Inflammation in Alzheimer's disease: insights from immunotherapy

More than 20 years after its initial formulation, the amyloid cascade hypothesis—which postulates that build-up of toxic amyloid-β species initiates a series of events that culminates in neurodegeneration and symptoms (Hardy and Higgins, 1992)—continues to dominate thinking on the pathogenesis of Alzheimer’s disease. Although the exact sequence of events linking amyloid-β accumulation to aggregation of hyperphosphorylated tau in different neuronal compartments, neuronal loss, synaptic dysfunction and symptoms remains unknown, there is now a substantial body of evidence implicating neuroinflammation in the pathogenesis of Alzheimer’s disease. Thus activated microglia accumulate around amyloid plaques both in the brains of individuals with Alzheimer’s disease and in transgenic mice, and have been implicated in promoting neurodegeneration (Akiyama et al., 2000). Imaging studies using the 11C-R-PK11195 PET ligand provide evidence that activated microglial accumulate in the vicinity of amyloid plaque pathology, and that activated microglial burden correlates with declining cognition (Edison et al., 2008). Genome-wide association studies have identified a number of risk variants for Alzheimer’s disease implicated in inflammatory responses (Betens et al., 2013); exome sequencing has revealed polymorphisms in the microglial receptor TREM2 gene as a rare but significant risk for Alzheimer’s disease (Guerreiro et al., 2013; Jonsson et al., 2013); and recently, the CD33 risk allele has been shown to inhibit microglial clearance of amyloid-β (Bradshaw et al., 2013; Griciuc et al., 2013). Finally, an integrative network-based genetic analysis of Alzheimer’s disease brain has implicated disturbance in immune/microglial networks in the pathogenesis of the disease (Zhang et al., 2013).

If inflammation, and microglial activation in particular, are core features of Alzheimer’s disease, the exact mechanisms involved, and the roles of the different inflammatory components are far less clear. Microglia—the predominant macrophage species within the brain—can express different cell-surface receptors and change morphology in response to changes in local environment thus becoming ‘activated’ in numerous ways (Perry et al., 2010). It is likely that in the Alzheimer’s disease brain some activated microglial species may, in certain circumstances, adopt a proinflammatory profile with deleterious effects, promoting neuronal and synaptic damage. Conversely, a microglial reaction initiated in response to, and promoting clearance of toxic amyloid-β species may confer protection. Given evidence that reductions in the rate of clearance of amyloid-β42 are seen in sporadic Alzheimer’s disease (Mawuenyega et al., 2010), it may be that subtle alterations in normal inflammatory-mediated clearance of fibrillar or perhaps oligomeric amyloid-β (Frenkel et al., 2013) play important roles in the earliest stages of Alzheimer’s disease pathogenesis.

Targeting the inflammatory cascade in Alzheimer’s disease either to attenuate harmful effects or promote clearance of abnormal proteins is an attractive therapeutic option. To date, clinical trials of ‘anti-inflammatory’ drugs including non-steroidals and aspirin have yet to show definite benefits in Alzheimer’s disease (Jaturapatporn et al., 2012). After the remarkable demonstration that peripheral, active vaccination against amyloid-β42 leads to clearance of brain amyloid from the brains of transgenic mice carrying human Alzheimer’s disease mutations (Schenk et al., 1999) immunotherapy-based approaches aimed at promoting amyloid clearance have dominated attempts to modify the course of human Alzheimer’s disease over the last decade or so. The first such study in man (AN1792) was halted after 6% of those on active therapy developed significant brain abnormalities’—often asymptomatic and usually mild and reversible oedema/effusions (ARIA-E) or haemosiderin deposition.
of fibrillar amyloid pathology in 39 patients who died with sporadic Alzheimer’s disease treated with targeted immunotherapy provides evidence deleterious or protective immune responses in Alzheimer’s disease. In this context, studies such as this, which demonstrate that immune targeting of amyloid-β pathology can result in clearance of fibrillar amyloid-β, reduction in phosphorylated tau load as well as producing fundamental and long-lasting changes in the inflammatory milieu give cause for some optimism. Particularly given hints that these approaches may show some subtle benefits in more mildly affected patients (Karran, 2012), the move towards using vaccination in secondary prevention trials in individuals with presymptomatic familial disease (Reiman et al., 2011) or sporadic asymptomatic amyloidosis (Sperling et al., 2012) is particularly timely. More generally, studies such as this demonstrate how much can be gained by long-term follow-up and post-mortem examination of individuals participating in disease-modifying trials in Alzheimer’s disease and other neurodegenerative conditions; and how much we still have to learn about the multiplicity of roles inflammation plays in the pathogenesis of Alzheimer’s disease.

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