Metabolic Control of Brain Ageing in Progressive Multiple Sclerosis (META_PMS)

G112716 to Stefano Pluchino, MD, PhD and Alexandra Nicaise, PhD
Dept of Clinical Neurosciences, University of Cambridge

Multiple sclerosis (MS) is the most common neurological disability affecting young adults. In the early stages of the disease, known as relapsing-remitting, symptoms appear and then partly, or completely go away. However, 80% of these patients go on to develop a progressive condition within 10-15 years of disease onset. The progressive condition is where there are no longer any remissions and symptoms progressively accumulate over time. This form of the disease is called progressive multiple sclerosis (PMS). During the progressive phase the brain is no longer able to repair what has been damaged, which causes the permanent loss of brain cells and the development of severe disability. Here, drugs that are effective in treating the relapsing-remitting form do not provide any positive benefit for patients with PMS.

The biggest risk factor in the development of PMS is ageing. Interestingly, there is now a suggested link between biological ageing and the development of PMS, as recent work has identified hallmarks of cellular ageing, known as senescence, in numerous cell types in the post-mortem tissue and *in vitro* with patient cell lines. Premature cellular ageing in the stem cell compartment of the PMS brain, with an increased accumulation of cell stress signatures, has been incriminated as a potential driver in the failure of brain repair after damage. Here, we hypothesize that dysfunctional, aged stem cells, secrete inflammatory factors impacting surrounding cells and promoting cellular degeneration. Furthermore, cellular metabolism, how cells generate energy, has been shown to regulate cell stress pathways and undergo reprogramming in aged cells, making it a promising target for therapeutic intervention.

In our current study, we aim to uncover metabolic signatures that may be dysregulated in stem cells of the PMS brain which may be causing the spread of inflammation and eventual neurodegeneration. To do so we have generated an all-human patient-based approach by reprogramming skin cells from patients with PMS into induced neural stem cells (iNSCs). iNSCs from PMS patients have been found to express senescence markers and are inflammatory compared to age-matched controls. Via untargeted metabolomics we have discovered that PMS iNSCs also display an altered bioenergetic profile, with increased mitochondrial and glycolytic functions compared to age-matched control iNSCs, and dysregulation in several metabolic pathways. To study how cell metabolism impacts their function we have begun to establish an all-human 3D organoid approach to study how PMS-specific cells can impact healthy surrounding cells, which may help elucidate how the disease becomes neurodegenerative and allow for testing of future therapeutics.

With the support from Ferblanc we have confirmed that there is a dysfunctional metabolic landscape in PMS-patient derived stem cells that may lead to and cause degeneration and lack of repair. Furthermore, we have started to develop a first of its kind all-human organoid approach to study how these dysfunctional cells influence healthy cells around them.

Most treatments developed to treat PMS have worked in animal trials but have failed in patients. Now with this all-human patient approach we have discovered a new metabolic pathway that has the potential to be targeted and reversed which may lead to the development of new types of treatments for this disease.