Examining changes in oxidative and inflammatory balance in the ageing brain

Pierrick Roger

Neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, are characterized by global atrophy of neuronal tissues leading to a progressive loss of motor or cognitive functions. These diseases disproportionately affect older populations with symptoms typically only becoming visible in the later stages of life. In fact, ageing is the greatest risk factor for neurodegenerative diseases. For example, the overwhelming majority of those affected by Parkinson's and Alzheimer's are over 65 years of age. What is it exactly that changes with age that can explain the late onset of such diseases? Which molecular mechanisms, if any, become dysregulated within neuronal cells making them more susceptible to disease as we age?

One of the leading theories of the mechanism behind ageing postulates that as the body ages, it accumulates oxidative damage – this is the oxidative theory of ageing. This damage is caused by the increased presence of endogenously produced reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion radicals. ROS cause damage to a whole range of macromolecules, including DNA, lipids, and proteins. Inflammageing, or the chronic inflammation observed in older organisms, is thought to be another mechanism underlying ageing. This inability to leave a pro-inflammatory status damages tissues and is influenced by several factors such as senescence of the immune system and the production of defective immune cells, but also an increase in oxidative stress.

Neurons, because they are post-mitotic cells, are particularly susceptible to harm caused by changes in oxidative or inflammatory status. Redox balance dysregulation and chronic inflammation have both been

linked to the development of a whole host of neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. The exact dysfunctions in the mechanisms regulating the redox and inflammatory balance associated with ageing in the brain have yet to be described in detail.

Tying into the University's Health and Wellbeing research theme, this project aims to interrogate the expression of genes associated with reactive oxygen species, and cytokine production and regulation over time in cells of the human brain. I will make use of publicly available whole transcriptome databases to determine whether these genes' RNA transcripts become enriched or impoverished with age and in which cell types these changes arise, whether in neurons themselves or surrounding glial cells. I expect there to be substantial alterations in the expression patterns of ROS- and cytokine-associated genes and that these changes will not be restricted to neurons but will also involve supporting glial cells.