**Semaphorin signalling during development**

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**Semaphorins and their receptors**

**Introductory signalling downstream of plexins**

The biology of semaphorin signalling is made possible by the ability of semaphorins to interact with plexins, which are transmembrane receptors associated with the cytoskeleton. Semaphorins can act as semaphorin receptors, providing a unique signalling capacity that is different from other signalling pathways. Domains marked with °, †, * or ‡ are not present in the indicated semaphorin subclass or are unique to vertebrates.

**Semaphorin binding receptors**

- **Sema6D receptor complex.** This complex contains Sema6D, which recruits Sema6D to plexins and binds to plexins, leading to the activation of plexins and downstream signalling.

**Modulatory co-receptors**

- **Neuropilins** are transmembrane proteins that modulate the interaction between semaphorins and plexins.

**Spatiotemporal regulation**

- **Local protein synthesis**
  - Semaphorins and plexins interact in space and time. These interactions can influence the balance of signal transduction.

**Diversification of semaphorins**

- **Reverse signalling**
  - Transmembrane semaphorins can function both as ligands and receptors, a process termed bidirectional signalling. Semaphorin reverse signalling, in which semaphorins act as receptors, contributes to neural and cardiac development.

- **Modulatory co-receptors**
  - Plexin-independent semaphorin receptors can contain modulatory co-receptors, including neuropilins, receptor tyrosine kinases, chemokine receptors and integrins.

**COMPETITION**

- **Complementary signal interactions**
  - Competition between different semaphorins can occur and contribute to neural and bone development. During bone development, these interactions control the balance between bone-resorbing and bone-forming.

**Semaphorins as semaphorin receptors**

- **In the Drosophila olfactory system, the regulatory effects of secreted Semaphorins and proteins are mediated by the transmembrane Semaphorin receptor by acting as a receptor.**

**Abbreviations:** AL, antennal lobe; APF, after puparium formation; BD, basic domain; CUB, complement C1r/s homology domain; ECM, extracellular matrix; GTPases, guanosine triphosphatases; mTOR1, mechanistic target of rapamycin complex 1; miR, microRNA; NSP-1, nucleoside triphosphate synthetase 1; PDGF, platelet-derived growth factor; R-Ras, Rac-related GTPase; RhoA, Ras-related C3 botulinum toxin substrate 1; RhoGDI, Rho guanosine diphosphate dissociation inhibitor; Rho-kinase, Rho-associated protein kinase; Rnd, Ras-related in neurons; SEK, stress-activated kinase; SEMA, semaphorin; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VIM, vimentin; Wnt, wingless-related integration site.