Defining the role of astrocytes in neuronal health and the implications of neuroinflammation

Supervisory team:
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Host institution: University of Bristol / University of the West of England; UWE
Submit applications for this project to University of Bristol

Project description:
As we age, we become increasingly at risk of developing neurodegenerative diseases. This is due to the inability of neurons to regenerate, and the 'wear and tear' of a lifetime causing changes to the biology of neurons that ultimately leads to their death. This loss of neurons underpins the symptoms of neurodegenerative diseases.

A key feature of many age-related neurodegenerative diseases is proteinopathy, where proteins that are normally present in the nervous system becomes neurotoxic, often due to their aggregation. One such protein is alpha-synuclein, which is required in neurons for the release of synaptic vesicles. However, in certain people, as they age alpha-synuclein aggregates inside particular neurons in the brain. These aggregates disrupt critical cellular functions, eventually leading to death of the neuron. Depending which region of the brain is affected this results in either Parkinson's disease or Lewy body dementia (LBD). Alpha-synuclein aggregates propagate through the brain, as the abnormal protein is transferred between cells, priming its own aggregation in neighbouring neurons, and leading to further neuronal loss. We still do not understand why alpha-synuclein aggregation occurs in certain people as they age, or how aggregates are able to 'spread' from cell-to-cell leading to disease progression. However, new evidence shows that neuroinflammation is key. Neuroinflammation increases as we age and is further increased in people with Parkinson's and LBD. Neuroinflammation involves astrocytes, which are normally help maintain homeostasis in the nervous system, being critical for the function and survival of neurons. However, in neuroinflammation, astrocytes become 'reactive', they no longer provide support, instead exerting toxic effects on neurons. Preventing astrocyte reactivity prevents neurodegeneration.

In our labs we use human stem cell derived astrocytes and neurons, that represent the parts of the brain affected in Parkinson's and LBD. Using these we have shown that in response to neuroinflammation, reactive astrocyte cells release substantially increased levels of alpha-synuclein. This is the first evidence connecting reactive astrocytes to alpha-synuclein. This project will investigate how changes astrocyte proteostasis in response to neuroinflammation alter alpha-synuclein processing and release. Human stem cell differentiation combined with genetic models, cutting edge imaging techniques and high content proteomics will be used to define this relationship.

***Please note**: This project is in collaboration with the University of Bristol and the University of the West of England (UWE) and subject to a **joint degree award**. Successful applicants will be registered at both these institutions, and graduates will be awarded a joint degree from these two institutions upon successful completion of the PhD programme.*

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.