This Week in The Journal

Semaphorins and Plexins Interact in Discrete Ways to Regulate Proper Circuit Development

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During development, axon guidance molecules called semaphorins bind their plexin receptors to enable processes that are critical for the formation and functioning of circuits in the brain. These processes include the positioning and cohesion of axons into their target brain regions, which may rely on axon fasciculation (bundling) and defasciculation (unbundling). Two papers from this issue elucidate the role of semaphorins and plexins acting on axon fasciculation, defasciculation, and the arborization of axons into their target brain regions.

The ability to control skilled movements is regulated by corticospinal (CS) neurons, which project axons from the sensorimotor cortex to the spinal cord. In rodents, CS axons remain tightly fasciculated in the brain, and evidence suggests that this fasciculation enables them to transverse the spinal cord. Gu et al. explored whether this is the case and what role semaphorins and plexins play in this process, if at all. First, they investigated where subtypes of semaphorins and plexins are expressed in this circuit; they found that plexin-A1 and -A3 receptors (PlexA1 and PlexA3, respectively) are expressed in CS neurons, whereas their ligands semaphorin-5A and -5B (Sema5A and Sema5B, respectively) are expressed in the medulla. The medulla is the location where CS axons decussate before targeting the spinal cord. In the absence of semaphorin and plexin binding in the medulla, the authors discovered that some CS axons prematurely defasciculate. This results in CS axons aberrantly transversing spinal gray matter instead of projecting further down the spinal cord through the spinal white matter. To determine the behavioral consequences of this, Gu et al. used mutant mice with altered Sema5A/Sema5B or PlexA1/A3 expression. They found that these mice could not properly perform skilled movements. Furthermore, stimulating areas of motor cortex associated with hindlimb muscle movement in these mice produced abnormal activation of forelimb muscle. These data provide compelling evidence for semaphorin and plexin interactions directly impacting circuit functionality by regulating the fasciculation process.

Authors of another study from this issue demonstrated that semaphorins and plexins may act in a more intricate and complex manner than previously thought. Their findings came from investigating the role of semaphorin-6D (Sema6D) and PlexA1 in regulating axon positioning and cohesion of a different circuit. Before retinal ganglion cells arborize into their target areas, their axons fasciculate in the optic tract. Using mutant mice with altered Sema6D and PlexA1 expression, Prieur et al. observed that interactions between Sema6D and PlexA1 must occur for proper retinal axon positioning and cohesion in the optic tract at the surface of the dorsolateralgeniculate nucleus (dLGN; a target area for retinal axons). This finding supports the data of Gu et al.: semaphorin and plexin interactions must occur for proper defasciculation and arborization of axons into their target regions. Notably, Prieur et al. further found that the level of downregulation of Sema6D, PlexA1, or both correlated to the proportion of resultant irregular retinal projections. This is the first demonstration of semaphorins and plexins acting in a dose-dependent manner. Ablation of Sema6D or PlexA1 from the retinas of mice via in utero electroporation of Sema6D or PlexA1 shRNA not only validated that the two are required for retinal ganglion axon positioning and targeting, but also revealed that even retinal ganglion cells not targeted by shRNA do not properly innervate the dLGN. Prieur et al. suggest that their newfound discovery of non–cell-autonomous Sema6D and PlexA1 activity may be due to axon–axon interactions formed between retinal ganglion cells.

Together, these studies enable a broader understanding of how semaphorin and plexin interactions permit optimal development of circuits, or at least those that regulate vision- and movement-related behaviors. Unraveling the mechanisms mediating neural circuit formation is not only critical for understanding how proper circuit development regulates behavior but may also inform research exploring novel mechanisms underlying developmental disease states.

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