

Elucidation of the Signaling Pathway of MERTK

Background

Mer Tyrosine Kinase (MERTK) is a receptor which mediates efferocytosis – removal of apoptotic cells by phagocytes such as macrophages. MERTK plays a critical role in homeostasis, with mutations in MERTK associated with the development and progression of atherosclerosis, the buildup of cholesterol-laden plaque in the sub-arterial space. Indeed, one MERTK allele is associated with 66% (heterozygous) to 75% (homozygous) protection from atherosclerosis, while other alleles and SNP's pre-dispose to atherosclerosis and autoimmunity. Complications resulting from atherosclerosis, including heart attack and stroke, are currently the second leading cause of mortality in Canada. Despite the importance of MERTK in atherosclerosis and other clinical conditions, little is known of its signaling or regulation. My project is focused on identifying the downstream signaling pathway triggered by MERTK activation and determining how atherosclerosis alters signaling through this pathway.

Methods

MERTK will be activated in human macrophages under homeostatic conditions and associated downstream signaling molecules identified. These signaling molecules will then be prioritized based on their known function, and their roles elucidated through efferocytosis assays using cells treated with inhibitors against the proteins of interest. Finally, the activity and expression of key signaling molecules will be assessed in a model of atherosclerosis.

Expected Results

My project will potentially reveal the signaling pathway utilized by MERTK for efferocytosis and clarify MERTK's role in atherosclerosis development and progression.

Discussion/Conclusion and Interdisciplinary Reflection

The findings generated by this project may lead to the development of putative therapies aimed at treating cases of advanced atherosclerosis and its associated complications.