The role of BACE1 in cerebrovascular disease

Hannah A Taylor[1], Eva M Clavane[1], Jane M Brown[1], Laura C Matthews[2], Paul J Meakin[1]

[1] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds

[2] Leeds Institute of Medical Research, University of Leeds

Cardiovascular disease is a known risk factor for dementia, associating two of the most abundant age-associated diseases. Around 7.6 million people are living with heart and circulatory diseases within the UK, presenting a substantial number of people with a potentially modifiable risk of dementia. Understanding the molecular mechanisms acting upon the cerebrovasculature could therefore provide a therapeutic target for vascular dementia and have a huge impact on public health.

The beta secretase 1 (BACE1) enzyme is a clinically relevant therapeutic target for Alzheimer's Disease, and a well-established causative molecule in the development of amyloid beta (Aβ) plaques in the brain, including in cerebrovascular vessels. BACE1 and Aβ have been shown to regulate peripheral blood vessel function, suggesting the same might be true in the brain. My project therefore aims to investigate whether increased BACE1 activity and/or Aβ deposition in the cerebral vessels leads to vascular dysfunction and may be a mechanism behind the increased risk of dementia for individuals with cardiovascular disease.

Due to the low substrate specificity that BACE1 has for its perceived main substrate, amyloid precursor protein (APP), I investigated novel substrates of BACE1, which may play important roles in pathological changes in BACE1 expression and activity. I used a datamining and bioinformatics approach to identify pathways controlled by BACE1. Through stratification and comparison of publicly available proteomics and RNA sequencing datasets, I identified 533 BACE1 regulated proteins, of which, 119 were predicted as BACE1 substrates. Of this list, 26 BACE1 dependent proteins were differentially expressed in vascular dementia, including the L1 family of cell adhesion molecules. Comparison with genes differentially expressed in endothelial cells in Alzheimer's Disease, identified seven members of the PTPR family as novel BACE1 substrates, including PTPRD. Experimental validation observed a significant 1.95 fold increase ($p<0.05$) in PTPRD expression in BACE1 knockout primary isolation brain endothelial cells when compared with wild type. The analysis was repeated in human brain endothelial hCMEC/D3 cells, a cell line derived from human temporal lobe microvessels. In hCMEC/D3 cells treated with a BACE1 inhibitor (M3), a 1.31 fold increase in expression of PTPRD was observed ($p>0.9999$). Dysregulation of receptor-type protein tyrosine phosphatase signalling is frequently observed in disease, including diabetes and cardiovascular disease, which are associated with an increased risk of dementia. The Netrin receptor DCC (DCC) protein was also found to increase in response to BACE1 knockout in endothelial cells compared to wild type by 1.53 fold ($p<0.05$), and in response to BACE1 inhibitor treatment (M3) in hCMEC/D3 cells by 1.11 fold ($p>0.9999$). The Netrin-1/DCC interaction has been shown to be involved in inducing angiogenesis via endothelial cell nitric oxide. This computational analysis has therefore identified novel BACE1 substrates which may play important roles in cerebrovascular disease, with the potential for further analysis to unveil additional substrates. Further analysis of these novel associations with BACE1 may provide a greater understanding of BACE1 in health and cerebrovascular disease and contribute towards targeting BACE1 for therapeutic benefit in the treatment and/or prevention on vascular dementia.