COBRE
Investigators

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Title of project: CXCR4 Controls Neurite Extension through Direct Regulation of Actin Dynamics

Summary:

The external cues that guide the migration of developing neurons and outgrowth of neurons upon differentiation have been intensely studied for decades. CXCR4, a chemokine receptor, has been implicated in the regulation of chemotaxis, neuronal migration, and axonal guidance. Neuroblastoma cells, which are of neural crest origin, are capable of differentiating into more mature sympathetic neurons in culture, and insulin-like growth factor I (IGF-I), has been shown to promote both migration and neurite outgrowth in these cells. In addition, neuroblastoma cells often express high levels of CXCR4, are responsive to CXCL12 and, depending upon the level of differentiation, are capable of producing fully extended axons. The mediator of the cytoskeletal changes seen in during process extension is actin polymerization.
We have shown that in the neuroblastoma cell line, SHSY-5Y, both CXCR4 and IGF I receptors are involved in neuronal outgrowth, however, treatment with ligands for these receptors results in different cellular morphologies. CXCR4 stimulation stimulated the cells to take on a more differentiated neuronal form and directly involved actin, while IGF-IR stimulation resulted in a very immature neuronal morphology with shorter, broader processes. Based on these results, our overall hypothesis is that CXCR4 promotes neuronal migration and neurite extension through direct regulation of actin dynamics. Our preliminary data suggest that activation of CXCR4 by CXCL12 in cultured neuroblastoma cells promotes the elongation of neurites, and we have found CXCR4 along these projections.
In this work we will be testing three specific hypotheses:
1) Cellular context, including the extracellular matrix present and the concentration of CXCL12 ligand to which the cells are exposed play a large role in determining the signaling pathways that are activated, and thereby the ability of the cells to migrate;
2) CXCR4 activation by CXCL12 promotes an increase in neurite length in neuroblastoma cells;
3) CXCR4 regulates elongation of neuronal processes through interaction with actin using the actin binding protein Dbn