Interaction of Regulatory Factor X (RFX) factors and the mineralocorticoid receptor (MR) in neuronal differentiation and ciliogenesis in embryonic and adult neurogenesis

Supervisory team:
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Project description:

Glucocorticoid hormones play very important functional roles in the body. They regulate metabolism, the immune system as well as many brain functions to maintain health and wellbeing. Dysregulation of glucocorticoid hormone function is known to enhance vulnerability for developing mental health disorders like major depression, anxiety and post-traumatic stress disorder. Presently, however, the molecular underpinnings of these glucocorticoid effects on the brain have still not been clarified. The brain structure mostly investigated is the hippocampus because of its role in stress coping and learning and memory processes.

Glucocorticoid hormones act on the hippocampus through interaction with two intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which act like ligand-dependent transcription factors. Recently, we conducted so-called chromatin immunoprecipitation (ChIP) analysis on the hippocampus to identify, for the first time, the genes with which MR and GR interact under baseline and stress conditions (see Mifsud & Reul (2016) Proc. Natl. Acad. Sci. USA 113:11336-41; Mifsud et al. (2021) Nature Communications 12: 4737). Amongst many findings, we discovered that, the MR in particular, is involved in neuronal differentiation and cilia function. Cilia are hair-like protrusions from cells, including neurons, that play critical roles in sensory and developmental processes. Both neuronal differentiation and ciliogenesis are part of the adult neurogenesis process taking place in the dentate gyrus, a highly plastic region of the hippocampus. Indeed, MR is thought to play a role in the neuronal differentiation phase of dentate neurogenesis but exactly how is presently unknown. We were able to confirm that MR is critical for neuronal differentiation and ciliogenesis in human foetal neuronal progenitor cells (hfNPCs; Mifsud et al., 2021). We also discovered that, most likely at the genome, MR interacts with so called Regulatory Factor X (RFX) factors, which are critical for ciliogenesis. These novel findings provide a solid rationale and basis for the in-depth investigation of the connection between MR and RFX factors in relation to neuronal differentiation and ciliogenesis as part of the embryonic and adult neurogenesis process.

The successful PhD student will apply various state-of-the-art technologies including epigenetic (ChIP), molecular (RNA, genome analysis, gene silencing), biochemical (co-immunoprecipitation (Co-IP)), neuroanatomical (RNAscope, double/triple immunofluorescence), cell culture (hfNPCs, iPSCs), and bioinformatics (R, Bioconductor, Ingenuity Pathway Analysis) technologies and methods. The project will be supervised by Professor Johannes Reul, Dr Oscar Cordero Llana, Professor James Uney, and Dr Karen Mifsud, in collaboration with Professor David Stephens, at the University of Bristol, Bristol, UK.