Ultrastructural analysis of neuroinflammation

For: MSc or PhD Students; 12 months

Program supported: Aging in Place

Academic Collaborator	NRC Principal Investigator	Associated NRC Research Centre
University of Alberta	Marianna Kulka (Researchgate)	Nanotechnology Research Centre

Project Description:

Neuroinflammation requires extensive communication between nerve and immune cells. Identification of these bidirectional links is thus a critical step in designing effective therapeutics. Mast cells, microglia and astrocytes engage in crosstalk that accelerates disease progression and contributes to pathogenesis across both the peripheral (neuropathic pain, fibromyalgia) and central (Alzheimer disease, Parkinson disease) nervous systems; such interactions become exaggerated with aging and stress. Therefore, understanding how these cells communicate has become a very active area of research. The host interdisciplinary team currently examines communication pathways between mast cells, microglia and astrocytes and has identified several receptor-mediated signaling networks (MrgprX2, SCF, PrP) that may contribute to these complex interactions.

Our previous work has shown that activated mast cells shuttle the high affinity IgE receptor to lipid rafts, specialized nanostructures on cell surfaces that facilitate signaling. Other work has shown that these structures also arrange into phalloidin-positive cytoneme-like structures, also called tunneling nanotubes. Our hypothesis is that cytonemes facilitate communication between mast cells and microglial cells. To test this hypothesis we have three objectives: (1) examine the formation of cytonemes in resting and activated mast cells and microglial cells, (2) determine cell-cell synapses of mast cells and microglial cells, including interactions of cytonemes, and (3) design janus nanoparticles composed of latrunculin (which sequesters globular-actin) to block these cytoneme-based interactions and disrupt cellular synapses.

Much of this project will rely heavily on transmission electron microscopy (EM) and fluorescent microscopy. Working as a part of our interdisciplinary team, the student supported by this program will co-develop and optimize state-of-the-art EM approaches, including biological sample preparation. The student will examine these neuroinflammatory communication synpases in unprecedented detail and determine whether nanoparticle disruption of these processes is a feasible therapeutic approach for treating neuroinflammatory disease.

This internship will further develop new cryoEM protocols and optimize existing strategies to examine multi-cell interactions, particularly in terms of cytoneme-mediated communication networks. These approaches typically require months of optimization for each set of complex biological samples; this internship would accelerate our development of these techniques for neuroinflammatory research and could significantly reduce optimization times. This internship/project would further support M. Kulka's project "Molecular understanding for early diagnosis of the diseases of aging" currently supported under the Aging in Place Challenge Program, in collaboration with Dr. M. Cuperlovic-Culf (DT) and J.K. Sandhu (HHT).

The student will join an active team of experts in EM at NANO, have access to the extensive electron microscopy facility, including internationally-recognized experts in electron microscopy research and development. The student will be supported by NANO's Biomedical Team, who are experts in cell biology, neurobiology, organic chemistry and cryoEM.

Student Profile:

- Background knowledge of basic microscopy and principles of sample fixation
- Background knowledge of basic neurobiology and cell biology
- Basic laboratory experience, including preparation of buffers
- A MSc in microscopy or cell biology is preferred