Neuroscience Graduate Program

presents:

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IN A THESIS PROPOSAL

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2:30PM IN AUDITORIUM K-307 (3-6408)

SOX9 as a novel target for improving regeneration following stroke

Functional recovery following stroke has been attributed to neuronal plasticity and axonal sprouting in the peri-infarct area. Currently no drug treatment can promote axonal regeneration in stroke patients. Astrocytic production of chondroitin sulfate proteoglycans (CSPGs) in the peri-infarct area is one of the major barriers for axonal sprouting. In addition, astrocytes are also the major sources of CSPGs in the perineuronal nets (PNNs), which are inhibitory extracellular matrix (ECM) structures prohibiting plasticity in the normal adult brain. SOX9 is known as a key transcription factor for the upregulation of proteoglycans in several other cell types. In cultured astrocytes, SOX9 has been found to play pivotal roles in the upregulation of CSPG biosynthetic genes (CBGs), *Xylt1*, *Xylt2* and *C4st*. In addition, by quantitative PCR (qPCR) screen of published SOX9 target genes, I found that *Hapln1*, which encodes an important ECM protein for CSPG organization, and negatively regulates adult plasticity, is highly enriched in astrocytes. Furthermore, our preliminary data demonstrate that SOX9 is highly upregulated in the peri-infarct areas following middle cerebral artery occlusion (MCAO) and its expression is restricted to reactive astrocytes. Therefore, I hypothesize that SOX9 upregulation in astrocytes in the peri-infarct area drives increased production of CSPGs by increasing the expression levels of its target genes. Deletion of SOX9 in astrocytes after MCAO is postulated to improve axonal regeneration. First, I will use chromatin-immunoprecipitation-sequencing (ChIP-seq) technique to perform a genome-wide analysis of SOX9 target genes in astrocytes, which will generate an unbiased understanding of SOX9 in regulating ECM related genes (**Aim1**). To study the role of SOX9 following stroke in vivo, I will generate tamoxifen inducible SOX9 knock-out mice by crossing $SOX9^{fl/fl}$ mice with Cx30-CreERT mice, in which CreERT is driven by the astrocyte specific gene Cx30 promoter. In **Aim 2**, I will compare the post-stroke expression of CBGs, HAPLN1 and CSPGs between Cx30-CreERT/$SOX9^{fl/fl}$ mice and $SOX9^{fl/fl}$ littermates using immunofluorescence, qPCR and western blotting. In **Aim3**, I will compare post-stroke plasticity and axonal regeneration between the above two groups using anterograde tracing technique. Through these experiments, I hope to establish whether SOX9 can serve as a target for post-ischemic suppression of inhibitory ECM production.