


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 (Bettens 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-β1–42 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-steroidal aspirin have yet to show definite benefits in Alzheimer’s disease (Jatuprapatponn et al., 2012). After the remarkable demonstration that peripheral, active vaccination against amyloid-β1–42 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.
(ARIA-H), that may reflect immune-related flux of amyloid pathology in/out of vessels (Sperling et al., 2011). Amyloid-β vaccination has been shown to alter Alzheimer’s disease biomarkers including levels of CSF tau (Blenow et al., 2012). Finally, significant reduction in brain amyloid-β pathology has been demonstrated in the few treated patients that have thus far come to post-mortem (Holmes et al., 2008).

Despite the significant progress that has been made in identifying inflammation as a core feature of Alzheimer’s disease, many fundamental questions remain. It is as yet unclear which aspects of the inflammatory response in Alzheimer’s disease contribute to the pathological process, and which may be protective. The influence of systemic inflammatory events on neurodegeneration remains to be clarified (Perry et al., 2010). Exactly how amyloid-β immunotherapy interacts with the ‘normal’ immune repertoire in humans is unclear. The relationship between inflammation, amyloid and tau pathology remains uncertain. And most importantly, it is not yet known whether, if given early enough, treatments that modify neuroinflammatory responses can lead to demonstrable benefits for patients.

Given the limitations of current animal and cellular models of Alzheimer’s disease, examining the brains of humans with Alzheimer’s disease treated with targeted immunotherapy provides a unique opportunity to address many of these questions directly. In this issue of Brain, Zotova et al. (2013) present a detailed pathological comparison of the Alzheimer’s disease and inflammatory brain pathology of 39 patients who died with sporadic Alzheimer’s disease, 11 of whom had undergone active amyloid-β vaccination as part of the AN1792 trial. They demonstrate a number of important differences between the vaccinated and untreated groups. Those vaccinated against amyloid-β had substantial (82%) reductions in fibrillar amyloid-β42 load compared with those who did not receive treatment, demonstrating that, as previously reported (Holmes et al., 2008), peripheral vaccination against amyloid-β has clear and significant effects on its primary target within the brain. Treated individuals also showed significant (40%) reduction in phosphorylated tau burden in neuronal cell processes [although not in neurofibrillary tangles (Boche et al., 2010)], suggesting that in some way immune targeting of amyloid-β pathology has effects on other, likely downstream, pathologies involved in Alzheimer’s disease pathogenesis. Although there was no difference in total microglial load, vaccinated individuals showed significantly reduced levels of a range of activated microglial species, including those involved in innate immunity and antibody-mediated amyloid-β removal, suggesting a general downregulation of inflammation despite, on average, several years elapsing between vaccination and death. Whereas most activated microglial species were distributed widely throughout the cortex, clustering of activated microglia implicated in phagocytosis, i.e. those expressing macrophage scavenger-receptor A (El Khoury et al., 1996), was seen in the vicinity of amyloid plaques; and in the immunized group alone these clusters correlated with amyloid-β42 load. Finally in immunized but not immunized cases, brain phosphorylated tau load correlated with multiple markers of microglial activation, including those implicated in endocytosis of extracellular material, phagocytic activity, and binding of IgG and immune complexes.

Taken together, these observations provide further evidence that peripheral amyloid-β immunization can significantly alter core aspects of Alzheimer’s disease pathology, and diffuse downregulate microglial responses for prolonged periods after treatment has finished. The significant relationship and clustering of microglia-bearing phagocytic markers around amyloid plaques, in some cases years after treatment, suggest that therapeutic strategies directed towards modulating these and related microglial species may be beneficial; and that once initiated, such therapies may have self-sustaining effects. Conversely, it may be that other more widely distributed activated microglial species may be exerting more deleterious effects: the significant relationship between microglial activation and phosphorylated tau load in untreated individuals but not in vaccinated cases, and the reduction in phosphorylated tau load in the latter group provide tantalizing clues to a possible role for neuroinflammation to link amyloid with tau pathology. Particularly given the reduction in both amyloid and (to a lesser extent) phosphorylated tau burden in the immunized group, immune therapies targeting amyloid-β may—as predicted by the amyloid cascade hypothesis—reduce downstream degeneration, perhaps mediated through alterations in microglial activation.

Despite these intriguing insights, much remains unknown. A more detailed understanding of the full repertoire of microglial responses in Alzheimer’s disease may pave the way for more specific and targeted therapy either to promote normal clearance mechanisms, or prevent toxic bystander damage. It is uncertain whether other immune-based therapies targeting amyloid-β result in similar pathological effects to those seen in AN1792. And it is unclear how an individual’s specific genetic profile may influence deleterious or protective immune responses in Alzheimer’s disease.

Recent high profile failures of immunotherapy trials have provoked considerable reflection on the future of such approaches in Alzheimer’s disease. In this context, studies such as this, which demonstrate that immune targeting of amyloid-β 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.

Acknowledgements

This work was carried out at the NIHR Queen Square Dementia Biomedical Research unit. The authors acknowledge the support
References


