Project Details	
Project Code	MRC21IIRCa Peters
Title	Glial functions of the frontotemporal dementia and motor neuron disease associated gene TBK1
Research Theme	Infection, Immunity & Repair
Summary	Disruptive mutations in TBK1 occur in the devastating neurodegenerative disorders Motor Neuron Disease and Frontotemporal Dementia. Despite defined roles in immunity, our understanding of glial functions of TBK1 are limited. To better define glial activity of TBK1 in inflammation, phagocytosis and neurodegeneration this interdisciplinary project will combine high-throughput confocal microscopy of mammalian glia with in vivo disease modelling in Drosophila.
Description	Frontotemporal dementia (FTD) and the motor neuron disease amyotrophic lateral sclerosis (ALS) are devastating neurodegenerative disorders for which there are presently no effective therapies. In their familial forms, ALS and FTD have some common genetic origins, including the disruptive loss of function mutations in the ser/thr-protein kinase TANK Binding Kinase 1 (TBK1). TBK1 has known functions in the immune system, responding to stimulation of toll-like receptors to drive transcriptional regulation of cytokine release and activating autophagy receptors required for clearance of phagocytosed material. Despite these defined immune functions, how disruption of the expression and activity of TBK1 alters the function microglia, the resident immune cell of the brain, is less characterised. This project will combine mammalian microglia cell culture and Drosophila in vivo modelling to understand if TBK1 contributes to ALS/FTD relevant glial biology. We ultimately aim to determine if manipulation of glial TBK1 represent a potential therapeutic intervention for these neurodegenerative diseases. Aim 1.) Define the role of TBK1 in immune and autophagy functions of mammalian microglia in vitro. Using cell culture of mammalian microglia in which TBK1 function has been disrupted, the student will examine how TBK1 contributes to viability, morphology, immune response and phagocytosis/autophagy associated functional phenotypes of microglia. First the student will test for changes in viability and morphological features of TBK1 disrupted microglia, followed by molecular techniques to understand TBK1 activation, immune signalling cascades and stimulated cytokine release. Next, the student will use state-of-the-art imaging techniques to conduct assays to understand how TBK1 contributes to phagocytosis of extracellular material by microglia and activation of autophagy. Aim 2.) Understand how TBK1 contributes to in vivo glial function in development and ageing in a invertebrate model system. Drosophila melanogaster express Ik2, a well-conserved TBK1 homolog making fruit flies an excellent in vivo model organism for testing macrophage/glial roles in development and ageing. The student will generate flies where Ik2/TBK1 is reduced in glia and assess for ALS/FTD associated phenotypes, including deficits in larval and adult motor behaviour, changes in lifespan and neuronal health in ageing adult flies. To identify Ik2/TBK1 associated functional changes in immune cell activity, the

	student will use an advanced microscope technique to assess deficits in phagocytosis and autophagy of apoptotic corpses in the developing nervous system in live fly embryos. Finally the students will assess how Ik2/TBK1 contributes to glial phagocytosis of injured axons within the central brain of ageing adult flies. Our innovative approach will use a combination of mammalian cell culture and invertebrate model systems to provide insight into the importance of TBK1 in immune cell function in the brain. The study will provide the student with a broad training in highly translatable in vitro assays, developing techniques which will be suitable for future therapeutic screening, and establish a simple invertebrate model system for assessing glial genes associated with ALS/FTD.
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