The BERNICE GRAFSTEIN LECTURE

Sponsored by the Department of Physiology & Biophysics of WCMC and the Graduate Program in Neuroscience

given as part of the

PROGRESS IN NEUROSCIENCE SERIES

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)

Thursday, 3/6/14, 4 PM, coffee at 3:45 PM
Weill Auditorium

Cocktail Reception in Griffis Faculty Club to follow, 5:15 PM

Immune Mechanisms Underlying Synaptic Pruning in Health and Disease

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Research abstract:

Emerging evidence indicates that microglia, immune cells that reside in the brain, are altered in some individuals with autism, but it is not yet known whether they play a direct role. Are microglia simply responding to changes in the brain environment? Or could they play an active or even causal role in autism? Understanding their normal function in brain development is providing important insight. Recent work from our laboratory has demonstrated a surprising new role for microglia and molecules traditionally associated with innate immune system function, complement cascade proteins, in elimination and refinement of CNS synapses. In my talk I will present evidence that microglia actively participate in synaptic pruning by phagocytosing developing synapses. Our recent studies in the mouse visual system support a model in which 'weaker' or less active synapses in the developingbrain are 'tagged' by complement and then eliminated by microglia, the only resident brain cell to express complement receptor 3 (CR3/cd11b). An important question raised by these findings is what signals regulate the timing and initiation of microglia – mediated pruning? Our recent findings identify the cytokine, TGFB as a key regulator of microglia mediated pruning during development, Mice lacking TGF-β receptor II (TGFbRII) in retinal neurons have reduced C1q expression in RGCs, reduced synaptic localization of complement, and phenocopy refinement defects observed in complement deficient mice, including reduced eye specific segregation and microglial engulfment of RGC inputs. These data implicate TGF-β in regulating neuronal C1q expression to initiate complement- and microglia-mediated synaptic pruning. Our findings have important implications for understanding mechanisms underlying synaptic and microglia dysfunction in neurodevelopment disorders and CNS neurodegenerative diseases involving synapse loss and dysfunction, including Alzheimer's Disease.

Recent relevant publications:

1) Schafer D, Lehrman E. Kautzman A, Koyama, R, Mardinly A, Greenberg ME, Barres BA, and **Stevens, B (2012).** Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement- dependent manner Neuron, 74; 1-15. PMCID:PMC3528177

2) Schafer DP and **Stevens, B.** Phagocytic glial cells: Sculpting synaptic circuits in the developing nervous system Curr Opin Neurobiology (in press).

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