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Mechanisms controlling axon responses to Class III Semaphorins during the development of neuronal connectivity
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Context

The integrity of nervous processing critically relies on the correct wiring of axonal networks and increasing numbers of neurological diseases are found to originate from developmental impairments. Numerous work showed the importance of transcription factors in the generation of distinct neuron sub-populations and the formation of their connectivity. Many guidance cues and axonal receptors downstream from these transcriptional programs, with specific functional properties and expression patterns, have been found to control the trajectories of axon tracts towards their various target tissues. However and in spite of this diversity, it is difficult to conceive that these factors are in sufficient number for achieving the degree of specificity underlying neuronal connectivity.

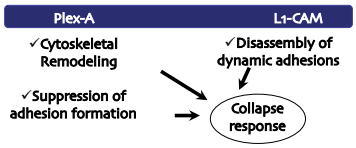
Objectives

Modulations of neuronal growth cone responses to guidance cues over navigation emerge as key mechanisms for increasing pathway choices. We explored the mechanisms by which neuronal growth cones vary their sensitivity to members of a wide family axon guidance cues, The Semaphorins (Sema3s). The receptors mediating the effects of Sema3s share a typical multimolecular structure, with ligand binding sub-units, the neuropilins (Nrps), recruiting signaling co-receptors, Plexin-A family members and L1-CAMs, a sub-group of IgSuperfamily Cell Adhesion Molecules (IgSFs), which our lab identified as novel Nrp co-receptors in previous work.

Our program consisted in investigating the specific role of L1-CAM co-receptors and in exploring whether regulations at the receptor complex level underlie the modulations of axon responsiveness to Sema3s during the formation of neuronal circuits. Our studies have been conducted on chick and mouse models, combining ex vivo and in vivo experimental paradigms, biochemistry and imaging.

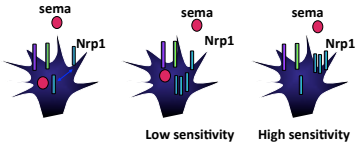
Results

Understanding the respective role of L1-CAM and Plexin-A coreceptors of Sema3A

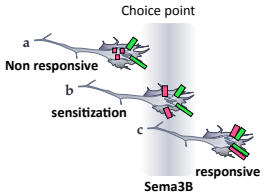


L1-CAM and Plex-A1 activate complementary downstream signaling to induce the growth cone collapse.

Uncovering novel regulatory pathways to set the sensitivity to Sema3s



Sema3A can be co-expressed with Nrp1 in the neuron. This negatively regulates Nrp1 level at the cell surface to set the growth cone sensitivity to Sema3A.



Plex-A1 (in red) can processed by calpain1so the growth cone is unresponsive to Sema3B. At a choice point, local cues suppress calpain activity allowing Plex-A1 to accumulate at the surface, assemble with Nrp2, thus switching on the responsiveness to Sema3B.

Conclusion/perspectives

The sensitivity of the axons to Sema3s can be regulated by various mechanisms, through remodeling of the receptor complex composition and sub-unit celll surface availability. This enables the growth cone to vary its responsiveness and adapt it to an environmental context continuously changing over navigation Such regulations might also operate in other biological and pathological contexts implicating the Semaphorins, such as cell migration and cancer cell dissemination.

Publications

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