The 22nd iCeMS SEMINAR

June 25, 2009

16:00-17:00

Lecturer: **Prof. Flora M. Vaccarino**
Child Study Center and Department of Neurobiology
Yale University

Injury and Recovery in the Developing Brain

Please see the second page for the seminar abstract.

Venue: Seminar Room (#A207)
Second Floor of the Main Building
iCeMS Complex 1

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Held by: iCeMS (Institute for Integrated Cell-Material Sciences), Kyoto University

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To model brain injury in premature infants, we developed a model of chronic perinatal hypoxia in the rodent. The type and evolution of injury in these animals are similar to those observed in premature children. After a week of hypoxia from P3 to P11, there is a global decrease in brain volume, a loss of neurons and an enlargement of the brain ventricles. Interestingly, the neuronal loss recovers in the ensuing weeks in normoxic conditions. This is in part attributable to the genesis of new cortical, hippocampal and olfactory bulb neurons. Most of the newly generated cortical neurons are phenotypically excitatory as they express the transcription factors Tbr1 and neurofilaments that react to the SMI-32 antibody. In contrast, hypoxic-reared animals show an enduring loss of cortical inhibitory GABAergic interneurons expressing the calcium binding proteins calretinin and parvalbumin, loss that may be responsible for persisting behavioral abnormalities. Hypoxic rearing upregulates several growth factor signaling pathways, among which are the fibroblast growth factor receptors (FGFR). Transgenic mice lacking a functional FGFR-1 gene in radial glial cells and astrocytes (FGFR-1 cKO) fail to recover after hypoxic injury. Adult FGFR1 cKO mice reared in hypoxia have a persisting loss of excitatory cortical neurons and a greater loss on inhibitory neurons than wild type hypoxic-reared animals. To further investigate the type of precursor cells that generate neurons in the early postnatal brain, we traced the lineage of astroglial cells in GFAP-CreERT2 transgenic mice, which express a tamoxifen-inducible Cre in GFAP+ cells, to determine their fate after injury. This experiment reveled that GFAP+ cells were the ancestors for new neurons in the cortex, hippocampus and olfactory bulb. In the hypoxia recovery period these astroglial cells generated more neuronal precursors in the SVZ and white matter, and more neurons and oligodendrocytes in the cortex. The experiments also revealed that, differently than the hippocampal neurons, most of the cortical neurons were transient but their survival could be improved by recovery in environmental enriched conditions.

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