PROGRESS IN NEUROSCIENCE
PINs

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 09/19/13, 3:45 PM
Weill Auditorium

Presentation 1: Progranulin Deficiency Promotes Post-Ischemic Blood-Brain Barrier Disruption

Katherine Jackman, Post-Doctoral Fellow
Iadecola Laboratory, BMRI/WCMC

Abstract: Loss of function mutations of progranulin (PGRN) are linked to frontotemporal dementia, but little is known on the involvement of PGRN deficiency in brain injury. PGRN is implicated in neurovascular development, inflammation and Wnt signaling, a pathway involved in blood-brain barrier (BBB) formation. We examined the role of PGRN in the cerebrovascular and tissue damage produced by ischemia-reperfusion. PGRN+/- and -/- mice underwent middle cerebral artery occlusion (MCAO) with monitoring of cerebral blood flow. MCAO resulted in ~60% larger infarcts in PGRN+/- and -/- mice at 72hrs, independent of hemodynamic factors or post-ischemic inflammation. Rather, massive hemorrhages and BBB disruption were observed, unrelated to degradation of tight junction (TJ) proteins or matrix metalloproteinases. By electron microscopy, TJ were 30-52% shorter, fewer and less interlocking, suggesting a weaker seal between endothelial cells. Intracerebral injection of PDGF-CC, which increases BBB permeability, resulted in a more severe BBB breakdown in PGRN+/- & -/- than wild type mice. We describe a previously unrecognized involvement of PGRN in the expression of key ultrastructural features of the BBB. Such a novel vasoprotective role of PGRN, in concert with its well-established prosurvival properties, may contribute to brain dysfunction and damage in conditions associated with reduced PGRN function.

References:
Yin, F., et al. (2010). Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. J Exp Med 207 (1): 117-28.

Iadecola, C & Anrather, J. (2011). The immunology of stroke: From mechanisms to translation. Nat Med 17 (7): 96-808.

Presentation 2: A Novel Molecular Mechanism for the Inhibition of Neurotransmitter Release

Daniel Radoff, Post-Doctoral Fellow
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Abstract: Synaptic plasticity is thought to underlie such diverse processes as learning and memory, and impaired synaptic transmission my precede neuronal loss in neurodegenerative diseases such as Parkinson's and Huntington's. While much is known about the mechanisms modifying neurotransmitter release, significant aspects remain poorly understood. SNARE proteins mediate the majority of fusion events in a cell through a mechanism conserved across over 600 million years of evolution. A small, soluble protein named complexin inhibits synaptic vesicle fusion through its so-called Accessory Helix (AH). Using *in vitro* systems, several mechanisms have been proposed explaining how the AH actually inhibits fusion, most of which require that the AH prevents the SNAREs from properly assembling. But none of these mechanisms holds across evolution, despite the conservation of the proteins involved. We have, for the first time, used an *in vivo* system to identify a universal mechanism describing how complexin can inhibit synaptic vesicle fusion.

References:
Martin JA, et al. "Complexin has opposite effects on two modes of synaptic vesicle fusion." Curr. Biol. 2011 Jan 25;21(2)97-105.Kummel D, et al. Nat Struct Mol Biol 2011 Jul 24; 18(8):927-33

Kümmel D, et al. "Complexin cross-links prefusion SNAREs into a zigzag array." Nat Struct Mol Biol. 2011 Jul 24;18(8):927-33.

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