Regulation of the netrin-1 receptor DCC by Ser/Thr phosphorylation

Nathalie Lamarche-Vane, Dept of Anatomy and Cell Biology, McGill University

Netrins are a small family of secreted proteins that guide growing axons during neural development. They are found in multiple vertebrate and invertebrate species and show highly conserved functions as axon guidance cues. In vertebrates, netrin-1 was identified on the basis of its ability to promote commissural axon outgrowth from explants of embryonic spinal cord. It is a bifunctional molecule attracting and repelling different classes of axons. The Down's syndrome Cell Adhesion Molecule (DsCAM) and the Deleted in Colorectal Cancer (DCC) have been identified as netrin-1 receptors mediating attraction of axons, however DCC can also participate in repulsion. The UNC5 family of proteins plays a role in the repulsive effects mediated by netrin-1, either alone or in combination with DCC. The signaling pathways that mediate the response of axons to netrin-1 are still incompletely understood. The importance of these guidance molecules in the development of neurodegenerative diseases, such as Parkinson and Alzheimer's diseases, mental retardation, and spinal cord injuries prompted us to investigate the intracellular machinery regulated by netrin-1. We are interested to investigate the molecular mechanisms underlying the effects of netrin-1 leading to a coordinated and directed response of growth cone navigation.

The receptor DCC is a tyrosine kinase-associated receptor, but it is also phosphorylated on Serine and Threonine residues in response to netrin-1. By mass spectrometry analysis, we mapped four phosphorylated Ser/Thr residues in the cytoplasmic tail of DCC. This project will be to determine the role of these phosphorylated residues in the regulation of DCC function using site-directed protein mutants and cell biology approaches.

Contact:
Dr. Nathalie Lamarche-Vane
Dept. of Anatomy and Cell Biology
McGill University
Email: nathalie.lamarche@mcgill.ca