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Neurite pruning and neuronal cell death: spatial regulation of shared destruction programs

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During development, neurons are initially overproduced and excess neurons are eliminated later on by programmed cell death. In a more refined developmental process termed pruning, excess axons and dendritic branches are removed while the cell body remains intact. In mature animals, axons that become disconnected as a result of injury are eliminated through a series of events collectively known as Wallerian degeneration. Recent evidence points to unexpected similarities between these three types of obliterative processes, as they share common regulators. These findings provide new ideas on how cellular destruction programs are spatially regulated in neurons.

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Introduction

It is well established that regressive processes are important for the establishment of accurate neuronal connections during development [1–3]. However, from a mechanistic point of view our understating of these events lags behind our knowledge of progressive phenomena such as neuronal migration, axon guidance and synapse formation. Unlike other organs and tissues in which cell death accounts for almost all regressive events during development, in many cases, the complex cellular structure of neurons undergoes a more limited refinement. In these cases, the soma is spared but pruning of long neuronal processes and synapse elimination allow the formation of new connections [2,4]. Previous studies suggested that differential genetic programs are employed by the neuron for its death or for pruning of its neurites [2,4,5]. However, recent studies provide evidence indicating that the cell is much more economical, and that neurite pruning and programmed cell death have many shared elements. Therefore, the cellular outcome does not rely on the genetic program that is activated, but rather on how the cell regulates it spatially.

Naturally occurring neuronal cell death and neurite pruning

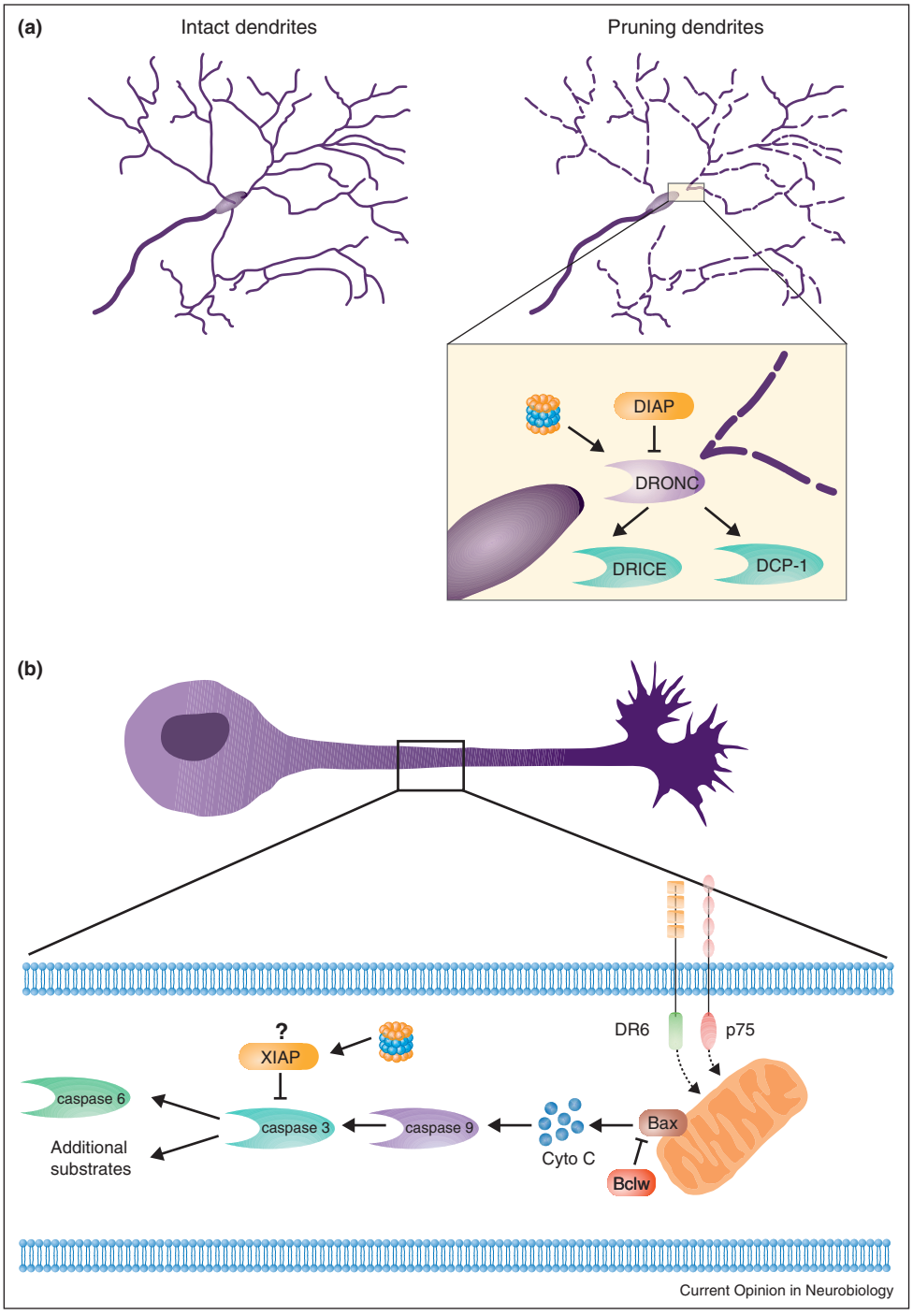
Programmed cell death (PCD) was the first major regressive event that was recognized to shape the nervous system during development. It is now well established that neurons die throughout the vertebrate nervous system at specific developmental stages, resulting in loss of up to 75% of the neurons in certain neuronal nuclei [3]. The roles of PCD during development of the nervous system in multiple model organisms have been extensively reviewed. PCD may act to match the number of neurons to the target field they innervate or to eliminate misguided axons. Notably, however, genetic manipulations of the apoptotic machinery in the mouse resulted in significantly increased numbers of neurons in the CNS, but did not cause severe behavioral abnormalities [3]. This suggested that other forms of PCD may compensate for the apoptotic system, or that other mechanisms allow proper wiring in the face of higher numbers of neurons.

The removal of axonal process and synapses is a widespread developmental phenomenon in vertebrates that ranges from elimination of axonal arbors in the neuromuscular junction (NMJ) to the stereotyped pruning of long axonal projections in the brain [2,4,6]. Interestingly, several cellular mechanisms have been shown to control these events. These include axonal retraction, local degeneration and axosome shedding [7–10]. Most of these processes are not recapitulated by *in vitro* systems, hampering elucidation of the molecular mechanisms that govern them. The most commonly used *in vitro* setup to study axonal pruning is the Campenot chamber. This allows the selective withdrawal of trophic support, mainly NGF (nerve growth factor), from the axons, which results in induction of axonal degeneration without cell death [11]. Remodeling of the *Drosophila* nervous system during metamorphosis provides a unique invertebrate system in which the power of the fly's genetics can be used to uncover the mechanisms of axonal and dendritic pruning. In all of the *Drosophila* studies so far, neuronal process pruning is executed by local degeneration [12–14].

The role of the apoptotic system in neurite pruning

The first indication that the apoptotic system has a role in neurite pruning in addition to its function in PCD came

Figure 1



The apoptotic system regulates neurite pruning in mammals and flies. **(a)** Developmental pruning of sensory neurons dendrites in *Drosophila* is regulated by the apoptotic system. Upon pruning induction, the caspase inhibitor DIAP1 is degraded by the proteasome, which leads to activation of the initiator caspase Dronc. This induces the severing of sensory dendrites from the cell body (arrow heads) and the activation of two effector caspases (DCP-1 and DRICE) that promote the degeneration of the dendrites (arrows). **(b)** Apoptotic machinery executes axonal pruning induced by trophic deprivation and activation of the death receptors DR6 and p75. The pro-apoptotic BAX protein initiates activation of the apoptotic system through release of mitochondrial cytochrome-C, subsequent activation of the initiator caspase-9 and the effector caspase-3, and caspase-6. The anti-apoptotic protein BclW, which binds to BAX, and the caspase-3 inhibitor XIAP, negatively regulate this pathway.