Published in final edited form as:
Mol Neurobiol. 2010 August ; 42(1): 25–31. doi:10.1007/s12035-010-8128-2.

A Perspective on Neuronal Cell Death Signaling and Neurodegeneration

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Keywords

Cell Death; Apoptosis; Axonal Transport; Kinesin; Dynein; Neurodegeneration; Kinases

Loss of neurons is typically the readout used for studies of neuropathological conditions ranging from stroke and traumatic brain injury to adult-onset neurodegenerative diseases such as Alzheimer's and Parkinson's[1]. One result is that studies of neurodegenerative disease often become descriptions of progressive neuronal cell death, and many therapeutic strategies focus on preventing cell death [2, 3]. Unfortunately, successes in reducing or preventing neuronal cell death have not translated to effective treatments for any neurodegenerative disease [4–6]. The problem is that neurodegenerative diseases are not caused by cell death signaling pathways. Although apoptotic pathways will eventually be activated and neurons lost as the disease progresses, the clinical symptoms of neurodegenerative diseases reflect abnormalities in synaptic function and the loss of synaptic connections, rather than the loss of neurons. Conflating the shared molecular mechanisms of cell death with unique disease-specific pathogenic mechanisms of neurodegeneration may be interfering with the search for effective therapies.

Although the final common steps in cell death pathways (i.e., nuclear fragmentation, etc.) are shared between neuronal and nonneuronal cells[7, 8], the sequence of events leading to cell death in neurons may include steps not found in nonneuronal cells[9]. Neuron-specific features may involve an extended period of time, often months or years, in contrast with the rapid progression of apoptosis observed in non-neuronal cells[10]. These initial neuron-specific steps manifest as a loss of synaptic function, a process initiated at a considerable distance from the neuronal perikaryon. Complicating the situation further, components of cell death signaling pathways can play roles in neurons unrelated to cell death, such as regulating aspects of synaptic function and plasticity[11–13].

Neuron-specific cell death features

A brief consideration of some unique aspects of cell death in neurons may be useful. Both extrinsic and mitochondrial-based pathways of apoptotic cell death can be observed in neurons[8, 10, 14], depending on the triggering stimulus. The initiators of cell death may be as diverse as failure to establish trophic relationships with a target cell, stroke and traumatic brain injury, or neurodegenerative disease, regardless of whether they are environmental, familial or sporadic in origin. Both apoptotic and necrotic cell death may be observed in neurons [8], but here we will focus on apoptotic mechanisms. Perhaps the most obvious

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difference between neuronal and non-neuronal cell death is the time that takes to complete apoptosis. The final stages of apoptotic cell death are rapid and similar in both neuronal and nonneuronal cells. However, in neurons the early stages begin in the distal axon and presynaptic terminals and progress slowly. Months or even years may elapse between the first decrements in neuronal function and the initiation of a final apoptotic sequence.

The ways in which cell death pathways are managed in neurons differ from nonneuronal cells. The enormous size and complex functional architecture of neurons requires additional layers of complexity, which are seen both in development and in pathological states. Cell death plays a critical role in sculpting the functional architecture of the nervous system during development [9, 15]. During development, programmed cell death via apoptosis assures that appropriate matches exist between neurons and their target cells. Nuclear changes are late events and the first steps leading toward developmental neuronal death typically occur in synaptic and axonal compartments. If these steps are limited in scope and extent, synaptic and axonal changes might lead to pruning of nonproductive synaptic contacts or axonal branches[9]. Such pruning is essential for establishing sensory maps in the cortex such as those corresponding to visual space [16]. The atrophy of an axonal branch follows shutdown of synaptic function and degeneration of the presynaptic terminal, with subsequent degeneration of the distal axon. The distal axonopathy seen in early stages of neurodegenerative disease follows a similar sequence but involves a most or all of the presynaptic terminals in an affected neuron. The result is a classic dying-back neuropathy[17–19].

The sequence of events associated with loss of presynaptic function and degeneration of distal axons may be prolonged for years after the first decrement in synaptic function take place [10, 20]. This is in large part due to the size and complex morphology of neurons, which create an abundance of heterogenous microdomains and provide new arenas for cell death-related molecular components to perform diverse functions. In some neurons, activation of kinases or caspases in a presynaptic compartment may occur a meter or more away from the nucleus. This topographic separation prevents the interaction with key downstream targets required for the progression and execution of apoptosis. Under these conditions, the critical apoptosis executioner caspase-3[11, 12, 21] and pro-apoptotic kinases like JNK [22–25] may be activated in a pre- or postsynaptic compartment, but apoptosis does not result. A growing body of evidence indicates that some components of cell death pathways may play important roles in normal neuronal functions like the synaptic plasticity that underlies learning and memory[11–13].

However, a failure in the trophic relationships of neurons with target cells does trigger apoptosis in neurons[26–28]. This is due to the uniquely symbiotic relationship between a given neuron and the hundreds or thousands of other cells that interact with that neuron. Important interactions are associated with presynaptic and postsynaptic specializations as well as with diverse glial cells. Target cells (i.e., muscle cells, other neurons, etc.) act as a source of neurotrophins, which in turn promote survival of neurons innervating these targets. The neuron integrates these various relationships in ways that are incompletely understood. This integration is essential not only for neuronal survival, but also for determining size, morphology and various functional aspects of the neuron. Moreover, these trophic relationships are tightly tied to neuronal activity, so only productive relationships are preserved[29, 30].

Synaptic function and neurotrophin-dependent neuronal survival

How then does a neuron progress to apoptosis either in development or in slowly progressing adult-onset neurodegenerative diseases like Alzheimer’s, Parkinson’s and

Amyotrophic Lateral Sclerosis? In both, the apoptotic process occurs as a dying-back neuropathy or distal axonopathy[31], following a characteristic sequence of events (Figure 1). Lack of effective synaptic activity coupling neurotransmitter release to neurotrophin uptake will initiate degeneration of the presynaptic terminal[9, 17]. Loss of synaptic activity may result from reductions in critical components for neurotransmitter release in the presynaptic compartment or by failure of appropriate responses (i.e., trophic support) from target cells. In disease states, deficiencies in presynaptic components may be more common, while during development inadequate neurotrophin supplies from nonresponsive targets is more likely. For example, blockade of neurotrophin uptake during development interferes with the establishment of ocular dominance columns[32]. Similarly, both uptake and retrograde transport of neurotrophins by sensory neurons in dorsal root ganglia is needed to prevent cell death of these sensory neurons[33]. Survival of motor neurons in the spinal cord is also dependent on neuronal activity[34] and activity dependent release of neurotrophins is critical for their biological actions[35]. Although a full review of the actions of neurotrophins on synaptic plasticity[36, 37] and neuronal survival is beyond the scope of this perspective, a number of reviews have considered this issue[35, 38–41]. Regardless, both formation and maintenance of neuronal connections are closely linked to establishment of trophic relationships with target cells.

In a healthy connection, the release of neurotrophins from target cells leads to binding of neurotrophins to neuronal receptors, uptake of receptor-neurotrophin complexes into the neuron, and eventually transport of these complexes to the distant neuronal cell body. There is a close relationship between synaptic function and neurotrophin support, so neurotrophin uptake correlates with the release of neurotransmitter from the synapse [42, 43]. In turn, elevated neurotransmitter levels at the synapse stimulates release of neurotrophins from the target cell and helps maintain postsynaptic structures as well as enhancing endocytosis in the presynaptic terminal[43]. For neurotrophic influences to be effective, receptors with bound ligand must be endocytosed and processed into a signaling endosome for return to the cell body[44–47]. Both local and perikaryal signaling by neurotrophin receptors are important in the maintenance of presynaptic function [29, 30]. An appropriate supply of synaptic components and neurotrophin receptors from the neuronal perikaryon to synapses and the corresponding return of signaling endosomes to the neuronal cell body are both essential processes for neuronal survival. From these observations, it is clear that the intracellular trafficking of synaptic and trophic factor components along axons plays a critical role in maintaining neuronal viability.

Axonal Transport: A vital supply line for synapses

As discussed above, synaptic activity and neurotrophic factor support represent critical cellular processes underlying the neuronal survival. An understanding of apoptotic cell death in neurons thus requires an analysis of molecular mechanisms underlying maintenance and functionality of synapses. Neurons are uniquely dependent on intracellular transport of proteins and organelles[18, 48]. Human neurons may be a meter or more in length and even small mammalian neurons are significantly larger than nonneuronal cells. Their large size imposes certain demands on a neuron, but the polarization and complexity of neuronal morphologies creates further challenges. A typical neuron has thousands of pre- and post-synaptic specializations. Some of these may be maintained for decades and others must be rapidly adjusted in response to local signals. The ability of synapses to respond to localized signals requires alterations in their biochemical composition. Despite periodic reports that small amounts of protein synthesis may occur in axons (particularly growing axons), >99.9% of the proteins in axonal domains and >80% of the proteins in dendrites of mature neurons are synthesized in cell bodies and transported to sites of utilization [48]. As a result, neuronal cells face daunting logistical challenges in the coordinate synthesis, packaging,

transport and targeting of proteins to pre and postsynaptic compartments. To fullfill this need, neurons must continually synthesize, transport and deliver remarkable amounts of membrane proteins, mitochondria, cytoskeletal elements, and cytoplasmic enzymes via axonal transport mechanisms [48]. This dependence of axons and synapses on delivery of material from the cell body was recognized as early as Ramon y Cajal[49], although the responsible molecular motors were not discovered until the 1980's[50]. At that time, advances in digital video microscopy methods permitted real time visualization of individual membrane bounded organelles (MBOs) moving along single microtubules (MTs) in living cells for the first time. Application of video microscopic methods to axoplasm isolated from squid giant axons[51] produced real time images of MBOs translocating on MTs and allowed biochemical and pharmacological characterization of fast axonal transport (FAT) [51–56]. Studies of FAT in axoplasm led to the discovery of conventional kinesin, a new class of molecular motor that defined a superfamily of proteins [55–58]. Subsequently, a cytoplasmic form of dynein [59] was identified. Although there are exceptions, most kinesins move toward the plus end of MTs and dyneins are minus end motors. The polarized distribution of MTs in the axon allows for kinesins to move MBOs from the cell body towards the cell periphery in the anterograde direction and for dyneins to move MBOs from the cell periphery towards the cell body in the retrograde direction [60, 61].

Cumulative evidence indicates that *conventional kinesin* is the main molecular motor involved in the anterograde FAT of various MBOs, including mitochondria, synaptic vesicles, and plasma membrane components. Signaling complexes (i.e., activated neurotrophin receptors) and MBOs carrying degradation products (i.e., lysosomes and multivesicular bodies) are transported retrogradely to the neuronal cell body by the multi-subunit molecular motor cytoplasmic dynein [44, 50]. However, the complexity of neuronal cell biology has also raised the issue of differential regulation of kinesins and dyneins [18, 62]. Coordination of kinesin and dynein-based FAT represents a critical component underlying synaptic function and plasticity [63]. As discussed below, an establishment of functional relationships between synaptic activity, trophic support and axonal transport has shed important insights on the mechanisms underlying neuronal dysfunction and death in various human neurodegenerative diseases.

Axonal transport and Dysferopathies

Adult-onset neurodegenerative diseases are among the most difficult and puzzling disorders of the nervous system. Genes associated with these diseases have been identified and characterization of pathogenic mutations constituted major breakthroughs. However, identification of mutant genes often failed to illuminate specific pathogenic mechanisms. Biological roles for the associated gene product were often not apparent. Some diseases were associated with multiple mutations in a given gene or with mutations in different unrelated genes that all resulted in comparable pathologies. Many diseases existed in both familial and sporadic forms with indistinguishable clinical presentation. Moreover, a number of these mutant proteins were expressed in a variety of neuronal and nonneuronal cells, but only specific neuronal populations would be affected. Few of the identified mutations explained either the unique vulnerability of neurons in these diseases, or why affected neurons functioned normally for decades before appearance of pathology. However, one class of neurodegeneration-associated genes were illuminating

Recently, evidence that alteration in motor function may underlie some neuropathologies has accumulated [18, 62, 64–67], and these typically manifest as neurodegenerative diseases with the features of a dying back neuropathy[19]. For example, loss of function mutations leading to a 50% reduction in the kinesin-1 isoform kinesin-1A (representing approximately 10% of total kinesin-1 in motor neurons) leads to a form of spastic paraplegia[68, 69], a

disease involving gradual degeneration of upper motor neurons. Similarly, mutations in the cytoplasmic dynein heavy chain subunit [67, 70] or dynactin[71] result in late onset neurodegeneration of specific neuronal populations. Curiously, some mutations in dynein heavy chain lead to motor neuron degeneration[67] while other mutations produce degeneration of sensory neurons[70]. Although mutations in motor proteins are rare and can account for only a small fraction of neurodegenerative diseases, recent evidence indicates that FAT may be affected in a much larger fraction of neurodegenerative diseases. These alterations occurred through changes in the activity of protein kinases involved in regulation of FAT [19]. Diseases that involve compromises in FAT as an intrinsic element in their pathogenesis may be categorized as dysferopathies (from the Greek “fero” meaning to transport or carry)[19, 72].

The complexity of neuronal cell biology raised the issue of differential regulation of kinesins and dyneins [18, 62]. Altered protein phosphorylation is a common feature of neurodegenerative diseases, and several kinase and phosphatase activities have been implicated in the regulation of FAT through phosphorylation of motor protein subunits (reviewed by Morfini et al[18, 62]). These kinase pathways affect a variety of cellular activities, including pro-apoptotic pathways. However, in cases where adult-onset, slowly progressive neurodegeneration is observed, compromised FAT is likely to be a primary lesion leading to loss of neuronal connectivity and eventually to neuronal cell death. Significantly, kinases activated in some of these dysferopathies include ones with pro-apoptotic activity, including JNK, P38, PKC, and GSK3β[73–79].

For example, Alzheimer’s disease neurons with familial Alzheimer’s disease mutations in presenilin-1 (PS1) increased activity of GSK-3β, a regulator of kinesin-based motility in neurons[80] and a facilitator of apoptosis[73]. Analysis of FAT in PS-1 mutant neurons showed a 20%–30% reduction in kinesin-based motility[81]. The tau filaments present in the neurofibrillary tangles characteristic of both familial and sporadic Alzheimer’s brains[82] also activate GSK3β in neurons and affect FAT[83]. Subsequently, oligomeric forms of the Aβ peptide associated with the amyloid characteristic of Alzheimer’s was found to activate casein kinase 2, which also inhibits FAT[84] and leads to failure of synaptic transmission[85]. In some cases, CK2 may be antiapoptotic in some cellular contexts[79], but in Alzheimer’s elevated CK2 activity has the paradoxical effect in shutting down FAT and hastening loss of synaptic connectivity.

Similarly, polyQ expansion diseases like Huntington’s disease and spinal bulbar muscular atrophy lead to activation of the stress activated protein kinase JNK3, which phosphorylates kinesin and reduces FAT[86, 87]. JNK family kinases are well known pro-apoptotic kinases, although they can also be protective in some situations[77, 78]. In neurons, this dual role may depend on different JNK isoforms, because JNK1 activity appears to be essential and constitutive, while stressors activate JNK3 (a neuron-specific JNK) and neuronal damage [88]. Significantly, JNK3 inhibits FAT, while JNK1 does not[87]. Finally, exposure to certain toxic agents like MPTP lead to a form of Parkinson’s disease[89, 90]. MPTP and its metabolites activate caspase 3[72, 91], but this occurs in primarily in axons and terminals where dopamine transporters are enriched. When caspase 3 activated in the axon or the terminal, it cleaves and activates PKCδ[72, 92], which in turn alters FAT and leads to failure of neurotransmission[72, 93]. Thus, activation of pro-apoptotic signals in neurons can lead to deficits in FAT that eventually result in loss of synaptic function and distal axonopathy.

Summary

Although neuronal cell death through apoptotic pathways represents a common feature of dysferopathies, the canonical apoptotic changes familiar from non-neuronal cells are late

events. Loss of neuronal function occurs at a much early time, when synaptic-based neuronal connectivity fails. In this context, apoptotic pathways may normally serve a clean-up role, rather than a pathogenic one. Reframing the consideration of cell death in the nervous system to include the early stages of axonal degeneration provides a better understanding of the roles played by various apoptotic signaling pathways in neurodegenerative diseases. Focusing on disease-specific mechanisms that initiate the sequence that eventually leads to neuronal loss should facilitate development of therapies that preserve neuronal function as well as neuronal numbers.

Acknowledgments

This work was supported by grants from NINDS (NS23868) and MDA to S.B, and from the Huntington's Disease Society of America to (G.M.).

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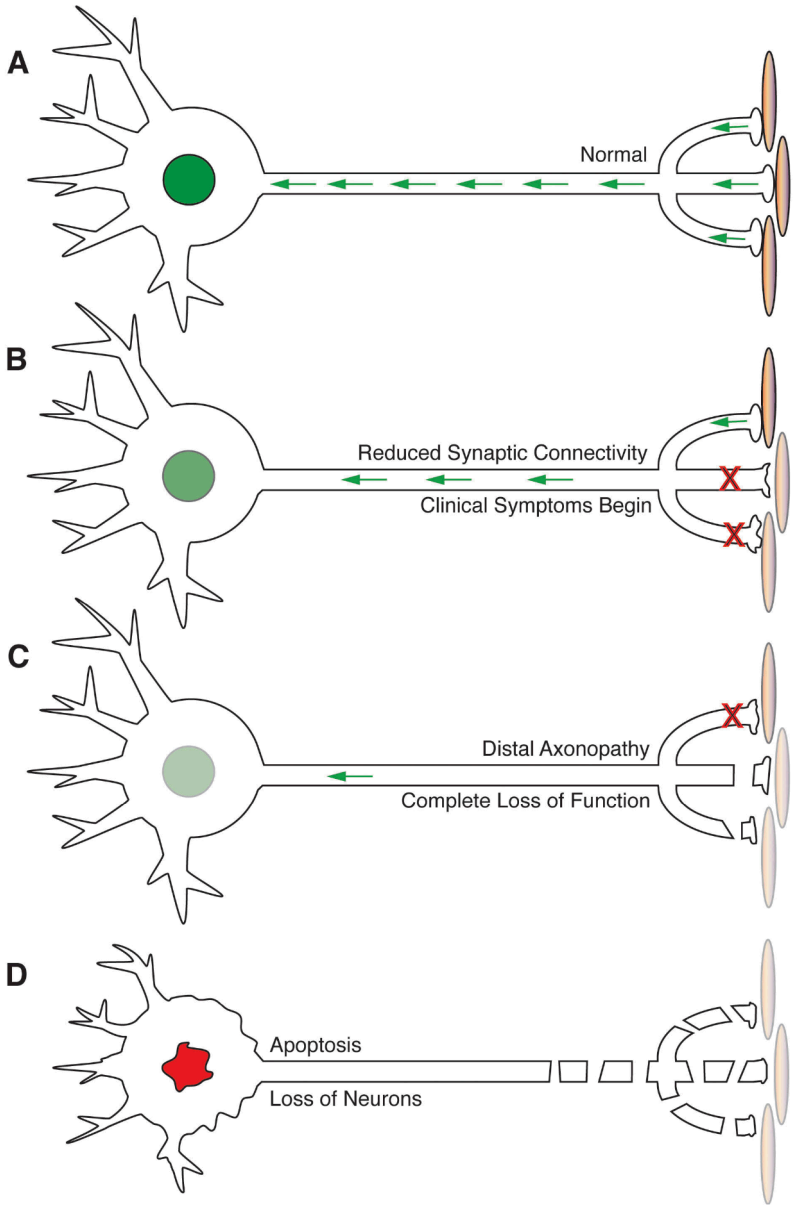

Figure 1. Stages in neuronal death as a dying back neuropathy

A) In the intact nervous system, neurons and targets are well matched, so activity and neurotrophic support (green arrows) are well-coordinated. B) When the activity at a given synapse is compromised, then presynaptic terminals are retracted and neurotrophin return is reduced. Changes in gene expression may occur, but the perikaryon is still intact at this stage. C) When the number of functional synapses falls below a critical threshold, the remaining presynaptic terminals are typically shut down and retracted. Consequently, target-derived neurotrophin supplies are no longer sufficient to maintain the distal axon or to sustain neuronal viability. D) As the distal axon atrophies, the neuronal perikaryon begins to exhibit the characteristics of classical apoptotic cell death, including pycnotic nuclei, shrinkage of cell body, TUNEL staining and blebbing of the plasma membrane. The time from the earliest changes in synaptic function seen in B to the clear activation of apoptotic pathways in D may be months or years.