ALZHEIMER'S DISEASE
Alzheimer's disease; It's time for a cure
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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 brains 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 $A\beta_{40}$. However, in AD, APP is often cleaved into the 42 amino acid fragment ($A\beta_{42}$), 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. However, to date, therapies targeted at reducing Aβ have disappointingly had little success in clinical trials. 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. Furthermore, as a hallmark, the first Aβ imaging ligand, which detects neuritic plaques, has been approved as a diagnostic tool for AD and is now being used in the clinic. 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. Indeed, functional processes such as inflammation and neuronal cell loss have been shown to be early events in the disease cascade in several mouse models of AD. Additionally, postmortem studies have shown extensive neuronal loss and neuroinflammation in the hippocampus and cortex of the brain in AD patients. Numerous mouse model studies have shown that cell loss and inflammatory processes occur well before plaque formation and cognitive dysfunction. Furthermore, there is a strong correlation between cognitive function and inflammation in mouse models of AD. Therefore, treatments that target the dysfunctional processes which prelude AD could potentially be beneficial in protecting against degeneration in AD.

Anti-inflammatory treatments, such as non-steroidal anti-inflammatories, have been clinically trialed in AD. Although effective, they have often failed as their non-specificity can cause unwanted side effects. In addition, plausible reasons for their failure may be due to incorrect timing and/or the length of the intervention. Numerous studies have shown that the delivery of anti-inflammatory drugs to mouse models of AD has neuroprotective effects, enhances brain regeneration, improves memory and learning, clears inflammation and can also delay the onset of plaque deposition. This gives exciting indication that antiinflammatory drugs could be a more viable treatment option for AD. What is lacking, however, is the specificity of the target. An increased knowledge of inflammatory and neuronal cell signaling in AD is required to conceive a specific therapy that could benefit cognitive output in AD patients without side effects.

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.