| Project Details | |
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| Project Code | MRCNMH24Ex Piers |
| Title | Effect of Alzheimer's disease risk variants on microglial cell state transitions in response to pathology |
| Research Theme | Neuroscience & Mental Health |
| Summary | Microglia are strongly linked to Alzheimer's disease (AD), supported by significant cell-type specific genetic association. However, there is a substantial gap in our understanding of how genetic variation affect microglial response to pathology. This project will use culture models to uncover the mechanisms associated with microglial activation states using a multidisciplinary approach including microscopy, electrophysiology, epigenetics, and bioinformatics. |
| Description | A significant proportion (~25%) of Alzheimer's disease (AD) risk loci map to genes preferentially expressed in microglia and associate with pathways key in regulating microglial activation and cellular state. It is also well established that the epigenome plays a pivotal role in the regulation of microglial activation states. We previously identified deficits in microglial response to inflammatory modulators and effects on activation states if cells harboured TREM2 mutations associated with AD, providing an excellent model of sub-optimal microglial activation. The project will use human iPSC-derived microglia and neurons to study: "How AD risk variants alter the ability of microglia to respond to pathological insults" Objectives and learning outcomes for the student: 1. Develop expertise in iPSC culturing to generate complex models to assess microglial response to pathology 2. Develop skills in electrophysiology and super-resolution imaging to assess differences in microglial physiology and cellular states when harbouring genetic variants 3. Develop bioinformatic skills to identify new regulatory pathways that are altered in disease variant microglia, affecting cell state transitions Research Plan: Aim 1: Validation of iPSC culture models and development of co-culture techniques to study microglia response to pathology. 1a. UEx: The student will learn how to generate and differentiate iPSC lines into microglia and cortical neurons using validated KOLF2.1J iPSC line and isogenic genome edited daughter lines that harbour disease-associated mutations. The KOLF2.1J has been utilised by several international collaborations including the iPSC Neurodegenerative Disease Initiative (iNDI) consortium as a model system, enabling cross-site validation. The student will usw immunocytochemistry (ICC) and quantitative PCR (qPCR) to validate lineages and test basal functionality with ELISA and Seahorse. 1b. UB: The student will establish co-cultures of isogenic human iPSC-derived microglia and neurons and study microglial responses to disease-related pathology using electrophysiology (DW) and live imaging (TP). Specifically, the student will prepare neuron-glial combinations of known risk variants associated with microglial function, such as rs75932628 (TREM2) and familial AD (fAD) mutations in PSEN1 (e.g., PSEN1E276A) in neurons, known to increase the pathological Aβ ratio and compare these to an array of control combinations: wildtype (WT) neurons + WT microglia; WT neurons + risk variant microglia; fAD neurons + WT microglia. These combinations will enable the student to delineate how microglia respond to pathological changes in Aβ known to affect synaptic |

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| | integrity, and how these responses are altered when microglial cell state transitions are sub-optimal. Aim 2: Mapping the regulatory landscapes of microglial activation. UEx: To identify the regulation associated with sub-optimal microglial responses to pathology, genome wide patterns of DNA methylation and gene regulation will be studied in the co-culture combinations (Aim1b). DNA will undergo quantitative genome wide profiling for methylation by microarray profiling and collected RNA will be used for transcriptome profiling. Established pipelines for data analysis will be utilised, and data correlated with open-source datasets from diverse models (GSE98969) and patient cohorts (KL/NC). Identified regulatory pathways will be validated in culture using genetic manipulation. The combinatory strategy will provide the student with opportunities steer the project in multiple directions depending on their interests, including a focus on the underlying regulatory differences associated with sub-optimal microglial phenotypes, fundamental changes in glial physiology when harbouring risk variants and how this may contribute to pathogenesis, or the study of microglial cell state transitions in response to pathology using live super-resolution microscopy. |
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