MSc DEFENCE – Friday, July 8th, 2016
Student: Adam Yu
Title: NEUROINFLAMMATORY CONDITIONS MODULATE ARNT2 AND RME-8 EXPRESSION WITHIN THE CNS
Time and location: 1:00 pm PDT; Djavad Mowafaghian Centre for Brain Health, Room 3402C, 2215 Wesbrook Mall, UBC
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ABSTRACT

Microglia are the primary immune cells found within the central nervous system (CNS), playing a vital role in neuronal function, trophic support and also modulating immune or inflammatory responses to pathogens or damage during disease. Microglia are essential to repair processes influencing axonal health and remyelination. However, the study of microglia is limited as significant yields of microglia through tissue culture are difficult to obtain. We show that the addition of granulocyte macrophage colony-stimulating factor (GM-CSF) during the culture of embryonic microglia yields significantly greater cell numbers. GM-CSF cultured microglia exhibit a non-differentiated phenotype similar to *in vivo* microglia and represent a useful model for disease and reparative processes in the CNS.

Using our primary microglial model, we investigated two proteins, Aryl hydrocarbon receptor nuclear translocator 2 (ARNT2) and receptor-mediated endocytosis – 8 (RME-8). ARNT2, a transcription factor for several proteins but most notably for the neuronal growth factor, brain derived neurotrophic factor (BDNF), has been primarily studied in neurons. Our studies show regulation of ARNT2 in astrocytes and immune cells (microglia and splenocytes) under inflammatory conditions. In the experimental autoimmune encephalomyelitis (EAE) model, splenocytes exhibited lower ARNT2 expression than those from healthy controls. Lipopolysaccharide and interferon-γ increased otherwise low ARNT2 expression in microglia.

RME-8 is a protein that is important in endosomal trafficking. Mutations in RME-8 have been linked to Parkinson's disease and essential tremor. However, RME-8 has yet to be characterized within the CNS. Motor neurons, astrocytes and ependymal cells expressed RME-8 in healthy control mice; RME-8 was increased and co-localized with CD68 positive cells in immune infiltrates in EAE mice. Our results show the uptake of dextran in RME-8 mutant knock-in microglia is decreased, indicating the importance of this protein in phagocytic processes.

These results show that microglia can be effectively cultured from embryonic tissue with the addition of GM-CSF in comparison to previously established protocols and are similar to microglia *in vivo*. Furthermore, inflammatory mediators influence expression of ARNT2 and RME-8 and may highlight roles for each in neuroprotection or phagocytic function respectively, thereby influencing inflammatory neurodegenerative or reparative processes relevant to several diseases in the CNS.