# Semaphorins and Plexins in Axonal Navigation: Implications for Neural Circuit Assembly

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Short Communication

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## ABOUT THE STUDY

Semaphorins and their receptors, plexins, play major roles in axonal guidance, serving as key regulators in the development of neural circuits. These molecular cues provide both attractive and repulsive signals to navigating axons, ensuring precise connectivity in the nervous system. The formation of precise neural circuits is essential for the proper functioning of the nervous system. Axonal navigation, a critical process in neural development, is orchestrated by extracellular guidance cues that direct axons to their appropriate targets. Among these, Semaphorins, a large family of secreted and membrane-bound proteins, have emerged as crucial regulators.

### Semaphorin family: Diverse roles in axonal guidance

Semaphorins are categorized into eight classes based on structural and functional properties. Classes 1 and 2 are found in invertebrates, while classes 3–8 are specific to vertebrates. These molecules exhibit diverse roles in axonal guidance, ranging from repulsive to attractive cues, depending on the cellular context and receptor composition. Class 3 Semaphorins (Sema3), the most extensively studied, are secreted proteins known to regulate axonal repulsion. Sema4 and Sema6 membrane-bound Semaphorins, provide contact-dependent signals crucial for neural circuit refinement.

Semaphorins' ability to act as both attractive and repulsive cues highlight their versatility. For instance, Sema3A induces growth cone collapse in specific neuronal populations, steering axons away from inappropriate targets, while Sema3C acts as an attractive signal in certain contexts, promoting axonal extension toward target regions.

### Plexins: Intracellular signal transduction

Plexins, the primary receptors for Semaphorins, are transmembrane proteins that mediate intracellular signaling upon ligand binding. They are classified into four subfamilies: Plexin-A, Plexin-B, Plexin-C and Plexin-D. Plexin-A receptors often associate with Neuropilins, co-receptors that enhance

Semaphorin binding and signaling specificity. Upon Semaphorin binding, Plexins undergo conformational changes that activate intracellular signaling cascades.

Plexin-B family members are unique in their ability to interact with receptor tyrosine kinases. For example, Met (Metabolic equivalent) and ErbB2 (Erb-B2 Receptor Tyrosine Kinase 2), broadening the scope of Semaphorin-Plexin signaling in neural and non-neural tissues. This versatility highlights Plexins' integral role in both developmental and pathological processes.

### Semaphorin-plexin signaling in neural circuit assembly

The Semaphorin-plexin axis is essential for establishing neural circuits by guiding axons, dendrites and synaptic connections. In the developing spinal cord, Sema3A-mediated repulsion ensures proper segregation of motor and sensory axons. Similarly, in the visual system, Sema6A guides retinal ganglion cells to their appropriate targets in the brain.

Beyond axonal guidance, Semaphorin-Plexin signaling influences synapse formation and pruning. Studies suggest that aberrant Semaphorin-Plexin signaling can disrupt neural circuit assembly, contributing to neurodevelopmental disorders such as autism and schizophrenia. Understanding these mechanisms opens avenues for therapeutic interventions to restore proper connectivity.

Semaphorins and Plexins are integral to the intricate process of axonal navigation and neural circuit assembly. Their ability to mediate diverse signaling outcomes underscores their central role in neural development. Dysregulation of Semaphorin-Plexin signaling has been implicated in a wide range of neurological disorders, emphasizing the importance of further research into these pathways. Advances in molecular biology and neurotechnology have unveiled promising therapeutic strategies, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) based gene editing and targeted small molecules, to modulate Semaphorin-Plexin interactions. These approaches could help restore neural connectivity and alleviate the impacts of developmental and degenerative disorders. Ongoing investigations are expected to deepen our understanding of these pathways, offering transformative insights into neural circuit formation and inspiring innovative treatments for neurological diseases.

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