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The GAP between axon pruning and repulsion

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Abstract

Stereotyped axonal pruning and growth cone repulsion, modulators of neuronal connectivity, share many ligands and receptors systems. Riccomagno et al. (2012) show in *Cell* that common ligands can link functionally specialized downstream pathways, demonstrating that the Rac GAP β2-Chimaerin is needed in Semaphorin-mediated axonal pruning but not growth cone repulsion.

During development, axonal connectivity is established through the interplay of positive and negative influences on axon extension. Quite a few ligands and receptor systems have now been implicated as mediators of chemoattraction or chemorepulsion of axons, mostly acting through the modulation of growth cone guidance. Elegant neuroanatomic studies subsequently showed that the pruning of axons after they are formed is an additional developmental mechanism that shapes connectivity. On the basis of context, two distinct types of neurite pruning have been identified in the developing mammalian central nervous system (CNS) – activity-dependent pruning and stereotyped pruning (Kantor and Kolodkin, 2003; O'Leary, 1992). Activity-dependent pruning is a means by which axons making weak connections with targets are eliminated, whereas stereotyped pruning is defined as the removal of entire anatomic axonal connections as a population at a particular developmental time. The molecular mechanistic differences between growth cone repulsion, activity-dependent pruning, and stereotyped pruning have been unclear, but in the case of growth cone repulsion and stereotyped pruning, there is significant overlap between the involved ligands and receptors (Bagri et al., 2003; Li and Pleasure, 2005).

The first identified examples of stereotyped pruning involved the development of long axonal tracts connecting the cortex, brainstem, and spinal cord. In these examples, early long straight projections are then modified by timed sprouting of collateral axons from the long shaft, followed by removal of the now redundant longer projections (O'Leary, 1992). This mechanism is likely an evolutionary holdover from simpler nervous systems that allows a fairly simple set of scaffolding projections to be modified into more refined anatomic connectivity. However, the best understood example of stereotyped pruning in the vertebrate brain is in hippocampal formation (Bagri et al., 2003). In the adult dentate projection, essentially all of the axons of the granule neurons (so-called mossy fibers) project to the stratum lucidum layer of CA3. However, at earlier stages of development the mossy fiber projection is split between the stratum lucidum and the stratum oriens (Figure 1). The stratum oriens axon bundle, sometimes called the infrapyramidal tract (IPT), is remodeled by stereotyped pruning to generate the adult structure. Previous studies showed that ligands such as Sema3F and its receptors Neuropilin 2 (Npn-2) and Plexin A3 (PlexA3) are required for the pruning of these axons (Bagri et al., 2003; Faulkner et al., 2007; Sahay et al., 2003). In this developmental context, recent work from Riccomagno and colleagues (2012),

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published in *Cell*, provides molecular insights into how the machinery of axonal retraction is specialized between axonal pruning and growth cone repulsion.

This recent work from Riccomagno et al. (2012) rests on careful consideration of the intracellular signaling events downstream of Sema3F signaling. The intracellular domain of PlexA3 recruits diverse signaling molecules through its phosphotyrosine residues, Rho GTPase binding domain, and Rac GTPase activating protein (GAP) domains. It also recruits p190, a Rho-GAP with Semaphorin regulated GAP activity, which leads to restructuring of the actin cytoskeleton (Barberis et al., 2005). Signaling through the much smaller intracellular domain of the Sema3F receptor Npn-2, however, has been less studied. Most of the existing work is confined to analysis of the SEA motif at the end of the Npn-2 carboxyl terminus that binds PDZ proteins. Riccomagno et al. (2012) now presents genetic and cell biological evidence that the short intracellular domain of Npn-2, not the SEA domain shared by Npn-1, recruits β2Chn, a Rac-specific GAP. The authors propose that Sema3F activation of Npn-2 releases β2Chn to the axonal membrane. Previous studies showed that the enzymatic GAP activity of β2Chn is regulated by binding lipid activators found in the axonal membrane (Canagarajah et al., 2004). This provides a possible link between Semaphorin ligand signaling and the membrane dynamics necessary for regulating membrane cytoskeletal and trafficking events. Strikingly, although β2Chn is required for stereotyped axonal pruning, its loss does not inhibit Sema3F-mediated axon repulsion, even though this process was believed to employ similar signaling molecules through the same ligands and receptors. To show that β2Chn activity is also sufficient on its own to drive IPT pruning, the authors examined a knock-in line with a hyperactive form of β2Chn expressed from the native allele. Indeed, these mice, in homozygous form, had accelerated IPT pruning compared to control mice, thus β2Chn activity alone is sufficient to enhance IPT pruning. The authors further confirmed that $\beta2Chn^{-/-}$ mutant and $Npn\text{-}2^{+/-}$; $\beta2Chn^{+/-}$ transheterozygous mice show the same infrapyramidal axonal pruning defects as previously observed in the mutant mice with Sema3F-Npn-2-PlexA3 signaling defects. In wildtype mice, Rac-GTP disappears from the axonal shafts of dentate axons that are going to be subject to stereotyped pruning in the following few days under the control of Sema3F treatment, but in the mutant mice Rac-GTP puncta are maintained in these axons. This implies that membrane reorganization events under the control of Rac-GTP are likely to be important preceding steps to the actual removal of the superfluous axons. It is possible that the Rac-GTP puncta that are lost are involved in the retrograde axonal transport of membrane complexes being removed from the axon that is to be pruned.

Are there other signaling pathways whose activity has been implicated in the regulation of IPT pruning? Activation of Rac G-proteins mediates reverse signaling via Ephrin B3 in the dentate, and activated transmembrane Ephrin B3 in the dentate granule neurons recruits Grb4 and activates Rac during stereotyped IPT pruning (Xu and Henkemeyer, 2011). The superficial contrast between these signaling cascades, whereby Ephrin B3 activates Rac-GTP signaling on an acute timescale whereas Sema3F signaling downregulates Rac-GTP signaling over longer-term exposure while both effects are required for stereotyped pruning, may be misleading. It is likely that there are nodes of crosstalk between Ephrin-reverse signaling and Semaphorin-induced axonal pruning that remain to be discovered. Interestingly, there has been a documented role of another Chimaerin family member, αChimaerin, in Ephrin signaling that may hint at future mechanisms for signaling interplay in the control of IPT pruning. Axonal pruning is likely to be a multistep process involving several roles of signaling pathways involved in membrane dynamics. The Rac-GTP family is large and involved in many types of membrane trafficking. To begin axon pruning, preexisting synaptic complexes become simplified and components are packaged into membrane bound particles for retrograde transport. These events occur in different membrane compartments and are likely to be mediated by Rac-dependent signaling

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pathways. Impairment of any step might make axons unable to be pruned. The complexity of the pruning process does seem to stand in some contrast with the more binary process of signaling that regulates growth cone repulsion. Thus, the identification of signaling components specifically involved in the process of pruning and not repulsion will be important for full molecular understanding of the two processes. The identification of β2Chn by Riccomagno and colleagues (2012) provides a new molecular handle on distinct machinery and will likely not be the last example.

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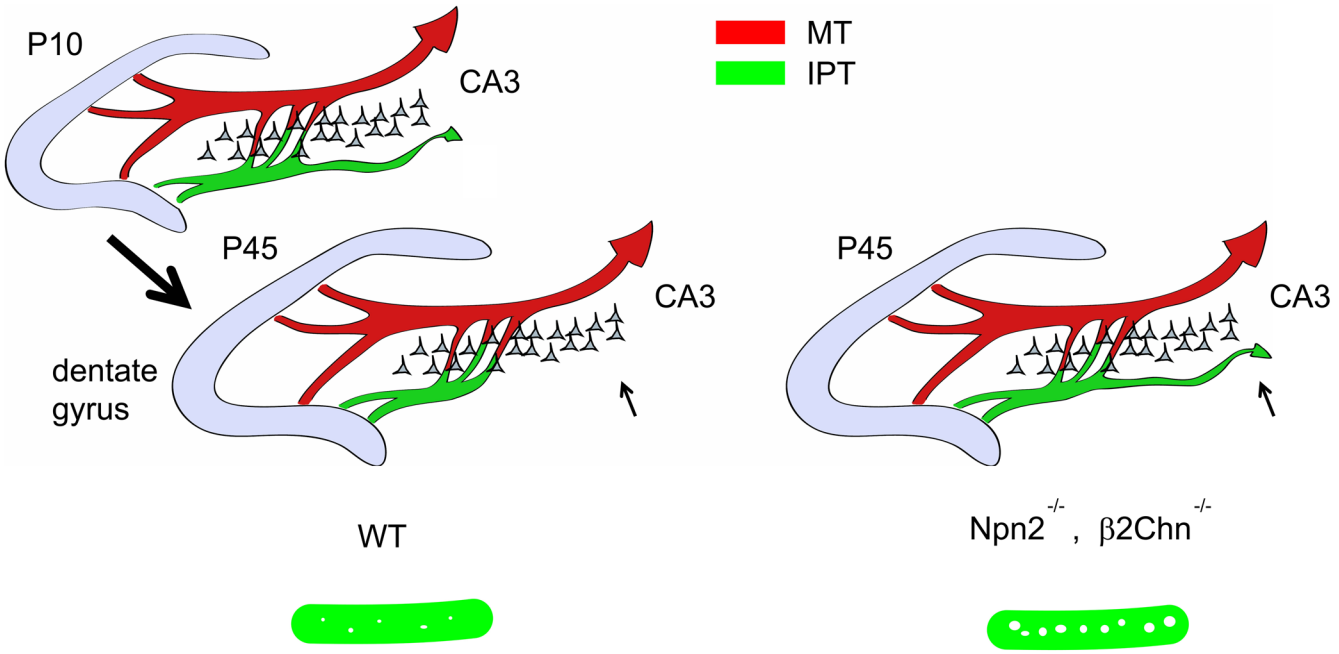

Figure 1. Stereotyped axonal pruning in the dentate gyrus

Initially the granule neurons project mossy fibers in both the main and infrapyramidal tracts (MT and IPT) to terminate on CA3 dendrites. By the second month of life these axons are remodeled by pruning so that the IPT is lost. In Npn-2 and β2Chn mutant mice, the IPT fails to be pruned (arrows indicate the location of the IPT in wildtype and mutant mice). Below are schematic diagrams of Rac-GTP puncta shown as white spots in a green axon. In axons destined for pruning in wildtype mice, the density of puncta falls prior to axonal pruning, whereas in mutant mice the puncta density remains high. (Modified from Kantor and Kolodkin, 2003).