Alzheimer’s disease; its time for a cure

Alzheimer’s disease (AD) is a debilitating neurodegenerative disorder symptomatically characterised by impaired memory and alterations to personality. Unfortunately, little is known about the causes of AD, early detection is limited, and there is currently no cure. Slowing the rate of progression of AD and enhancing the brain’s own ability to regenerate are current key focal points in establishing a treatment for AD. However, there is still a vast amount unknown about this complex disorder and further investigation into normal and diseased brain function is essential.

Pathologically, AD is characterised by the abnormal cleaving of the amyloid precursor protein (APP) resulting in amyloid beta (Aβ) deposition. In the normal state, cleavage of APP results in a 40 amino acid fragment termed Aβ_{40}. However, in AD, APP is often cleaved into the 42 amino acid fragment (Aβ_{42}), which is more fibrillogenic. This fibrillogenic form is often what results in the formation of plaques within the cortex, hippocampus and amygdala. These areas are involved in memory, learning and higher thinking. As a result of degeneration in these areas, patients exhibit cognitive dysfunction.

Aβ deposition and the subsequent plaque load have gained enormous attention as both a hallmark and a therapeutic target for AD. As such, many developed therapies have been based around preventing the production of, or increasing the clearance of, the Aβ peptide (Liu B et al, 2013; Demattos RB et al, 2012; Liu YH et al, 2012). However, to date, therapies targeted at reducing Ab have disappointingly had little success in clinical trials (Liu B et al, 2013; Demattos RB et al, 2012; Liu YH et al, 2012). This is potentially due to therapies being delivered too late in the disease progression, though this may also give indication that Aβ is not a central component of the disorder. Despite this, intense debate amongst the scientific community remains as to the clinical relevance of Aβ as both a cause and a hallmark of AD. This is because there is often little correlation between plaque deposition and cognitive status.

Whilst the hallmarks of AD include plaque deposition, other cellular processes also occur. Numerous mouse model studies have shown that cell loss and inflammatory processes occur well before plaque formation and cognitive dysfunction (Wright et al, 2013). Additionally, analysis of human brain tissue from AD patients and studies conducted in pre-clinical animal models of AD indicate that disease onset may also be associated with inhibition of neurogenesis (Mu Y and Gage FH, 2011; Rodrigues JJ et al, 2008; Li B et al, 2008). Neurogenesis is the process by which new neurons are formed from populations of stem cells in the adult brain. It has been shown that neurogenesis is critical to brain function playing an important role in memory and learning (Geihig CS et al, 2012; Blaiss CA et al, 2011; Ohira K et al, 2010; Cho KO et al, 2010; Sun D et al, 2007; Bonfanti L et al, 2011). Therefore, agents or approaches that stimulate neurogenesis in the adult brain could be therapeutically significant in Alzheimer’s disease.

With the predicted exponential growth rate of AD worldwide, there is now an eager need for a deeper understanding of AD pathology. A marker for early detection is essential, and treatment options are critically required. It is plausible that memory loss and other clinical signs of AD are late stage events,
occurring well after the development of neuroinflammation and neuronal cell loss. Therefore, regardless of the ultimate therapeutic approach it is reasoned that therapies will certainly need to be started early in the disease cascade. We are now at a stage where there is a pressing need to identify early markers and create treatments for individuals living with AD that are viable and target specific. Further research into early biomarkers and cell signaling dysfunction are crucial to understand this devastating disorder.

References: