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Axon & dendrite degeneration: Its mechanisms and protective experimental paradigms

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Abstract

Accumulating evidence suggests that axon and dendrite (or neurite) degeneration both in vivo and in vitro requires self-destructive programs independent of cell death programs to segregate neurite degeneration from cell soma demise. This review will deal with the mechanisms of neurite degeneration caused by several experimental paradigms including trophic factor deprivation and Wallerian degeneration as well as those under pathological conditions. The involvement of autophagy and mitochondrial dysfunction is emphasized in these mechanisms. The mechanisms through which protective agents including the Wld^s protein rescue neurites from degeneration or fail to do so will be discussed.

Keywords: Axon; Dendrite; Degeneration; Wallerian degeneration; Mitochondria; Energy impairment; *Wld^s* mutant mouse

It is generally thought that the destruction of a neuronal network occurs as a result of the loss of impaired neurons, indicating that axon or dendrite degeneration is likely to be a secondary and passive event. However, accumulating evidence has indicated cases in which axons are initially impaired by degenerative insults in certain neurodegenerative diseases (Raff et al., 2002; Coleman, 2005). Elimination of axons without loss of their parent neurons, sometimes referred to as ''axon pruning'', provides an important mechanism for neuronal plasticity during development of the nervous system (Luo and O'Leary, 2005). Research from this standpoint that pays a close attention to axon degeneration mechanisms has been flourishing (Raff et al., 2002). Here in this short review we will summarize some of recent progress on the mechanism of axon and dendrite degeneration (here called neurite degeneration) and consider mechanisms through which protecting agents rescue neurites from degeneration. Other comprehensive and extensive reviews will be found elsewhere (Coleman and Perry, 2002; Raff et al., 2002; Korhonen and Lindholm, 2004; Coleman, 2005; Buki and Povlishock, 2006; Wishart et al., 2006; Conforti et al., 2007a,b).

During development of the nervous system, neurons extend axons to make synaptic contacts with target tissues from which target-derived neurotrophic factors are released to promote neuronal survival and hypertrophy (Reichardt, 2006). Trophic signals from targets or others play a critical role in causing inappropriate axons and dendrites to undergo degeneration. In vivo, neuritic branches and synapses are also eliminated, without somal death, for the establishment of precise topographic maps (Luo and O'Leary, 2005). Accumulating evidence suggests that these types of neurite degeneration both in vivo and in vitro require self-destructive programs independent of cell death programs to segregate neurite degeneration from cell soma demise (Finn et al., 2000; Raff et al., 2002; Ikegami and Koike, 2003; Berliocchi et al., 2005; Song et al., 2006; Wang et al., 2006a,b). These studies also suggest that axonal or dendritic degeneration occurs through a common form of degeneration among various degenerative processes including Wallerian degeneration in which axons distal to the cut site undergo a rapid degeneration after nerve transection, neurite degeneration caused by microtubule-disrupting agents or trophic factor deprivation as well as some

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diseases such as multiple sclerosis, gracile axonal dystrophy (GAD) (Coleman et al., 2005). The principal convergence points in axon degeneration mechanisms may include mitochondrial dysfunction and cytoplasmic Ca^{2+} deregulation, each of them being dealt with in this review.

1. General aspects of somal and neuritic degeneration in a model of developmental neuronal death

Before discussing on the relationship between somal and neuritic degenerations we shall outline the mechanism of cell somal death that occurs following withdrawal of trophic factor support from the target. Towards to this goal, researchers employ an in vitro model of rat or mouse sympathetic neurons that have been grown in the presence of NGF in which subsequent NGF deprivation triggers a classic apoptotic death that recapitulates naturally-occurring cell death in these neurons during the first week of life (Chang et al., 2002; Putcha and Johnson, 2004). This cell death exhibits certain characteristics of apoptosis, including cytoplasmic shrinkage, nuclear blebbing, and chromatin condensation. The caspase family of cysteine proteases has a critical role in executing apoptosis as shown in Fig. 1 (left, apoptotic death). In this mitochondria-dependent pathway of apoptosis, caspase activation is regulated mainly by the release of cytochrome c from the intermembranous space of mitochondria. The Bcl-2 family of proteins contributes to regulating cytochrome c release by integrating and conveying pro- and antiapoptotic signals to the mitochondria. Once in the cytosol, cytochrome c initiates a cascade of caspase activation by promoting the oligomerization of APAF-1 and the activation of procaspase-9 (Fig. 1). Other mitochondrial proteins including Smac/DIABLO are also released into the cytosol during apoptosis and may contribute to the regulation of caspase activities. In sympathetic neurons, BAX, one of the Bcl-2 family proteins, plays a pivotal role in triggering cell death (Putcha and Johnson, 2004). If this apoptotic pathway is prevented, another caspase-dependent pathway involving caspase-2 will be activated. However, under conditions where caspase activities are completely inhibited by the use of pharmacological, genetic or other means, neuronal death is delayed, but still occurs. As shown in Fig. 1(right, non-apoptotic or auphagic death) caspase inhibition causes the neurons to die in a manner that is dependent

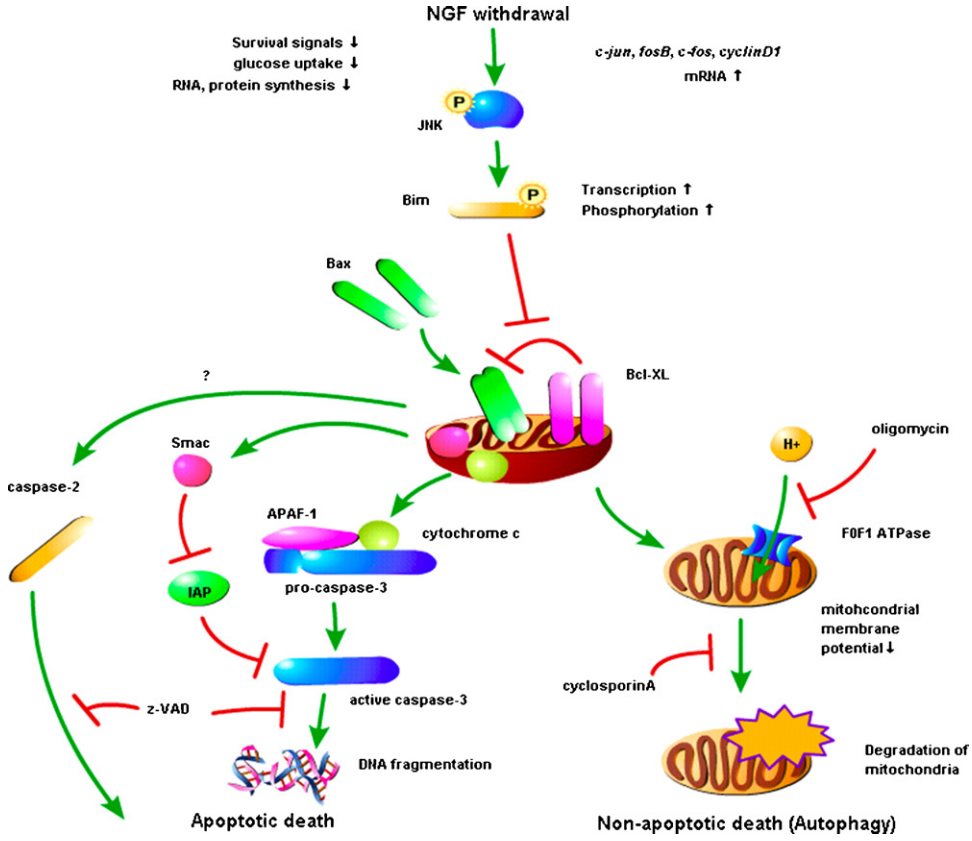

Fig. 1. Mechansims of cell somal death caused by trophic factor deprivation. NGF deprivation triggers a classic apoptotic death in cultured sympathetic neurons (Chang et al., 2002). The caspase family of cysteine proteases has a critical role in executing apoptosis as shown in the left pathway (apoptotic death). Caspase activation is regulated mainly by Bax transfer from cytosol to mitochondria and subsequent release of cytochrome c. Once in the cytosol, cytochrome c initiates a cascade of caspase activation by promoting the oligomerization of APAF-1 and the activation of procaspase-9. Other mitochondrial proteins including Smac/DIABLO are also released into the cytosol during apoptosis. Caspase-2 will be activated under conditions where the major pathway is inhibited. Cellular ATP levels are maintained during apoptosis, and cytochrome c release occurs without mitochondrial permeability transition. However, under certain conditions where caspase activities are inhibited, neuronal death will proceed via the right pathway (non-apoptotic, autophagic death) where mitochondrial permeability transition plays a pivotal role. Details of this pathway remain elusive, but electron microscopic observations suggest that it has been essentially characterized by autophagy. Study on any interplay between key players in apoptosis and autophagy during neuronal degeneration remains unexplored, although EM studies suggest that autophagic vesicle formation occurs in parallel with apoptosis caused by NGF deprivation (Xue et al., 1999; Chang et al., 2004) or colchicine treatment (Mitsui et al., 2001).