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NEURONAL CELL DEATH

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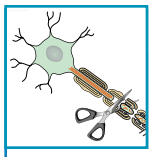

Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC. Neuronal Cell Death. *Physiol Rev* 98: 813–880, 2018. Published February 28, 2018; doi: 10.1152/physrev.00011.2017.—Neuronal cell death occurs extensively during development and pathology, where it is especially important because of the limited capacity of adult neurons to proliferate or be replaced. The concept of cell death used to be simple as there were just two or three types, so we just had to work out which type was involved in our particular pathology and then block it. However, we now know that there are at least a dozen ways for neurons to die, that blocking a particular mechanism of cell death may not prevent the cell from dying, and that non-neuronal cells also contribute to neuronal death. We review here the mechanisms of neuronal death by intrinsic and extrinsic apoptosis, oncosis, necroptosis, parthanatos, ferroptosis, sarmoptosis, autophagic cell death, autosis, autolysis, paraptosis, pyroptosis, phagoptosis, and mitochondrial permeability transition. We next explore the mechanisms of neuronal death during development, and those induced by axotomy, aberrant cell-cycle reentry, glutamate (excitoxicity and oxytosis), loss of connected neurons, aggregated proteins and the unfolded protein response, oxidants, inflammation, and microglia. We then reassess which forms of cell death occur in stroke and Alzheimer's disease, two of the most important pathologies involving neuronal cell death. We also discuss why it has been so difficult to pinpoint the type of neuronal death involved, if and why the mechanism of neuronal death matters, the molecular overlap and interplay between death subroutines, and the therapeutic implications of these multiple overlapping forms of neuronal death.

I. INTRODUCTION

A. The Meaning of Death

Physiologically, cell death is a highly regulated and crucial homeostatic mechanism required to maintain tissues, organ size, and function. One cell type that is for the most part exempt from the daily flux of cell birth and death is the neuronal cell, as following the developmental period, postmitotic neurons are required to be long-lived to maintain proper circuits. However, during the developmental period, cell death occurs in both mitotic neuronal precursor and postmitotic differentiated neuronal populations (86, 369, 585). Developmental programmed cell death plays an important role in the generation of functional circuitry within the nervous system through several mechanisms, such as elimination of neurons migrating to ectopic positions or innervating inappropriate targets, and competition of neurons for limiting amounts of pro-survival factors produced by targets (including glia) to achieve optimal target innervation (86).

While removal of excessive neurons in the developing nervous system is essential for formation of functional circuitry, aberrant neuronal cell death is one of the principal causes of acute and chronic neurodegenerative disease. Given the critical importance of neuronal death in the pathogenesis of neurodegenerative disease, it is perhaps not surprising that a PubMed search for "neuron AND cell death" returns over 40,000 results. Interest in neuronal death boomed in the 1990s with the discovery of molecular mechanisms governing apoptotic death and excitotoxic death. Despite this extensive research, novel observations regarding neuronal cell death continue apace, both refining and redefining known paradigms of cell death such as apoptosis and uncovering hitherto undescribed forms of cell death such as necroptosis, phagoptosis, ferroptosis, and pyroptosis.

Three important concepts have emerged from the recent literature on neuronal cell death: *1*) that there are many ways in which a neuron may die, *2*) that there exists extensive cross-talk (and at times ambiguity) between various

modes of cell death, and *3*) that neuronal cell death is not merely a "cell autonomous" event but it is often aided or triggered through interactions with neighboring neuronal and glial cells. In this review we aim to summarize the known mechanisms of neuronal cell death, both old and new, and examine the existing evidence that these various forms of cell death might play a role in the pathogenesis of neurological diseases.

Do neurons die in different ways from other cells? Yes and no, there are clearly similarities and differences from other cells. The complex wiring of the nervous system during development has resulted in programmed cell death of neurons that fail to wire correctly. The excitability of neurons causes a high ATP turnover and thus a sensitivity to ischemia-induced death. The presence of voltage-gated sodium channels makes neurons susceptible to sodium overload and swelling, while voltage-gated calcium channels make neurons susceptible to calcium overload. Glutamate-gated channels make neurons susceptible to excitotoxity. Long axons and dendrites make cellular transport challenging, and make those axons susceptible to rupture. The postmitotic nature of most neurons means they need to survive for decades with accumulating damage to proteins, lipids, DNA, and organelles. The inability to divide may also make neurons susceptible to death induced by cell-cycle reentry, and also makes neuronal death more important as postmitotic neurons cannot divide to replace lost neurons. However, neurons also undergo most of the common forms of cell death experienced by non-neuronal cells, although in their own inimical way, shaped by the unique life- and death-style of neurons.

B. A Brief History of Neuronal Cell Death and Cell Death Types

In 1842, Karl Vogt (701) first noted the requirement for physiological cell death when studying metamorphosis of amphibians. Neuronal cell death was first noticed as a loss of neurons during development. The first reports were in 1889 and 1892 by Beard(40, 41), who found a loss during development of a specific population of sensory neurons in the spinal cord of fish and skate. In 1906, Collin (128) reported cell death of dorsal root ganglion and motor neurons during embryonic development of chicks. In 1926, Ernst (197) reported that during development in vertebrates there was a substantial loss of neurons in the retina, trigeminal nerve, facial nerve, dorsal root ganglion, and anterior horn of spinal cord. He proposed that during normal development, neurons were overproduced and then excess eliminated by cell death in three phases during: *1*) regression of vestigial organs, *2*) morphological modifications of organ buds, and *3*) tissue remodeling. In 1951, Alfred Glücksmann (254) named these three phases of developmental cell death: phylogenetic, morphogenetic, and histogenetic cell death. Glücksmann also discussed neuronal cell death as a result of experimental limb amputation. Then in 1958, Hamburger (275) showed that after limb amputation in chick embryos, motor neurons were lost as a result of cell death rather than failure to divide or differentiate. In 1961, Hughes (308, 309) found that during tadpole development there was a large overproduction of motor neurons, most of which were then lost as a result of cell death, and cell death could be increased by limb amputation.The general concept of "programmed cell death" was formulated by Lockshin and Williams in 1964 (427). Subsequently, the concept of programmed cell death during development of the nervous system was expanded to a wide range of different neurons and organisms so that it is now widely accepted that about half of the neurons produced during development are lost by neuronal death during development (523).

In 1972, Kerr, Wyllie, and Currie (342) distinguished two types of cell death (apoptosis and necrosis) in human pathology samples based on cell morphology. They identified necrotic cells as swollen cells with swollen organelles, which subsequently burst to release their contents into the extracellular space. In contrast, apoptotic cells underwent nuclear and cytoplasmic condensation, followed by cell fragmentation and phagocytosis by phagocytes.

At about the same time as Kerr, Wylie, and Currie distinguished apoptosis and necrosis in pathology samples, Schweichel and Merker (607) distinguished three types of cell death during development and in response to toxins: type 1, condensation and fragmentation of single cells undergoing phagocytosis by neighboring cells; type 2, primary formation of lysosomes in dying cells, followed by phagocytosis by neighboring cells; and type 3, disintegration of cells into fragments that disappeared, without involvement of lysosomes or phagocytosis. Both papers helped establish the idea that cells could die in different ways. The paper of Kerr, Wylie, and Currie led to the bipartite distinction between apoptosis and necrosis, while Schweichel and Merkers' classification led to the tripartite distinction between *1*) apoptosis, *2*) autophagic cell death, and *3*) necrosis. Note however that Schweichel and Merkers' type 1 death is also consistent with phagoptosis, and type 2 death may be consistent with lysosomal cell death, paraptosis, or granulovacuolar degeneration.

In the late 1970s and early 1980s, Sulston mapped developmental cell death in *Caenorhabditis elegans*, including in the nervous system (654, 655), and in the 1990s, Horvitz and colleagues identified the genes and biochemical pathway carrying out this death, and showed that these were homologous to the genes and biochemical pathways carrying out apoptosis in mammals (reviewed in Ref. 292). The nematode pathway started with expression of Egl-1, which displaced Ced-4 from the inhibitor Ced-9, and Ced-4 was then able to recruit and activate Ced-3, which was a (caspase) protease degrading multiple cellular proteins.

This established the basic molecular machinery of apoptosis and led to the award of the Nobel prize to Sulston and Horvitz as well as Brenner (who presciently established the nematode as a model organism) in 2002.

The past decade or so of cell death research has been dominated by the discovery of different forms of necrosis. Until recently, necrosis was largely considered to be unregulated from a molecular perspective, and thus could not be targeted for pharmacological blockade. However, it is now understood that there are multiple different mechanisms that drive necrotic death in regulatable way, raising hopes for therapeutic targeting of such forms of death in pathologies such as stroke which feature a high number of neurons dying by necrosis.

Currently multiple forms of cell death are distinguished **(TABLE 1)** and defined either by *1*) the stimulus that induces death (e.g., excitotoxicity) or *2*) the mechanism that executes cell death (e.g., apoptosis). However, this distinction is not always clear. So, for example, excitotoxicity may induce cell death by one or more of the known execution mechanisms or its own unique mechanism. Also the execution mechanisms can be regarded as cell death "induced by" the identified executioner, e.g., apoptosis can viewed as cell death induced by Bax/Bak pores or caspase activation. Necrosis has come to mean plasma membrane rupture, but this is the terminal event for almost all forms of cell death, including apoptosis in pure cell cultures and in vivo when cells fail to be cleared by phagocytes (originally termed "programmed cell necrosis"), so it does not really indicate the mechanism involved.

C. The Structure of This Review

The structure of the rest of this review is to *1*) review the mechanisms that execute neuronal cell death, *2*) review how neuronal death is induced by significant stimuli, and *3*) review how stroke and Alzheimer's disease induce cell death.

II. MECHANISMS EXECUTING NEURONAL CELL DEATH

A. Apoptosis

1. Apoptosis by the extrinsic/death receptor pathway

Kerr et al. (342) first described apoptosis in terms of morphological changes which include chromatin condensation, nuclear membrane breakdown, cell shrinkage, and formation of small vesicular bodies near the cell surface, named apoptotic bodies.

Apoptosis is triggered by two principal pathways: the intrinsic (or mitochondrial) pathway and the extrinsic (or death receptor) pathway **(FIGURE 1)**. The extrinsic apoptosis pathway is triggered by the ligation of tumor necrosis factor (TNF)-family death receptors at the cell surface. Receptor ligation can result in recruitment of Fas-associated death domain protein (FADD), which in turn binds procaspase-8 molecules, allowing autoproteolytic processing and activation of caspase-8 to occur (465). Once activated, caspase-8 may in turn activate downstream effector caspases by direct proteolytic cleavage or indirectly by cleavage of the BH3-only protein Bid to produce tBid which translocates to mitochondria to induce Bax activation and mitochondrial outer membrane permeabilization (MOMP) as discussed below. TNF-α and Fas ligand can induce apoptosis of some neurons during inflammation (see sect. III*H*), and a Fas-dependent apoptotic pathway was described for motor neurons, involving p38, nitric oxide (NO), and from thence classical caspase-dependent apoptosis (267).

Table 1. *Comparison of different types of neuronal cell death*

Type of Neuronal Cell Death	Initiators	Mediators	Inhibitors	Outcome	ATP Fall	DNA Break	Pores
Apoptosis extrinsic	TNF-α, FasL	Caspases 8 + 3,6,7	Bcl-2	Phagocytosis	No	200 bp	No
Apoptosis intrinsic	Multiple	Caspases 9 + 3,6,7	Bcl-2, IAPs	Phagocytosis	No	200 bp	Mito outer
Necroptosis	TNF, IAP	RIPK1/3, MLKL	Caspase-8	Necrosis via MLKL	No	No	Plasma membrane
Parthanatos	DNA damage	PARP-1, PAR, AIF	Caspase-3	Necrosis via ATP $\downarrow$	Yes	Yes	No
Ferroptosis	Iron, glutamate	Fe^{2+}, ROS	GTH, GPX4	Necrosis via ROS	No	No	No
Pyroptosis	Inflammation	Caspase-1, gasdermin		Necrosis Inflam	No	No	Plasma membrane
Oncosis	Ischemia	Calpain I, ATP		Necrosis via ATP $\downarrow$	Yes	No	No
Lysosomal	Calcium, ROS	LMP, cathepsin $\downarrow$	HSP	Necrosis inflam	No	No	Lysosome
Autophagic	Stress	Beclin, autophagy	Bcl-2	Various	Yes	No	No
Phagocytic	Inflammation, stress	PS, CRT, opsonins	CD47	Phagocytosis	No	No	No
MitoPore	Calcium, ROS	Cyclophilin, ANT	ATP	Necrosis via ATP $\downarrow$	Yes	No	Mito inner

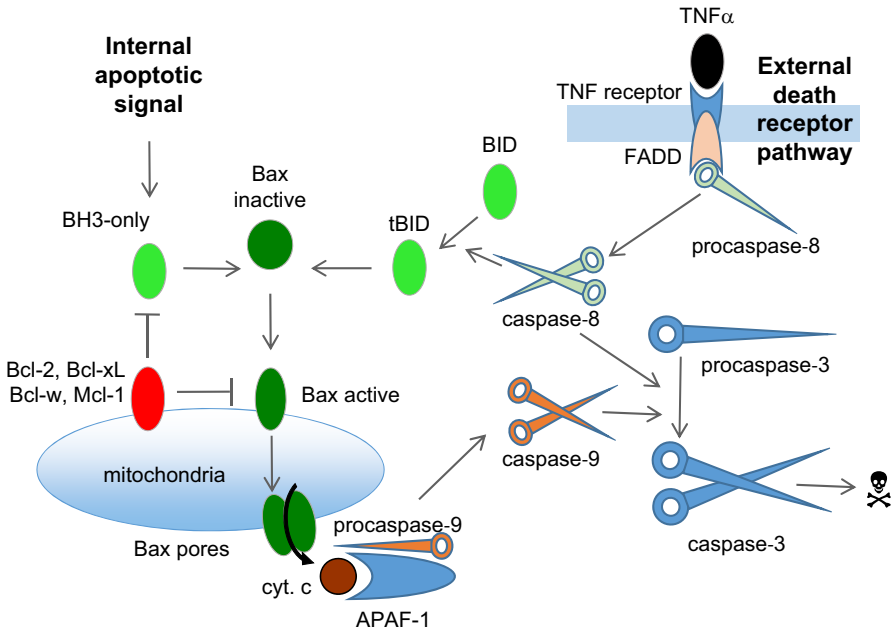

FIGURE 1. Overview of apoptosis. The internal (mitochondrial) pathway of apoptosis is triggered within the cell, causing expression or activation of BH3-only proteins that activate Bax (and/or Bak in some cells) to form pores in the outer mitochondrial membrane, releasing cytochrome *c* to bind APAF-1, activating caspase-9 to cleave and activate downstream caspases, which degrades cellular proteins. The external (death receptor) pathway starts outside the cell with death ligands activating death receptors to activate caspase-8, which either cleaves downstream caspases or cleaves and activates the BH3-only protein Bid. Anti-apoptotic proteins, such as Bcl-2, hold inactive Bax or BH3-ony proteins.

Biochemical evidence such as increased caspase-8 cleavage has long indicated that extrinsic apoptosis may play a causal role in neuronal death in stroke and seizure models (284, 293, 401), but definitive proof of caspase-8 requirement for death in these models was lacking as deletion of caspase-8 (and FADD) is embryonic lethal in mice, due to a recently discovered pro-survival function of the FADD-caspase-8 containing complex in suppression of the regulated necrosis pathway necroptosis (see sect. II*B1*) (333, 518, 687, 792). However, Krajewska et al. (364) addressed this issue through the generation of mice lacking expression of caspase-8 specifically in neuron cell types and showed that neuron-specific caspase-8 deletion rendered neurons resistant to apoptosis induced by TNF-α receptor ligation in vitro and resulted in increased neuronal survival associated with reduced activation of caspase-3 following traumatic brain injury or seizure-induced brain injury. Thus inhibition of the extrinsic pathway holds promise for development of novel neuroprotective agents in acute neurodegenerative pathologies.

2. Apoptosis by the intrinsic/mitochondrial pathway

The intrinsic apoptosis pathway centers on the regulation of MOMP by the Bcl-2 family proteins **(FIGURES 1 AND 2)**. Members of the Bcl-2 family share homology within at least one of up to four Bcl-2 homology (BH) domains which are required for the homo- and heterotypic interactions that determine the decision to undergo MOMP. The pro-apoptotic members Bax and Bak contain BH1–3 and are thought to be almost entirely essential for the execution of apoptosis via the intrinsic pathway (107, 722, 807), although a novel but as yet unknown Bax/Bak-independent intrinsic apoptotic pathway has recently been reported (787). Neurons are unique in that Bak is expressed as an alternately transcribed product (N-Bak) that is translationally repressed and does not participate in apoptosis (318). Thus the induction of intrinsic apoptosis in neurons is entirely dependent on Bax expression and activation, and indeed deletion and inhibition of Bax prevents aberrant neuronal cell death in a number of in vitro and in vivo models of neurodegeneration (146, 147, 153, 244, 258, 330, 466, 636, 670, 695, 732, 736, 738). Of note, Bok, a Bcl-2 family member, was recently described to induce MOMP and apoptosis in non-neuronal (146) cells following disruption of proteasome or the endoplasmic reticulum-associated degradation pathway (426). Unlike Bax and Bak, Bok appears unresponsive to signals from other Bcl-2 family proteins, is constitutively active, and is regulated primarily through degradation. The significance of this mechanism in neurons is uncertain however, as although Bok is highly expressed in mouse brain, its expression was demonstrated to be dispensible for proteasome- and excitotoxicity-induced neuronal cell death, even in the absence of Bax expression (146). Thus regulation of MOMP and intrinsic apoptosis in neurons appears to center on control of Bax activation.

In healthy primary neuronal culture, the majority of Bax molecules exist as cytosolic monomers in which the NH_2-terminal alpha helix α1 and the COOH-terminal α9 are constrained and embedded within the protein structure. Both α1 and α9 helices become exposed upon receipt of an apoptotic stimulus. Exposure of the COOH-terminal α9 mediates targeting of Bax to the outer mitochondrial membrane. Following mitochondrial translocation, Bax projects its NH_2 terminus and forms dimers and then homo-oligomers that result in MOMP and cytochrome *c* release (143, 167, 239, 345). The exact mechanisms by which Bax oligomers induce MOMP and cytochrome *c* release are not fully understood; however, several recent studies have pro-

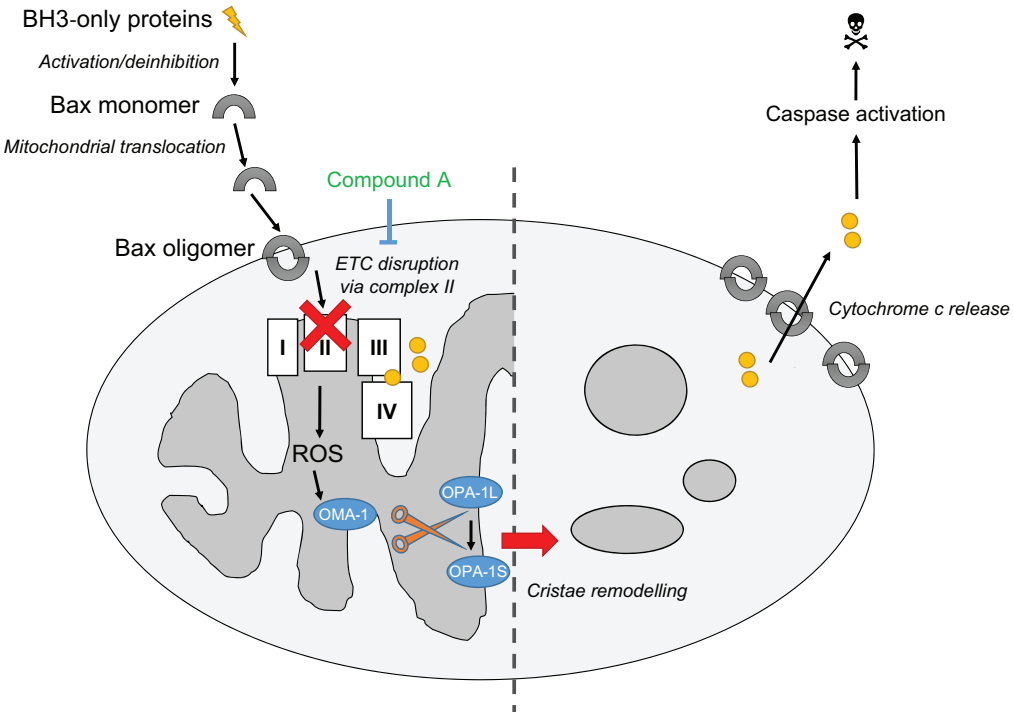

FIGURE 2. Bax signaling at the mitochondria. BH3-only proteins activate Bax to oligomerize and form pores in the outer mitochondrial membrane, causing cytochrome *c* release and inhibition of complex II, inhibition of respiration and ROS production, activating the protease OMA-1 to remodel the inner mitochondrial membrane, which enables greater cytochrome *c* release, which triggers caspase activation and apoptosis.

vided novel mechanistic insights. Central $\alpha 5$ and $\alpha 6$ helices of Bax may insert in plane with the outer mitochondrial membrane, potentially inducing curvature and MOMP (52, 249, 724). Upon induction of apoptosis, Bax forms ring structures of various size and shape likely to represent pores, which are devoid of other mitochondrial proteins (262, 591). Formation of Bax rings on the mitochondria alone is not sufficient for maximal cytochrome *c* release, and other proteins involved in mitochondrial structural dynamics such as Drp1 are implicated (262).

Indeed, activation of the mitochondrial protease OMA1 downstream of Bax oligomerization may drive cristae remodeling and cytochrome *c* release by cleavage and activation of OPA1 (327). This mechanism appears to be present and relevant in neuronal populations (362). OPA1 is cleaved in primary neurons undergoing apoptosis and in the central nervous system (CNS) during oxygen-glucose deprivation, implicating this mechanism during stroke (21, 430). OPA1 dysfunction has also been linked to neurodegeneration in Parkinson's disease, as complex I-inhibiting parkinsonian toxins induce disruption of OPA1 complexes, facilitating cytochrome *c* release and sensitizing dopaminergic neurons to apoptotic stimuli (559). In what is likely to become a seminal study, Jiang et al. (328) recently described a novel, Bax/Bak-dependent apoptotic mechanism involving disruption of complex II of the electron transport chain and subsequent reactive oxygen species (ROS) generation driving OMA1 activation and downstream OPA1 processing **(FIGURE 2)**. Using a pharmacological screen of over 200,000 compounds, they identified compound A, which through covalent modification of succinate dehydrogenase B was able to stabilize complex II and prevent Bax/Bak-induced complex II disruption, preventing OPA1 cleavage and crista remodeling which in turn reduced cytochrome *c* release and downstream apoptotic signaling. Critically, while conventional caspase inhibitors provided only a temporary block of cellular demise following Bax activation, compound A resulted in long-term survival and proliferation of cells, despite activation and oligomerization of Bax at the mitochondria (see sect. II*B3*). Importantly, compound A was demonstrated to exert substantial neuroprotective effects in a rat model of 6-hydroxydopamine-induced Parkinson's disease. Thus inhibition of Bax-mediated disruption of the electron transport chain in neurons undergoing apoptosis holds significant promise as a therapy in neurodegenerative disorders.

As outlined above, clearly, the regulation of Bax oligomerization is paramount in determining death commitment point. Bax is held in check through inhibitory interactions with anti-apoptotic Bcl-2 family members (34, 675, 777), although other non-Bcl-2 family proteins may also inhibit Bax such as humanin (265), 14-3-3 (513), clusterin (791), and parkin (100).

BH3-only proteins are a pro-apoptotic group of Bcl-2 family proteins that induce apoptosis by causing deinhibition of Bax. The exact mechanism whereby BH3-only protein activation results in Bax translocation to the mitochondria and subsequent MOMP is controversial (178). It is clear that different BH3-only proteins display selective binding to anti-apoptotic Bcl-2 family members (104, 344, 373). For example, while the BH3-only proteins Bim, Bid, and Puma bind with high affinity to all anti-apoptotic Bcl-2 proteins [with the possible exception of Bcl-B/Diva, although the

significance of this is unknown in neurons (562)], other BH3-only proteins show remarkable specificity. Binding of BH3-only proteins to anti-apoptotic Bcl-2 proteins can displace Bax and deinhibit it, allowing Bax homo-oligomerization and MOMP to occur. The ability of Puma, Bim, and Bid to bind with high affinity to all anti-apoptotic Bcl-2 proteins may provide an explanation for their relatively high potency in terms of inducing apoptosis compared with other BH3-only proteins (729). It has also been postulated that in addition to de-inhibition of Bax, certain BH3-only proteins are capable of directly binding to and activating Bax, and that this "direct activation" is necessary for induction of MOMP (344, 345, 391, 566, 690) **(FIGURE 1)**. Studies from Walensky and colleagues shed light on the potential mechanisms of "direct activation" of Bax, identifying a site involved in Bax activation by BH3 peptides that is spatially distinct from the site involved in interaction with anti-apoptotic Bcl-2 family members (239, 240).

Generation of mice deficient for all three proposed direct activator BH3-only proteins, Bim, Bid, and Puma, resulted in partial but not complete phenocopy of Bax/Bak double knockout mice (566). Although this study highlights the relative importance of this subset of BH3-only proteins in causing apoptosis in a variety of cell types, the lack of complete phenocopy of the Bax/Bak double knockout argues against the absolute requirement for direct activation for Bax activation or indicate that other direct activators may exist (for which there exists some experimental support) (110, 690, 697). However, recent use of CRISPR technology to generate cells deficient for all eight BH3 proteins (Puma, Bim, Bid, Bad, Bmf, Hrk, Noxa, Bik) demonstrated that Bax/Bak-dependent apoptosis could be triggered in the absence of BH3-only proteins by simultaneous knockdown of Mcl-1 and Bcl-xL. Thus direct activation does not appear to be an absolute requirement for induction of intrinsic apoptosis, while de-inhibition of Bax/Bak does (516). Open questions regarding the de-inhibition model remain however, such as the observations that mitochondrial localization plays an important role in the activation of Bax by Puma, Bim, and tBid (431, 719, 728, 778).

In vitro studies in primary neuronal cultures have highlighted the importance of the BH3-only proteins Puma and Bim in causing apoptosis in response to a plethora of toxic stimuli, including DNA damage, reactive oxygen species, endoplasmic reticulum stress, proteasomal inhibition, amyloid-β, and excitotoxic stress. Based on current evidence (or to be strictly accurate a lack of published evidence) other BH3-only proteins such as Noxa and Hrk do not seem to play such a dominant role in neuronal apoptosis (12, 49, 130, 150, 213, 298, 460, 646, 719, 732). Evidence supporting a causal role for Puma, Bid, and Bim in causing neuronal death in vivo has been reported in models of neonatal hypoxic-ischemic injury, cerebral ischemia, and seizure-induced death, although the importance of these individual proteins varies depending on the stimulus, time points examined, and region of the brain involved (for review on this topic, see Ref. 195 and more recently Ref. 455). Furthermore, a novel BH3-only protein, Bcl-2-like molecule short form (Blm-s), was recently discovered and found to be enriched in immature postmitotic neurons, rendering them susceptible to apoptotic stimuli (420).

In sum, Puma, Bim, Bid, and Bax-mediated MOMP can drive neuronal loss in a variety of experimental neuropathologies, particularly in young animals. While BH3-mimicking compounds such as ABT-199 have been successfully developed for the induction of apoptosis in tumor cells, the generation of compounds with the ability to block Bax activation by BH3-only proteins potentially represents more of a challenge. Some progress has been made towards development of small molecule inhibitors of Bax. A compound that inhibited Bax-mediated MOMP and cytochrome *c* release was reported to protect hippocampal neurons in vivo following global ischemia, although hemolytic side effects of this compound have hindered further development (229, 299). As mentioned above, Bax can interact with a number of non-Bcl-2 family proteins in the cytosol, and a pentapeptide derived from the protein Ku70 was shown to exhibit neuroprotective effects in an in vivo model of global cerebral ischemia (277). The recent identification of an antibody that can activate mitochondrial Bax but prevent mitochondrial translocation of cytosolic Bax raises hope that development of further Bax-inhibiting compounds may be feasible (316). As discussed above, the recent discovery of a compound that can inhibit cytochrome *c* release and apoptosis as well as promote long-term survival downstream of Bax activation holds significant promise for the development of neuroprotective apoptosis inhibitors (328).

3. Apoptotic neuronal death after MOMP

Upon induction of MOMP, several apoptogens including cytochrome *c*, Htra2, Smac/Diablo, apoptosis inducing factor (AIF), and endonuclease G (Endo G) can be released from mitochondria to the cytosol. Of these apoptogens, the role of cytochrome *c* in induction of apoptosis is best understood. Once in the cytosol, cytochrome *c* binds to Apaf-1 and, together with dATP, forms a large heptameric molecular structure, the apoptosome, that then recruits pro-caspase-9. Recruitment of pro-caspase-9 molecules to the apoptosome allows autocleavage to produce mature caspase-9 which in turn cleaves and activates pro-caspase-3 (64). Caspase-3 and other executor caspases cleave a plethora of target proteins, mediating the systematic disassembly of cells undergoing apoptosis (for an up-to-date list of caspase substrates, see the searchable database at http://cutdb.burnham.org/ and Ref. 313). Some of these substrates are proteins whose cleavage by caspases is thought to potentiate their toxicity in neurodegenerative diseases (82).

Neurons control apoptosome assembly and activity through several mechanisms. The oxidation state of cytochrome *c* affects its ability to induce apoptosis, with oxidized cytochrome *c* more potent in induction of caspase activity and apoptosis than reduced cytochrome *c* (74). The generation of reduced glutathione (GSH) by preferential oxidation of glucose via the pentose phosphate pathway in neurons may therefore result in reduction of cytosolic cytochrome *c* to an extent sufficient to inhibit induction of caspase activity and subsequent apoptosis even after MOMP and cytochrome *c* release have occurred (297, 689). Indeed, in mature cultures of sympathetic neurons, when cytochrome *c* release was induced by nerve growth factor (NGF) deprivation in the presence of a caspase inhibitor, then readdition of NGF resulted in cytochrome *c* being resynthesized and refilling the mitochondria and the neurons were rescued (205). It is relevant to note that neuronal expression of caspase-3, caspase-9, and Apaf-1 is strongly reduced during maturation (305, 359, 735, 746, 804). Synaptic activity can also suppress expression of Puma, Apaf-1, and caspase-9, while in developing mice, blocking synaptic activity causes neuronal apoptosis via induction of Puma expression (392).

Generation of mice lacking expression of either Apaf-1 (97, 773), caspase-9 (268, 371), or caspase-3 (372, 733) has demonstrated the importance of the intrinsic apoptotic pathway for apoptosis both in vivo and in vitro. Deletion of any of these genes causes decreased apoptosis during brain development, resulting in hyperplasia in the CNS. Due to these extreme phenotypic effects, studies examining the genetic requirement for these proteins in causing neuronal loss in disease models has been limited, although a causal role for caspase-3 in ischemic death has been reported (383). In addition, cells derived from animals lacking expression of either Apaf-1, caspase-9, or caspase-3 display resistance to apoptosis induced by a variety of apoptotic stimuli, the exception being activators of the extrinsic apoptosis pathway.

It must be noted that inhibition of caspases by pharmacological means often offers only temporary rescue from cell death, with ensuing dissipation of the mitochondrial membrane potential resulting in the induction of alternative modes of cell death. However, work using mice harboring a point mutation in cytochrome *c* that inhibits apoptosome formation but not oxidative phosphorylation has demonstrated that apoptosome formation can play an important role in induction of death of motor neurons following injury in vivo, even if this protection was not as complete as that offered by inhibition of MOMP by deletion of Bax or overexpression of Bcl-2 (279, 338). Apoptotic cell death can be resistant to caspase inhibitors also because MOMP releases AIF from mitochondria, and AIF can cause DNA cleavage and caspase-independent cell death (see sects. II*B2* and III*E*). Moreover, apoptosome assembly requires ATP, and thus neuronal apoptosis does not occur if ATP falls below a certain threshold, as may occur during ischemia or experimental oxygen-glucose deprivation (502). For these reasons, it would seem that development of inhibitors of apoptosis that block MOMP would provide a more effective neuroprotective strategy than inhibition of caspase activity downstream of MOMP.

4. Secondary necrosis and phagocytosis following apoptosis

Apoptotic cells are normally recognized and engulfed by neighboring cells and phagocytes in a process called efferocytosis (from the latin *effere* for "to take to the grave"), preventing the escape of intracellular components from dying cells into the extracellular milieu and thereby avoiding unnecessary and potentially neurotoxic inflammatory responses. The main mechanism for mediating this engulfment is caspase cleavage of the transporters for phosphatidylserine, resulting in cell surface exposure of phosphatidylserine, which is recognized as an "eat me" signal by phagocytes (see sect. II*E*).

In situations where efferocytosis capacity is impaired or overwhelmed, apoptotic cells undergo a process termed secondary necrosis in which the plasma membrane ruptures and intracellular contents are released, triggering inflammatory responses. One mechanism by which apoptosis can cause necrosis in neurons is caspase cleavage of the plasma membrane calcium pump, resulting in calcium overload of the cell (606).

More recently it was found that DFNA5, a gasdermin D-related protein, can form necrosis-inducing pores at the plasma membrane following caspase-3-dependent cleavage, in a manner analogous to the cleavage and activation of gasdermin D by caspase-1/11 during pyroptosis (577). The discovery of a pore-based plasma membrane rupture mechanism in secondary necrosis may explain some of the phenotypic similarities of this death compared with necroptosis and pyroptosis, and further supports the notion that more undiscovered mechanisms of necrosis are likely to exist (685). It is not inconceivable that these proteins may be cleaved by other proteases to yield an active pore-forming fragment.

B. Necrosis

In 1858, Virchow used the word *necrosis* to refer to the passive, degradative changes to cells and tissues as a result of pathology (698), and some pathologists still use the term to refer to the general degradative changes to tissues after pathology or death. However, Kerr et al. (342) contrasted the cellular features of necrosis with those of apoptosis and noted that necrotic cells rupture and release of intracellular contents triggering an inflammatory response, whereas ap-

optotic cells were removed (by phagocytosis) before rupture, preventing inflammatory damage to neighboring cells. Thus, in the brain, necrosis may represent a "double whammy" of irreversible neuronal loss coupled with initiation or potentiation of potentially damaging neuroinflammation.

More recently, the meaning of the term *necrosis* has become synonymous with rupture of the plasma membrane, and it has become clear that there are many different mechanisms that can lead to this end. Regulated (or programmed) necrosis has been distinguished from unregulated necrosis on the basis that regulated necrosis is genetically controlled and involves active cellular processes that can in principle be blocked, whereas unregulated necrosis involves passive processes (for example, as a result of tissue trauma or toxins acting directly on the plasma membrane) that may be difficult or impossible to block (684). However, this distinction is currently poorly defined and could simply reflect our ignorance of further mechanisms of "unregulated" necrosis. The various forms of regulated necrosis include necroptosis, parthanatos, ferroptosis, pyroptosis, autolysis, and mitochondrial permeability transition.

Oncosis is a term sometimes used by pathologists to refer to cell death accompanied by swelling of the cells and their organelles (721). The name oncosis is derived from the Greek word "swelling," and was coined by von Recklinghausen in 1910 (440). It may be an example of unregulated necrosis, although this depends on the definition. Oncosis is typically seen in infarcts after tissue ischemia. Thus "oncosis" has overlap with "necrosis" as defined by Kerr, Wylie, and Currie. The term is often used to mean "cell death induced by ischemia," but note that ischemia can induce many different forms of cell death (see sect. IV*A*). We will use the term *oncosis* here to refer to necrotic cell death mediated by ATP depletion and cell swelling. This is an important form of cell death induced by ischemia, but can also be induced by mitochondrial dysfunction and/or excessive ATP consumption **(FIGURE 3)**. Ischemia deprives cells of energy substrates, leading to ATP depletion, followed by failure of the sodium pump, leading to *1*) swelling of the cell that may eventually rupture the plasma membrane, and *2*) plasma membrane depolarization that can open voltage-gated sodium and calcium channels. ATP depletion also causes failure of the calcium pumps, elevating cytosolic calcium, which can induce necrosis via activation of *1*) proteases, *2*) phospholipases, and *3*) mitochondrial permeability transition. There are number of calcium-activated phospholipases that may contribute to neuronal death induced by stroke or Alzheimer's disease (599). In the brain, ATP depletion also results in release from neurons and astrocytes of glutamate, which, together with neuronal depolarization, activates NMDA receptors that flood the neuron with calcium and sodium (excitoxicity) (see Ref. 691 and **FIGURE 3**). These processes contribute to neuronal death during ischemia, but may also contribute to death of astrocytes after focal cerebral ischemia or persistent oxygen-glucose deprivation (93, 115, 227).

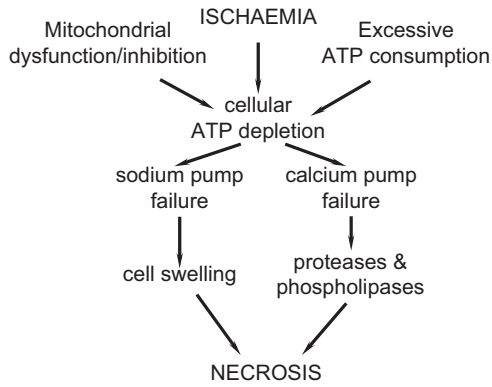

FIGURE 3. Oncosis. Ischemia, mitochondrial dysfunction, and/or excessive ATP consumption cause cellular ATP depletion, resulting in 1) failure of sodium pump resulting in cell swelling to rupture, and 2) failure of calcium pumps resulting in calcium activation of proteases and phospholipases that degrade the cell.

1. Necroptosis

The best-characterized form of regulated necrosis is necroptosis. Necroptosis is defined as a necrotic cell death dependent on the kinase activity of Receptor Interacting Kinase 1 (RIP1), kinase activity of RIP3, and expression of the pseudokinase Mixed Lineage Kinase Domain-like (MLKL) (231). Upon receipt of a necroptosis-inducing stimulus, RIP1 phosphorylates and activates RIP3, which in turn phosphorylates and activates MLKL, forming a complex termed the necrosome (133, 231). Activation of the necrosome results in the oligomerization of phosphorylated MLKL at the plasma membrane, cell rupture, and necrosis **(FIGURE 4)**. This is due to pore-forming activity of the MLKL oligomer or modulation of Na^+ or Ca^{2+} channels (181, 300, 484, 710, 737). Phosphorylation of MLKL and formation of the necrosome are currently thought to occur primarily during necroptosis and are thus considered cellular markers of necroptosis (684). However, in specific cellular contexts, necroptosis proteins RIPK1, RIPK3, and MLKL can participate in alternative processes including activation of the inflammasome (133). Therefore, absolute proof of necroptosis requires verification that activation of the necrosome occurs in concert with necrosis that can be inhibited by pharmacological or genetic inhibition of RIPK1, RIPK3, or MLKL. Notably, RIPK1 also has pro-survival functions that are independent of its kinase activity, and via this route it is capable of inhibiting developmental necroptosis mediated by ZBP-1/RHIM/RIPK3/MLKL (408, 501).

The interplay between necroptosis and apoptosis signaling is complex. In many non-neuronal cells, including microglia, immune stimuli such as TLR3/4 ligation or TNF-α

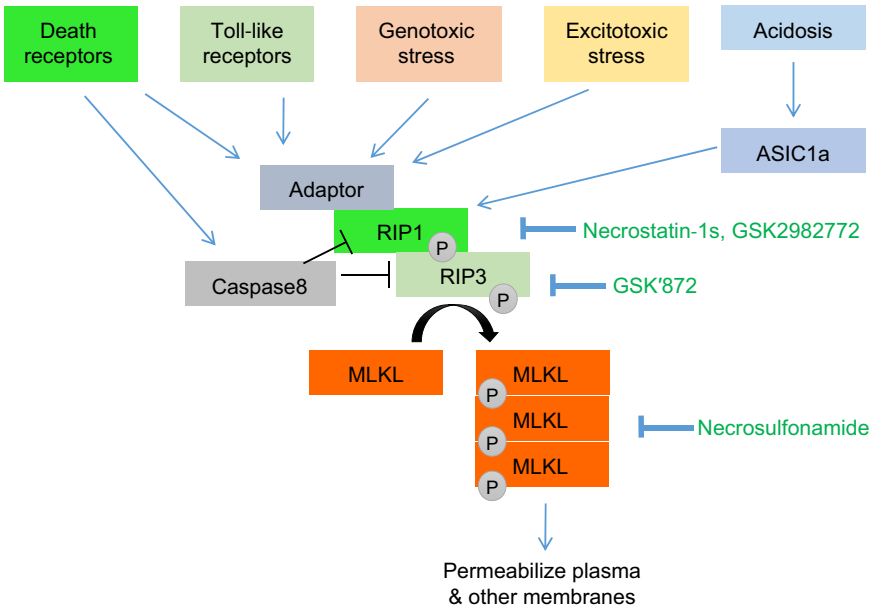

FIGURE 4. Necroptosis. Activation of death receptors or Toll-like receptors activates NF-κB-mediated inflammation via ubiquinated RIPK1, but deubiquinated RIPK1 can form a complex with RIPK3 that can induce necrosis if and only if caspase-8 is inhibited, preventing cleavage of RIPK1. RIPK1 phosphorylates RIPK3, which phosphorylates MLKL1, which permeabilizes membranes.

signaling induce caspase-8-mediated suppression of necrosome formation, and in these contexts, caspase-8 inhibitors can trigger necroptosis (216, 347). Evidence regarding this interplay in neurons is mixed. Studies on the HT22 hippocampal cell line have shown that TNF-α in combination with caspase inhibitors elicits necroptosis dependent on RIP1 kinase activity, RIP3 expression, and MLKL expression. Necrosome formation is present and requires Akt/mTOR activity, which may be unique to neuronal cell types (415, 416). The relatively high susceptibility of primary cortical neurons to 24(*S*)-hydroxycholesterol-induced necroptosis has been linked to the near undetectable levels of caspase-8 protein in these cells (751). In contrast, primary cerebellar granule neurons and forebrain neurons do not undergo necroptosis following stimulation with TNF-α or TLR3/4 ligands in combination with caspase inhibitors, suggesting unique mechanisms governing necroptosis induction in certain postmitotic neuronal populations (216, 347). These intricacies are further illustrated by the recent finding that primary hippocampal neurons undergo TLR7-dependent necroptosis triggered by miR-21-containing extracellular vesicles, without requirement for caspase inhibition (768). Human embryonic stem cell-derived motor neurons undergo RIP1 kinase and MLKL-dependent necroptosis when exposed to astrocytes derived from sporadic ALS patients or SOD1 mutant mice. Intriguingly, this death is also dependent on Bax but not on caspase activity, potentially placing Bax upstream of a necroptosis-inducing pathway in motor neurons. Of note, RIPK3 kinase activity appears required to suppress RIPK1 and caspase-8-mediated apoptosis in specific non-neuronal contexts and several RIPK3 kinase inhibitors, while inhibiting necroptosis can induce apoptosis (444). Thus care is required when interpreting the outcomes of experiments where necroptosis and apoptosis are inhibited (133).

Many studies have demonstrated neuroprotective effects associated with chemical or genetic inhibition of necroptosis signaling in models of neurodegeneration. In in vivo models of stroke, necroptosis inhibition results in reduced infarct size and protection of CA1 hippocampal neurons (156, 693, 769). Necroptosis of CA1 hippocampal neurons is associated with increased expression of RIPK3, which is prevented by RIPK1 inhibition (769). Upregulation of RIPK3 protein following stroke in vivo and following oxygen-glucose deprivation of primary hippocampal neurons occurs in an NMDAR-dependent manner and is required for necrosis, implying necroptosis can be triggered by excitotoxic stress (693). This conclusion is supported by reports that RIPK1 inhibition inhibits glutamate-induced excitoxic death of cortical neurons and HT22 cells (406, 741). Inhibition of necroptosis results in reduced neuroinflammation following neonatal ischemia-reperfusion injury, consistent with earlier reports in non-neuronal systems that necroptosis is pro-inflammatory (101). In a model of acidosis, which occurs after stroke, cortical neurons undergo RIP1-dependent necroptosis (717). Acidic conditions induced association of RIP1 with acid-sensing ion channel 1a (ASIC1a), which was required for RIPK1 activation and necroptosis. This association of ASIC1a and RIP1 along with RIP1 phosphorylation and activation was detectable in mouse brain following experimental stroke, indicating its potential physiological relevance. Necrostatin-1 is neuroprotective in models of spinal cord injury and does not exert anti-apoptotic activities in this context (337, 415, 715). In keeping with seeming absence of inhibition of Nec-1 on neuronal apoptosis, dual blockade of apoptosis and necroptosis has been shown to increase neuroprotection in vivo compared with inhibition of individual death modalities (715, 742). Necrostatins are also neuroprotective in models of traumatic brain injury, and the neuroprotective effect of controlled hypothermia in traumatic brain injury may be re-

lated to inhibition of RIPK1, RIPK3, and MLKL protein (419, 776). As discussed above, necroptosis of motor neurons may contribute to pathology in amyotrophic lateral sclerosis (ALS) (563). Necroptosis in glial cells, particularly oligodendrocytes, may also play an important role in ALS. Optineurin (mutations of which are associated with ALS) deficiency sensitizes oligodendrocytes to die by RIPK1-, RIPK3-dependent necroptosis, which in turn triggers an inflammatory cascade resulting in axonal damage and pathology (315).

In sum, neuronal necroptosis may play a critical role in acute and chronic neurodegenerative disorders. Inhibition of necroptosis appears to exert neuroprotective effects through rescue of neurons. In addition, necroptosis inhibition is associated with reduced neuroinflammation, which could be due to reduced DAMP release from rescued neurons, but may also be related to non-cell death-related immunomodulatory functions of necroptosis pathway signaling (488). Another major caveat of this body of work is that the majority of studies have implicated necroptosis through the use of Nec-1, an inhibitor of RIP1 kinase activity that also inhibits IDO activity (686). A more specific Nec-1 derivative, 7-Cl^{-}O-Nec-1 (662), is available, but further studies using genetic inhibition and novel pharmacological regulators of necroptosis are required to definitively confirm the importance of necroptosis in neurodegeneration. Furthermore, the specific mechanisms that govern the initiation of neuronal necroptosis are relatively poorly understood and are likely to be numerous. As these are elucidated they could offer further opportunities for therapeutic intervention. Finally, in a manner analogous to the delay (but not prevention) of apoptotic death by caspase inhibitors, it has been noted that inhibition of RIPK3 and MLKL in non-neuronal cells may prevent RIPK1-dependent necroptosis but only delay death which remains RIPK1-dependent and resembles apoptosis (565). Thus it will be important to further study whether necroptosis inhibition can provide long-term neuroprotection in neurodegenerative models in vitro and in vivo.

2. Parthanatos

Parthanatos (from Thanatos, the Greek personification of death) is a type of regulated necrosis that is dependent on the activity of poly(ADP-ribose) polymerases (PARP) (200). PARP-dependent death requires AIF translocation from the mitochondria to the nucleus and subsequent chromatin degradation (109, 141, 704, 780) **(FIGURE 5)**. The product of PARP activity, PAR, induces AIF nuclear translocation and also causes bioenergetic collapse through inhibition of the glycolytic enzyme hexokinase, resulting in necrosis (8, 14). NAD^{+} depletion resulting from excessive PARP activity further compromises cellular metabolic processes to promote death (8). PARP-1-induced AIF nuclear translocation also requires cyclophilin A, which complexes with AIF upon mitochondrial release (668, 803). Inhibition of cyclophilin A-AIF complex formation prevents glutamate-in-

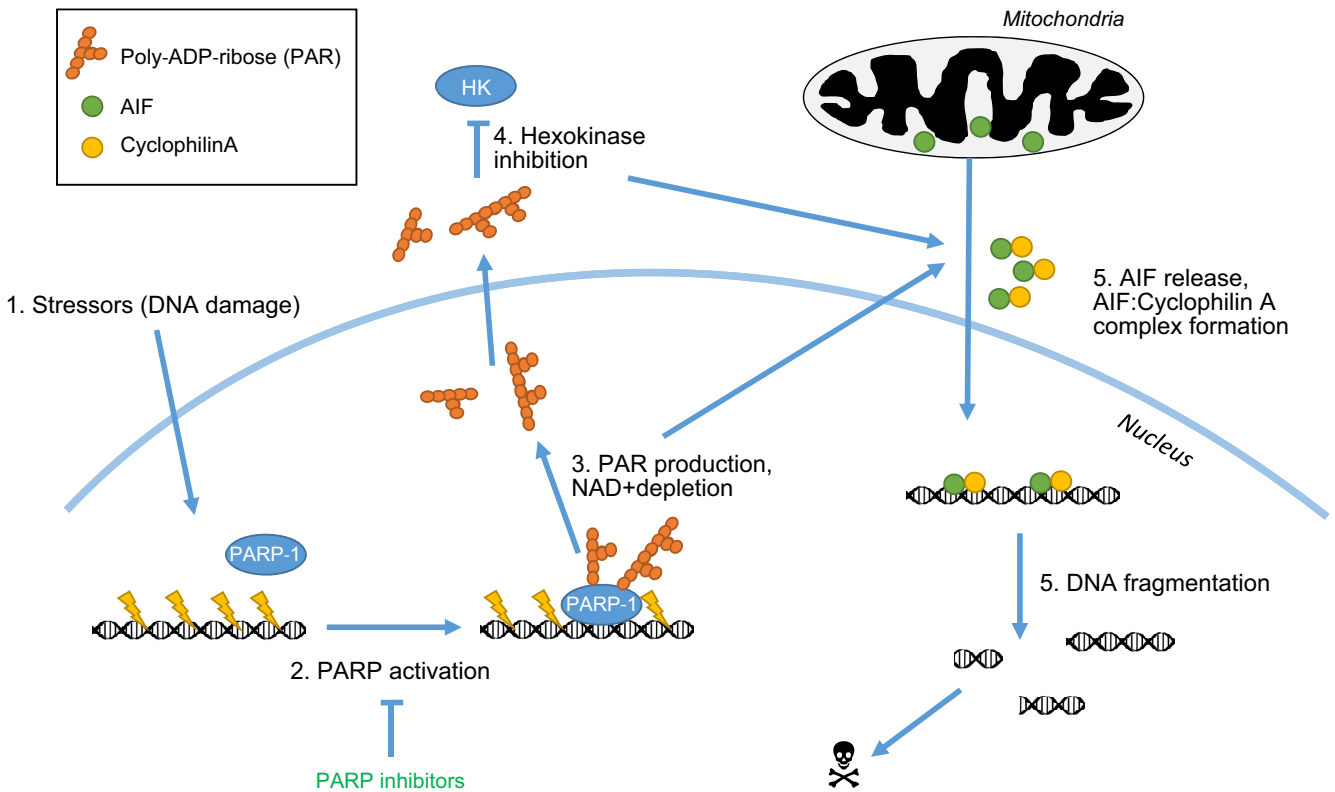

FIGURE 5. Parthanatos: poly ADP-ribose polymerase 1 (PARP-1)-mediated cell death.

duced death of HT22 hippocampal cells (182). AIF release downstream of PARP activation in neurons can also involve the BH3-only proteins Bid and Bnip3 (141, 182, 379, 433) and/or activation of mitochondrially localized calpain (92, 702).

Considerable evidence exists to support a role for parthanatos in various neurodegenerative disorders. Genetic or pharmacological inhibition of PARP-1 and (in some cases) PARP-2 reduces AIF nuclear translocation and neuroprotection in models of stroke (92, 141, 191, 194, 403, 433), excitotoxic stress (374, 379, 448, 702, 704, 793), Parkinson's disease (348, 449, 781), and traumatic brain injury (649). Furthermore, genetic or pharmacological modulation of AIF also offers neuroprotection in models of stroke, excitotoxicity, and traumatic brain injury (109, 182, 635, 672, 713, 803). In addition, increased AIF activation and nuclear translocation is observed in relevant nervous system regions of patients with Parkinson's disease (84), Alzheimer's disease (385, 781), and ALS (625). Of note, combined inhibition of parthanatos and apoptosis (downstream of MOMP) results in increased and prolonged neuroprotection (109, 541), supporting the notion that inhibition of multiple cell death modes may be required to achieve significant long-lasting neuroprotection.

3. Ferroptosis

Recent work has led to the identification of ferroptosis, an iron-dependent form of regulated necrosis that may also be triggered in neurons by excitotoxic stress. Ferroptosis is morphologically and biochemically distinct from apoptosis, necrosis, necroptosis, and autophagic cell death and was initially identified as a mode of death responsible for the toxic action of a novel group of compounds (e.g., erastin) that displayed selective lethality towards Ras-transformed cell lines (175, 745, 764). Induction of ferroptosis with erastin results in cell death lacking the chromatin condensation and nuclear shrinkage of apoptosis as well as the cellular and organellar swelling of necrosis, and it can occur in the absence of any obvious alterations in autophagy. Morphologically, mitochondrial shrinkage may be a unique hallmark distinguishing it from alternative forms of death (175). Ferroptosis appears to require the iron-dependent lipid peroxidation of polyunsaturated fatty acids, and although the mechanisms that result in necrosis downstream of lipid peroxidation remain unclear, they may involve AIF release from mitochondria and nuclear translocation (530, 613, 761). Thus ferroptosis may share late-stage death-inducing mechanisms with parthanatos. In many cell types, including neurons, glutathione peroxidase 4 (Gpx4) plays a critical role in preventing excessive lipid peroxidation in a glutathione-dependent manner, and inhibitors of Gpx4 can trigger ferroptosis (762). Indeed, Gpx4 is essential for embryonic development, and induced whole-body knockout of Gpx4 in adult mice results in rapid death accompanied by loss of hippocampal neurons (772). Further refinement of these studies using neuronal-specific inducible knockout mice shows that motor neurons are particularly sensitive to Gpx4 depletion, undergoing nonapoptotic neuronal death with hallmarks of ferroptosis (103). Gpx4 knockout-induced motor dysfunction is partially delayed by dietary supplementation with the lipid-based antioxidant vitamin E. Of note, neuronal death induced by Gpx4 knockout is accompanied by astrocyte and microglial proliferation and activation, consistent with a role of ferroptosis as an immunogenic form of necrotic cell death (103, 772). Conditional deletion of Gpx4 in forebrain neurons resulted in neurodegeneration and cognitive dysfunction (273).

Supply of glutathione to Gpx4 is dependent on export of glutamate and import of cystine via system x_c^-, inhibition of which also triggers ferroptosis (176) **(FIGURE 6)**. Thus, during excitotoxic stress, excessive extracellular glutamate may serve to inhibit system x_c^- resulting in excitotoxic death with features of ferroptosis (288, 763). Importantly, ferroptosis may be inhibited pharmacologically through iron chelation (e.g., deferoxamine) or by antioxidant moieties capable of scavenging lipid ROS (e.g., ferrostatins, liproxstatin-1, vitamin E). In addition, the 5-lipoxygenase inhibitor zileuton was shown to inhibit both glutamate and erastin-induced ferroptosis in HT22 hippocampal cells to a similar extent to ferrostatin-1, and lipoxygenase inhibitors have been demonstrated to possess neuroprotective activity in vivo and in vitro (133, 424). Dixon et al. (175) demon-

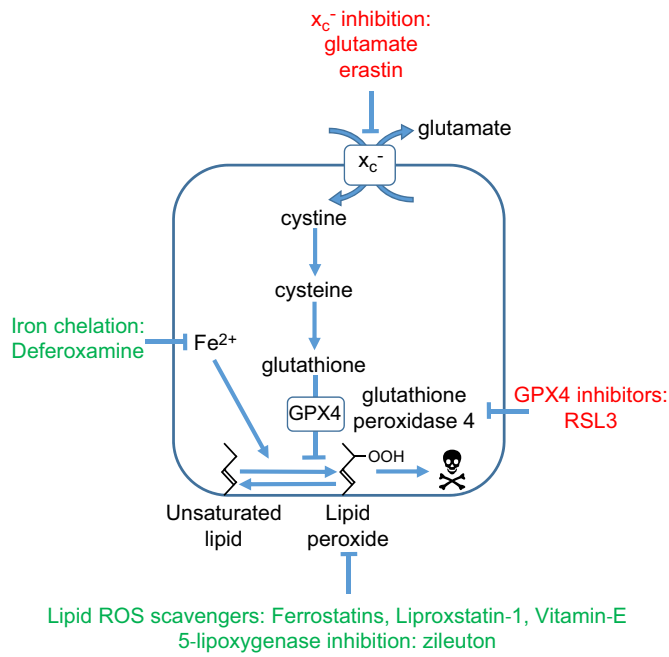

FIGURE 6. Ferroptosis. Ferroptosis results from excessive peroxidation of membrane lipids, promoted by reduced iron (Fe^{2+}) and inhibited by glutathione peroxidase 4, which depends on glutathione, which in turn depends on cystine supplied by the cystine/glutamate exchanger (X_c^-). Red text indicates inducers of ferroptosis, and green text indicates inhibitors of ferroptosis.

strated using organotypic hippocampal slice cultures that ferrostatin-1 is equally effective as MK-801 (an inhibitor of the NMDA receptor and glutamate-mediated excitotoxicity) at reducing overt neuronal cell death following excitotoxic stimulation. Consistent with the above findings, NMDA-mediated excitotoxic death is also prevented by iron chelation. Previous studies have demonstrated that iron chelation using chemical and genetic means can prevent neuronal death in a number of models of neurodegeneration, including excitotoxic death, Parkinson's disease, and ALS (102, 339, 711, 806). Knockdown of cysteinyl-tRNA synthetase in PC12 cells prevents glutamate-induced ferroptosis by boosting intracellular cysteine and glutathione levels even when system x_c^- is inhibited, providing further scope for the therapeutic modulation of ferroptosis (288).

Recent studies have identified ferroptosis inhibition as a potential therapeutic strategy in Huntington's and Parkinson's disease. Overexpression of huntingtin exon-1 fragment with an expanded pathogenic polyglutamine repeat (Q73) in corticostriatal brain slices resulted in death of medium spiny neurons by ferroptosis (634). Dopaminergic neurons are sensitive to erastin-induced ferroptosis and the induction of ferroptosis by several stimuli relevant to Parkinson's disease including MPP^+ and paraquat. Transcriptional markers associated with ferroptosis are increased in Parkinson's disease substantia niagra samples, and ferrostatin-1 blocks 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neuronal loss and accompanying motor impairment in a mouse model (177). This study also revealed a Ras-independent pathway of ferroptosis induction in dopaminergic cells, which required protein kinase C (PKC)-α activity.

4. Cell death by mitochondrial permeability transition

Cells can die as a result of mitochondrial permeability transition (mPT), and this is a distinct form of cell death. mPT defines a large increase in the permeability of the inner mitochondrial membrane in response to elevated concentrations of calcium, usually resulting in uncoupling of oxidative phosphorylation, cellular energy depletion, and necrotic cell death. The permeability transition is caused by opening of a so-called mitochondrial permeability transition pore (mPTP), a nonselective pore with a diameter of ~1.4–2.3 nm (287), which makes the inner membrane freely permeable to protons, metal ions, and all small molecules (<10,000 Da). The molecular components of the pore remain unclear, as many previously proposed candidates for this role [the voltage-dependent anion channel (VDAC), phosphate carrier, the translocator protein TSPO, etc.] were ruled out by experiments on genetic inactivation of these proteins in cells and mice. Currently, the general consensus is that mitochondrial matrix enzyme cyclophilin D (a peptidyl-prolyl *cis-trans* isomerase) is an essential component of mPTP (reviewed recently in Ref. 47). To form a pore in mitochondrial inner membrane, cyclophilin D must interact with one or several transmembrane proteins such as the adenine nucleotide carrier, the phosphate carrier (270), the F_0F_1-ATP synthase (251), and/or the spastic paraplegia protein 7 (SPG7) (619). There are studies indicating that complex I of the mitochondrial electron transport chain may also be involved in mPTP at least in some types of cells (such as astroglial cell lines) as inhibitors of complex I, such as rotenone, piericidine, or metformin, can also desensitize mPTP to Ca^{2+} (397). However, the mechanism linking complex I to pore formation is unclear. It is also hypothesized that mPTP could be formed by multiple different oxidized/denatured/misfolded proteins of the mitochondrial inner membrane (289).

An elevated concentration of calcium ions in the mitochondrial matrix is an essential trigger of mPTP opening, which is also facilitated by ROS, inorganic phosphate, intracellular acidification, decreased mitochondrial membrane potential, and decreased ATP, among others **(FIGURE 7)**. These factors alone are not sufficient to trigger mPTP opening, but rather they sensitize the pore to calcium so that mPTP occurs at lower (ambient) concentrations of calcium ions. mPTP opening can be suppressed by drugs, such as cyclosporin A that binds to cyclophilin D, preventing its binding to the adenine nucleotide carrier and/or other pore components (139, 269). There is some controversy regarding the effect of cyclosporin A on brain mPT: some authors argue that neuronal mPT is not inhibitable by cyclosporin A (31, 367), whereas others have reported that cyclosporin A blocks mPT in brain mitochondria at least in the presence of low levels of ADP (252, 278). mPT is also inhibited by adenine analogs, such as 3-methyladenine, but this also blocks formation of autophagosomes (743) and inhibits kinases that regulate survival and death in neurons (334, 744).

mPTP opening results in *1*) depolarization of the inner membrane, causing *2*) cessation of ATP production by oxidative phosphorylation and *3*) reversal of ATP synthase, hydrolyzing cytosolic ATP entering into the mitochondrial matrix, *4*) hence depletion of all cellular ATP, *5*) swelling of the mitochondrial matrix, which can *6*) rupture the outer membrane, *7*) releasing cytochrome *c* and Endo G, which can *8*) irreversibly halt respiration and induce cell death (87, 162). However, induction of mPT and subsequent rupture of the outer membrane and cytochrome *c* release appears less robust and less sensitive to cyclosporine A in brain mitochondria than in other tissues (15, 192). There is also evidence that mPTP opening may cause degradation of NAD(H) due to PARP activation resulting in energy depletion and cell death (332). In general, opening of mPTP results in necrotic/oncotic cell death due to energy depletion (39, 489). However, in some circumstances, mPT can trigger apoptosis due to cytochrome *c*

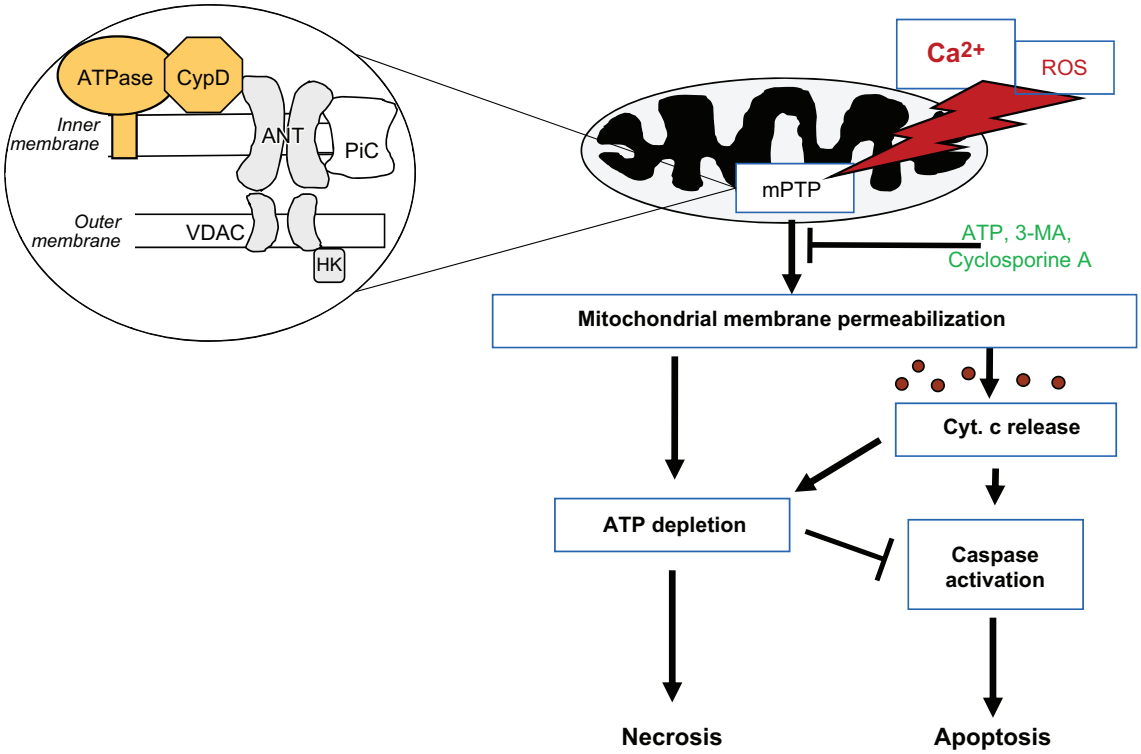

FIGURE 7. Cell death by mitochondrial permeability transition. Calcium and ROS trigger formation of the permeability transition pore (mPTP) in the inner mitochondrial membrane, consisting probably of the adenine nucleotide carrier (ANT) and cyclophilin D (CypD), or possibly the phosphate carrier (PiC) or ATP synthase, and regulated by VDAC and hexokinase on the outer membrane. mPTP causes ATP depletion and thus necrosis, but also may cause cytochrome *c* release to trigger apoptosis if sufficient ATP is still present.

release (189, 592), and this is more likely to occur if cellular ATP can be maintained by glycolytic ATP production (11, 26, 390).

mPT is promoted in cellular environments with high cytosolic levels of calcium, ROS, and low levels of ATP. Such conditions can occur during reperfusion of ischemic tissue, including the brain. Thus neuronal cell death induced by ischemia/reperfusion of brain can be partly prevented by blocking mPTP opening with cyclosporine A or its nonimmunosupressive derivatives or genetic knockout of cyclophilin D (399, 483, 602). There is some evidence that brain ischemia can also cause mPT leading to necrosis by translocation of p53 to mitochondria where it forms a complex with cyclophilin D (688). Neuronal cell death induced by high glutamate (excitotoxicity) can also be partially prevented by blocking mPT. There are studies suggesting that mPT may be involved in pathogenesis of Alzheimer's disease as the absence of cyclophilin D protects against beta amyloid-induced mitochondrial dysfunction and neuronal death, and also improves learning and memory functions in mouse models of Alzheimer's disease (183). Neurotoxic beta amyloid oligomers have been shown to sensitize mPTP in isolated brain mitochondria so that the pore can open at physiological levels of Ca^{2+} (474).

5. Lysosomal cell death (autolysis)

Lysosomal cell death (LCD) (also known as autolysis) is defined as cell death resulting from lysosomal membrane permeabilization (LMP). LCD is executed mainly by proteases released from lysosomes into the cytosol, including particularly cathepsins B, D, and L, but also other hydrolases (5). Release of DNase II can also cause nuclear degradation (674) **(FIGURE 8)**. Diagnosis of LCD as the cause of cell death is imprecise as it can be triggered by events that activate other cell death pathways and occur alongside, and cross-react with, other cell death mechanisms. Several signals have been shown to induce LMP, including increased dihydroceramide induced by Δ9-tetrahydrocannabinol (296), lysosomal p53 (206, 261), phospholipase A_2 activity (731), lysosomal pore formation by Bax or tBid (61, 799), DNA damage-regulated autophagy modulator 1 (DRAM1) (264), and cleavage of the lysosomal membrane protein Lamp2 (696). Given the disparate mechanisms that cause LMP, the systematic study of the causes of LMP in each neurodegenerative disease or condition requires specific study.

Proteins released by LMP can contribute to neurodegenerative diseases (615, 755). Ischemia can induce the calcium-activated protease calpain I to localize to lysosomes and

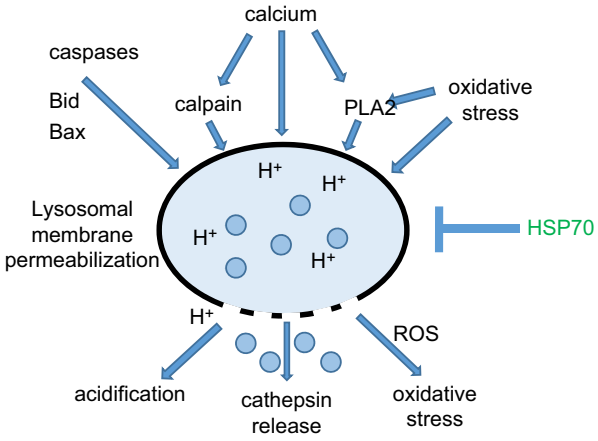

FIGURE 8. Lysosomal cell death. Multiple stimuli can cause lysosomal membrane permeabilization (LMP), releasing cathepsin proteases that induce cell death by multiple routes. LMP may also cause the release of calcium, which activates calpain, as well as DNase II and other hydrolases (e.g., lipases).

cause LMP in neurons (731, 754, 756, 765), including in primates (757). Heat shock protein 70 (Hsp70) can stabilize lysosomes against LMP (5), so calpain degradation of Hsp70.1 may be one means by which calpain permeabilizes lysosomes in the postischemic brain (586).

Aside from inhibiting LMP directly, the most widespread method to prevent LCD has been to inhibit the hydrolases that are released from the lysosomes (463, 784). For example, LCD of motor neurons in models of motor neuron disease was reduced by blocking cathepsins (718, 734), and LMP accompanying photoreceptor cell death in models of genetic blindness was reduced by calpain and cathepsin inhibitors (576). Interestingly, LCD was also reported to follow LMP induced by mitochondrially derived prooxidants during dopaminergic neuronal cell death in the MPTP model of Parkinson's disease (where drug conversion to MPP^+ by monoamine oxidases causes specific toxicity to dopaminergic neurons). In this instance, LMP and loss of lysosomes caused a secondary block in autophagosome activity (157, 694), which was recovered by inducing lysosomes biogenesis and/or reactivation of autophagy, both of which regenerated the lysosomes and ameliorated the toxicity.

6. Pyroptosis

Pyroptosis is a form of regulated necrosis mediated by caspase-1 **(FIGURE 9)** and first described in macrophages infected by intracellular bacteria (68). Pyroptosis requires cleavage of pro-caspase-1 to active caspase-1 within the inflammasome, a cytosolic protein complex normally consisting of one of several sensor proteins [NLRP1, NLRP3, NLRP4, or AIM2 (absent in melanoma 2)], which form homooligomers when they bind pathogen-associated molecules. These then normally recruit the adaptor protein ASC, which then recruits and activates pro-caspase-1, which autocleaves to give rise to active caspase-1 (NLRP1 and 4 may also recruit and activate pro-caspase-1 directly). Once active, caspase-1 can proteolytically cleave pro-interleukin (IL)-1β to IL-1β and cleave pro-IL-18 to IL-18 to induce inflammation. However, active caspase-1 or caspase-11 can also cleave gasdermin D to form pores that directly permeabilize the plasma membrane (and possibly other membranes) causing necrosis (106, 290, 340, 421, 442, 622).

Activation of caspase-1 within neurons has been implicated in neuronal death in some conditions (161). For example, following hypoxia/ischemia, neuronal caspase-1 promoted Bid cleavage and hence activated mitochondrial permeabilization in cortical neuron cultures, linking into an apoptotic downstream effector pathway (796). In addition, isolated embryonic neurons were found to undergo pyroptosis induced by synthetic dsDNA and DNA from human subjects after traumatic brain injury activated AIM2, ASC, caspase-1, and pannexin channels that was blocked by probenecid and Brilliant Blue FCF, indicating a nonapoptotic death mechanism (2). Inhibition of neuronal caspase-1 with

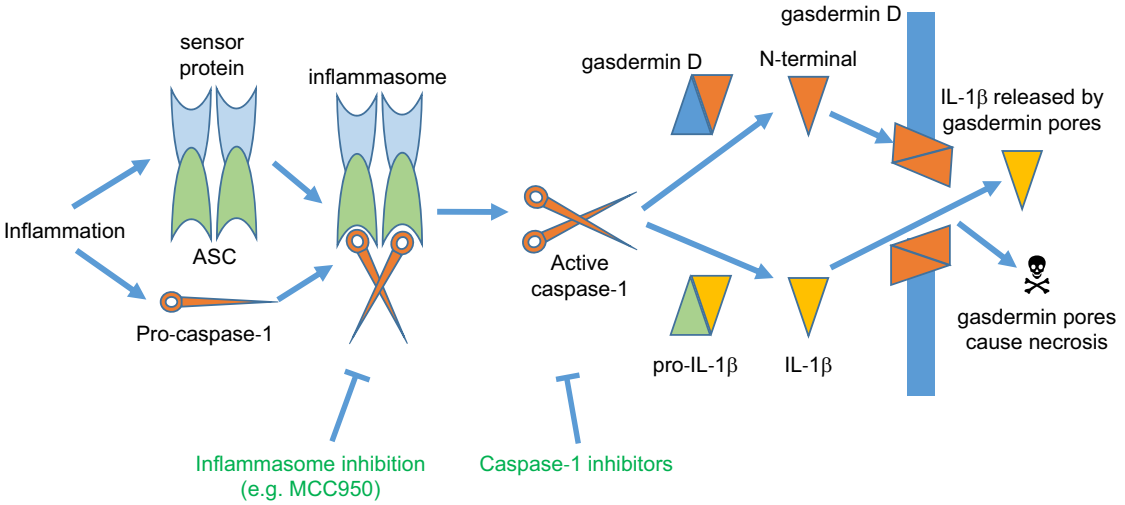

FIGURE 9. Pyroptosis. Inflammation causes expression and activation of the inflammasome, causing activation of caspase-1, which cleaves *1*) pro-IL-1β to IL-1β, a key inflammatory cytokine, and *2*) gasdermin D (and/or DFNA5) to an NH_2-terminal fragment that oligomerizes into pores.

a dominant negative form of the enzyme also reduced neuronal death induced by brain ischemia or trophic factor withdrawal (218). Caspase-1 inhibition also protected dorsal root ganglion neurons against trophic factor-induced cell death (228) and prevented neuronal death in SOD1 models of ALS (217). Knockdown of NLRP1 or caspase-1 reduced neuronal loss in a model of temporal lobe epilepsy (665) and in an amyloid model of Alzheimer's disease (666). However, inhibition of caspase-1 also blocks release on IL-1β and inflammation so that it is not always clear whether neuronal death is induced by inflammation or pyroptosis (or both). If the finding that pyroptosis, and only pyroptosis, is mediated by gasdermin D can be generalized to all cell types, it will be easier to distinguish between these possibilities.

C. Autophagic Cell Death and Autosis

Autophagy normally functions to prevent cell death, but if excessive can cause cell death **(FIGURE 10)**. Autophagy is a process of cell "self-eating" whereby cell constituents are delivered to the lysosome for digestion and recycling. It was given the name by Christian de Duve, who was first to show that autophagy is a regulated process (165, 166, 355). It is used by all eukaryotic cells to ward off starvation by providing anabolic substrates, and for a variety of specialized purposes, e.g., in phagocytes to enable phagocytosis of dead cells in the developing retina and to enable cavitation of embryoid bodies (461, 554). It is also used to isolate, neutralize, and eliminate invading pathogens and hence pathogens can subvert the autophagic machinery to avoid these fates (407, 538, 569). The best-studied type of autophagy is macroautophagy, where delivery of cell constituents to lysosomes occurs via vesicles known as autophagosomes. Autophagosome formation is initiated through a cascade of signals targeted at three distinct multi-protein complexes comprising autophagy-related (ATG) genes and additional proteins that are not homologs of the yeast ATG repertoire (519) but are found in multicellular organisms. Upon activating the complex containing the vacuolar protein sorting PI3-kinase VPS34, PI3P hot spots are generated at the endoplasmic reticulum (368, 395) and an orderly recruitment of the other complexes initiates the budding of a nascent double-membrane structure known as an omegasome (368). Upon omegasome release, further ATG family proteins are recruited that ultimately lipidate Atg8 [MAP-LC3 (LC3) and/or its homologs GABARAP or Gate-16 in mammalian organisms] leading to vesicle growth around the organelle or segment of cytoplasm to be engulfed to form a complete vesicle, the autophagosome (368, 519). Further

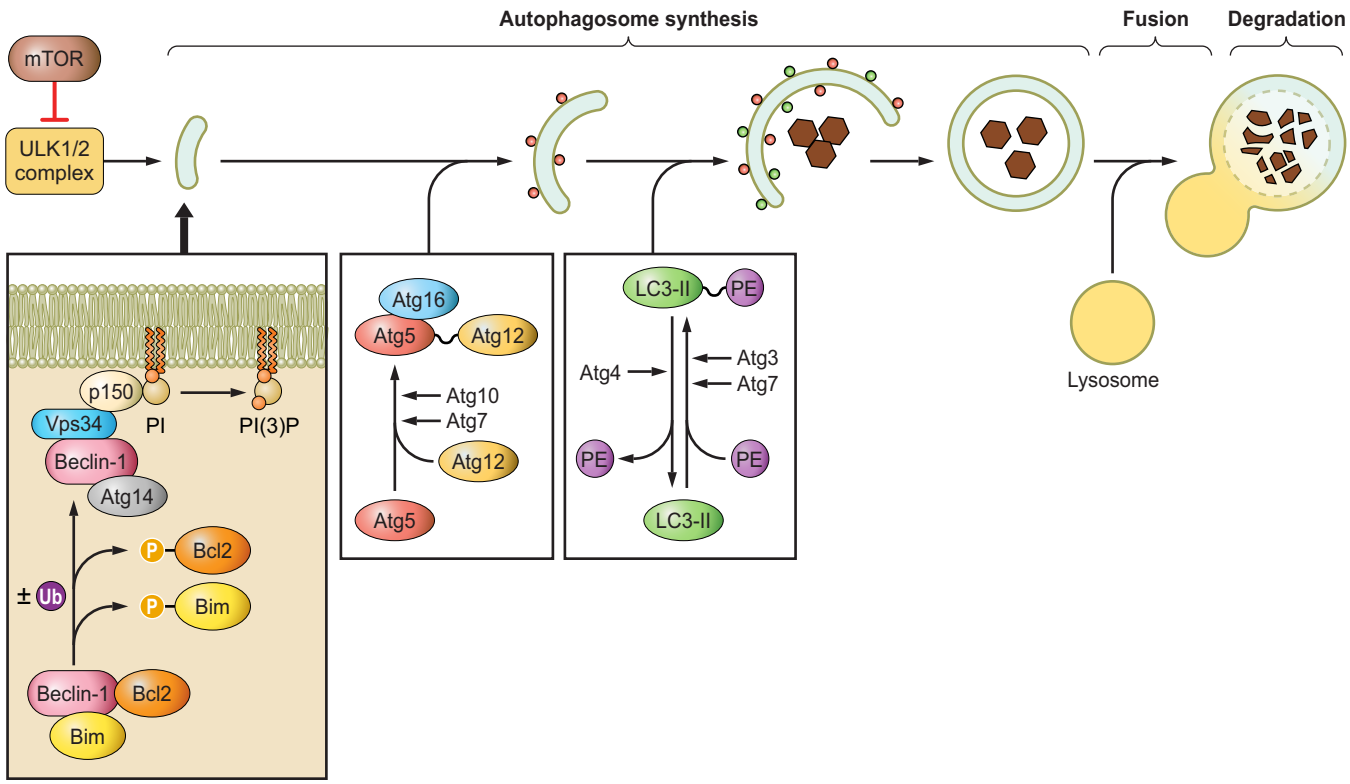

FIGURE 10. Autophagy and autophagic cell death. Autophagy normally promotes survival during starvation or growth factor withdrawal, but, if excessive, can cause autophagic cell death, characterized by the accumulation of autophagic vacuoles. Note the cross talk between autophagy and apoptosis as Beclin-1 is held via its BH3 motif in an inactive state by binding to anti-apoptotic Bcl2 family members or to Bim when it is tethered on microtubules.

proteins then drive the fusion of the autophagosome with endosomes or lysosomes, known as amphisomes or autolysosomes, respectively (285, 326, 620).

Autophagy is an active process, so the key test for the existence of operative autophagy is to demonstrate the presence of autophagic flux. This was realized when the first measurements of, and controls over, autophagy were described (256, 610–612) and is probably the biggest impediment to demonstrating that autophagy is ongoing, or is impaired (or both), in whole animal models and post-mortem human tissue. Accumulation of autophagosomes is not a sufficient sign, since they can accumulate due to increased production or decreased destruction. A surrogate marker often used to demonstrate autophagic flux in tissue extracts is the disappearance of the autophagic substrate p62/SQTM1 (51, 532). p62 is a member of a family of adaptor proteins with LC3 interacting region (LIR) motifs that link LC3 or its congeners on autophagosomes to ubiquitylated proteins in the cytoplasm or on organelles destined for autophagic degradation (48). p62 is often found bound to misfolded protein aggregates that accumulate in neurodegenerative diseases (257), while the LIR-domain proteins NDF2 and optineurin, but not p62, play a major role in mitophagy of mitochondria marked for degradation by the Pink1 (PARK6)/Parkin (PARK2) pathway, where mutations are implicated in Parkinson's disease (382, 543). However, loss of p62 can be extremely difficult to detect, and this is not sufficient to indicate autophagic flux, so demonstrating causality between autophagic flux and ACD in tissues and the brain in particular is not straightforward. This is especially true now that there is evidence that certain ATG genes can have roles in other cell processes (124, 368, 375, 800) and that some types of autophagy may possibly bypass key ATG genes (114, 368), such as Beclin-1 in neurons (114). Another type of autophagy that has been especially implicated in Parkinson's and Huntington's disease is chaperone-mediated autophagy, where proteins are delivered to lysosomes by binding via a KFERQ motif to the Hsp70-cognate protein Hsc70, and imported into the lysosomes via Lamp2a (140). Dysfunction of this pathway, or mutations that disable proteins, such as alpha-synuclein, from binding to Hsc70, can lead to the build-up of misfolded alpha-synuclein, proteostasis, and cell death. Chaperone-mediated autophagy is a mechanism in its own right, and since it does not display macroautophagic features, it has not been incorporated into the definition of autophagic cell death.

Knockout of key ATG genes, such as Atg5 or Atg7, that are necessary for autophagosome formation, showed that basal autophagy plays a central role in preventing neurodegeneration due to build-up of misfolded proteins and proteostasis in mice (282, 314). However, early studies of mechanisms of cell death (607), and later studies of neuronal cell death in the developing brain (118), showed that there is a distinct type of cell death that is nonapoptotic, but rather replete with autophagosomes, autolysosomes, and lysosomes. This was defined as autophagic cell death (ACD) as distinct from apoptosis (type 1) alongside a third ill-defined mechanism that does not involve lysosomes (type 3).

Since autophagosomes accumulate in many instances of cell death, including those involving apoptosis (744), the question whether ACD exists as a separate entity has been under intense debate. The foremost problem lies in the definition of ACD. The most restricted definition is that to qualify as ACD, death must be mediated and executed solely by autophagy without the involvement of any other cell death machinery (e.g., apoptosis, necroptosis); hence, inhibition of essential autophagy genes upstream of autophagosome formation should result in cell rescue exclusively (621), without impairing cell death by any other mechanisms such as apoptosis. Proving that no other execution pathway is triggered is difficult, especially when the cause of death is unknown. One example was reported by Levine and colleagues, who found that overexpression of a peptide from Beclin-1 (ATG6) promoted excessive autophagy and this was sufficient for autophagy-dependent death, which they termed "autosis" (422, 423). This death was prevented by knockdown of key ATG genes (Atg13 and Atg14, as well as Beclin-1), but not by inhibition of key apoptotic (Bax/Bak) or necroptotic (RIPK1/3) death commitment genes. Interestingly, death was mediated by hyperactivation of the Na^+-K^+-ATPase, which depleted ATP and hence caused necrosis. Importantly, death was rescued by cardiac glycosides that inhibit the Na^+-K^+-ATPase. However, this death did not require fusion with lysosomes, or at least lysosomal activity, so it was not dependent on a complete autophagic flux, and this death was not mediated by autophagic elimination of catalase, as had previously been found in apoptosis-deficient (Bax/Bak knockout) cells (779). The Beclin-1-induced ACD had a similar morphological profile to that observed in 7-day-old rats exposed to a carotid-occlusion model of ischemia/reperfusion, and partial rescue of the rats was obtained using the cardiac glycoside neriifolin. However, the evidence presented for autophagy being the causal agent of death in this study is weak. There are, however, other examples where knockdown/knockout of autophagic genes (e.g., Atg7 or Beclin-1) prevents neuronal death induced by brain ischemia (358, 553, 739). It is doubtful that Na^+-K^+-ATPase hyperactivity can be classified as an exclusive ACD-execution mechanism, and it is still unclear how autophagy activates the Na^+-K^+-ATPase. Note that autophagy normally functions to supply cellular ATP, and the Na^+-K^+-ATPase is the main user of ATP in most cells, including neurons, so that inhibition of the Na^+-K^+-ATPase preserves cellular ATP.

A less extreme view of ACD is one where autophagy genes are necessary for death commitment but are not sufficient to execute it. This was the original intent of the term *ACD*

(119, 553). One might argue that autosis falls into this category as well since lysosomal activity is bypassed and Na^+-K^+-ATPase is not part of the autophagy machinery, as far as we know. There are now some documented cases where inhibition of key ATG genes inhibit or delay cell death (see Refs. 225, 396 for more details). Interestingly, each case describes a completely separate upstream initiator-signaling pathway in a different organism or cell type; the key intermediates that link between these signals and the process are not always identified. Indeed, there are numerous studies where apoptotic cell death occurs coincidentally with features of autophagy (744) but whether autophagy is necessary has not been examined in all cases. In the nervous system, possible examples of ACD include reduced retrograde neuronal death induced by the toxin 6-hydroxydopamine after Cre-recombinase excision of Atg7 in adult dopaminergic neurons (108). Similarly, reduced dopaminergic neuron death was found in MPTP-treated mice in which Atg7 is conditionally knocked out (CKO) in adult dopaminergic neurons (509). Photoreceptor death in a genetic (rd10) model of photoreceptor degeneration was increased by the induction of autophagy with rapamycin, but cell death execution was ascribed to lysosomal permeabilization rather than autophagy per se (576). However, there are numerous examples where deficient autophagy may lead to neurodegeneration (462). Even in the same adult Atg7 CKO mice where dopaminergic neurons were more resistant to MPTP, there were fewer dopaminergic neurons compared with wild-type mice (509). Likewise, survival of retinal ganglion cells after optic nerve axotomy was worsened by deletion of essential autophagy genes (Atg4B, Atg5) in the ganglion cells and improved by autophagy induction (575).

In the original definition of ACD, numerous lysosomes were found to accumulate and "turn" autophagosomes into lysosomes. Indeed, Schweichel and Merkel (607) used the appearance of these lysosomes to differentiate between the various forms of cell death as described above (see section I*B*). They also noted lysosomal rupture as the final step in this type of necrosis, so death execution itself may have been mediated by LMP.

In fact, the least clear aspect of ACD is the role of lysosomes. This is especially important as lysosomal activity impairment is suggested to be a major cause of cell death in Alzheimer's disease (510, 511) and other neurodegenerative diseases (234, 615). Yet diseases of lysosomal dysfunction, such as lysosomal storage diseases, do not necessarily implicate a causal relationship between cell death and autophagy. Clearly, any lysosomal dysfunction will lead to dysfunctional autophagy, and both excessive autophagy and defective autophagy can kill a cell. Even if knockdown of key autophagy genes rescues cells from death, clear cases of ACD will be difficult to find and diagnose, especially in whole organisms and post mortem human brains.

D. Paraptosis

Sperandio et al. (641) defined "paraptosis" as a form of cell death, distinct from apoptosis and necrosis, characterized by cytoplasmic vacuolation. They had found this form of cell death when overexpressing the insulin-like growth factor 1 receptor (IGF-1R), and they subsequently found that paraptosis induced by IGF-1R could be blocked by inhibition of IGF-1R kinase activity, or by inhibition of mitogen-activated protein (MAP) kinase activity, or by overexpression of AIP-1/Alix (642). In the CNS, it has been found that overexpression of p44, an isoform of p53, causes activation of IGF-1R, memory defects, and neuronal death, apparently by paraptosis and autophagy (539). Cytoplasmic vacuolation has been seen in retinal ganglion cells after retinal ischemia and reperfusion injury in rats, but it is not known whether inhibition of this process prevents neuronal death (723).

However, it remains unclear whether paraptosis is really a distinct form of cell death, as cytoplasmic vacuolization may occur as a result of multiple mechanisms, including autophagy, disruption of lysosomal function, and mitochondrial permeability transition. Thus the observation of cytoplasmic vacuolization is not sufficient to diagnose paraptosis. The cytoplasmic vacuolation of paraptosis has most often been associated with vacuolation of the endoplasmic reticulum, and hence endoplasmic reticulum stress and the unfolded protein response (UPR). And UPR-induced cell death is generally thought to be apoptotic (see sect. III*F*). So it is still unclear whether there is a mechanistically distinct form of cell death corresponding to the term *paraptosis*. In principle, inhibition of cell death by expression of AIP-1/Alix could be used to diagnose paraptosis, but apart from the original paper (642), AIP-1/Alix has rarely been shown to block cell death, an exception being amyloid beta toxicity in *C. elegans*, but the latter was attributed to boosting protein turnover (286). Indeed, AIP-1/Alix (product of the PDCD6IP gene, not to be confused with AIP1, product of the DAB2IP gene) was originally described as a regulator of apoptosis, but also regulates vesicular trafficking, so it is probably not specific to paraptosis. Another potential distinguishing feature of cell death by paraptosis is a requirement for protein synthesis, not required for most forms of cell death other than for some cases of intrinsic apoptosis, where inhibition of de novo synthesis of BH3-only proteins (e.g., Puma, Bim, Bid) prevent neuron death (164, 343, 732, 736).

Cytoplasmic vacuoles are also seen in degenerating neurons with hyperphosphoryated tau in Alzheimer's disease and other tauopathies (see sect. IV*B6* for more details). However, whether this process of "granulovacuolar degeneration" has anything to do with paraptosis is unknown.

E. Cell Death by Phagocytosis (Phagoptosis)

Cell death by phagocytosis ("phagoptosis" for short) refers to a cell dying as a result of being phagocytosed by another cell **(FIGURE 11)**. The key discriminating characteristic of this form of cell death is that inhibiting phagocytosis of the cell prevents death of the cell. Dead or dying cells are rapidly phagocytosed (so-called "secondary phagocytosis"), and inhibition of phagocytosis in this case will not prevent cell death, but rather cause dead cells to accumulate. However, in a variety of circumstances, viable cells are phagocytosed resulting in their death (sometimes called "primary phagocytosis," synonymous with "phagoptosis"), and in this case inhibition of phagocytosis will prevent cell death (77).

Phagoptosis has some similarities to "entosis." Entosis was originally defined as the process of one cell invading into another cell without cell death (529), but it can lead to death of the invading or invaded cell, so we have the concept of "entotic cell death" (366) or "cell-in-cell death" (716). Entosis and entotic cell death can in principle be distinguished from phagocytosis in that entosis requires cadherins, while phagocytosis requires the phagocytic receptors described below. Neurons are not known to undergo entosis.

Phagocytosis consists of three main steps: recognition, engulfment, and digestion. Recognition by phagocytes of target cells to phagocytose is mediated by phagocytic receptors (e.g., vitronectin receptor, Mertk, CR3) that recognize "eat me" signals (e.g., cell surface phosphatidylserine or calreticulin), "don't eat me" signals (e.g., cell surface CD47 or sialylation), or opsonins (e.g., Gas6, MFG-E8, or complement factors) on the surface of the target cell. The engulfment phase of phagocytosis may depend on activation of P2Y6 receptors on phagocytes by its ligand UDP coming from the engulfed cell (77).

Phosphatidylserine can be irreversibly exposed on the surface of apoptotic cells as a result of caspase cleavage-mediated activation of a phosphatidylserine scramblase Xkr8 (659) and caspase cleavage-mediated inhibition of a phosphatidylserine translocase (flippase) ATP11C (609). However, phosphatidylserine can be reversibly exposed on viable cells as a result of calcium activation of the scramblase TMEM16F (658, 660) or temporary lowering of ATP, which is required for translocase activation. Glutamate also causes rapid and reversible phosphatidylserine exposure on neurons, which results in their phagocytosis by activated microglia if present at the time of phosphatidylserine exposure, but such neurons survive long-term if activated microglia are not present (495). Phosphatidylserine-exposed neurons are recognized either via the opsonin MFG-E8 and vitronectin receptors on microglia (212) or the opsonin Gas6 and MerTK/Axl receptors on microglia (493). An alternative "eat me" signal is exposure of calreticulin on the cell surface (235), which can result from endoplasmic retic-

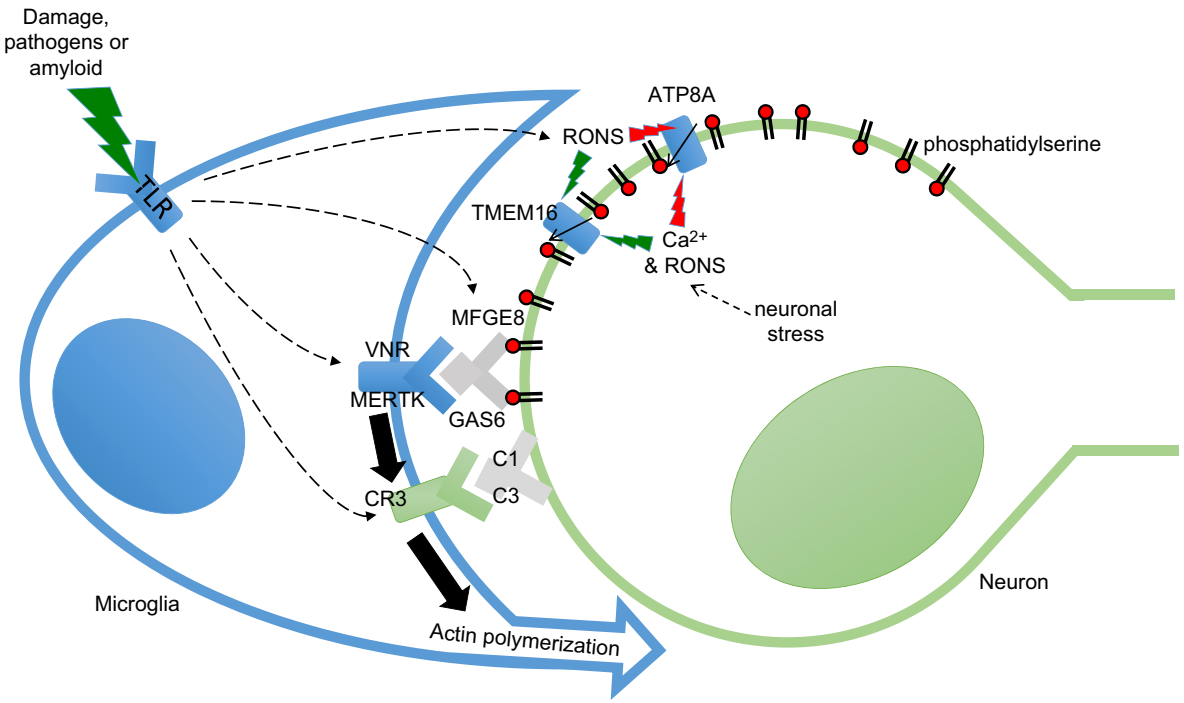

FIGURE 11. Phagoptosis is cell death resulting from phagocytosis of the cell. Neuronal stress can result in exposure of "eat me" signals such as phosphatidylserine, which bind opsonins such as MFG-E8 or GAS6 that engage phagocytic receptors VNR (vitronectin receptor) and MERTK, respectively. Complement factors C1 and C3 binding to neurons can induce uptake via CR3. Phagoptosis is increased in inflammatory conditions that stress neurons and increase phagocytosis.

ulum stress, and can evoke phagocytosis via LRP receptors on phagocytes including microglia (214). Complement component C1q can act as a opsonin by binding a variety of cell surface factors, including phosphatidylserine, calreticulin, or a desialylated surface, and inducing phagocytosis via generation of C3b/iC3b or direct binding to phagocytic receptor CR3 on microglia (410). Sialylation of the cell surface acts a "don't eat me" signal, blocking phagocytosis via Siglec receptors on microglia (714), and desialylation enables phagocytosis of neurons, partly by C1q opsonization and phagocytosis via CR3 (410), and potentially also galectin-3 opsonization and phagocytosis via MerTK (512, 770).

Inflammatory activation of microglia by Toll-like receptor TLR ligands, TNF-α, or amyloid-β in vitro induced slow neuronal loss in culture via microglial phagocytosis of viable neurons (495, 497). Upon activation, microglia released sublethal amounts of ROS and reactive nitrogen species (RNS) that caused reversible phosphatidylserine exposure on neurons, which evoked their phagocytosis by microglia (495). Blocking phagocytosis by inhibiting either phosphatidylserine, MFG-E8 binding or production, vitronectin receptors (VNR), calreticulin, MerTK, or P2Y6 receptors is sufficient to rescue neurons following microglial activation in vitro and in vivo (212, 493, 495, 497).

In vivo, injection of lipopolysaccharide (LPS) into the brain caused delayed neuronal loss, accompanied by microglial phagocytosis of neurons, and was prevented by either inhibiting vitronectin receptors, genetic knockout the opsonin MFG-E8 (212), or inhibiting P2Y6 receptors (494). Transient brain ischemia also caused a delayed neuronal loss, accompanied by microglial phagocytosis of neurons, which was prevented by genetic inactivation of either MFG-E8 or MerTK (493). Other examples that implicate phagoptosis are the loss of retinal rod cells (sensory neurons) by microglial phagocytosis in a model of retinitis pigmentosa, which was prevented by removing microglia or blocking vitronectin receptors (785) and loss of hippocampal neurons with age was accompanied by microglial phagocytosis of neurons, blocked by genetic ablation of C3 (623).

In models that are more relevant to neurodegenerative diseases, loss of dopaminergic neurons in substantia nigra in an accepted inflammatory (LPS) model of Parkinson's disease was accompanied by microglial phagocytosis of neurons, which were rescued by genetic ablation of complement component C3 (58). Loss of dopaminergic neurons was also reduced by inhibiting microglial phagocytosis in an MPTP model of Parkinson's disease by blocking VNR (536) or Rho-associated protein kinase (ROCK) (33) and in a 6-hydroxydopamine model by knockout of the phagocytic adaptor protein DAP12 (452). Blocking exposed phosphatidylserine with annexin V was sufficient to prevent neuronal loss in a histamine model of Parkinson's disease (574) and knockout of the phagocytic receptors Mer and Axl increased survival in a genetic synuclein model of Parkinson's disease (209). Knockout of these receptors also increased the number of neuronal precursors in the mice and microglia have also been found to phagocytose live neural precursor cells in rat and monkey cortex (142).

One form of frontotemporal dementia can be caused by inactivating mutations in the progranulin (*PGRN*) gene. In a *C. elegans* model of TDP-43 toxicity where progranulin was knocked down, a more rapid disappearance of stressed-but-viable neurons was measured, suggesting that neuronal loss in frontotemporal dementia may be due to phagoptosis that is normally inhibited by PGRN (589). The known association of progranulin polymorphisms with Alzheimer's disease, Parkinson's disease, and ALS raises the possibility that altered phagocytosis and phagoptosis may play a role in the pathogenesis of these diseases.

Thus there is tantalizing evidence that neuronal cell death by phagoptosis is common during development and pathology. Phagoptosis may have been overlooked simply because it leaves no cell corpse to diagnose the cause of cell death. The true frequency of neuronal cell death by phagocytosis in physiology and pathology awaits our ability to block phagocytosis or phagocytic signaling to determine whether this prevents cell death.

III. NEURONAL DEATH INDUCED BY VARIOUS IMPORTANT STIMULI

Types of cell death can be distinguished based on either *1*) the molecular mechanism executing death within the cell or *2*) the stimulus inducing cell death. This distinction is not always clear, but is useful, for example enabling us to ask which execution mechanisms are involved for a particular stimulus.

A. Neuronal Cell Death During Development and Its Prevention by Survival Factors

That cell death is necessary for proper development of multicellular organisms has long been appreciated (786). However, it was the discovery of NGF led by Cohen and Levi Montalcini (393, 394) and the evidence that NGF is necessary for the survival of sympathetic neurons and nociceptive sensory neurons during development that heralded the molecular underpinning of regulated cell death in neuronal development in vertebrate (chick) and mammalian systems. The neurotrophic hypothesis was proposed (552) to provide a formal framework for the work by Bueker (81), Hamburger (274), and Levi-Montalcini (393); it stipulates that neurons are generated in excess and their survival is dependent on competition for limiting amounts of neurotrophic factors (NTFs) synthesized by their target fields,

or lack of such factors if the axons go awry. Overall validation of the neurotrophic hypothesis was provided by the discovery of the other neurotrophin family members brain-derived neurotrophic factor (BDNF), NT3, and NT4/5 (149) and their specific Trk tyrosine kinase receptors (361), which accounted for all classes of sensory neurons in the periphery. Further important families of survival-supporting factors for other types of neurons during development or injury were then discovered, such as the glial-derived neurotrophic factor (GDNF) family alongside their specific receptor subunits and signaling receptor Ret tyrosine kinase (4, 30), the LIF/CNTF cytokine family important after injury and their composite receptors (30, 571), and IGF-1 (507) among others. Good evidence soon accrued from studies of knockout and transgenic mice (637) that NTFs are both necessary and sufficient to support the survival of defined subsets of neurons (for a comprehensive list of source references, see Refs. 361). This intense period coincided with the discovery of the key players in apoptosis (Bcl-2 family members, Apaf-1, and caspases 9, 3/7) and ample evidence quickly accrued that neurons in the PNS that depend on NTFs for their survival die by apoptosis when NTFs are absent.

There is convincing evidence that cell death of many neuronal progenitor and postmitotic neuron populations in the CNS also occurs by apoptosis (369), although the survival factors that control cell death of each neuronal population are still not resolved, including the intrinsic factors that govern the survival of motor neurons from birth to when they reach their final position and number (259, 524). Indeed, there is evidence that appears to contradict the NTF hypothesis in that developmental death of the GABAergic interneuron population in the developing cortex is determined cell intrinsically (158, 639) by an internal timer, similar to the case in the *C. elegans* nervous system (134, 135, 617, 782). The mechanisms of such a timer have been studied in detail in *Drosophila* (750) and involve mainly sequential transcription factor switching, interwoven with recruitment of different signaling pathways. However, the signals that govern the initial loss of apoptosis repression and/or elevation or activation of proteins involved in apoptosis execution are still not known. Even in the nematode *C. elegans*, the death of some neurons is not cell-autonomous as it requires phagocytosis by neighboring cells to execute death, i.e., phagoptosis contributes (329).

In the mammalian CNS, a broad distinction has been made between apoptotic mechanisms in postmitotic neurons versus dividing neural progenitor populations, revealed by crossing mice with deficiencies in key mediators of the intrinsic apoptotic pathway. For example, in certain postmitotic neurons, there was an epistatic relationship between anti-apoptotic Bcl-xL and pro-apoptotic Bax, with widespread neuronal cell death induced by knockout of Bcl-xL being rescued by knockout of Bax (627). Likewise, apoptosis due to Bcl-xL deficiency was abrogated by knockout of caspase-3 (369, 581). However, Bax knockout was not sufficient to prevent most cell deaths among the neural progenitor population, whereas a marked brain hyperplasia was reported in caspase-3 knockout mice (369). Some of these differences are due to the fact that different populations of dying neurons/neuron progenitors are place and time restricted. At each stage of development, cell death is restricted to one or two sites and involves a small number of cells (369). Malformations indicating disturbances of cell death are also strain dependent in mice; for example, forebrain overgrowth (fog) mice have a spontaneous mutation in Apaf-1 that has partial loss of function (302). These mice produce notable forebrain and facial defects with spina bifida-like syndromes on a 129S1 background, but these malformations, and those due to Apaf-1 knockout, disappeared when mice were crossed into other genetic backgrounds, such as pure C57Bl/6. Despite these caveats, it is clear that numerous instances of cell death during development follow an apoptotic program. However, the fact that Bax knockout (and Bax + Bak double knockout mice) lacking neuronal apoptosis can survive and reproduce suggests that not all developmental neuronal death is due to apoptosis.

The various roles of programmed cell death in brain development are extensively reviewed in Reference 750. The authors (Y. Yamaguchi and M. Miura) note that the purpose of apoptosis during early brain development is not simply to match the number of neurons to the size of their targets, it is also used to sculpt organs, among other functions (750). For example, in mixed BL6/129S1 mice, where Apaf-1 knockout gives rise to brain malformations, loss of Apaf-1 or caspase-3 prevented apoptosis in the anterior neural ridge (514). Interestingly, the "undead" cells produced FGF8 continuously and caused failure of ventricle expansion, although this was not due to the overgrowth of the neuroepithelium but rather to lack of CSF accumulation. This finding shows how careful one must be before attributing the lack of cell death as a cause of a malformation. Notably, not all neurons that failed to die by apoptosis remained viable. Some cells that died nonapoptotically displayed swollen nuclear envelopes, swollen endoplasmic reticulum, and an accumulation of vacuolar structures and autophagosomes in the cell body. Lack of Apaf-1 also prevented cell deaths necessary for closure of the neural tube, suggested to be due to inability of a thicker epithelium to meet in the mid line (514). Cells dying with such swollen organelles aligns with the "nonlysosomal vesiculate" type 3B suggested by Clarke (118), most probably a subtype of necrosis with autophagic features. Likewise, Oppenheim found that motor neurons in Apaf-1 knockout mice (525) undergo "quantitatively normal PCD by a caspase-independent pathway involving autophagy and not requiring AIF." It will be interesting to examine which, if any, signals and genes would be required to rescue neurons undergoing alternative pathways of death

of neurons that would normally undergo apoptosis. As pointed out by others (749, 750), crucial evidence regarding how each class of neurons dies in the CNS in development is still lacking.

Axon pruning is also part of a normal developmental process. As mentioned in section I, neurons have unique morphologies, not least having extended cytoplasms enlarged by long thin axons and arborized dendrites. Recently it has been questioned whether axon pruning during contact remodeling occurs via the same mechanisms as "dying back" neurodegeneration, which occurs in diseases such as ALS, and which eventually cause cell body death. There is little mechanistic evidence that the two share the same molecular pathways. Earlier work suggested that axon death occurs via different mechanisms to that of cell body death, but this has been overridden by the finding that both types of death require caspase 3 (632) and at least in vitro, loss of trophic support in the axon compartment initiates events that requires active participation of the cell body; in this particular model, elevation of Puma was reported to be confined to the cell bodies but led to an eventual Bax-dependent anterograde pro-degenerative program (631). It now appears that Puma is expressed in the axons (in sensory neurons) but is held in check by the dual specificity phosphatase DUSP16/MKP-7, which negatively regulates the transcription factor p53, the cause of Puma upregulation. However, loss of Puma increases skin innervation density without affecting neuronal number, but DUSP16 loss increases cell body loss without impacting on skin innervation. It is clear that an intricate interplay between survival factors and death mechanisms is ultimately what determines the final sculpting of the developing nervous system (450).

B. Cell Death Induced by Loss of Connected Neurons (Transneuronal Degeneration)

Death of neurons can lead to the death of neurons connected to those neurons, a process known as transneuronal degeneration or secondary neuronal loss. This degeneration can occur to neurons either downstream (anterograde) or upstream (retrograde) of dead neurons. Thus anterograde transneuronal degeneration results from loss of synaptic inputs to neurons, while retrograde transneuronal degeneration results from loss of synaptic outputs. In principle, this loss can occur as a result of loss of the synapses, dendrites, axons, or neurons.

In general, transneuronal degeneration is more prevalent in young than adult animals, and this appears to be due to much reduced expression of Apaf-1 and caspase-3 in neurons of adult animals (479, 746). For example, unilateral removal of the cochlea (inner ear) of 5-day-old mice resulted in caspase-3 activation in neurons of the anteroventral cochlear nucleus a few hours later, and subsequent neuronal loss that was prevented by overexpression of Bcl-2; while removal of the cochlea in 30-day-old mice resulted in no neuronal loss in the anteroventral cochlear nucleus (479), presumably due to the lack of apoptotic gene expression. However, neurotrophic factors may also play a role. Striatal lesion induced neuronal loss in ipsilateral substantia nigra pars compacta in postnatal day 7 (P7) rats but not P15 rats, and this correlated with upregulation of BDNF in pars compacta after lesions in P15 rats but not P7 rats, while blocking BDNF receptors allowed lesion induced neuronal loss in P15 rats (90). Retinal ganglion cells are susceptible to retrograde transneuronal degeneration from the lateral geniculate nucleus and optical cortex in adult animals including humans, although again neuronal loss is much greater in young animals (291, 534).

Synaptic activity, via activation of NMDA receptors, can suppress expression of Puma, Apaf-1, and caspase-9, while in developing mice, blocking synaptic activity causes neuronal apoptosis via induction of Puma expression (392). Whether this can occur in adults is less clear.

In adults, unilateral excitotoxic lesions of the striatum cause progressive degeneration of neurons in the substantia nigra pars reticulata and thalamus, and this death is not apoptotic in adults (647). Similarly, unilateral lesions of the anteromedial cortex cause mild atrophy in the ipsilateral striatum and substantia nigra pars reticulata. This degeneration can be prevented with GABA agonist or glutamate antagonists, suggesting an imbalance in excitatory and inhibitory inputs, causing excitotoxicity (54, 155, 747). Transient middle cerebral artery occlusion in adult rats leads to secondary loss of neurons in the thalamus, part of which may be due to loss of protective GABAergic input from the globus pallidus (172). Ablation of occipital cortex in adult mice induces apoptosis of neurons in the dorsal lateral geniculate nucleus, 7 days later, which is prevented by knockout of Bax, neuronal NO synthase (nNOS), or cyclophilin D, suggesting that NO/peroxynitrite activates mitochondrial permeability transition, inducing apoptosis (454).

Brain ischemia or trauma apparently cause transneuronal degeneration via gap junctions between neurons so that gap junction inhibitors or knockout of gap junction genes protect (45). Transneuronal transfer of protein aggregates might contribute to Alzheimer's disease and other protein aggregate diseases (653). Inflammation may contribute to some cases of transneuronal degeneration (53).

Synapses are lost before neurons in a variety of neurodegenerative diseases, including Alzheimer's disease, and this could in principle cause transneuronal degeneration. However, it is unclear whether this significantly contributes to the neuronal loss.

In summary, transneuronal degeneration is more common in young animals due to the susceptibility of young neurons to apoptosis and neurotrophin dependence. Where it occurs in adult animals, transneuronal degeneration appears to be mainly via excitoxicity.

C. Axon Death and Cell Death Induced by Axotomy (Wallerian Degeneration and Sarmoptosis)

Axotomy leads to different death mechanisms in different neuronal compartments **(FIGURE 12)**. The best understood is Wallerian degeneration, the near-universal, nonapoptotic degeneration of all axonal structures distal to a site of injury, typically over 1–2 days (42, 434) followed by a more prolonged glial reaction to clear debris and promote regeneration, at least in peripheral nerves. There are only two exceptions. One is axons where Wallerian degeneration is greatly delayed by a genetic mutation acting autonomously within neurons (see below). The other is axons in some invertebrates that appear to survive for prolonged periods by glial support. In contrast, loss of the cell soma after axon injury depends on cell type, injury location, and developmental stage. For example, while retinal ganglion cells (RGCs) die 2–3 wk after optic nerve injury (43), sensory and motor neurons survive after sciatic nerve injury, at least in adults. Sciatic nerve injury in neonates, or motor axon injury at a very proximal site (ventral root avulsion), does however cause motor neuron death (1). These RGC and motor neuron death mechanisms are clearly apoptotic (98, 593), so the likely explanation is that death is caused by the loss of retrograde trophic support. In contrast, there is clear evidence that Wallerian degeneration of distal axons is nonapoptotic (85, 204, 725), and a genetic variant that delays Wallerian degeneration does not alter apoptosis in the cell body (154). The absence of apoptotic (caspase-mediated) death in Wallerian degeneration may be explained by the recent finding that the cell body is a necessary convergence point for factors that are required for axon demise (450, 631).

Knowledge of the Wallerian degeneration mechanism has been transformed by the identification of genetic mutations that delay it by ~10-fold. The identification of Wallerian degeneration slow (Wld^s), a mutant fusion protein, revealed a key role for NAD-related metabolism (438). Based on this, a wild-type NAD synthesizing enzyme, NMNAT2, was shown to be lost rapidly after axotomy and essential for axon survival (247). When NMNAT2 expression is constitutively blocked, axons fail to grow beyond a short distance, and if knocked down after axons have grown, these axons degenerate through the Wallerian pathway (246). In essence, removing NMNAT2 spontaneously activates the Wallerian pathway even without injury. NMNAT2 matches many of the properties of the "neuronal trophic substance" postulated by Lubinska (434) long before the discovery of Wld^s mice (435), a substance whose delivery from cell bodies to axons was expected to prevent pathway activation. How NMNAT2 loss subsequently causes Wallerian degeneration is an area of current debate. The decline in NAD (706) appears to be neither sufficient nor necessary, so current models include a rise in its precursor NMN (170), another metabolite yet to be identified (596), or a combination. NMNAT proteins are also reported to have an additional chaperone activity (790), although it is well established that their role after injury is related to their conventional NMNAT activity (18, 20, 132).

Importantly, the Wallerian mechanism is not limited to injury. Uninjured, wild-type axons degenerate in a Wld^s-sensitive manner after NGF withdrawal, exposure to vincristine, or a range of Parkinson mimetics, genetic impairment of axonal transport, inflammation, ischemia, and other stresses (131). A likely common feature of many of these is impaired delivery of NMNAT2 to distal axons, thereby triggering a pathway similar to that when NMNAT2 supply is stopped by physical injury. However, levels of this essential survival protein could also be limited by impaired protein synthesis, aberrant mRNA processing, accelerated turnover, oxidative damage, and other mechanisms. The ability of Wld^s to prolong axon survival in many circum-

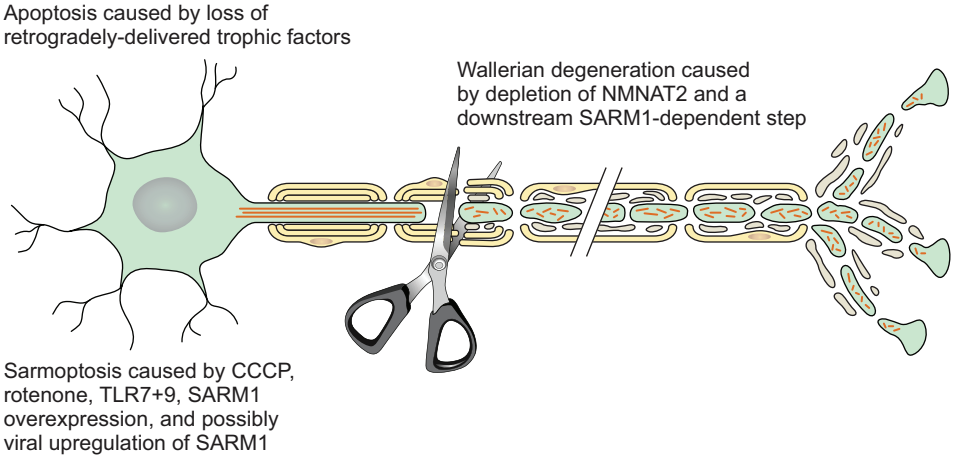

FIGURE 12. Neuronal death induced by axotomy.

stances strongly suggests that NMNAT2 is a limiting factor for survival, which likely underlies the involvement of this pathway in many disease models.

In a surprising development, loss of the TLR-adapter protein SARM1 was found to phenocopy the Wld^s phenotype in both mouse and *Drosophila* neurons (528). SARM1 is required downstream of NMNAT2 loss for Wallerian degeneration to occur, either directly on this pathway or on a separate branch that converges downstream of NMNAT2 (248). Dimerization of its TIR domain also depletes NAD (241), potentially exacerbating the effect of NMNAT2 degradation after injury, although it remains unclear whether similar dimerization activates the intact protein or what causes this activation. Accelerated removal of existing NAD after axon injury is consistent with such a mechanism (596), so it is important to establish the nature of this NAD depletion. The existence of a protein whose role it is to kill axons is perhaps the best evidence of an "active" mechanism of programmed axon death.

Although axon injury, or a blockade of axonal transport, triggers SARM1-dependent axon degeneration, the role of SARM1 in cell death is not restricted to axons. The mitochondrial toxins CCCP and rotenone lead to SARM1-dependent death of neuronal cell bodies and their axons, a process that has been termed "sarmoptosis" (656). However, loss of mitochondrial membrane potential appears to be a late event in injury-induced axon degeneration, downstream of SARM1 (428), and mitochondria are dispensable for Wallerian degeneration to occur (353), suggesting these mitochondrial changes may be epiphenomena. It is also unclear whether SARM1 needs to localize to mitochondria to cause sarmoptosis, as there are conflicting reports on this (242, 533) and despite many reports that SARM1-GFP localizes to mitochondria, the nonmitochondrial location of the endogenous, untagged protein suggests this could be an artifact of overexpression or GFP fusion (528).

Sarmoptosis can also be triggered by SARM1 overexpression, or expression of a constitutively active form lacking the NH_2-terminal ARM domain, which is proposed to have an autoinhibitory function. Importantly, SARM1 is upregulated by some viruses (482), raising the prospect that this could be the basis of some viral neuropathies. Activation of TLRs 7 and 9 is another way to activate SARM1-dependent neuronal death, linking this mechanism to tissue injury and the release of damage-associated molecular patterns (DAMPs) (481, 482), and SARM1 is also sufficient to promote cell death in a growing range of other cell types (533). Thus it appears that the profound influence of SARM1 in Wallerian degeneration reflects a wider cell death mechanism that is triggered specifically in axons by a failure to deliver NMNAT2 by axonal transport but can be triggered in other ways in the soma and elsewhere.

D. Cell Death Induced by Aberrant Cell Cycle Reentry

"Mitotic catastrophe" refers to cell death induced by aberrant mitosis (94, 682, 700). Postmitotic neurons can undergo mitotic catastrophe as a result of "aberrant cell cycle reentry" (136, 210, 582), and this has been suggested to contribute to neuronal death in neurodegenerative diseases (616, 677, 783). Aberrant cell cycle reentry may be triggered by an oxidative stress-induced DNA damage response, resulting in expression of the transcription factor E2F-1, which can induce neuronal apoptosis (207). It is possible that cell cycle reentry in neurons is triggered by DNA damage to aid DNA repair because cell cycle reentry causes reexpression of proteins involved in DNA repair (679). Alternatively, activation of NMDA receptors by glutamate can induce cyclin D, resulting in aberrant cell cycle reentry (188). However, postmitotic neurons may elicit a p53-dependent apoptotic DNA damage response pathway in response to pro-oxidants or camptothecin, a topoisomerase inhibitor, without actually initiating a cell cycle reentry response (13, 215, 476, 732).

E. Cell Death Induced by Glutamate (Excitotoxicity and Oxytosis)

Glutamate and aspartate are the main excitatory neurotransmitters in the CNS, playing vital roles not just in neurotransmission, but also neural development, synaptic plasticity, and learning and memory. However, in 1971, Olney (521) reported that high levels of glutamate or aspartate induce cell death of neurons expressing glutamate receptors, a form of cell death he termed "excitotoxicity." Excitotoxicity is thought to contribute to neuronal cell death in stroke, trauma, and epilepsy (221). Excitotoxicity has been attributed to apoptosis, AIF, calpain I, oncosis, autophagy, lysosomal membrane permeabilization, mitochondrial permeability transition, ROS and RNS production, PARP activation, ferroptosis, and phagoptosis **(FIGURE 13)**, making its comprehension and treatment challenging (221, 325)!

Glutamate-induced neuronal damage is mainly mediated by NMDA receptors (112, 437), particularly extrasynaptic NMDA receptors (283, 712), and blockade of NMDA receptors can reduce brain ischemia-induced neuronal death (633). Activation of NMDA receptors requires both high extracellular glutamate and membrane depolarization, conditions occurring particularly during ischemia. Activation of NMDA receptors opens a cation channel within the receptor resulting in neuronal depolarization and calcium loading. The resulting neuronal death is mainly due to the

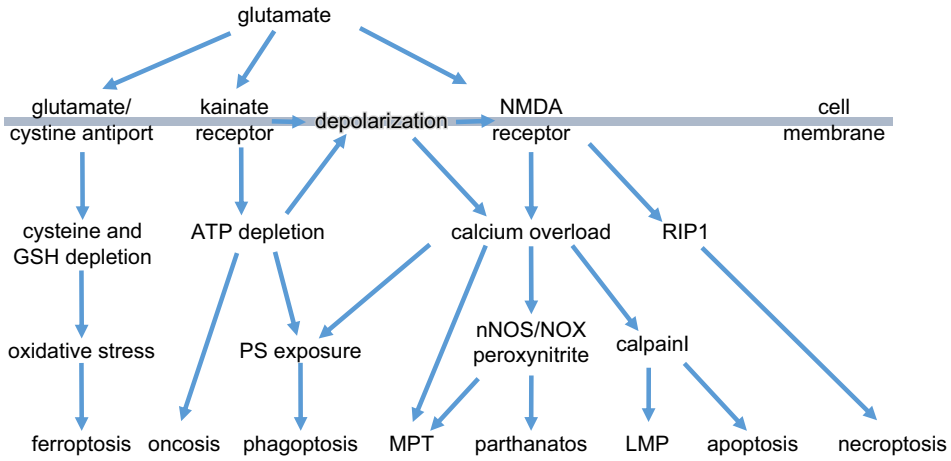

FIGURE 13. Excitotoxicity. Glutamate induces neuronal death by multiple mechanisms. Autophagic cell death may also contribute. Outcome is dependent on neuronal type, stimulus strength and duration, preconditioning, age, gender, etc.

high, sustained rise in cytosolic calcium (112), thereby causing activation of nNOS, activation of calpain I, and/or activation of mitochondrial permeability transition pore.

nNOS can localize to NMDA receptors by binding to PSD-95 so that calcium entering via activated NMDA receptors directly activates nNOS, and disrupting this interaction prevented excitoxicity in culture and reduced brain damage induced by focal cerebral ischemic in mice and rats (801). The mechanisms by which NO from nNOS can induce neuronal death are discussed in the next section, but note that nNOS is expressed in only 1–2% of cortical neurons (66). One mechanism by which NO from nNOS can induce neuronal death during excitoxicity is thought to be by a NO reaction with superoxide to produce peroxynitrite, which damages DNA, thereby activating PARP, resulting in parthanatos (191). Hence, neurons from PARP-1 knockout mice are resistant to glutamate- or NO-induced death, and knockout mice are resistant to transient cerebral ischemia (191). Activation of the NMDA receptor can also activate the NADPH oxidase in neurons to produce superoxide, contributing to neuronal death so that inhibition or knockout of the oxidase prevented excitotoxic neuronal death in culture and in vivo (67, 69, 570). Of note, mild intracellular acidosis, which may occur in neurons during oxygen deprivation, can uncouple NMDA receptor activation from NADPH oxidase and thus limit excitotoxic death during ischemic brain insults (377).

Calpain I is a cysteine protease highly expressed in neurons, which is activated when cytosolic calcium rises into the micromolar range. Activated calpain I can cleave Bax and Bid, causing release of cytochrome *c* and AIF from mitochondria (145, 708). Cytochrome *c* can induce caspase activation via the apoptosome, and calpain I may also cleave and activate caspases directly (708). Calpain I also cleaves AIF to a truncated form (tAIF) that translocates to the nucleus to induce DNA cleavage (92, 702). Calpain activation can also cause lysosomal membrane permeabilization (LMP), which releases toxic cathepsins into the cytosol (see section II*B5*), and this has been implicated in postischemic death of neurons in monkeys (754, 755). However, activation of NMDA receptors may also cause LMP independent of calpain activation (758). During excitotoxicity and brain ischemia, activated calpain I also cleaves and inactivates the plasma membrane sodium/calcium exchanger in neurons, resulting in calcium overload and necrosis, prevented by inhibiting calpain or expressing an exchanger not cleavable by calpain (32). Neurons express a natural calpain inhibitor, calpastatin, whose deletion makes neurons more vulnerable to, and whose overexpression suppresses, excitotoxic cell death (663).

ACD may also have a role in excitotoxic neuronal death. NMDA treatment of cultured cerebellar granule neurons induced autophagy, and inhibition of autophagy with 3-methyladenine or Atg7 knockdown reduced the delayed neuronal death (584). Kainate treatment of cultured primary neurons increased autophagic flux, and autophagy inhibitors or knockdown of Atg7 or Beclin-1 reduced neuronal death (250). Exactly how cell death is executed is not clear. Much of the literature pertaining to ACD in excitotoxicity in vivo comes from studies of ischemia/hypoxia and stroke and is discussed elsewhere (163, 553).

Activation of neuronal NMDA receptors can induce mPT, via increased calcium and ROS and RNS, and blocking mPT with cyclosporine A can reduce the resulting death of neurons (601). Cyclosporine A can also protect neurons against excitoxicity in vivo, but protection is strongly dependent on the strain of mice (595). Genetic knockout of the mPT component cyclophilin D reduced neuronal death induced by low glutamate levels, but not that induced by high glutamate (402), emphasizing the fact that glutamate induces neuronal death by multiple mechanisms.

Glutamate-induced neuronal death is usually via activation of NMDA receptors, but can also be via activating non-NMDA glutamate receptors (549) and/or inhibiting the cystine/glutamate antiporter (604). Glutamate inhibition or reversal of the latter antiporter can deplete neurons of cystine, resulting in ferroptosis, hence ferrostatin was found to

block glutamate-induced cell death in organotypic rat brain slices (175). Glutamate-induced cell death mediated by inhibition of the cystine/glutamate antiporter and consequent oxidative stress was termed "oxytosis" or "oxidative glutamate toxicity" (604, 667). Note, however, that reversal of the cystine/glutamate antiporter during ischemia can cause glutamate release that contributes to excitotoxicity (638).

Phagoptosis may also contribute to glutamate-induced neuronal loss in some conditions, as subtoxic glutamate was found to cause reversible exposure of phosphatidylserine on neurons, which were subsequently phagocytosed by microglia if present, and genetic inhibition of phagocytic genes prevented neuronal loss in vivo induced by transient brain ischemia (493). Apoptosis can contribute to NMDA receptor-mediated excitoxicity in young rats and mice, but not in adults (548), probably due to loss of caspase-3 expression in neurons with age (305). Transneuronal degeneration may spread excitotoxic neuronal death via gap junctions between affected neurons so that gap junction inhibitors or knockout of gap junction genes protect (45).

The plethora of independent and intersecting mechanisms that lead to neuronal cell death in excitotoxicity makes the notion of treatment daunting. It was thought that treatment of the acute damage due to lack of oxygen in stroke would be unlikely to succeed, but the damage that follows due to excitotoxicity in the penumbra may be preventable. Several targeted treatments in rodent models have been successful, not least inhibition of the NMDA receptor with MK-801, but thus far, these treatments have failed to ameliorate the damage in humans (472, 740).

F. Cell Death Induced by Protein Aggregates and/or Unfolded Protein Response

Protein aggregates are a major cause of neuronal dysfunction and death in the neurodegenerative disorders, which include Alzheimer's disease (tau and amyloid β), Parkinson's disease (α-synuclein), Huntington's disease (huntingtin), prion diseases (prion protein), and ALS (superoxide dismutase 1, TDP-43, FUS). In each disease, an unusual misfolding of proteins causes protein deposition as structured or amorphous aggregates that may involve inclusion body formation (360), triggering degenerative signals in the neurons. Despite the different proteins involved in each neurodegenerative disease, the neuronal reactions leading to neuronal death may have common elements, including membrane permeabilization, activation of neurotransmitter receptors, kinase activation, oxidative stress, cell cycle reentry, unfolded protein response, and synaptic loss (439) **(FIGURE 14)**.

The neurotoxicity of extracellular Aβ can be mediated through binding to a variety of receptors, including NMDA receptors, α7 acetylcholine nicotinic receptors (α7n-AchChR), p75 neurotrophin receptor (p75NTR), the β-adrenergic receptors, the tyrosine kinase ephrin type-B receptor 2 (EphB2) and ephrin type-A 4 (EphA4) receptors, insulin receptors, and the Fcγ receptor II-b (208). Excessive activation of NMDA receptors by Aβ oligomers may mediate both inhibition of long-term potentiation and induction of neuronal death via excitoxicity (400). Oligomeric forms of both Aβ and α-synuclein can permeabilize the membrane bilayer, resulting in calcium overload, oxidative stress, mitochondrial permeabilization, and neuronal death, but whether this occurs at levels found in the human brain is less clear (16, 208). Oligomeric Aβ causes synaptic dysfunction and loss, which may cause secondary neuronal loss (72). Oligomeric Aβ can also activate microglia to phagocytose synapses (303) and neurons (497).

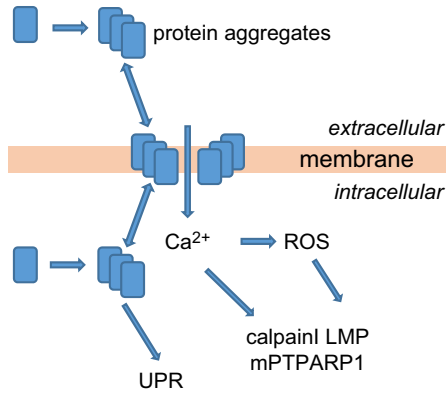

FIGURE 14. Neuronal death induced by protein aggregates. Protein aggregates can trigger the unfolded protein response (UPR) or form membrane pores that elevate calcium and ROS levels, which can trigger cell death by multiple mechanisms. Protein aggregates can also clog protein import into organelles, induce stress granule formation, interfere with RNA and heat shock proteins, and impair the proteasome/autophagy, but how these connect to specific cell death pathways is not clear.

Parkinson's disease and dementia with Lewy bodies (DLB) are characterized by Lewy bodies, composed mainly of aggregated α-synuclein, a physiological presynaptic protein. Smaller aggregates may cause synaptic dysfunction, which may secondarily cause loss of neurons (605). In Parkinson's disease, α-synuclein pathology affecting the substantia nigra is closely correlated with death of substantia nigra dopaminergic neurons innervating the striatum and motor symptoms. Oligomeric α-synuclein can form pores that nonspecifically permeabilize membranes, elevating cytosolic calcium (381). Extracellular α-synuclein oligomers can activate NMDA receptors and thereby inhibit long-term potentiation (173). Extracellular and intracellular α-synuclein aggregates can also activate microglia and astrocytes, which may contribute to neuronal loss (80). α-Synuclein may also directly or indirectly increase ROS levels in cells and induce mitochondrial damage, which may contribute to neuronal death (16).

Tau aggregates are associated with a variety of "tauopathies" including Alzheimer's disease, progressive supranuclear palsy, chronic traumatic encephalopathy, and frontotemporal dementia. Soluble tau becomes abnormally phosphorylated and forms oligomers and larger filamentous aggregates (445, 643). Misfolded, hyperphosphorylated tau causes bundling of filamentous actin, dysfunctional mitochondria, oxidative stress, and DNA damage, which may trigger cell cycle reentry and subsequent apoptosis. Tau aggregates may also cause defects in axonal transport and nuclear depletion of REST and SFPQ. At the synapse, tau localizes Fyn to the NMDA receptor in dendritic spines, facilitating an Aβ-mediated influx of calcium and subsequent excitotoxicity (219, 564) (for further discussion, see sect. IV*B*).

The accumulation of aggregated/misfolded proteins within the cell or endoplasmic reticulum can induce "endoplasmic reticulum stress" and a UPR, which if sufficiently high and sustained can induce cell death. Cell death induced by the unfolded protein response is generally thought to be apoptotic, mediated by activation of endoplasmic reticulum protein kinases PERK and Ire1. PERK blocks most protein translation by phosphorylation of eIF2a, but enables expression of the proapoptotic protein CHOP (CCAAT/-enhancer-binding protein homologous protein), which transcriptionally downregulates the anti-apoptotic protein Bcl-2. Ire1 activates a JNK signaling pathway, stimulating apoptosis. Endoplasmic reticulum stress-induced death of cultured cortical neurons and motorneurons in an ALS mouse model occurs via a p53-independent, Puma-dependent apoptotic pathway (213, 215, 343). Note however that endoplasmic reticulum stress is also associated with paraptosis and cytoplasmic vacuolation (see sect. II*D*).

UPR has been implicated in prion diseases (272), Alzheimer's disease (44), Parkinson's disease (464), and Huntington's disease (185), and inhibiting UPR prevents neurodegeneration in mouse models of these diseases. However, PERK activation has also been suggested to be neuroprotective in a tauopathy model (via Nrf2 activation) (79), and it is unclear how UPR leads to neurodegeneration; it could be due to apoptosis, synaptic loss leading to "dying-back" degeneration (766), loss of protein synthesis, a combination of all of these, or something else (211).

G. Cell Death Induced by ROS and RNS

ROS are reactive molecules derived from oxygen, of which the most relevant are superoxide (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical ($OH^\cdot$), lipid radicals ($L^\cdot$), and lipid peroxides (LOOH). RNS are reactive molecules derived from NO, of which the most relevant are NO, peroxynitrite (ONOO-), nitrogen dioxide (NO_2), and *S*-nitrosothiols (RSNO). Reactive molecules are molecules that can react directly with other molecules without the requirement for enzymes. Because of this, the reactions of reactive molecules are difficult for the cell to control. ROS and RNS have been implicated in neuronal death by multiple means in almost all types of neuropathology and neurodegenerative diseases (123).

The main sources of ROS are *1*) plasma membrane NADPH oxidases (NOX, generating O_2^-) and lipoxygenases; *2*) peroxisomal oxidases (fatty acid oxidation, D-amino acid oxidase, L-2-hydroxyacid oxidase and urate oxidase); *3*) mitochondrial complex I and III; *4*) endoplasmic reticulum cytochrome *P*-450 and b5 enzymes, diamine oxidase, and Ero1; *5*) cytoplasmic NO synthases, lipoxygenases, and prostaglandin synthase; and *6*) extracellular xanthine oxidase (75). Superoxide-generating NADPH oxidases are expressed in neurons and activated by the NMDA receptor resulting in excitoxic neuronal cell death (67, 69, 570). Knockout or inhibition of NADPH oxidases protects neurons in multiple models of stroke (70, 354, 794), brain trauma (179), Parkinson's disease (111, 294, 795), and Huntington's disease (683). The NADPH oxidases that promote this neuronal death could be expressed in neurons, microglia, or vascular cells. Microglia express NADPH oxidase (594), where the oxidants produced mediate microglial activation (105, 321, 447), but the superoxide only becomes neurotoxic in the presence of NO, resulting in the production of neurotoxic peroxynitrite (27, 105, 446). Microglial NADPH oxidase can be activated by multiple inflammatory stimuli, including LPS, amyloid beta, and MAC1/CR3 ligands (105). Activation of microglial NADPH oxidase is necessary and sufficient to drive phagoptosis of neurons by the microglia (496). In the presence of free iron, superoxide and hydrogen peroxide produce hydroxyl radicals that can react with any organic molecule, damaging proteins, lipids, and DNA. The hydroxyl radical can react with membrane lipids and, via a chain reaction, generate multiple lipid peroxides that can be neurotoxic (123, 237). As noted above, glutamate-induced cell death mediated by inhibition of the cystine/glutamate antiporter and consequent oxidative stress was termed "oxidative glutamate toxicity" or "oxytosis" (604, 667) and can be mediated by ferroptosis (163).

The main sources of NO are *1*) nNOS (NOS-1) expressed by some neurons (65, 190), *2*) iNOS (NOS-2) expressed by microglia and astrocytes during inflammation only (243), and *3*) eNOS (NOS-3) expressed mainly by the endothelium (805). NO from eNOS is normally protective via vasodilation, while NO from nNOS and iNOS can be detrimental in specific circumstances (236). High, sustained levels are only produced by iNOS, during inflammation, while nNOS can produce transient and local NO when NMDA receptors are activated, as noted in section III*E*. High, sustained concentrations of NO induce energy depletion-induced necrosis via *1*) inhibition of mitochondrial respiration by decreasing the apparent affinity of cytochrome *c* oxidase for oxygen, *2*)

inhibition of glycolysis by depletion of glutathione, *3*) induction of mitochondrial permeability transition, and/or *4*) activation of PARP. If energy levels are maintained, NO can induce apoptosis, via oxidant activation of p53, p38 MAPK signaling, or endoplasmic reticulum stress (73). Low concentrations of NO can inhibit cell death via cGMP-mediated vasodilation, Akt activation, or inhibition of mitochondrial permeability transition (73). High NO may protect by *S*-nitro(sy)lation of caspases and the NMDA receptor. Neurons are sensitive to NO-induced excitotoxicity because NO rapidly induces both depolarization and glutamate release, which together activate the NMDA receptor (25). In hypoxic conditions, NO inhibition of cytochrome oxidase blocks energy production in neurons (25, 76). Thus, in culture, NO from nNOS can synergize with hypoxia to induce neuronal death (322) and NO from glial iNOS can synergize with hypoxia to induce neuronal death (446). Peroxynitrite exerts concentration-dependent neurotoxicity, inducing necrosis at high concentrations, apoptosis at lower concentrations (59), and phagoptosis at even lower concentrations (494, 495). NO/peroxynitrite-induced neuronal death may also be mediated by mitochondrial permeability transition (454, 598). Peroxynitrite can also damage DNA resulting in activation of PARP-1 to induce neuronal death (191, 608) so that neuronal death induced by NO, glutamate, and brain ischemia was prevented in PARP-1 knockout mice.

Note that PARP-1 activation as a result of oxidant-induced DNA damage causes neuronal death mainly by depleting its substrate NAD^+, resulting in cellular energy depletion (8). A different pathway involving SARM1 mediates axonal degeneration after axotomy by also degrading NAD^+ (see sect. IIIC), but also appears to mediate neuronal death and axonal degeneration induced by H_2O_2 or mitochondrial ROS (242, 656). Thus NAD^+ depletion is common to several instances of neuronal death induced by reactive oxygen and nitrogen species.

H. Cell Death Induced by Microglia and Inflammation

Microglia are the resident macrophages of the CNS and are capable of recognizing and phagocytosing dead neurons rapidly. Microglia play an important role in neuronal survival by several mechanisms including production of neurotrophic factors as well as the phagocytosis of dead cells, cellular debris, protein aggregates, and invading pathogens. Microglia in the healthy brain are "resting," i.e., immobile but with long, motile processes. However, if these microglia detect inflammatory stumuli (indicating the presence of pathogens or damage), they become "activated," motile, retract their processes, and express iNOS and pro-inflammatory cytokines. Microglial activation is a common feature of many neurodegenerative diseases (550). Activated microglia can kill neurons by releasing TNF-α, glutamate, cathepsin B and/or reactive oxygen and nitrogen species (RONS), which can cause apoptotic, excitotoxic, and necrotic death of surrounding neurons (55, 78, 346). Alternatively, if such agents are not sufficient to directly kill neurons, they may stress the neurons sufficiently to induce exposure and/or release of molecules (phosphatidylserine, calreticulin, UDP) provoking microglial phagocytosis of the stressed-but-viable neurons, resulting in cell death by phagocytosis (see sect. II*K*).

Proinflammatory cytokines such as IL-1β and TNF-α can induce neuronal cell death in culture and in vivo (253, 459), but in general, this is indirect toxicity mediated by activation of glia (498, 669). However, in those neurons that express TNF-α receptors, TNF-α can induce either *1*) apoptosis via activation of caspase-8, *2*) inhibition of apoptosis via activation of NF-κB, or *3*) necroptosis, if caspase-8 is inactivated (113, 363, 418). TNF-α can also induce release of glutaminase from neurons, generating glutamate from glutamine extracellularly, resulting in excitotoxicity (767). Interestingly, HIV-infected microglia and macrophages also release glutaminase, resulting in excitotoxicity (196, 307); cathepsin B released by activated microglia has been suggested to mediate the neurotoxicity of Aβ (233) and chromogranin A (351).

As mentioned in section III*G*, microglia express NADPH oxidase (PHOX), which regulates microglial activation and neurotoxicity. Its role in vivo has been highlighted by studies where knockout or inhibition of PHOX subunits prevented LPS-induced neuronal damage (51), 6-hydroxy-dopamine-induced neurodegeneration (295), neuronal death after transient ischemia (775), mortality in a mutant huntingtin model of Huntington's disease (683), and retinal degeneration (789). However, it is unclear in most studies whether this is due to inhibition of neuronal or microglial PHOX. iNOS is expressed in inflamed glia, and the resulting NO can protect neurons (446, 664) but causes neurotoxicity if *1*) PHOX is activated at the same time, producing superoxide that reacts with NO to give neurotoxic peroxynitrite (446, 626), or *2*) hypoxia greatly sensitizes mitochondrial cytochrome oxidase to inhibition by NO, resulting in energy depletion, glutamate release, and excitoxicity (28, 76, 255, 322, 515, 648).

IV. NEURONAL CELL DEATH IN PATHOLOGY

The next sections review specific aspects of neuronal cell death in two human pathologies, stroke and Alzheimer's disease, to reassess what forms of cell death are involved. The reasons for choosing stroke and Alzheimer's disease are partly that they are the most important pathologies involving neuronal cell death (in terms of total mortality, morbidity, and cost) and partly because they are very different pathologies, in particular stroke is an acute insult, inducing

cell death in minutes to days, while Alzheimer's disease is a chronic degenerative disease inducing cell death over years to decades. Nevertheless, they have some common attributes that point, perhaps, to therapeutic strategies.

A. Neuronal Cell Death in Stroke

1. Introduction to stroke

Stroke is one of the main causes of death and disability worldwide. Stroke is a disruption of blood supply in the brain, resulting in extensive neuronal death over a time course from 20 min to 10 days after the event (412). Human strokes are divided into hemorrhagic (caused by a blood vessel bursting) and ischemic (insufficient blood flow). And ischemic strokes are divided into thrombotic (vessel blocked by clot formed locally), embolic (vessel blocked by clot traveling in blood), and global ischemic (due to systemic low blood pressure, myocardial infarction). Stroke and stroke models can be further differentiated on how large the ischemic area is (local vs. global), how long the ischemic event lasts (transient vs. permanent), how low the blood flow falls, and the relative level of hypoxia and hypoglycemia (412). Different areas of the brain differ in their likelihood of undergoing a stroke event (due to the vagaries of the vasculature) and in their sensitivity to ischemic damage (5 min of ischemia is sufficient to cause delayed neuronal death of hippocampal CA1 neurons).

Hemorrhagic strokes result in tissue injury by *1*) compression and tearing of brain tissue by the hemorrhage; *2*) increased intracranial pressure compressing blood vessels locally and globally to cause ischemia; *3*) toxicity of blood-derived coagulation factors, complement components, hemoglobin, heme, and iron; and/or *4*) inflammation contributes to the secondary brain injury after hemorrhage. In general, it is thought that the main mechanisms of neuronal death in hemorrhagic stroke are excitotoxicity, toxicity of blood, oxidative stress, and inflammation (19, 705).

The brain tissue area affected by ischemic stroke can be conceptually divided into the core and penumbra, with the core being the central area experiencing the deepest level of ischemia, and generally becoming rapidly necrotic, whereas the penumbra is the surrounding areas experiencing a lower level of ischemia in which neurons are functionally depressed but still viable (see **FIGURE 15**). Nevertheless, cell death occurs even in this area but later, by more diverse mechanisms, and is generally thought to be more preventable (412) (**FIGURE 16**). The penumbra may comprise as much as half the total lesion volume (71) and may undergo dynamic changes. Shortly after ischemic insult, neurons of penumbra activate signaling pathways that promote survival lasting for several hours or even days; however, with time neuronal density in the penumbra adjacent to infarct core decreases along with activation of glial cells (22). As a result, infarct lesions may expand over time at the expense of the penumbra. Growth of ischemic lesions during the first 6–24 h after the insult has been observed by NMR imaging studies on patients (23, 24). Therefore, salvage of the penumbra neurons seems to be an important target for post-stroke therapies. Subsequently, neurons may die in other areas of the brain as a result of losing their connection to neurons in the infarct (known as secondary neuronal loss, selective neuronal loss or transneuronal degeneration, see sect. III*B*).

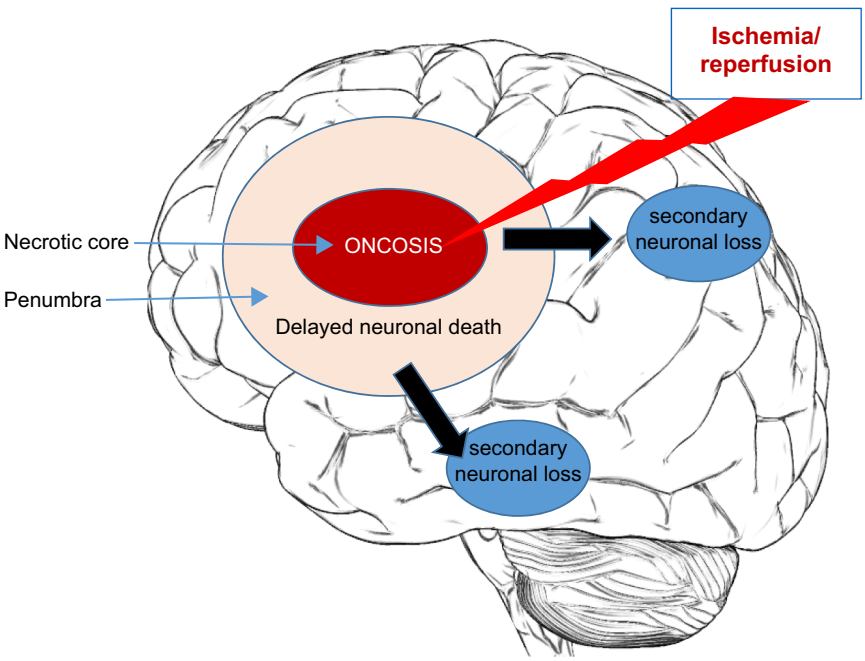

FIGURE 15. Brain ischemia. Brain ischemia induces a necrotic core, delayed neuronal death in the penumbra (where hypoxia is not so deep), and secondary neuronal loss in connected areas of the brain.

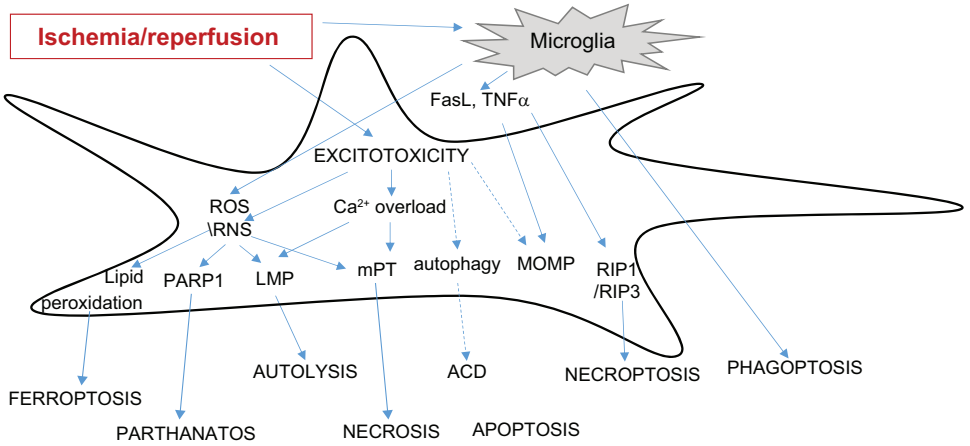

FIGURE 16. Forms of ischemia-induced neuronal death in penumbra.

2. Excitotoxicity in stroke

Ischemia-induced neuronal death is thought to be mediated by excitotoxic mechanisms that are triggered by excessive accumulation of excitatory amino acids such as glutamate and lead to excessive accumulation of intracellular Ca^{2+} (174, 266, 376). During ischemia, limitation of oxygen and glucose supply causes rapid ATP depletion in neurons leading to plasma membrane depolarization. This promotes activation of presynaptic and somatodendritic voltage-dependent calcium channels and the release of glutamate. At the same time, presynaptic reuptake of glutamate is suppressed, which further contributes to accumulation of glutamate in the extraneuronal space. High concentrations of extracellular glutamate together with membrane depolarization leads to activation of glutamate receptors, in particular the NMDA receptors (63), which, once activated, act as ion channels allowing entry of calcium into neurons. This results in cytoplasmic calcium overload, which in turn may activate various programs of neuronal death via opening of mPTP, activation of calpains, and other enzymes and signaling pathways (526).

3. Calpain I in stroke

It has been shown that cerebral ischemia in adult rodents causes activation of calpain I, the calcium-dependent cysteine protease (92, 702), and this contributes to subsequent neuronal death (37, 499, 573, 587). There are also studies showing that calpain I inhibitors prevent neuronal death when applied before (304, 388, 557, 771) or after an ischemic insult (36, 38, 405, 453). Calpain I-null mice showed decreases of cortical neural degeneration after traumatic brain injury (748). Calpain activation can cause apoptosis (708) or necrosis via lysosomal cell death (752, 754).

4. Parthanatos in stroke

During ischemia, excitotoxic mechanisms induced by action of glutamate on neuronal NMDA receptors may lead to production of peroxynitrite and other oxidants that cause DNA damage and activation of PARP-1, which may result in depletion of cytosolic NAD^+, inhibition of glycolysis, and cell death due to energy depletion (see above). Depletion of NAD^+ may also lead to mitochondrial depolarization and release of AIF. In various animal models of stroke, application of pharmacological PARP-1 inhibitors or deletion of gene have been shown to exert protective effects against ischemia-induced neuronal death (191, 475, 651), suggesting parthanatos as a possible mechanism operating during ischemia/reperfusion.

5. Lysosomal cell death in stroke

Yamashima and colleagues found that in primate global cerebral ischemia, the cathepsin B inhibitor CA-074 protects against neuronal death from lysosomal rupture and release of cathepsins into the cytosol of neurons in the hippocampus, which is the basis of their "calpain-cathepsin hypothesis." They subsequently found that hydroxynonenal causes phosphorylation of heat shock protein 1 (HSP-1, a form of HSP70), which is responsible for permeabilization of lysosomal membranes, allowing release of cathepsins into the cytosol and DNase II into the nucleus (reviewed in Ref. 753).

6. Mitochondrial permeability transition in stroke

Neuronal calcium overload, which occurs during ischemia or early in reperfusion and is accompanied by acidification, depletion of adenine nucleotides, mitochondrial depolarization and ROS generation, leads to abrupt calcium accumulation in mitochondria and subsequent opening of mPTP leading to neuronal death. There is extensive experimental evidence that mPTP-induced neuronal death is important component of ischemic brain injury and that specific mPTP inhibitor cyclosporine A reduces neuronal death and infarct size in animal models of cerebral ischemia (483, 680, 774). In a gerbil ischemia model, it has been shown that administration of cyclosporine A early at reperfusion blocked ischemia-induced release of cytochrome *c* from mitochondria (an indication of mPTP opening) and substantially re-

duced neuronal loss in CA1 region of hippocampus (180). In contrast, another immunosuppresive cyclophilin A inhibitor FK506 had no effect on ischemia-induced cytochrome *c* release and neuronal death, indicating that in this model neuronal death was mediated by mPTP-induced cytochrome *c* release rather than by other mechanisms related to cyclophilin A activation. Mitochondria from cyclophilin D-knockout mice have been shown to exhibit resistance to calcium-induced mPTP, and these mice were more resistant to ischemia-induced brain cell death than their counterparts expressing cyclophilin D, suggesting an essential role of mPTP in ischemic brain injury (602). There is some debate whether mPT occurs during ischemic insult itself or at reperfusion after prolonged ischemia as some of mPTP-promoting factors, such as ROS, act particularly at reperfusion (504). Contrary to the later prediction, recent in vivo study by Liu and Murphy (417) demonstrated that in mouse global ischemia model, cyclosporine-sensitive mPTP opening occurs as early as within 1–3 min of ischemic onset and recovers rapidly upon reperfusion. Most of the evidence on mPTP role in ischemic brain damage came from studies on animal models using cyclosporine A as neuroprotector. However, in a pilot phase II clinical trial cyclosporine A was not effective in reducing infarct size in patients (503). But this may be due to the timing of cyclosporine administration to the patients, penetration of the drug through the blood-brain barrier, the dosage of the drug, etc. It also should be noted that in most of studies the effect of cyclosporine A on ischemic brain injury was not 100% protective, suggesting that either other mechanisms of neuronal death are involved or other more powerful inhibitors (and acting on other possible components of mPTP) are needed.

7. Necroptosis in stroke

Ischemia initiates apoptosis in the penumbra; however, if apoptotic signaling is compromised, affected cells may still die by necro(pto)sis (409, 506). This form of cell death can be triggered by Fas ligands, TNF-α, or other proinflammatory mediators produced by activated astroglia and may contribute to brain injury during ischemic and hemorrhagic stroke (798).

Ischemic stroke in mice has been shown to cause necroptotic neuronal death which correlated with delayed ischemic brain injury, and both were reduced by intracerebral injection of a specific small molecule inhibitor of RIP1 kinase, Necrostatin-1 (156). In hemorrhagic stroke, neurovascular injury and related hemolysis of extravasated erythrocytes producing hemoglobin degradation metabolites may trigger neuroinflammatory response of surrounding astroglia resulting in activation of necroptotic pathway in neurons. In line with that, Necrostatin-1 has been shown to reduce cell death, hematoma volume, and neurobehavioral outcomes in a mouse model of intracerebral hemorrhagic stroke (350); however, this study did not identify cellular targets nor the mechanism of Necrostatin-1 protection. In another study on a similar model of intracerebral hemorrhage (99), it was shown that pretreatment with Necrostatin-1 reduced cell death with necrotic morphology along with reduction of levels of autophagy-associated proteins LC3-II and Beclin-1. In addition, such treatment enhanced levels of Bcl-2 and decreased levels of cleaved caspase-3. These data were interpreted as showing that there is interplay between various forms of cell death (necroptosis, apoptosis, and autophagy) in hemorrhagic stroke injury. Similarly in ischemic stroke model in mouse or simulated ischemia in cell cultures, Necrostatin-1 on its own only partially reduced infarct volume and cell death, but it acted synergistically with the antiapoptotic peptide humanin, suggesting that several forms of cell death contribute to ischemic stroke injury (740).

8. Apoptosis in stroke

Apoptosis appears to contribute to neuronal death induced by ischemia in young rodents, but not adult rodents. For example, caspase-3 is activated by focal cerebral ischemia in young (P7) mice, but not adult (P30) mice (245, 305, 414, 804).

For young rodents, there is evidence that apoptotic processes occur during and/or after brain ischemia. So, for example, components of the extrinsic pathway of apoptosis (Fas, Fas ligand, and TNF-α) are upregulated within a few hours postischemia in rodents (456, 579), while the levels of antiapoptotic proteins Bcl-2 and Bcl-xL levels are downregulated (720). Transient or permanent focal brain ischemia in rats has been shown to cause cytochrome *c* release from mitochondria to cytosol (222); note however that cytochrome *c* release could be due to Bax pores or permeability transition. Caspase-3 cleavage has been found after reperfusion of rodent brain (203, 492), and in human brain after stroke (558). Measures of apoptotic cell death peak 24–48 h after transient ischemia (456, 579). Caspase activation is found in the penumbra rather than the core after reperfusion (443), and caspase inhibitors protect after focal rather than global ischemia (398), suggesting that apoptosis is confined to the penumbra.

There is also evidence that blocking apoptotic processes during and/or after brain ischemia is neuroprotective. Transgenic mice lacking functional Fas ligand or TNF-α had reduced cerebral infarcts after middle cerebral artery occlusion, and hybrid mice with both changes had a 93% reduction in infarct volume 24 h after ischemia (456, 579). Neutralizing antibodies against both FasL and TNF-α gave a similar level of protection (456). Mice overexpressing Bcl-2 or Bcl-xL had smaller infarcts after focal cerebral ischemia (457, 727). Furthermore, mice with the Bid knocked out were protected against transient middle cerebral artery occlusion (545, 546), and an Apaf-1 inhibitor was neuroprotective in stroke models (91). Knockout or

inhibition of caspases is also neuroprotective (203, 398, 480).

However, much of the above evidence is ambiguous as to whether it supports a role for apoptosis in neurons or neuroinflammation in glia. TNF-α is a potent activator of neuroinflammation and can induce microglia to phagocytose neurons (498). FasL can mediate microglial killing of neurons (669). Caspases 8, 3, and 1 are all involved in microglial activation (83), and therefore, anything that blocks caspase activation is likely to block microglial activation and neuroinflammation.

9. Phagoptosis in stroke

Neurons in peri-infarct areas have been shown to reversibly expose phosphatidylserine (451), which can provoke microglial phagocytosis of such neurons via the opsonin MFG-E8 and phagocytotic receptors such as MerTK (see sect. II*E*). We found that MerTK and MFG-E8 are upregulated after transient focal ischemia, with levels peaking after 3 days (493). Mice lacking MFG-E8 or MerTK showed a marked reduction in brain atrophy 7–28 days after brain ischemia, compared with wild-type animals, leading to reduced motor deficits. Thus the brain damage induced by ischemia was reduced in the absence of phagocytic proteins. Complement can be activated in stroke and stroke models, and blocking complement activation is in general protective (9). However, it is unclear whether complement is acting to promote microglial phagocytosis of stressed but viable neurons in these models.

10. Autophagic cell death in stroke

Studies in rodents suggest that autophagy can mediate some of the deleterious effects of ischemia and stroke (reviewed in Refs. 163, 553). For example, knockout of Atg7 prevented neuronal death induced by brain hypoxia/ischemia (358). Secondary (transneuronal) death of thalamic neurons, induced by focal brain ischemia, was prevented by autophagy inhibitor 3-methyladenine or knockdown of Beclin-1 (739). However, other studies have found that autophagy can be protective in stroke; for example, activation of autophagy with rapamycin prevented hippocampal neuronal death induced by global ischemia (311). The precise context that leads to these different outcomes still needs to be determined.

11. Microglia and neuroinflammation in stroke

Stroke induces neuroinflammation, and neuroinflammation appears to play a role in delayed neuronal death after stroke (3). IL-1β is one of the main proinflammatory cytokines mediating neuroinflammation in the brain (485). There is little evidence that IL-1β can directly induce neuronal cell death; rather, it acts by amplifying neuroinflammation, resulting in microglial-mediated neuronal death or disruption of the vasculature (78, 485). Expression of pro-IL-1β is induced by inflammation, and cleavage to mature IL-1β is by caspase-1. Inhibition or knockout of caspase-1 is neuroprotective in focal stroke models (280, 281, 600), suggesting that IL-1β production is detrimental, although a neurodegenerative role for caspase-1-mediated pyroptosis is also possible. Double-mutant mice of IL-1α and IL-1β are highly resistant to ischemic brain damage (60). An IL-1 receptor antagonist was protective in animal models and a phase II clinical trial (193). Minocycline, which inhibits microglial activation, was neuroprotective in animal models and a phase II clinical trial (378).

12. Neuronal death in human brain after stroke

It is generally assumed that excitotoxicity is the main mechanism of ischemia-induced neuronal damage in human brains. It has been shown that levels of the excitotoxic amino acids glutamate and glycine in patients' cerebrospinal fluids and plasma were significantly elevated within 24 h of ischemic stroke onset and correlated with size of infarcted area and progression of neurological deficits (95, 96). However, practically all clinical trials on treatments designed to target excitotoxicity were not successful (see below). Concerning forms of neuronal death, the consensus is that in the central core of the ischemic area, cell death is oncotic/necrotic, sometimes is called pan-necrosis, indicating that all types of cells, neurons, astroglia, and endothelial cells die in this severely injured zone. Less evident is what happens in the surrounding penumbra, a hypoperfused area where neuronal activity is compromised but cells are still alive, at least at early time points. With the use of MRI and computed tomography, progression of the hypoperfused penumbra to infarction has been observed in patients during the early hours of acute stroke (50), suggesting that oncosis/necrosis may be progressing in the ischemic penumbra. Another study analyzing post mortem autopsy samples from patients with repetitive episodes of cerebral hypoxia due to cardiac arrest or severe hypotension has shown upregulation of active caspase-3, cytosolic distribution of cytochrome *c*, and occasional TUNEL staining in neurons of vulnerable brain regions 24 h post-ischemia, suggesting apoptotic neuronal death proceeding in the ischemic human brain (558). Signs of apoptosis were found to be less pronounced 3–7 days after ischemic insults. In a recent study on blood biomarkers of 80 patients 6 months after stroke, a correlation between TNF-α levels and caspase-8 and caspase-3 activation was observed suggesting that inflammatory and apoptotic processes may persist long after stroke (535). However, this study did not provide evidence on whether the apoptotic markers were directly related to neuronal death.

Difficulties in determining the type of neuronal death in humans after stroke are related to limitations of in vivo imaging methods identifying biomarkers of neuronal death,

and histopathology post mortem can identify cell death only within relatively short time periods after which no remnants of dying neurons can be detected due to phagocytosis of dead or dying neurons (35). Some investigators have introduced the concept of "selective neuronal loss" that refers to the death of single neurons within preserved extracellular matrix and tissue bulk and can be identified by counting neurons in certain brain areas (35). Such degeneration of hippocampal neurons has been detected by MRI within days after cardiac arrest in humans (224). In the ischemic penumbra in patients, neuronal loss was detected several days and months post-stroke (263, 490, 597). These and other similar studies demonstrated atrophy and possible reduction in neuronal counts in brains of stroke patients; however, they do not provide evidence for mechanisms and time course of neuronal death.

Data from clinical trials on pharmacological inhibitors of key enzymes in cell death pathways may provide useful information about mechanisms of neuronal death operating in human brains during stroke. As mentioned above, excitotoxicity is one of the main targets for neuroprotection in stroke. However, most of the clinical trials designed to investigate the effectiveness of inhibitors of NMDA receptors in stroke patients have failed (389, 477, 583). Indeed, almost all stroke trails have failed (www.stroketrials.org). There may be several possible reasons for such outcomes. First, NMDA receptors or other targets are necessary for normal brain function (413). Second, the time window for stroke patients may be short and not achievable in clinical settings. Third, excitotoxicity is not the main mechanism of neuronal death in human stroke.

Cell death occurring late after stroke may be a more practical target for prevention, making neuroinflammation potentially a good target, as it is upregulated many hours and days after stroke. Though clinical trials on minocycline as an anti-inflammatory drug for post-stroke treatment were terminated, there are several promising ongoing trials investigating effectiveness of antagonists of IL-1 and sphingosine-1-phosphate receptors and other immunomodulators in reducing infarct volumes and neurological deficits in stroke patients (692) (www.stroketrials.org). These studies provide more evidence that neuroinflammation is a driver of neuronal death in human brains after stroke.

Taken together, numerous experimental and clinical observations indicate an interplay of variety of cell death forms and mechanisms during ischemic as well as hemorrhagic stroke. Putative neuronal death mechanisms in ischemic penumbra as the main target for possible therapeutic interventions are summarized in **FIGURE 16**. We are still far from a clear understanding of cell death processes, factors, and causal relationships among them, particularly in stroke patients' brains. Understanding of the complexity of cell death mechanisms operating in post-stroke brains may suggest new strategies and therapeutic means that most probably must target several death signaling pathways.

B. Cell Death in Alzheimer's Disease

1. Introduction to Alzheimer's disease

Alzheimer's disease (AD), as distinct from stroke, is a disease whose time of onset is still obscure. AD is responsible for 60–80% of dementia cases, and symptoms include loss of recent memory, difficulties in concentration and planning, speech and writing, general confusion as to time and place, lack of judgment, and mood changes (29). Careful clinical assessment is still the only way of diagnosing AD and differentiating it from other forms of dementia, although positron emission tomography (PET) ligands for Aβ and tau are being continually developed to try to stage and differentiate AD noninvasively. Morphologically, advanced AD manifests post mortem as a significant shrinkage in cortical volume, with reduced sizes of gyri up to 50%, and increased sizes of sulci, especially throughout the cortex and hippocampus. This is caused by massive neuronal cell death, whose etiology is not clear. A major problem is that AD progresses over many years, so the number of neurons dying per day per area is very low and, hence, those neurons that die do not accumulate in sufficient numbers to investigate the underlying mechanisms of death. There has been extensive research into the causes and consequences of AD (122,744 papers listed in PubMed under "Alzheimer's Disease" in February 2017), yet there is little understanding of how neurons die in AD and there are no effective therapeutics. We focus here mainly on mechanisms of death reported in the human brain.

AD is characterized by two molecular hallmarks: the deposition of amyloid plaques and intracellular neurofibrillary tangles (NFT) composed of the protein tau **(FIGURE 17)**. Plaques consist of peptide fragments of APP, which is a type I membrane glycoprotein and is found associated with vesicles undergoing rapid axonal transport. It has also been reported to localize with lysosomes, mitochondria, and endoplasmic reticulum (ER), as well as the plasma membrane (352, 555). Through sequential cleavage steps by β and γ secretases, APP is processed to produce Aβ1–40/1–42, which form oligomeric structures that seed the formation of amyloid fibrils found in plaques. Evidence from numerous experimental systems suggests that oligomers of Aβ1–42 peptide are most prone to fibrillization and are the most toxic species, but whether this is true in the human brain is not known because probes that allow imaging of oligomers in the living brain are not available (for review, see Ref. 657). A recent analysis of plaques from AD brains shows that the most abundant forms of Aβ1–40/42 are further modified, pyroGlu being the most abundant NH_2-terminal residue (residue 3 in Aβ1–40/42); these are capable of decomposing further nonenzymatically but not sufficiently to

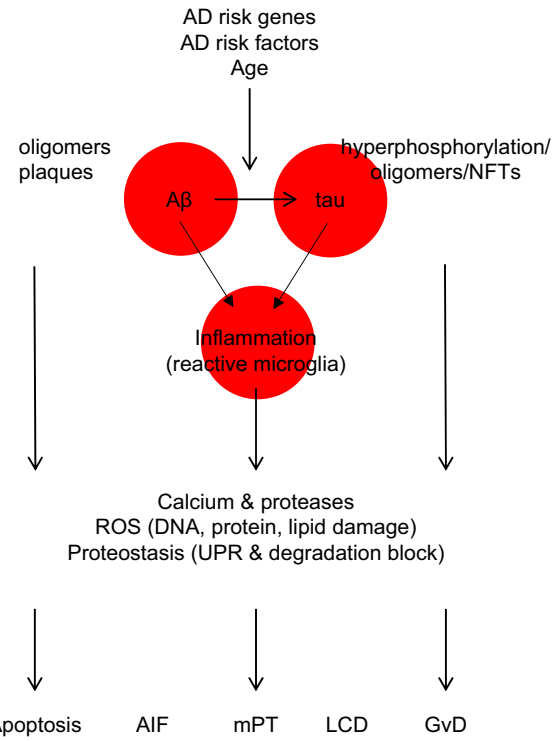

FIGURE 17. Alzheimer's disease pathology and links to neuronal death.

overcome enhanced Aβ production and fibril formation that occurs in AD (436). Aβ1–42 in particular can self-organize into fibrils without accessory protein involvement, but whether these alone form the fibrils in AD is not clear.

The highest genetic risk factor for the development of AD is the E4 isoform of the lipoprotein ApoE, ApoE4. Interestingly, in a comparison of ApoE4 and non-apoE4 carriers who were clinically diagnosed as having mild to moderate AD with cognitive impairment, only 37% had a higher plaque burden than controls though a higher proportion (43%) of those with intermediate levels of AD were associated with NFTs (470). These are necessarily qualitative studies further highlighting the difficulties in diagnosing AD rather than encouraging a switch in emphasis away from plaques as being an important component of AD pathology (590). Despite extensive evidence that Aβ1–42 in particular is toxic, it seems that proof that plaques are causal in the development of AD is still under debate. The best evidence that Aβ is causal in AD etiology is based on the high incidence and early onset of AD and dementias in individuals expressing familial mutations *1*) in the amyloid precursor protein (APP) itself; *2*) in the enzymes known as β and γ secretases that process it, notably the γ secretase activity of Presenilin-1/2; and *3*) in cases of APP gene triplications found in individuals with Down's syndrome (88, 580). These are borne out by studies in animal/cellular models: oligomeric Aβ has numerous death-inducing effects in cultured neurons (see sect. III*F* for brief overview), and many mouse models with familial mutations develop amyloid plaques and cognitive impairments, though not many show cell death (271, 517). However, amyloid deposits can also occur in other diseases, such as small vessel disease, so that the presence of plaques is not sufficient to indicate AD (7). Furthermore, APP-derived amyloid plaques are also found in aged individuals with normal cognitive abilities as observed by PET studies using with the ^{11}C-Pittsburgh compound B (PiB) (317, 540). That APP-derived peptides are nonetheless causal in cognitive decline is suggested by a study of APP variants in the Icelandic population, where the mutation A673T in the APP gene protected against cognitive decline in AD and elderly carriers. This substitution caused a ~40% reduction in Aβ1–40/42 production after transfection of APP into 293T cells, presumably by its being adjacent to the BACE1 cleavage site in APP (331). Interestingly, a A673V mutation was associated with very early onset of AD with enhanced Aβ production and fiber formation in the homozygous state, but it destabilized Aβ when in a heterozygous state, suggesting a dominant negative effect (169). It is important to remember that a precursor product relationship occurs between APP and Aβ (and other cleavage products of APP). Hence, a lot of emphasis has been laid on understanding intracellular APP metabolism. Uncleaved APP has important roles in neuronal development in *C. elegans*, *Drosophila*, and mammals, not least in neurogenesis, and soluble APPα (which cannot be converted to Aβ) has been reported to be neuroprotective (89, 802). Hence, there is an interplay between the toxic and nontoxic forms of APP that likely determine the overall toxicity of amyloid in AD **(FIGURE 17)**.

Almost all forms or hallmarks of death outlined in sections II and III have been recorded in studies of neuronal death induced by Aβ1–42. Most of these studies come from in vitro work. Mediators include death induced by ROS and RNS (reviewed in Refs. 336, 341, 425, 439, 441), PARP-1 (650), calcium dysregulation (160) and calpain (753), mPT (184), excitotoxicity (531), cell cycle reentry (616), various kinases (260, 439), and dysfunction of organelles including lysosomes, autophagosomes (726), and endoplasmic reticulum (137). Some of these studies are difficult to reproduce in culture most likely because of the lack of a standard way of preparing the amyloid peptide such that the monomeric, oligomeric, and fibrillar contents are defined and are maintained constant throughout the course of the experiment. It is still unclear which form of Aβ aggregates are the toxic species (168, 341, 760). Other problems include the wide range of concentrations of at least three orders of magnitude used when adding the recombinant amyloid, the duration of exposure, and the cell type being used; it is especially important to know whether the recipient cells contain tau and whether tau can form NFTs (56) as it is currently suggested that hyperphosphorylated or conformationally altered tau is an important mediator of amyloid toxicity (404, 788) (while normal tau may be neuroprotective (151)). Out of the 66 current transgenic mouse models incorporating

familial APP mutations with or without presenilin mutations (see http://www.alzforum.org/research-models), only 7 report neuronal cell loss, only 4 show tau hyperphosphorylation, and only 2 are reported to contain NFT. In these models, again, the precise composition of monomers, oligomers, and fibrils inside and outside the cells are not known.

While extracellular amyloid deposits are composed of a beta-sheet structure invariant of location, NFTs are intracellular and hence will have specific effects in different types of neurons **(FIGURE 17)**. NFTs consist of insoluble paired-helical filaments composed of hyperphosphorylated tau. Tau is a microtubule-binding protein and in the adult human brain consists of six isoforms due to alternative splicing of the MAPT gene that encodes for tau. These isoforms are distinguished by 0, 1, or 2 NH_2-terminal inserts (designated 0N, 1N, or 2N) and/or 3 (3R) or 4 (4R) repeats in the microtubule binding domain of tau (643). Tau stabilizes microtubules and impacts on axonal transport, but hyperphosphorylation of tau reduces its binding to microtubules; it is suggested that elevating the concentration of tau in the cytoplasm increases tau's likelihood to aggregate and form NFT. A landmark analysis of over 2,336 nondemented autopsy cases by Braak and Del Tredici (62) has suggested that AD begins with abnormal NFTs first appearing in the locus coeruleus, which then progresses through the transentorhinal and entorhinal cortices, to the hippocampus and the rest of the neocortex. In this scenario, interestingly, Aβ plaques appear in much older individuals than hyperphosphoryated tau and NFTs. Indeed, NFT can also accumulate in other types of dementias that do not manifest with Aβ plaques [e.g., frontotemporal dementia with Parkinsonism linked to c17 (FTDP-17T), corticobasal degeneration (CBD), Pick's disease (643)], and together with AD, this group of diseases is termed "tauopathies". These data led to the suggestion that tau/NFTs spread as the disease advances. However, it is not clear from these studies whether pathological forms of tau in, for example, young people would necessarily lead to AD (or to other tauopathies) in these people had they aged. Another explanation could be that this pattern of tau "spread" might be due to differential vulnerabilities of neurons in different regions, given that all neurons express tau (703). Nevertheless, the idea that NFTs can spread according to connectivity maps is supported by data from mouse models expressing a specific isoform of nonaggregating wild-type tau, where small seeds of NFT injected into a limited region of the hippocampus and overlying cortex induced NFT composed of the transgenic wild-type tau that propagated with time to distal sites (121, 122). In what form tau is released and spread is still under debate. Although the burden of NFT correlate with dementias, NFTs in different diseases form different types of filaments and are not expressed in the same types of neurons or are expressed in other cells. In keeping with this observation, tau aggregates derived from non-AD tauopathies injected into mice spread throughout distinct regions of the brain that were different from those derived from AD brains (120).

In AD, NFT are composed of roughly equal ratios of 3R and 4R tau. Numerous familial mutations relevant to AD and other tauopathies have been mapped in MAPT, albeit the frequency of these diseases compared with sporadic AD are very rare. Some mutations change tau's primary sequence, but others alter the ratio of 3R to 4R tau due to changes in alternative splicing, the surfeit of 4R over 3R tau being correlated with the toxic effects of NFTs. It was proposed some years ago from computational modeling that neurons can live for many years with NFTs (478), and data from a mouse tauopathy model expressing P301L tau in cortical neurons including the visual cortex suggest that neurons with NFT retain normal functional connectivity based on responses to visual cues and calcium measurements (370). As noted in the latter paper, only longitudinal studies can establish the true impact of NFT on neuronal survival and function. Since tau oligomers have been suggested to be more toxic than NFTs, it has been suggested that NFTs can be protective due to their ability to sequester tau (for review on mechanisms of tau toxicity, see Ref. 551). Whether NFTs might prevent more toxic species of tau from inflicting damage has also been explored, but the answer in the human brain is still uncertain (46, 380).

Many kinases have been implicated in the production of hyperphosphorylated tau, but so far none has been identified conclusively as being causal in this process. In addition to phosphorylation, tau can also be modified by other post-translational mechanisms, including lysine methylation and ubiquitylation (673) and acetylation (126), with acetylation being proposed to be a leading cause of degeneration in a mouse model of tau-mediated neurodegeneration (468). Autocatalytic cleavage has also been suggested to enhance tau toxicity as well as cleavage by proteases, e.g., caspases (138, 232, 384) or asparagine endopeptidase (797). However, most of the evidence for the importance of tau cleavage in promoting AD is based on post mortem examination, work with animal and cell models, or work with pure tau, and up to now the products of such cleavages only correlate with AD and are not necessarily causative (57, 643, 707).

Plaques are often decorated by microglia with proinflammatory signatures and reactive astrocytes, as well as degenerating dystrophic neurites containing hyperphosphorylated tau/NFT, suggesting two possible causes of neuronal cell death: *1*) direct interactions of neurons with Aβ/tau and *2*) activated glia. As summarized above, Aβ can cause toxicity by a variety, if not all, the pathways summarized in this review. Identifying Aβ receptors would help delineate molecular mechanisms. One proposed biochemical link between APP/Aβ and cell death is provided by the observation that APP binds to DR6/p75 (306, 335, 522). However, an emerging view is that intracellular Aβ can also mediate

neuronal death, and APP has been found in mitochondria and endoplasmic reticulum, two sources of signals that can lead to multiple mechanisms of cell death (487, 681).

2. Apoptosis in Alzheimer's disease

Research on apoptosis in AD had its heyday around the turn of the millennium (year 2000) and has not been revisited since. A series of studies investigated the extent of DNA end-labeling (TUNEL) in post mortem brains from advanced AD patients (Braak stages IV-V), and compared these with those from Parkinson's disease (PD), progressive supranuclear palsy (PSP), and CBD (323, 324, 644, 645). A frequency of ~1% TUNEL-positive cells in AD cases was found compared with 0.0005% in control brains, but less than 0.04% of the TUNEL-positive cells showed apoptotic morphology together with active caspase 3. TUNEL [terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling]-positive labeling indicates DNA strand breaks, which can have a variety of causes, but the high frequency and absence of coincidence with caspase-3 activation suggests that apoptosis is not the cause (58). However, interestingly, active caspase 3 (as detected with the antibody CM1) was localized in 40–90% of neurons containing granules in the hippocampus at Braak stages IV-VI, consistent with evidence of granuolvacuolar degeneration (GvD), although these appear to be living neurons (59) (see below for further discussion of GvD). Interestingly, a negligible number of TUNEL-positive neurons were found in sections from the relevant areas of degeneration in Parkinson's disease, PSP, or CBD. A qualitative assessment indicated that approximately threefold more cells were labeled for proteins implicated in apoptosis, e.g., cJun, Bcl-2, and Bcl-xL compared with control brains (57). c-Jun is involved in cellular stress responses, and Bcl-2 and Bcl-xL inhibit both apoptosis and autophagy (537), so changes in their expression do not indicate a mechanism of underlying death. A decrease in Bcl-2 was also reported in NFT-bearing neurons and an increase in Bax expression in neurons and microglia in AD brains (652), but the antibodies used measured total expression of Bax rather than NH_2-terminal exposure, a hallmark of active Bax recruitment to mitochondria and initiation of mitochondrial apoptotic events (see sect. II*A*). Moreover, the correlation between Bax-, TUNEL-, and NFT-positive neurons was poor. Although it was calculated that the frequency of apoptosis is compatible with the rate of progression of neuronal degeneration (645), that apoptosis is responsible for all death in AD has not been confirmed. It is interesting that there is no enhanced cell death in most animal models of beta-amyloidoisis. A potential explanation for differences in APP-dependent pathology between mouse models and human disease is the recent observation that human iPSC-derived neural precursor cells transplanted into a transgenic APP mouse model, but not wild-type mice, were more vulnerable to amyloid and/or environmental toxicity than the endogenous mouse neurons or mouse iPSC-derived neurons. Interestingly, the death of the human neurons was necrotic with no evidence for apoptosis (199). While neuronal death is prevalent in transgenic tauopathy mouse models, none is evidently purely apoptotic (10, 186). Caspase-3/6 can cleave tau at Asp-421 to a more toxic form (232, 572).Caspase-9 was found with dystrophic neurites within plaque regions in AD hippocampal brain sections, but its presence was reduced in neurons with NFTs (578). As noted by Jarero-Basulto et al. (319), it is not clear how caspases cleave misfoled tau and do so in time to allow tau to be incorporated into filaments over the lifetime of filament formation. To do so would require permanent capsase activity, which has yet to be reported. Hence, there may be nonapoptotic roles for caspase-3/6/9 in AD, but these must occur in living neurons, because had the neurons died as a result of caspase activity, there would be no evidence for tau truncation.

Synaptic loss appears to correlate better than neuronal loss with cognitive decline in AD, and recent studies have supported a view that sublethal nonapoptotic caspase activation localized to dendrites and axons may drive synaptic loss independently of apoptosis (312). As such, caspase inhibition can rescue cognitive decline in genetic mouse models of AD in which cognitive impairment occurs in the absence of neuronal cell death (144). Dendritic pruning involving localized caspase-3 activity has been described as a form of "subcellular apoptosis" (312), and it is hypothesized that this potentially important physiological caspase function becomes aberrantly activated during the early stages of AD (144, 505). Localized caspase-3 activation in dendritic spines is sufficient to induce dendrite loss but not neuronal apoptosis, and recent studies have shown that inhibitor of apoptosis protein (IAP) and proteasome activity may exert protective functions by preventing the conversion of dendrite-localized caspase-3 activity in dendritic pruning into conventional neuronal apoptosis (198).

3. AIF in Alzheimer's disease

As outlined above, AIF has been implicated in Parthanatos and certain types of necrosis (159, 547). An immunological study of AIF expression was conducted comparing early (Braak stages I-II) or late AD (Braak stages V-VI) stages in pyramidal neurons of the CA1–3 regions of the hippocampus, as well as cholinergic basal forebrain and amygdala (385). The results indicate AIF translocation to the nucleus in the CA1 region at the early Braak stages, as well as the amygdala and basal forebrain, which spread to the CA2 region in the advanced AD brains. However, there was no correlation with other markers of cell death, so it is not clear whether AIF translocation is causal in neuron death or whether it indicates dysfunctional mitochondria (or misdirection of newly synthesized AIF away from mitochondria) that are the primary cause of cell death. It would be interesting to check for other markers of parthanatos, e.g., poly-ADP ribosylation, although this modification can be directed at DNA in an innocuous manner. Interestingly, the

PAR modification has been suggested to mediate the neurotrophin signaling by relaxing DNA to allow enhanced transcription (699).

4. Lysosomal/autophagic/calpain-related death mechanisms in Alzheimer's disease

Current approaches to alleviation of neurodegeneration are targeting the beneficial capacity of autophagy to clear protein inclusions and restore catabolic metabolism (462). The risk of AD increases with age and, interestingly, Beclin-1 expression is decreased in human brains during aging (542, 624). In mice, heterozygous deletion of Beclin-1 decreased neuronal autophagy and resulted in neurodegeneration and disruption of lysosomes, whereas increasing Beclin-1 expression reduced both intracellular and extracellular amyloid pathology in APP transgenic mice (542). However, others reported that, in contrast to normal aging, there is a transcriptional upregulation of autophagic genes in the brains of AD patients, but whether this results in increased autophagic flux remains to be determined (411). Autophagic markers (LC3+ vacuoles and p62) were also found to accumulate with tau in human tauopathies, but the significance of this is not established (544). One potential conflict is that autophagy inhibition may decrease Aβ production (508) but may exacerbate other aspects of the disease.

There are more conclusive studies linking AD to lysosomal dysfunction. It has been suggested that lysosomal dysfunction is prevalent in AD and is the major cause of neurodegeneration. Lysosomal dysfunction has mainly been studied in the context of APP and amyloid formation and has been linked to mishandling of amyloid processing, and consequent defects in axonal transport, autophagy, handling of lipids, and cytoplasmic calcium overload (127, 458, 726), thus embroiling all the cellular organelles, leading to massive cell failure. The initiating point appears to be linked to failure of lysosome acidification. The V-type proton ATPase (V-ATPase) is a multimolecular complex that is situated in the lysosomal membrane and is essential for maintaining lysosome acidification, where the V0a1 subunit is indispensible for its function. Studying presenilin 1 (PSEN1) null blastocysts, neurons from mice hypomorphic for PSEN1 or conditionally depleted of PSEN1, or fibroblasts from AD patients with PSEN1 mutations, it was found that the presenilin1 holoprotein (which does not possess γ-secretase activity), which normally bound to the V-ATPase V0a1 subunit and enabled its glycosylation and hence appropriate targeting to the lysosomes, failed to glycosylate the V-ATPase V0a1 subunit and was consequently degraded, resulting in alkalinization of the lysosomal lumen (387). As a consequence, it has been proposed that the lysosomal hydrolases do not function properly causing buildup of undigested constituents. This in turn causes autophagy to be aborted with buildup up of autophagosomes in axons and cell bodies. Calcium is released from the lysosomes via calcium transporters into the cytoplasm, causing calpain activation and proteolysis of cellular proteins (386). In other studies, PSEN1 mutations have also been shown to release calcium from the endoplasmic reticulum, which might contribute to neuronal death (301). The notion that the calcium-activated protease calpain contributes to neuronal cell death is supported by the observation that expression of the calpain inhibitor calpistatin is reduced in neurons in AD brains, probably following cleavage by calpain and/or caspases, and that calpistatin expression rescues neurons in a mouse model of Aβ amyloidosis (471, 561). Calpistatin itself was also cleaved, leading to excess cytoskeletal fragmentation and axon degeneration in mice after physical injury, and this effect was rescued by expression of calpistatin (759).

A causal link between the absence of PSEN1 activity, lysosomal acidification, and reduced lysosomal calcium release is supported by the finding that delivery of acidic poly (lactic-co-glycolic) acid (PLGA) nanoparticles to PSEN1 knockout blastocysts or PSEN1 knockdown cells mediated by siRNA re-acidified the lysosomes and reduced calcium release (387). However, restoration of lysosomal calcium was not sufficient to reestablish lysosome function and autophagy. Hence, the root of the problem appears to lie in lysosomal pH mishandling. It should be mentioned that calpistatin expression also restored normal life span and delayed disease onset in a pure tauopathy (P301L) mouse model, where the mice developing pathology showed loss of calpistatin and generation of tau fragments and cytoskeletal breakdown (560). Familial AD caused by PSEN1 mutations is a rare disease (it is estimated that it accounts for $<0.25\%$ of all AD cases, although it occurs in 20–70% of early-onset autosomal dominant AD cases). Whether this sequence of events occurs in cases of sporadic AD, and in other tauopathies, remains unknown. There is evidence for accumulation of markers that may be explained by lysosomal dysfunction and/or LMP [for example, increased LC3 puncta, Lamp1, p62/SQSTM1, cytoplasmic cathepsin D (544)] but cause and effect or how these connect to cell death remain unclear.

5. Glia in Alzheimer's disease

Up to now, only cell-autonomous mechanisms have been explored as possible routes for neurodegeneration in AD. Astrocytes have been implicated as being causal in non-cell autonomous cell death of neurons in a mouse familial ALS model and in cultures of neurons and astrocytes from human cases of sporadic ALS, but not those from control individuals (563). Neuronal death was proposed to occur through necroptosis. Since ALS with frontotemporal dementiais characterized by dementia that can overlap with some tauopathies (202), it is not unreasonable to propose that glia are affected in AD and that they deliver a prodegenerative signal without which the neurons would not die.

One reason that there is great interest in microglia in AD is the finding from GWAS studies that TREM2, a microglial membrane protein implicated in innate immunity, is the second highest risk factor for sporadic AD (129). TREM2 is a phagocytic receptor on microglia, and TREM2 variants predisposing to AD appear to lose function, so one possible disease mechanism is that these variants have reduced ability to clear dead neurons and debris in AD, exacerbating neuroinflammation and disease progression. In mouse models of AD, eliminating microglia or microglial recruitment prevented neuronal loss without altering amyloid plaque burden (220, 640), indicating a role for microglia in neuronal death in such models. To examine whether microglial activation occurs in AD, a microglial PET marker that detects the microglial protein 18-kDa translocator protein TSPO (18)F-DPA-714, as an indicator of microglial activation, was delivered to a small cohort of individuals with prodromal AD or AD dementia or controls who were also imaged using the amyloid PET tracer (11)C-PiB, and evaluated for cognitive function. The results showed higher binding (18)F-DPA-714 in individuals with early-stage disease than those with more advanced disease. A longitudinal study over 2 yr showed that binding of (18)F-DPA-714 was higher in those individuals who seemed to decline less rapidly than those who declined more rapidly (276; see commentary in Ref. 349). At face value, these data suggest that "activated" microglia, if anything, are beneficial. However, another longitudinal study has shown an association between an increase in IL-1 receptor accessory protein (IL1RAP, a microglial protein regulating inflammation), increasing amyloid burden detected by PET and a declining cognitive performance (556). Clearly, more work needs to be done on the role of microglia and other glia in human AD.

6. GvD in Alzheimer's disease

An intriguing phenomenon that is a hallmark of AD brain histology is the appearance of neurons with numerous vacuoles that contain a single dense granule core, known as granulovacuoles (GV). Although these are a hallmark of advanced AD, inspection of NFT- and GV-bearing neurons in advanced AD (Braak stages V-VI) does not demonstrate a causal relationship between GVs and cell death (see Ref. 357 for a comprehensive discussion). GVs contain many lysosomal markers, so it has been suggested that GVs are the result of lysosomal dysfunction. GV are membrane-enclosed vesicles found in the cytoplasm of pyramidal neurons in the CA1/2 region of the hippocampus and in the cortex in AD and other tauopathies, and because their presence is closely correlated with the presence of hyperphosphoryated tau and dementia in AD, the process they represent is known as GvD. GvD is characterized by the intraneuronal accumulation of cytoplasmic vacuoles 3–5 μm in diameter, each containing a single granule measuring 0.5–1.5 μm^2. These granules contain epitopes for proteins such as neurofilament protein, phosphorylated tau, ubiquitin, tropomyosin, and vimentin. GVs were first described by Teofil von Simchowicz in 1911 as being associated with AD (630). One detailed structural study of GV in brains from individuals with AD dementia by electron microscopy has suggested the following steps: GV formation begins as vacuoles containing some flocculent electron-dense material surrounded by double membranes; the vacuoles then digest some of the material, leaving a dense core of undigested material, during which the inner membrane also disappears (520). With the use of casein-kinase-1∂ as a marker for GVs in AD samples from Braak stages IV-V, GVs were poorly associated with the autophagosomal markers p62 and LC3, but did associate with the lysosomal marker Lamp1 and more so with the chromatin-modifying protein/charged multivesicular body protein B2 (CHMPB2), primarily associated with the endosomal sorting complex, and TDP-43 granules (226). The absence of autophagosomal markers may have been due to the capture of cells at later stages of GV maturation or use of Gate-16 or GABARAP instead of LC3 as markers for autophagosome formation, or may indicate a depletion of autophagosomes by endo/lysosomal fusion. A connection between autophagy and GvD is further strengthened by the similarities between GVs and Rim vacuoles found in a chloroquine-induced muscle myopathy (491, 661). If GV were active autolysosomes and causal in degeneration, their presence might indicate a form of ACD. However, GV are also found in 40% of the hippocampi of nondemented aged individuals (357), so it is not clear that their presence leads invariably to cell death. Aside from tau and hyperphosphorylated tau, over 40 proteins have been detected with GvD granules (357). GVs also contain unusually high amounts of phosphorylated proteins (357), a feature hitherto unnoticed in disease models within or outside the nervous system where autolysosomes accumulate. Neurons bearing NFTs and GvD in AD brains have also been reported to be hypersialylated (486).

The importance of GV in AD pathology has been borne out by two studies: a recent study of GV degeneration in an unbiased sampling of the population of over 75-yr-old individuals from Cambridge City, UK showed a strong correlation between increased number of neurons with tau+ve vacuoles consistent with GvD, or increased incidence of NFT, and increasing dementia severity (310). However, when the analyses were controlled for additional neuropathologies [dystrophic neurites in neuritic plaques, Tar-DNA binding Protein-43 (TDP-43) and amyloid deposits], the associations between GVD and dementia lost significance. Thal et al. (671) have defined five progressive GVD stages based on the anatomical distribution of GVs, which emanate from the CA1/2 subiculum region of the hippocampus to several brain regions, not all associated with AD dementia. They find a high correlation between progressive GV spreading and all other measures of AD pathology including NFT, Aβ, and neuritic plaque pathologies, dementia, and cerebral amyloid angiopathy. GVD stages

were low and no different in controls, other tauopathies (AGD, PSP, CBD), TDP-43-dependent disease (ALS/FTLD), or sporadic PD. Hence, the pattern of distribution of GV with age is different from that of AT8+ve NFT, although it also progresses spatially. Thal et al. (671) further note that "the topographic distribution of GVD restricted to regions involved in response to chronic stress could indicate a link between GVD and chronically stressful influences."

If GVs were to represent the dysfunctional lysosomes discussed in section IV*B4*, this would support the notion that accumulation of GVs beyond a certain threshold could constitute the point of no return in neuronal death commitment in AD, as the name GvD implies. What is needed is to find the molecular link between tau, amyloid plaques, and GvD.

7. "Ballooned" neurons in Alzheimer's disease

Ballooned neurons constitute another degenerative morphological feature commonly found in tauopathies (171, 467, 473, 588, 676), including AD (17, 223, 618). That they signify neuronal degeneration is suggested by the finding that they are also expressed in other neurodegenerative conditions such as Creutzfeldt-Jakob disease (469). As the name implies, the tau+ve neurons swell and, typically, the nucleus is acentric; the cytoplasm showing strong staining for αB-crystallin (432, 678) and phosphorylated neurofilaments (171). One possible reason for this morphology is that the neurons swell because of the lack of matching between the rates of protein accumulation in the cell body due to inhibition of axonal transport and rates of protein degradation; this increases oncotic pressure causing water ingress. Does this signify a novel mechanism of cell death? Although these types of profiles appear with some regularity and are stereotypically placed in the different diseases, nothing is known about the molecular underpinning. With new laser capture devices it should be possible to extract enough samples from individual neurons showing this phenotype to analyze their expression profiles using deep sequencing technologies.

8. Clinical trials and therapeutics in Alzheimer's disease

Causal evidence in humans can sometimes be gleaned from clinical trials (193 listed for AD at www.alzforum.org/therapeutics on January 8 2017). Of the 54 published trials designed to clear or reduce amyloid plaques, there was no improvement over 12–24 mo follow-up, although it is important to note that the trials do not examine cell death but rather follow cognitive function and brain changes by MRI.

Some trials have targeted inflammation, while other sought to inhibit inflammation products such as receptor for advanced glycation end products (RAGE). A Cochrane Database Syst Rev study in 2012 assembled all the randomized controlled trials that met their inclusion criteria and assessed the efficacy of aspirin, steroidal, and nonsteroidal anti-inflammatory drugs (NSAIDs). From the 604 studies assembled, they concluded that "the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and COX-2 inhibitors) is not proven" (320).

Of treatments targeting tau aggregation, the methylene blue derivative LMTM failed to reach the end points in the AD trial and also in a frontotemporal dementia trial, assessed by cognitive examination, the Functional Activities Questionnaire, and change in whole-brain volume on MRI.

In moderate to severe AD, a pooled analysis of six trials found that memantine helped treat and prevent behavioral symptoms of AD (238, 730). Memantine's effect size is small, but it is an FDA-approved treatment for AD. Memantine is a low-affinity antagonist of NMDA glutamate receptors in the brain, preserving physiological activation of the receptor, but blocking excitotoxicity and the neurotoxicity of amyloid beta mediated by the NMDA receptor (152). Whether memantine reduces neuronal death in AD is unknown, but it does slow clinical deterioration, supporting a contribution of excitoxicity to neuronal death in AD.

9. Conclusions on neuronal death in Alzheimer's disease

Taken altogether, the mechanisms of cell death in AD are still a mystery. It is evident that understanding cell death in AD will be much more complicated than in stroke, partly because the stimulus that initiates the onset of cell death is not known, and the much longer time course of the disease that makes catching the neuron in the act of death more difficult.

V. DISCUSSION

A. Distinguishing Features of Different Forms of Neuronal Death

The ever-expanding repertoire of cell death modalities and the discovery of new means to inhibit them holds significant promise for the development of neuroprotective therapies. However, this burgeoning complexity also renders the identification and implication of the roles of unique cell death mechanisms in neurodegeneration both critical and immensely challenging. It is increasingly evident that there exists overlap between some forms of cell death and between cell death and other processes, making distinguishing between them experimentally tricky. For example, apoptosis has been diagnosed by *1*) changes in the level of Bcl-2 family proteins, *2*) caspase activation, *3*) DNA fragmentation,

Table 2. *Inhibitors (pharmacological and genetic) and markers for the identification of various forms of neuronal cell death*

Type	Pharmacological Inhibition	Genetic Inhibition	Markers
Apoptosis extrinsic	Caspase-8 inhibitor: Z-IETD-fmk	Conditional caspase-8−/−	Caspase-8 and -3 cleavage tBid, TUNEL+, PS exposure on nonnecrotic cell
Apoptosis intrinsic	Pan-caspase inhibitors: Z-VAD-fmk, Q-VD-OPh Complex II/SDH stabilizer: compound A	Caspase-3−/− Caspase-9−/− Bax−/− BH3-only protein-deficient mice	Bax NH_2-terminal exposure and oligomerization, cytochrome *c* release, caspase-3 cleavage, TUNEL+, chromatin condensation, PS exposure on intact cell
Necroptosis	RIP1 inhibitors: necrostatin-1s, GSK2982772 RIP3 inhibitors: GSK'872 (but can induce apoptosis) MLKL inhibitor: necrosulfonamide (human)	RIP3−/− MLKL−/− RIP1 D138N kinase-null knock-in RIP1 K45A kinase-null knock-in	MLKL phosphorylation and oligomerization at plasma membrane, accompanied by necrotic features
Parthanatos	PARP inhibitors	PARP-1−/− AIF−/−	PARP activation, high PAR deposition, AIF release
Ferroptosis	Iron chelators (deferoxamine) Lipid ROS scavengers (ferrostatins, liproxstatin-1, vitamin E) 5-Lipoxygenase inhibitor (zileuton)	Cysteinyl-tRNA synthetase knockdown	Excessive lipid peroxidation with necrotic features
Pyroptosis	Inflammasome inhibitors (MCC950) Pan-caspase inhibitors Caspase-1 inhibitor (Z-YVAD-FMK)	Caspase-1−/− Gasdermin-D−/−	Caspase-1 activation, accompanied by gasdermin-D cleavage and plasma membrane localization
Autophagic	Autosis inhibitors (cardiac glycosides)	Conditional ATG family−/− Beclin-1−/−	LC3+ve puncta in cytoplasm, autophagosomes by EM, morphological signature of autosis
Phagocytic	PS-inhibitors (PS blocking antibodies, annexin V, MFG-E8 D89E, cyclicRGD) CRT/LRP inhibitors (receptor-associated protein, blocking antibodies)	MerTK−/−, VNR−/− MFG-E8−/− P2Y6−/− CR3−/−	Engulfed (NeuN+) neurons within phagocytes
MitoPore	Cyclophilin D inhibitors (cyclosporine A)	Cyclophilin D−/−	Mitochondrial swelling (not selective)

See text for definitions.

or *4*) phosphatidylserine exposure. However, *1*) Bcl-2 family proteins regulate autophagy and a variety of other processes, *2*) caspase activation also occurs in inflammation and pyroptosis, *3*) DNA fragmentation occurs in most forms of cell death, and *4*) phosphatidylserine exposure occurs not only in most forms of cell death, but also during stress of viable cells.

The key distinguishing features of different forms of neuronal death are outlined in **TABLE 1**, and methods for distinguishing some of these forms are outlined below, in **TABLE 2**, and in Reference 429. Key diagnostic features include swelling and permeablization of the cell, mitochondria, or lysosomes; types of DNA damage; and activation of particular caspases, calpains, or cathepsins **(TABLE 1)**. For example, fodrin is cleaved into different sizes of fragments by caspase-3/7 and calpain I, and this is used as a diagnostic distinction between cell death mediated by these two proteases (629).

Some of the mechanisms of neuronal cell death and their interactions are depicted in **FIGURE 18**. A subset of cell death mechanisms are distinguished by the execution of

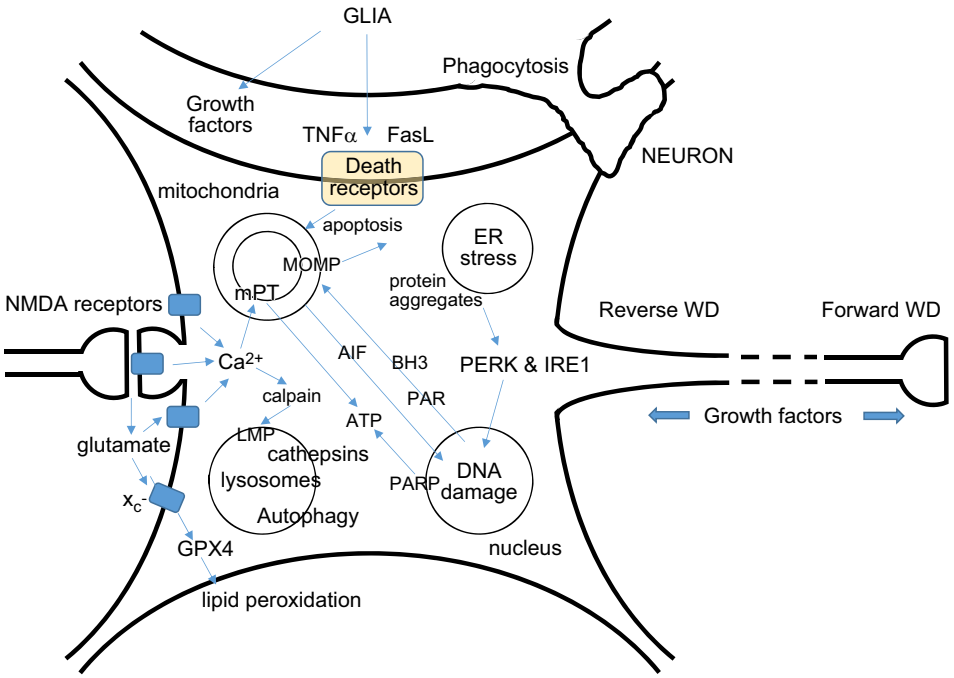

FIGURE 18. Summary of some mechanisms of neuronal death.

death by pores made of particular proteins lodged in particular membranes **(FIGURE 19)**.

To make sense of this ever-expanding field, we have distinguished between different mechanisms of cell death and different stimuli inducing cell death. In addition, we need to distinguish between processes associated with cell death (e.g., apoptosis) and cell death caused by those processes (e.g., apoptotic cell death), because apoptotic processes (e.g., caspase activation, DNA damage, phosphatidylserine exposure) may occur in the absence of cell death, or in some instances cell death may be accompanied by, but not caused by, these processes. Thus experimentally detecting a particular death mechanism does not mean it is the cause of cell death. To come to a clear conclusion, one needs causal data; for example, to conclude that apoptosis is the cause of death, one needs to block apoptosis and determine whether this prevents cell death. This is important because the majority of evidence from animals, and almost all evidence from human studies, is associative rather than causal, and is therefore of limited use in identifying mechanism of cell death.

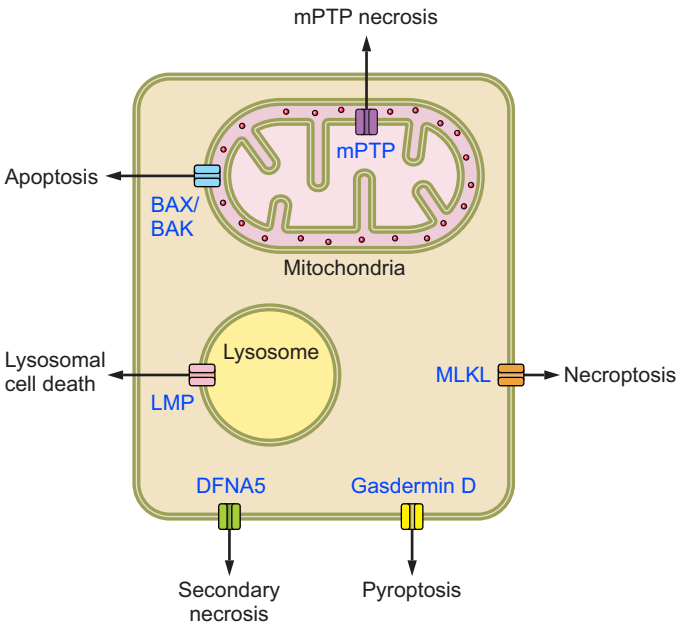

FIGURE 19. The pores of death.

In the absence of causal evidence, one strategy is to make use of markers that appear exclusively during discrete forms of cell death. For cell death modalities where such markers are not presently known, then a combinatorial approach combining several markers represents the best current approach. In the following section we discuss potential markers and attempt to highlight some of the potential traps facing researchers relating to the overlap and promiscuity of cell death-related signals.

1. Apoptosis markers

As discussed above, the diagnosis of apoptosis in post mortem tissue, in animal models, and in vitro culture is complicated by the considerable overlap of apoptotic mechanisms with alternative modes of cell death and further complicated again by nonapoptotic roles of apoptosis-related molecules. Extrinsic apoptosis involves the cleavage and activation of caspase-8 and downstream executioner caspases including caspase-3. Nonapoptotic roles of caspase-8, including the suppression of necroptosis, have been described; however, these roles do not necessarily involve or

require caspase-8 cleavage. Detection of cleaved caspase-8 and -3 and a positive TUNEL signal would provide a strong indication of neuronal death by apoptosis via the extrinsic pathway. In contrast, the intrinsic mitochondrial pathway of apoptosis requires Bax conformational activation and oligomerization, MOMP, cytochrome *c* release, and resultant caspase-3 activation. Thus diagnosis of intrinsic apoptotic cell death in post mortem tissue may best be achieved by detecting coincident presence of Bax activation (translocation and exposure of the NH_2 terminus at the mitochondria using conformation-specific antibodies), caspase-3 cleavage, and positive TUNEL signal. Further evidence should be sought, including cytochrome c release and cleavage of caspase substrates such as PARP and DFNA-5 (see below for markers of secondary necrosis). Where possible, inhibitory experiments should be conducted to confirm the presence and role of apoptosis. Extrinsic apoptosis, should mitochondria remain unpermeabilized, can be inhibited with conventional caspase inhibitors. In most cases (though see exception in Ref. 205), caspase inhibition does not prevent the intrinsic pathway BH3-only protein-induced MOMP however, and should MOMP occur, caspase inhibition will provide only temporary rescue before otherwise cryptic death mechanisms bring about neuronal demise. The recently described compound A, which inhibits Bax/succinate dehydrogenase-mediated cristae remodeling and cytochrome *c* release provides prolonged rescue from intrinsic apoptosis stimuli and may be of use in this respect (328).

2. Necroptosis markers

The phosphorylation of MLKL and the subsequent formation of MLKL oligomers at the plasma membrane represent potential markers that occur exclusively during necroptosis. Antibodies against phosphorylated MLKL have been developed and are available for studies using human and mouse tissues, and the application of these novel tools in the field of neurodegeneration is required. Upstream signaling events such as RIPK1 and RIPK3 phosphorylation are unlikely to occur exclusively during induction of necroptosis, as these two kinases participate in a number of immune-signaling related processes, although the relevance of these necroptosis-independent functions in neurons is unknown. Researchers employing animal models and in vitro cultures to model neurodegenerative processes should verify necroptosis by combining the use of necroptosis markers with genetic or pharmacological inhibition of necroptosis, the reagents for which are now numerous and widely available.

3. Parthanatos markers

Parthanatos involves massive production of PAR, and the translocation of PAR, AIF, and cyclophilin A to the nucleus to induce nuclear cleavage. Confirmation of AIF and cyclophilin A translocation to the nucleus may however not be sufficient to rule out occurrence of other forms of cell death, as AIF translocation appears to be a common execution mechanism and can occur in forms of cell death such as ferroptosis. Confirmation of AIF translocation, along with excessive PAR deposition and DNA cleavage, may be the best combination of markers for implicating Parthanatos in tissue samples. Confirmation of the role of Parthanatos in preclinical rodent and cellular models should be sought in the form of neuronal rescue by genetic or pharmacological PARP inhibition.

4. Ferroptosis markers

A bona fide marker of ferroptotic death is lacking. Excessive lipid peroxidation due to depletion of cellular glutathione appears to be a critical event in the induction of ferroptosis, and thus the coincidence of these two events along with confirmation of cellular demise could perhaps, with further characterization, prove useful in the detection of ferroptotic death. For now, confirmation of ferroptosis is limited to experimental models amenable to the various chemical inhibitors of ferroptosis described in the literature.

5. mPT markers

Large-scale mitochondrial swelling and disruption is a marker of mPT, but not entirely selective. Cyclosporine A and related cyclophilin D inhibitors are effective drugs against mPT-induced death in heart and muscle, but are less effective in inhibiting mPT in brain mitochondria.

6. Autophagic cell death markers

Increased appearance of autophagosomes is a common feature of multiple forms of cell death including autosis, apoptosis, and necroptosis. As such, the accumulation of autophagosomes in dying neurons does not indicate that a neuron is undergoing autophagic cell death, which is defined by an essential role of autophagy in the induction of cell death. Autophagosomes are commonly distinguished by the presence of LC3+ve puncta in the cell cytoplasm using antibodies, and backed up by showing the presence of autophagosomes by electron microscopy. Transgenic GFP-LC3 and RFP-GFP-LC3 mice are helpful and are available commercially (for a comprehensive discussion of methods, see Ref. 356). Application of compounds that cross the blood-brain barrier and activate autophagy in the CNS may help elucidate whether autophagy is being used for cell survival or death (462). However, the reliance on use of chemical or genetic means of autophagy inhibition to confirm ACD, along with the fundamental biological importance of the autophagic process, has rendered the development of useful markers of ACD challenging. The recent discovery of autosis (see also sect. IIG) has allowed the discovery of a morphological signature characterized by extensive autophagosome accumulation accompanied by appearance of

focal concave regions of the nucleus with surrounding swelling of the perinuclear space and separation of the inner and outer nuclear membranes. These unique ultrastructural features may allow histological evaluation of the incidence of autosis in post mortem tissue. Autosis can be chemically inhibited by the action of cardiac glycosides on Na^+-K^+-ATPase, and this class of compounds showed demonstrable neuroprotective effects in preclinical rodent models of stroke. However, at present, it remains unclear whether these compounds may provide neuroprotection through inhibition of the induction of autosis or by prevention of harmfully excessive ATP consumption by Na^+-K^+-ATPase. Furthermore, it is unclear at present whether autosis is the sole mechanism of ACD, or whether further autophagy-induced death mechanisms exist.

7. Lysosomal cell death markers

It is still difficult to determine whether LMP occurs in post mortem human brains because proteases/lipases/DNases that are normally packaged in lysosomes may accumulate in the cytosol due to lysosome rupture or to lack of a priori packaging due, for example, to reduced lysosome acidification (see detailed discussion in section IV*B4*). A novel assay for LMP has been proposed that involves the rapid translocation of galectins 1/3 to leaky lysosomes (6), but whether this event is specific to all cases of LMP, and whether this signals lysosomal cell death in neurodegenerative conditions, requires further analysis.

8. Paraptosis markers

There are no unique features or molecular markers that distinguish paraptosis from other forms of cell death. A requirement for protein synthesis may indicate paraptotic death, but since this is a feature shared with apoptosis, and the target of protein synthesis dependence was not elucidated, it is not a feature that can be used to define paraptotic death.

9. Pyroptosis markers

The cleavage of gasdermin-D by caspase-1 and its subsequent translocation to the plasma membrane in a necrotic cell may constitute the best unique marker of pyroptosis. Although caspase-1 (or caspase-11) activation is a critical component of the pyroptotic death cascade, along with upstream inflammasome activation, it does not constitute an exclusive marker of pyroptotic death in necrotic cells. Recent studies demonstrated that the formation of MLKL oligomers and plasma membrane permeabilization results in K^+ efflux-dependent NLRP3 inflammasome formation and associated caspase-1 activation. Thus caspase-1 activation in necrotic neurons may be associated with either pyroptosis or necroptosis, and researchers should seek to exclude necroptosis through confirming absence of MLKL phosphorylation or oligomerization at the plasma membrane, or preferably through measurement of gasdermin D activation as discussed above.

10. Secondary necrosis markers

As discussed above, secondary necrosis, previously considered to be a consequence of energetic collapse of uncleared apoptotic cells, was recently shown to occur through a regulated mechanism. The caspase-3-mediated cleavage of DFNA-5 results in the generation of an NH_2-terminal fragment that translocates to the plasma membrane, forming a pore in a manner similar to that of caspase-1-cleaved gasdermin-D. Of note, this mechanism remains to be demonstrated in neurons. Thus, contingent on further characterization, the appearance of an NH_2-terminal DFNA-5 fragment (detectable by Western blot) and the translocation of DFNA-5 to the plasma membrane may represent markers that could distinguish this form of necrosis from others. An inhibitor of DFNA-5-induced plasma membrane permeabilization does not exist at present, but mice deficient in DFNA-5 exist which will allow the initial characterization of the role of DFNA-5-mediated secondary necrosis in preclinical disease models.

11. Phagoptosis markers

The detection of phagoptosis is rendered particularly challenging by two considerations. First, the engulfment of viable neurons by microglia during phagoptosis results in rapid lysis, destruction, and recycling of the target in the phagocyte. Second, the molecular signals and machinery employed in the recognition, engulfment, and destruction of viable neurons during phagoptosis overlap completely with the mechanisms governing efferocytosis (phagocytosis of already dead neurons). At present, the sole means to visualize phagoptosis is thus through careful verification of the presence of completely engulfed neurons which may or may not lack morphological or histological markers of cell death (i.e., nuclear condensation and/or fragmentation and TUNEL positivity can be induced by DNA degradation in the lysosome). The role of phagoptosis in animal models and in vitro models may be revealed by demonstrating the long-term rescue of neurons using inhibitors of components of the efferocytosis/phagoptosis signaling machinery (e.g., phosphatidylserine exposure and recognition, calreticulin exposure, and recognition).

To summarize, pinpointing the mechanisms of cell death at play is complex and challenging. For the most part, it would appear that we cannot rely on individual markers for the diagnosis of the various types of cell death. As mechanisms are further elucidated, novel unique markers may become apparent, while other markers may become less useful than first thought.

B. Different Ways of Conceiving Cell Death Types

How we think about cell death and its different modes has changed over time. Some of the ways in which different modes of cell death have been distinguished include *1*) beneficial versus detrimental, *2*) accidental versus regulated/programmed/designed, *3*) absence or presence of phagocytosis of dying cell, *4*) absence or presence of inflammation, *5*) absence or presence of plasma membrane rupture, *6*) requirement for transcription/translation, *7*) cell autonomous versus non-cell autonomous, *8*) initiated inside or outside cell, *9*) initiating stimulus or execution mechanism, *10*) cell morphology, and *11*) biochemical pathway.

The group that has designated itself as the Nomenclature Committee on Cell Death has suggested doing away with morphological definitions of cell death and dividing it rather into "accidental" versus "regulated" cell death mechanisms, with programmed cell death being a subroutine of the latter (230). By accidental cell death they mean: "Cells exposed to extreme physicochemical or mechanical stimuli die [unavoidably] in an uncontrollable manner, as a result of their immediate structural breakdown." Regulated cell death is "initiated by a genetically encoded apparatus, correlating with the fact that its course can be altered by pharmacologic or genetic interventions . . . it can occur as part of physiologic programs or can be activated once adaptive responses to perturbations of the extracellular or intracellular microenvironment fail." A third category comprises a nonautonomous route where "the signals that emanate from the dead or phagocytosed cells can dysregulate neighbouring cells." In neurodegenerative it may be the case that the third category is the norm.

This is a meta-categorization of cell death types, but it cannot replace the necessity of distinguishing the different ways in which cells die. Also, the distinction between accidental and regulated forms of cell death is poorly formulated as *1*) all biological processes, including accidental death, are mediated by a genetically encoded apparatus; *2*) "accidental" in the sense of caused by human accident is a very small set, whereas "accidental" in the sense of not designed by evolution includes all disease; and *3*) distinguishing forms of cell death on the basis of whether they can be prevented or not depends on our current knowledge and the strength of the death stimulus, rather the type of cell death.

Categorizing cell death based on the stimulus used to induce cell death (as we have done in section II of this review) can be confusing, because the various stimuli overlap, and the type of death induced can depend on the stimulus amplitude, brain region, age, etc. However, if this is how the biology is, we should adapt our categories to the biology, rather than the other way around.

Different mechanisms of cell death can also overlap in their biochemical pathways, e.g., "lysosomal cell death" or mitochondrial permeability transition can be initiated by multiple other forms of cell death and can in turn trigger multiple other forms of cell death. Furthermore, a specific physiological stimulus or pathology may initiate multiple forms of cell death within a cell, e.g., excitotoxity or stroke. One approach to this challenging complexity is to focus on the points in cellular pathways where cell death can be stopped, the "death commitment points," rather than simply categorizing pathways of death.

C. Death Commitment Points

The death commitment point (dcp) in a cell death pathway is the last step in the pathway at which cell death can be prevented. In general, blocking that step or any step in the pathway upstream of that point prevents death, while blocking steps downstream does not prevent death. Defining the death commitment point of a cell death mechanism corresponds to identifying how that form of cell death can be prevented, and therefore how to causally diagnose that form of cell death. In pure cell populations, this is easy enough as cells die within a short period of time but in brains multiple interactions can occur within and between cells so each cell may have more than one dcp.

The concept of dcp traces its origins back to early studies on neuronal apoptosis, particularly those conducted in relation to NGF-withdrawal induced death of sympathetic neurons. These studies revealed that dcp is cell type, stimulus, and context dependent, even when studying a "simplified" model such as NGF-withdrawal-induced apoptosis. In most cases of intrinsic apoptosis, dcp appears to occur upstream of caspase activation, as caspase inhibitors provide only temporary rescue. Prior to caspase activation, cytochrome *c* release was considered as a potential dcp until it was found, in the context of NGF-withdrawal induced death of mature sympathetic neuron cultures, that mitochondria may recover from MOMP and reload with cytochrome *c* when caspases are inhibited and trophic factor signaling was restored (205). This ability to recover from cytochrome *c* release was context dependent and likely relates to as yet poorly understood signals associated with mitochondrial dysfunction and ability to restore ATP and protein synthesis. On this basis it might be argued that Bax oligomerization and subsequent induction of MOMP may constitute an important dcp. Yet, the recent discovery of Bax-mediated modulation of succinate dehydrogenase to induce cristae remodeling required for cytochrome *c* release and the observation that inhibition of this process (but not Bax oligomerization) can provide extended neuroprotection merits further investigation into the potential role of this step as an apoptotic dcp in neurons. It is not yet possible to conform to these definitions in most cases of neuronal cell death other than in development, since there are no significant markers

for any of these stages. In this regard, it may be easier to prevent dcp when the cell death stimulus is temporary (e.g., in the penumbra after stroke). In protein aggregation-prone neurodegenerative diseases, the stimulus is chronic so targeting dcp may need to be chronic to achieve long-lasting neuroprotection. Regardless, the implications of the concept of dcp are that one should develop therapeutics that target (pathways up to) dcp and not try to rescue neurons by inhibiting downstream pathways (unless there is an amplification feedback loop, where, for example, caspases activate proteins that aid in MOMP, in which case inhibiting caspases may allow time for treatment that prevents cell death). Here the neuroscience field diverges somewhat from the cancer field as the latter have no interest in defining dcp but rather try to overcome barriers to cell death. Nevertheless, studying the barriers to initiating tumor cell death might provide clues as to the steps that might be manipulated to implement and maintain neuronal survival.

Regarding alternative modes of cell death including the various forms of regulated necrosis, far less is understood regarding the intricacies of dcp. In terms of parthanatos, PARP inhibition has been shown to provide long-lasting neuroprotection both in vitro and in vivo. This may relate to the fact that hyperactivation of PARP appears to lie upstream of both mitochondrial permeabilization and release of AIF, as well as driving accompanying metabolic compromise through depletion of NAD^+ and disruption of glycolysis. Indeed, while AIF nuclear translocation appears to be an important executor mechanism in this and other forms of cell death, recent evidence suggests that early PAR-mediated inhibition of hexokinase drives both metabolic and mitochondrial dysfunction (including AIF release) and thus may constitute a critical dcp in neurons undergoing parthanatos.

Cell death by mitochondrial permeability transition is almost by definition prevented by blocking mitochondrial permeability transition, e.g., with cyclosporine A or knockout of cyclophilin D, so the death commitment point would be mitochondrial permeability transition itself. However, in practice, mitochondrial permeability transition is induced by complex stimuli, such as excitotoxicity or stroke, which also induce other forms of cell death so that the impact of inhibiting mitochondrial permeability transition can be limited (see sections on mPT above).

Ferroptosis is almost by definition prevented by iron chelators or some antioxidants, and the death commitment point should be some level of lipid peroxidation. However, again, iron chelators or antioxidants may have a limited impact on cell death induced by real, complex stimuli. Also, the mechanism of cell death downstream of lipid peroxidation is poorly understood, so the actual dcp is unclear and may depend on the stimulus and its intensity.

Necroptosis can be blocked by inhibition of RIP1 (e.g., with necrostatin), RIP3, or MLKL (e.g., with necrosulfonamide), and the permeabilization of membranes by phosphorylated MLKL could be the death commitment point. Further studies are required to establish the long-term neuroprotective effects of inhibition of each step of the necroptosis pathway to truly define its dcp, and recent studies suggest that activation of RIP1 and RIP3 may exert pathogenic effects independently of MLKL which could involve cell death (501). Pyroptosis is partly defined by being prevented by inhibition of caspase-1, and the death commitment point would be gasdermin D cleavage (by caspase-1) to form a pore-permeabilizing membrane, although the long-term neuroprotective effects of inhibition of gasdermin-mediated membrane rupture remain to be established. The commitment point to lysosomal cell death is lysosomal membrane permeabilization, but because this permeabilization can induce multiple forms of cell death, the dcp is in general unclear, and probably varies with stimulus and stimulus strength. For autophagic cell death, the dcp is unclear, partly because autophagy is required for cell life.

For cell death induced by stimuli and disease, the dcp becomes increasingly unclear and more likely to be located outside the dying cell itself.

D. Modeling Cell Death Kinetics

Can modeling cell death kinetics teach us anything about the cell death process? If cell death is a cell autonomous stochastic process, the kinetics of cell death are predicted to follow a simple first-order exponential, meaning that each cell's death is random and that a single intracellular event is responsible for the commitment to a degenerative process. The implication is that intervention at any stage of the disease is likely to rescue equally all the remaining living cells. However, if the probability of cell death increases over time, perhaps because each cell accrues sequential damaging events until this reaches a threshold that commits the cell to die, then cell death should follow a sigmoid pattern that begins with a lag followed by an ever-accelerating rate of death as time progresses. A test of these alternative hypotheses was conducted in a range of cellular and mouse models including Parkinson's and Huntington's disease (116). In almost all cases, the kinetics of death followed a first-order process, as was observed in the kinetics of death of cultured sympathetic neurons after NGF withdrawal by apoptosis (187). However, this model neglected the obvious lag time of different lengths that invariably occur until the onset of cell loss. To incorporate such a lag time, the same authors proposed a "stretched" kinetic model with a power constant beta (that can become 1st order when the added constant beta obtains a value of 1, but follows a sigmoid form when beta is >1), but this introduces factors that have no physical chemical basis. According to this model, each cell still has its own individual constant risk of death, but it is

different between cells "due to spatial differences in the cellular microenvironment" (117). An important implication is that therapeutic intervention that affects one cell may not rescue all the other remaining cells. It would be illuminating to examine the kinetic profile of death in AD, as has been done for the neurons in the caudal substantia nigra of patients with Parkinson's disease (201) and in ALS (148) because this can rule out simplistic models that postulate cell autonomous mechanisms and hint at differential vulnerabilities of neuronal classes, and interactions with the environment, as being crucial participants in the cell death process.

E. Future Research and Therapeutic Implications

Despites decades of research and thousands of papers, we have a poor understanding of how neurons die in pathologies, such as stroke and AD, and consequently a very limited capacity to prevent this neuronal death. In part, this knowledge gap is due to *1*) lack of techniques to image particular forms of neuronal death in patients in vivo and *2*) lack of treatments to specifically block particular forms of neuronal death in the brain in patients. If progress is to be made in this field, we need technical advances in these two areas.

Some progress has been made in imaging cell death in vivo, but mostly outside the brain (500, 567). Large molecule probes of phosphatidylserine exposure have been developed for in vivo imaging, but have limited brain penetrance. The phosphatidylserine-binding protein annexin V has been reported to penetrate beyond the blood-brain barrier, and report on neuronal phosphatidylserine exposure after stroke (451). However, this exposure was reversible in the penumbra, indicating that phosphatidylserine exposure is a marker of neuronal stress as well as apoptosis and necrosis. ApoSense have developed a set of novel small-molecule probes that apparently selectively accumulate in apoptotic cells, possibly due to scramblase activation, cell membrane depolarization, and cytoplasmic acidification (125). These compounds are reported to accumulate in the brain during ischemic cerebral stroke (568) and animal models of ALS and AD (628). However, it is not entirely clear what these probes are reporting on. In AD, recent advances in PET imaging have allowed a glimpse into the prevalence and distribution of amyloid plaques and NFT in individuals, and mapping the advancement of the disease using longitudinal measures (349, 365, 527, 603, 614, 709). None so far has been combined with markers of cell death.

Treatments currently available to block particular forms of neuronal death in the brain are listed in section VC above and elsewhere, and others are in development. There is some tension between *1*) using treatments selective to particular forms of cell death, which gives most information about the form of cell death involved, and *2*) using treatments that block all forms of cell death involved, for maximal therapeutic benefits, irrespective of selectivity. For neurological diseases, such as stroke and AD, multiple forms of cell death are likely involved so that multiple therapeutics or nonselective treatments may be the most beneficial.

Taking the particular case of neurodegenerative diseases driven by aggregated proteins, it would be useful to determine the receptors for the various toxic species of these proteins as a first step. The ability to culture complex human neuronal networks from embryonic stem cells and inducible pluripotent stem cells, along with advances in high-throughput gene editing technologies, may provide a means to address this area. Mitochondrial, ER, and lysosomal dysfunction have been implicated in all types of neurodegeneration; it is clear that such events will ultimately cause cell death, but, in AD, the precise molecular link between with Aβ and NFT and these organelles needs to be defined. The same holds true for all protein-aggregate prone pathologies. Once the initiating events are defined, then painstaking and systematic research will be needed to link these up to the point of death commitment.

Further understanding of the types, mechanisms, and roles of neuronal death in physiology and disease is urgently needed, but given the rapid progress in recent years, this understanding is likely to be transformative.

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