

PhD Oral Defense



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**27 April 2018, Friday
11am – 12pm**

**MD10 Anatomy Museum
Level 2, Seminar Room**

Molecular and Epigenetic Regulation of Microglia Activation with Special Reference to its Roles in Glioma Progression

Microglial cells, the resident immune cells of the central nervous system, are activated upon encountering pathological stimuli such as infection, brain injury, ischemia and neurodegeneration. This study has focused on understanding the molecular and epigenetic regulation of microglial activation in glioma tumours and neuroinflammation. Here, the role of the TGF β signalling pathway in microglia was explored, as glioma-derived TGF β has been shown to induce a tumour-supportive phenotype in microglia. SMAD4, which is a co-mediator of the TGF β pathway, was found to be upregulated in glioma-associated microglia. Stable knockdown of SMAD4 in microglial cells resulted in a decrease in MMP9 expression, abrogated migration of microglia towards glioma conditioned medium and suppressed glioma cell viability in vitro. Further, a microRNA, miR-146a, which targets SMAD4, was found to be downregulated in glioma-associated microglia. Overexpression of miR-146a in microglia was found to significantly downregulate MMP9 expression levels in microglia and suppressed migration of microglia towards glioma conditioned medium. The results demonstrate that SMAD4, epigenetically regulated by miR-146a, promotes the migration of microglia towards a glioma microenvironment and glioma cell viability in vitro. The second part of the study focused on the role of the post-translational modification SUMO-1 in the regulation of the NF- κ B pathway in activated microglia. SUMO-1 was found to be significantly upregulated in activated microglia and was found to be expressed in the amoeboid microglial cells of the post-natal rat brain. SUMO-1 inhibition suppressed pro-inflammatory gene expression in activated microglia, via downregulation of the NEMO subunit. Taken together, this study identified SMAD4 and SUMO-1 as regulators of microglial functions in glioma microenvironment and neuroinflammation.