

Uncovering the function of a novel gene involved in neurodegeneration

Dementia consist of a spectrum of disorders, where neurodegeneration affects memory, comprehension, learning capacity, language, and sometimes emotional control and motivation. The mechanisms by which neurons die in neurodegeneration is frequently due to accumulation of protein or lipid clusters, but the mechanisms are poorly understood. Recently, a novel gene named TMEM184b has been identified as a potential mediator of neurodegeneration. Researchers showed that the neurons of mice lacking TMEM184b accumulate membrane lipids, which caused cell death. The protein encoded by the TMEM184b gene is predicted to localise to membranes, suggesting that it is important for membrane homeostasis in neurons. Interestingly, I have noticed that the amino acid sequence of the TMEM184b protein encodes a specific signal (a dileucine motif) that is known to control the localisation of membrane proteins. Furthermore, there are nearby serine amino acids that could represent another signal that regulates the trafficking of the protein. I hypothesise that these signals found in other membrane proteins are responsible for the correct function of TMEM184b. I aim to investigate my hypothesis by making mutant forms of TMEM184b that lack these predicted signals. If my hypothesis is correct it will give a better awareness into how TMEM184b controls membrane homeostasis in neurons and perhaps how these mechanisms are disrupted in neurodegeneration. In the previous paper I read, the phenotype of the mice are really close to dementia symptoms so knowing more about this protein and gene would maybe enable us to have a better understanding of dementia pathway.

I wanted to combine, for my project, my interest for neurodegeneration diseases and cell signaling. The TMEM184b gene appears to be implied in neurodegeneration but only a few research have studied it and it is still relatively unknown. By studying this specific gene, I want to bring my contribution for a better understanding of dementia and neurodegeneration. On top of that, I find genetics fascinating. A slight alteration or expression of a specific gene can have significant consequences on our health.

In Dr Evans' laboratory, I aim to undertake cloning approaches to mutate the predicted dileucine or serine motifs in the TMEM184b gene. Plasmids encoding the mutated TMEM184b will be expressed in a neuronal cell line and fluorescence microscopy will be used to assess the effects of the mutations on the cellular localisation of the protein. I will then assess the physiological effects of the mutants on cell viability and cell morphology through fluorescence microscopy again.

My project links to the Health and Well-being theme of the university by underpinning the process and the system of a gene linked with the pathology of dementia. With 850,000 people suffering from dementia in the UK and numbers set to rise in the future, this disease can not be neglected. I am not aiming to find a cure for dementia, but my research could contribute to our understanding of neurodegeneration and highlight the fundamental role of the TMEM184B gene.