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Highlights

For better or worse: Immune system involvement in Alzheimer's disease

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ABSTRACT

In this issue of the *Biomedical Journal*, we explore the key role of the immune system in the development of Alzheimer's disease. We also learn more about the link between two disorders related to metabolic imbalances, with findings that could help to inform future screening programs. Finally, we would like to highlight some big news for our journal: the Biomedical Journal will be indexed in the Science Citation Index and receive its first official impact factor from this year.

Spotlight on reviews

For better or worse: immune system involvement in Alzheimer's disease

Alzheimer's disease and other forms of dementia are likely to become the biggest health challenge of the 21st century. Understanding the pathogenesis of the disease, and in particular, how various components of the immune system are involved in disease progression will be essential to combatting this epidemic. This issue of the *Biomedical Journal* includes two review articles [1,2] describing the unseen battleground at the front line of the pathology: how a well-intended innate immune response ultimately drives pathology and how adaptive immune responses can either put on the brakes or shift things up a gear.

Worsening in cognitive function in Alzheimer's patients correlates with the accumulation of microscopic lesions to the brain: extracellular aggregates of amyloid beta called "plaques" and intracellular aggregates of hyperphosphorylated Tau protein called "tangles". Both types of lesions are believed to be highly toxic to neurons [3,4], although how exactly these aggregates exert their devastating effects is still not completely clear. As Laurent et al. [1] describe, Tau is an incredibly complex protein to study, with 85 putative phosphorylation sites which can be phosphorylated by a staggering 30 kinases [5], not to mention a string of other post-translational modification sites. Normally a microtubule-associated protein, once hyperphosphorylated, Tau can detach from the cellular apparatus to form various conformations of insoluble intracellular tangles. However, Tau may also be actively secreted from neurons into the extracellular space [6]. A recent functional magnetic resonance imaging study of Alzheimer's patients showed that brain regions with the highest concentrations of damaging Tau were those connected functionally to one another, suggesting that Tau propagates along synapses to spread like an infection in the brain [7].

So how then does the immune system respond to this "infection"? The presence of plaques and tangles is sufficient

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to activate the brain's resident phagocytic immune cells, the microglia [8,9]. Microglia help to clear debris and toxic materials from the brain and produce inflammatory cytokines such as IL-1β and TNF-α. Initially, they appear to help to clear amyloid deposits but as the disease progresses, microglia become overwhelmed with take on a strong pro-inflammatory phenotype [10]. This creates a vicious cycle of chronic inflammation, which both promotes the accumulation of pathological variants of Tau and amyloid beta [11] and slows the replacement of damaged neurons by impairing neuronal differentiation [12]. This chronic inflammation is a hallmark of AD and polymorphisms in genes related to innate immune are linked to condition [13].

Besides activated glial cells spitting out cytokines, the brain of AD patients is also infiltrated by adaptive immune cells, called to the site of lesions by inflammatory chemoattractant molecules named chemokines. Most chemokines are overexpressed in Alzheimer's disease [14] and Martin and Delarasse [2] review their function in the pathogenesis of AD. For example, in a mouse model of AD, intra-hippocampal injection of amyloid beta peptides induced brain microvascular endothelial cells to express the chemokine receptor CCR5, enabling $CD8^+$ T cells expressing CCL3 (the ligand of the CCR5 receptor) to traverse the blood brain cell barrier [15]. In this case, T cell infiltration was pathogenic because blockade of CCR5 or CCL3 rescued cognitive impairment and CD8+ T cells have been shown to promote neuron death by releasing lytic granules containing granzyme A, B or perforin [16].

However, not all adaptive immune cells are detrimental in AD and their effect likely depends on the subset involved (Fig. 1). Strikingly, in a mouse model of AD, complete ablation of adaptive immune cells accelerated the accumulation of amyloid beta plaques and exacerbated neuroinflammation [17]. Specifically, it appeared that loss of IgG-producing B cells impaired microglial phagocytosis, thereby exacerbating amyloid deposition whereas re-introduction of IgG reversed these effects.

Thus, understanding the role of the immune system in Alzheimer's disease requires a systems approach, taking into account microglia, the diversity of peripheral immune cells and multiple other immune components all of which interact to contribute to disease pathology. "Untangling" these relationships will take some years to come.

Spotlight on original articles

Link between subclinical hypothyroidism and metabolic disease

Obesity, Diabetes, High blood pressure. The presence of these, or other conditions, together may lead to a diagnosis of metabolic syndrome (MetS), which puts individuals at a high risk of developing cardiovascular disease [18]. In this issue of the *Biomedical Journal*, Liu et al. [19] investigate how another metabolism-related disorder, subclinical hypothyroidism is linked with MetS, in a large study that could help inform national guidelines for SCH screening.

Thyroid hormones act on every cell in the body to regulate energy metabolism. Their secretion is initiated by thyroid-stimulating hormone (TSH) and controlled via a negative feedback loop. In 3–8% of the general population [20], levels of TSH are elevated even though serum thyroid hormone levels are within the normal range. This condition, called subclinical hypothyroidism (SCH), often progresses to clinically overt hypothyroidism during which the pituitary gland no longer produces sufficient levels of thyroid hormones, despite elevated TSH. There is still some debate whether SCH is associated with an increased risk of cardiovascular disease, with studies reporting both positive [21] and negative findings [22]. However, several metabolic abnormalities that are considered risk factors for cardiovascular disease are detected in patients with SCH [23]. These abnormalities are also present in individuals with MetS and the two disorders appear to show

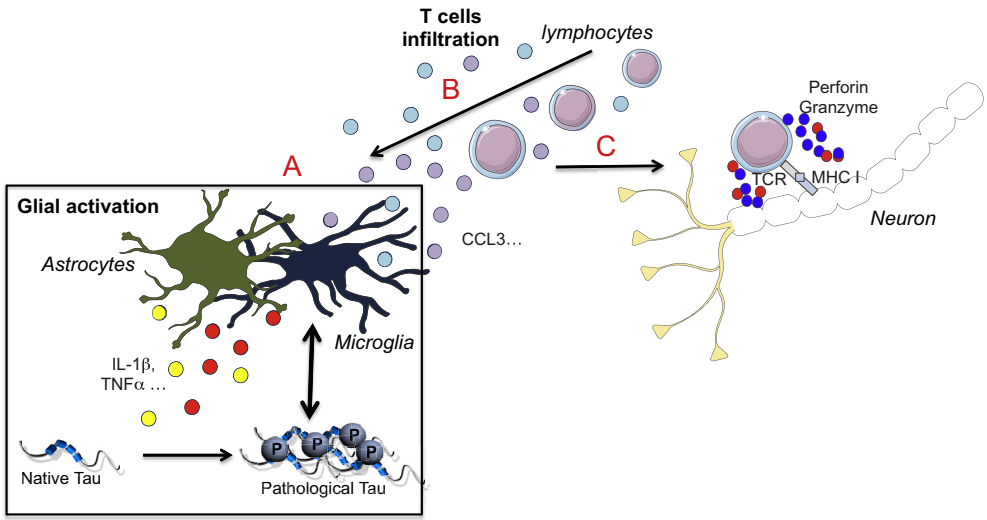

Fig. 1 T cell infiltration in tauopathies/AD. The CCL3/CCR5 pathways promotes the infiltration of lymphocyte populations to the site of brain lesions. These populations may exert beneficial or detrimental effects, depending on the subset involved. Figure kindly provided by Laurent et al. [1].

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