

MSc DEFENCE Tuesday, September 18th, 2018

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Title: AXL RECEPTOR TYROSINE KINASE REGULATES APOLIPOPROTEIN E EXPRESSION

Time and location: 12:00 pm PST; Room 3402, The Djavad Mowafaghian Centre for Brain Health, 2215 Wesbrook Mall, Vancouver, BC

Supervisor: Dr. Cheryl Wellington

ABSTRACT

Alzheimer's disease (AD), the leading cause of dementia, is a chronic neurodegenerative disease. One of the hallmarks of AD is the accumulation of amyloid plaques in the brain. Apolipoprotein E (apoE), which carries lipids in the brain in the form of lipoproteins, plays an undisputed role in AD pathophysiology. The *APOE* gene is the most validated genetic risk factor for late onset AD, and has well-established associations with amyloid deposition and clearance from the brain. We and others have shown that lipidation of apoE can assist amyloid clearance, raising interest in augmenting apoE function as a proposed therapeutic strategy for AD. A high-throughput phenotypic screen was conducted using a CCF-STTG1 human astrocytoma cell line to identify small molecules that could upregulate apoE secretion. A subset of AXL receptor tyrosine kinase inhibitors, which we term AXL modulators were identified as positive hits. The objective of this thesis is to dissect the mechanism of action (MoA) by which AXL modulators upregulate apoE expression. We initially understood their dependency on AXL by treating *AXL*^{-/-} CCF-STTG1 cells generated using CRISPR-Cas9 method with the lead compound. We then determined if Liver X Receptor (LXR) activity was required utilizing LXR knock-out (KO) mouse embryonic fibroblasts (MEF) cells. Immunoblotting analysis of AXL protein indicated the ability of AXL modulators to promote AXL receptor cleavage and stabilize the intracellular domain (ICD). To investigate the role of AXL-ICD in apoE homeostasis, various Axl variants, including WT AXL, kinase-dead AXL mutant, Axl-ICD, and AXL N-terminal fragment were stably reconstituted in *AXL*^{-/-} CCF-STTG1 cells. ApoE baseline expression was significantly upregulated only upon reconstitution of ICD-containing AXL variants. In summary, AXL protein plays a significant role in apoE homeostasis through its intracellular domain.