MSc DEFENCE – Monday, March 30th, 2015
Student: Yuda Shih
Title: **DIFFERENTIAL REGULATION OF OLIGODENDROCYTE DEVELOPMENT AND MYELINATION BY PROTEIN TYROSINE PHOSPHATASE ALPHA AND WNT SIGNALING**
Time and Location: ***10:00 am, Room 2108, CFRI, Visitor Address: Entrance #18, 938 West 28th Avenue, Vancouver, BC***
Supervisor: Dr. Catherine Pallen

Abstract

Oligodendrocytes (OLs) are the myelinating cells of the central nervous system (CNS). The myelination process is preceded by molecular and morphological differentiation of oligodendrocyte precursor cells (OPCs) into mature myelinating OLs. PTP□ is a brain-enriched tyrosine phosphatase that regulates many cellular processes, including OPC differentiation. Our laboratory has previously demonstrated that PTP□ null OPCs have impaired differentiation and brains of PTP□ KO mice are hypomyelinated. In this study, I observed defective myelination in OL/neuron co-cultures where WT and K□ OPCs were introduced to neurite beds formed by dorsal root ganglion neurons for 14 days and immunostained for myelin basic protein (MBP), a component of the myelin sheath, and neurofilament (NFH), an axonal protein. MBP/NFH co-localization was used as an indicator of potential myelination. Co-localization is significantly reduced by ~50% in co-cultures with K□ OPCs as compared to WT OPCs. Additionally, co-cultures with K□ OPCs exhibit a reduced ability to elongate MBP/NFH immunopositive segments, suggestive that in co-cultures with KO OPCs the ability to elongate axo-glial contacts, a prerequisite for myelination, is impaired. This coincides with a reduction in MBP immunopositivity from KO OPCs, indicating a differentiation defect in the absence of PTP□.

Pharmacological modulation of several signaling pathways has recently been shown to affect OL differentiation, myelination and remyelination. XAV939 is an inhibitor of canonical Wnt signaling and is known to promote OL differentiation and remyelination. Therefore, I investigated whether inhibition of Wnt signaling can remediate PTP□-dependent impairments in OL differentiation and myelination. I observed that inhibiting Wnt signaling can partially rescue PTP□-dependent impairments in differentiation; however, inhibition of Wnt signaling could not remediate the defects in elongation of MBP/NFH immunopositive segments in co-cultures with K□ OPCs. While these studies reveal no apparent common molecular candidates between PTP□and Wnt signaling that may regulate OL differentiation, the findings described suggest that PTP□ has at least two distinct roles during oligodendrocyte development: to promote OL differentiation by regulating MBP expression, forming and elongating of axo-glial contacts, both of which are prerequisite for myelination.

PhD DEFENCE – Tuesday, March 31st, 2015
Student: Melissa McConechy
Title: ***PPP2R1A* MUTATIONS IN GYNAECOLOGIC CANCERS: FUNCTIONAL CHARACTERIZATION AND USE IN THE GENOMIC CLASSIFICATION OF TUMOURS**
Time and Location: ***9:00am, Room 9299, Gordon and Leslie Diamond Health Care Centre, 2775 Laurel Street.***
Supervisor: Dr. David Huntsman

ABSTRACT

Endometrial carcinoma is the most common gynaecological cancer in developed countries, and ovarian cancer is the most lethal. The current pathologic classification system lacks reproducibility, which has hampered the development of new treatment approaches for this cancer.

Objectives: To determine the role of somatic *PPP2R1A* mutations in subtype specific classification of gynaecological tumours. In addition, mutational profiles from multiple genes will be used to improve subtype classification of endometrial carcinomas. Lastly, the functional effect of a *PPP2R1A* mutation on PP2A subunit interactions will be determined, in the context of endometrial cancer cell lines.

Methods: Next-generation sequencing and Sanger sequencing was used to determine the presence of mutations in endometrial and ovarian carcinomas. PPP2R1A isogenic endometrial specific cell lines were generated using somatic cell gene knockout by homologous recombination. Co-immunoprecipitation coupled to mass spectrometry was used to determine the effects of the PPP2R1A W257L mutation on the ability to interact with PP2A subunits.

Results: Subtype-specific somatic *PPP2R1A* mutations were identified in endometrial serous carcinomas. Low-grade endometrial endometrioid carcinomas were defined by mutations in the genes: *ARID1A, PTEN, PIK3CA, CTNNB1*, and *KRAS*, whereas high-grade endometrioid also harbor *TP53* mutations. Endometrial serous carcinomas harbor mutations in *PPP2R1A, FBXW7, PIK3CA* and *TP53*. Consequently, the molecular profiles proved useful in assisting classification of seven tumours with overlapping morphological features that cause irreproducibility in diagnoses. Proteomic analysis of the isogenic cell lines determined that the PPP2R1A W257L mutation disrupts the interaction with PPP2R5C and PPP2R5D B subunits. In addition, PPP2R1A mutated protein caused an increased interaction with the endogenous PP2A inhibitor SET/I2PP2A.

Conclusions: The integration of mutational profiles and other genomic features will be used to improve clinical and pathological classification in endometrial tumours that are difficult to diagnose. *PPP2R1A* mutations are likely playing an important role in the transformation of gynaecological carcinoma, by disrupting PP2A subunit interactions with tumour suppressor functions. Increased interaction of mutant PPP2R1A with SET/I2PP2A adds another layer of complexity to the tumour suppressive role of PP2A. In the future, targeting the PP2A complex with novel therapeutics could provide an alternative method for treating these gyneacological cancers with poor outcomes.