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Semaphorin signalling during development

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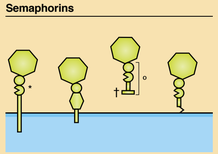
Semaphorins and their receptors

Semaphorins exist as secreted, transmembrane or GPI-anchored proteins and have been found in invertebrate (subclasses 1, 2 and 5) and vertebrate (subclasses 3-7) species, as well as in DNA viruses (subclass V). They signal predominantly through plexins. Four subclasses of plexins have been identified (A-D) and subclass-specific interactions exist between semaphorins and plexins. Semaphorins may also use integrins, neuropilins or other semaphorins as receptors. Domains marked with °, †, * or ‡ are not present in the indicated semaphorin subclasses or semaphorin receptor subclass.

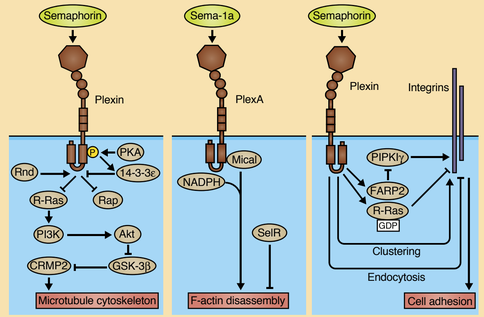
Ligand-receptor interactions

Semaphorin class	Semaphorin binding receptor
1	PlexA
2	PlexB, Sema-1a
3	plexin As, plexin D1, Neuropilins
4	plexin Bs, plexin Ds, Nrp1, CD72, TIM-2
5	plexin As
6	plexin As
7A	plexin C1, Integrins
V	plexin C1



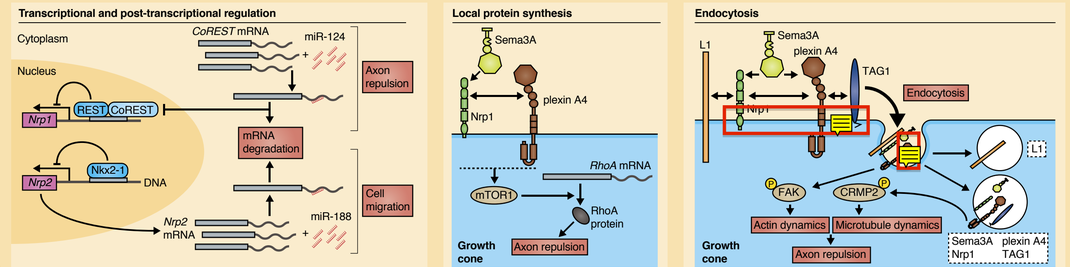
Intracellular signalling downstream of plexins

The binding of semaphorins to plexins leads to plexin GAP domain activation and signalling through cytosolic protein kinases, GTPases and cytoskeleton-associated proteins. Downstream of *Drosophila* PlexA, Mical and SelR antagonistically regulate F-actin disassembly. Plexins also regulate cell-cell and cell-substrate adhesion by influencing integrin activity, endocytosis and clustering.



Spatiotemporal regulation

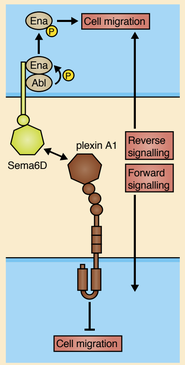
Spatiotemporal regulation of semaphorin signalling component expression occurs at different levels. Transcription factors (e.g. REST/CoREST and Nkx2-1) modulate gene expression, whereas microRNAs (e.g. miR-124 and miR-188) are important post-transcriptional regulators that stimulate mRNA degradation. Regulation also occurs locally in specific subcellular compartments (e.g. by local protein synthesis or endocytosis).

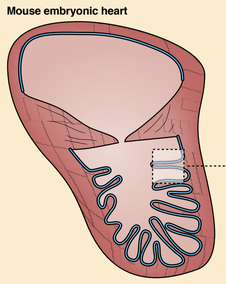


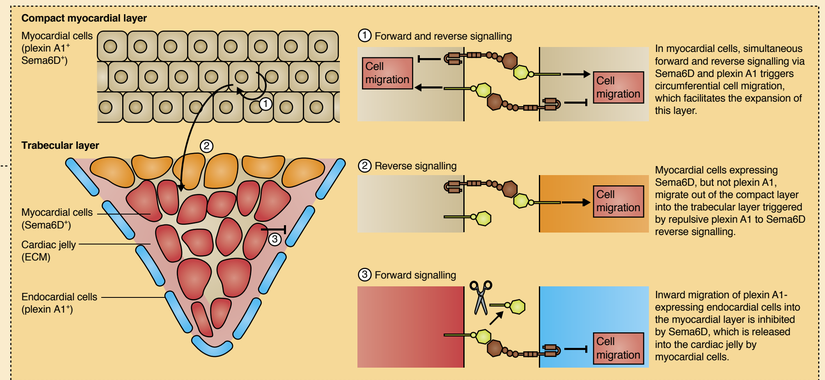
Diversification of semaphorin signalling

Reverse signalling

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

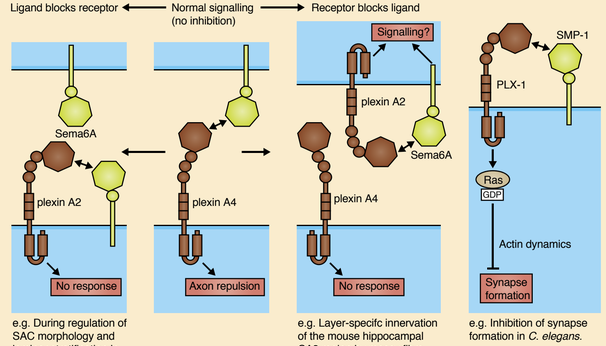


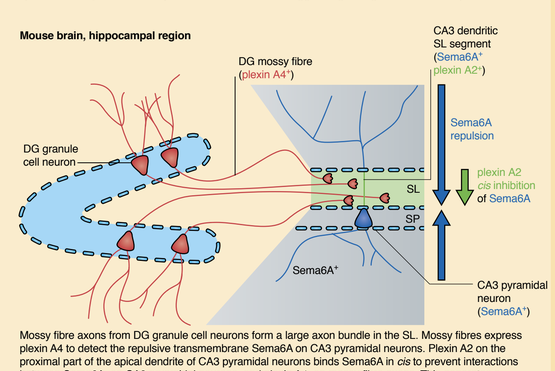




Cis inhibition and activation

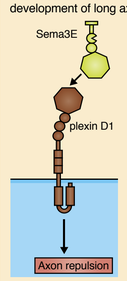
Semaphorins and plexins interact in *trans* but also in *cis*. These *cis* interactions can inhibit or activate plexin signalling. Two modes of *cis* inhibition have been described: (1) semaphorins bind plexins in *cis* to prevent signalling in *trans* with semaphorin ligands on adjacent cells; and (2) plexins bind semaphorins in *cis* to prevent signalling in *trans* with plexins on adjacent cells. By contrast, *cis* activation triggers signalling downstream of plexin.



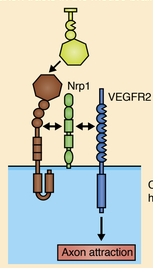


Modulatory co-receptors

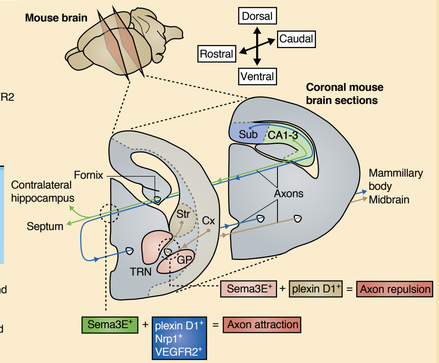
Plexin-dependent semaphorin receptors can contain various co-receptors, including neuropilins, receptor tyrosine kinases, immunoglobulin superfamily members and proteoglycans. These co-receptors provide them with unique signalling capacities and often determine the response to a specifc semaphorin. This is exemplified by Sema3E and its receptor plexin D1 during the development of long axon tracts in the mouse brain.



Axons from Cx and Str neurons express plexin D1 and are repelled by Sema3E expressed in the GP and TRN.

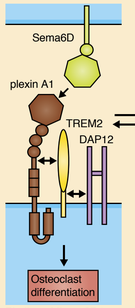


Axons from Sub neurons express plexin D1, Nrp1 and VEGFR2 and are attracted by Sema3E secreted by neighbouring axons derived from CA1-CA3 pyramidal neurons.

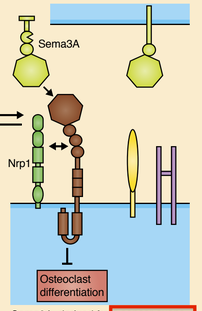


Competitive ligand interactions

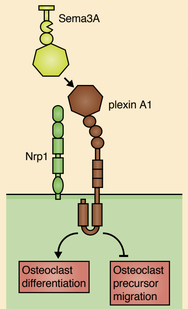
Competitive interactions between different semaphorins also occur and contribute to neural and bone development. During bone development, these interactions control the balance between bone resorption and formation.



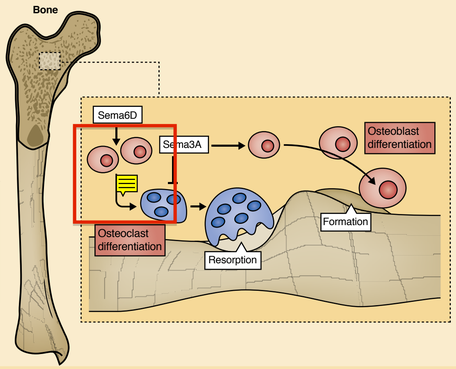
Binding of Sema6D to a plexin A1/TREM2/DAP12 receptor complex stimulates osteoclast differentiation and bone resorption.



Sema3A, derived from sensor axons innervating the bone, and the receptor Nrp1 sequester plexin A1 from the Sema6D receptor complex. This inhibits Sema6D-mediated osteoclast differentiation.

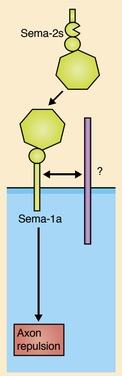


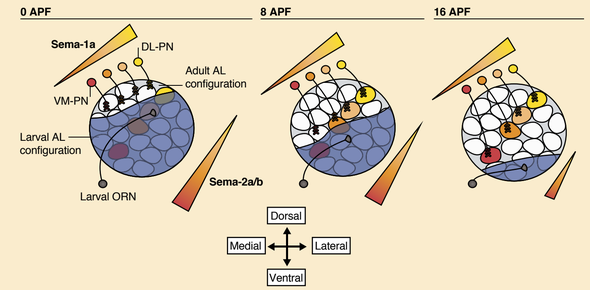
Binding of Sema3A to Nrp1/plexin A1 promotes osteoblast differentiation and inhibits the migration of osteoclast precursor cells.



Semaphorins as semaphorin receptors

In the *Drosophila* olfactory system, the repulsive effects of secreted Sema-2 proteins are mediated by the transmembrane semaphorin Sema-1a acting as a receptor.





Larval ORNs, which secrete Sema-2a and Sema-2b, project to the AL. These axons slowly degenerate as the fly develops, giving rise to a temporally receding Sema-2 gradient in the AL.

Sema-1a expression in PNs is required to sense this Sema-2 gradient; PN dendrites expressing high levels of Sema-1a are repelled into the dorsolateral AL, whereas weak Sema-1a expression allows ventromedial PN dendrites to extend towards the ventromedial AL.

Abbreviations: AL, antennal lobe; APF, after puparium formation; BD, basic domain; CUB, complement C1r/s homology domain; Cx, cortex; DG, dentate gyrus; DL, dorsolateral; CA1-3, cornu ammonis region 1-3; ECM, extracellular matrix; FV/VIII, homology to coagulation factors V and VIII domains; GAP, GTPase-activating protein; GP, globus pallidus; GPI, glycophosphatidylinositol; Ig, immunoglobulin-like; IPT, Ig-like, plexins, transcription factor; L1, L1 cell adhesion molecule; MAM, Meprin, A5, Mu domain; ORN, olfactory receptor neuron; PN, projection neuron; PSI, plexin-semaphorin-integrin; RBD, Rho-GTPase binding domain; SAC, starburst amacrine cell; SL, stratum lacunosum; SP, stratum pyramidale; Str, striatum; Sub, subicullum; Tr, thrombospondin; TRN, thalamic reticular nucleus; VM, ventromedial.