Last Stop, Cell Death

Caspases and Synaptic Plasticity

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Discussions of cell death in the nervous system, whether the cell death occurs as part of neuronal development, trauma, or a neurodegenerative disease, naturally focus on the final stages of somal death. Through these observations, we learn that the final common steps in cell death pathways (i.e., nuclear fragmentation, etc.) are generally shared between neuronal and nonneuronal cells (D'Amelio et al., 2010). Depending on the triggering event, both extrinsic and mitochondrial-mediated apoptotic cell death may occur (Mattson & Bazan 2006). Activation of cell death pathways in the cell soma initiates a standard apoptotic sequence, including nuclear fragmentation and disruption of translational machinery (see main text). However, the size and shape of neurons means that pre- and postsynaptic specializations may be located at some distance from the cell soma. Neuronal cell death may take considerably longer to complete than apoptosis. Final stages of apoptotic cell death are similarly rapid in both neuronal and nonneuronal cells, but if the first steps leading to cell death begin in the distal axon and presynaptic terminals, months or even years may elapse between the first decrements in neuronal function and initiation of a final apoptotic cascade (Brady & Morfini, 2010).

The ways in which cell death pathways are managed in neurons differ from nonneuronal cells. The complex architecture of neurons adds layers of complexity that are seen both during development and in pathological states. In development, programmed cell death plays a critical role in establishing functional connections in the nervous system by assuring that appropriate matches exist between neurons and target cells (Raff et al., 2002). Activation of cell death signaling components during development is typically initiated in synaptic and axonal

compartments. If these steps are limited in scope and extent, synaptic and axonal activation of apoptotic signaling leads to pruning of nonproductive synaptic contacts or axonal branches (Raff et al., 2002). Atrophy of an axonal branch follows loss of synaptic function and degeneration of the presynaptic terminal. However, loss of too many connections triggers apoptosis in the cell body. An analogous loss of synaptic function and subsequent axonopathy is seen in many adult-onset neurodegenerative diseases, producing a classic dying-back neuropathy (Morfini et al., 2009).

The distance of synaptic specializations from the cell soma allows caspases and other components of cell death signaling pathways to play roles in neurons unrelated to apoptosis (D'Amelio et al., 2010). If an executioner caspase is activated in a pre- or postsynaptic compartment, apoptosis does not follow as a matter of course. Instead, caspases may regulate aspects of axon growth, synaptic function and plasticity. Activation of caspase may occur in the growth cones of developing axons (McLaughlin, 2004) and during remodeling of synapses associated with learning and memory (D'Amelio et al., 2010). The separation between distal axon and soma prevents the interaction of caspases with key downstream targets required for the normal progression of apoptosis. Instead, the caspases may act on cytoskeletal proteins, kinases and other signaling molecules (Chan & Mattson, 1999; Morfini et al., 2009). As a result, activation of neuronal caspases affects hippocampal synaptic plasticity and long-term potentiation and song response habituation in zebra finches, as well as neuronal apoptosis (D'Amelio et al., 2010).

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