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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].

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So how then does the immune system respond to this "infection"? The presence of plaques and tangles is sufficient 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 substantial overlap. Here, Liu et al. [19] heat up the discussion

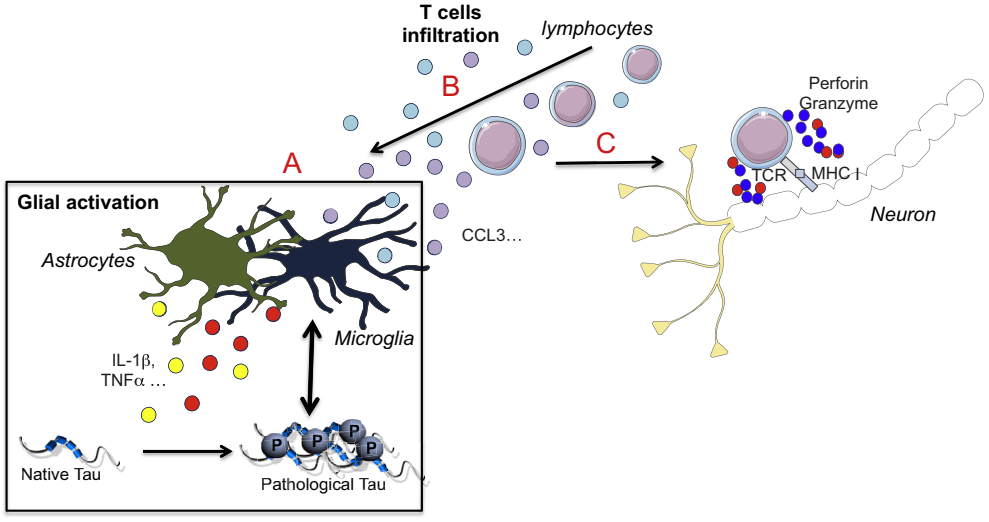

Fig. 1 T cell infiltration in tauopathies/AD. The CCL3/CCR5 pathways promotes the infiltration of lymphocyte populations to the site of brain lesions. These populations may exert beneficial or detrimental effects, depending on the subset involved. Figure kindly provided by Laurent et al. [1].

on the link between MetS and SCH by investigating the co-existence of the two conditions in a cross section of the general Taiwanese population.

Liu et al. reviewed the medical records of 22,324 people receiving an annual health check up at a Taiwanese hospital and identified 203 new cases of SCH based on TSH levels (the "SCH group"). All healthy subjects without known prior systemic disease were included in the "normal thyroid" (NG) group. For both groups, information was collected about health and lifestyle factors, clinical measurements, biochemical analysis of blood metabolites. The prevalence of metabolic syndrome was diagnosed as having at least three of five risk factors: abnormal waist circumference, high triglyceride levels, high blood pressure, and high fasting glucose concentration [24].

Body mass index was similar between the two groups. However, systolic blood pressure was significantly higher in the SCH group than in the NG group. Regarding the criteria used to diagnose MetS, the SCH were more likely to have elevated triglyceride levels than the NG group. This finding probably explains why the overall prevalence of MetS was significantly higher in the SCH group than in the NG group in both men and women, after adjustment for age and BMI. The levels of some blood metabolites, including cholesterol were significantly different between the SCH and NG group in women but not in men.

Thus, these findings reaffirm the association between SCH and MetS, but longer term follow up is required to determine the significance of detecting SCH early. These and later findings should inform national guidelines for SCH screening, and subsequent monitoring of MetS and cardiovascular risk factors in the identified cases, in particular in the elderly, who are more prone to develop SCH.

Also in this issue

News

The Biomedical Journal *receives an impact factor*
We are very pleased to announce that the Biomedical Journal will be indexed in the Science Citation Index Expanded (SCIE), a multidisciplinary index comprising 8,500 major journals. This means that from around June 2018, the Biomedical Journal will receive an official impact factor. This is an important milestone for us, and is a recognition of the contribution that our publications make towards scientific discourse in the biomedical field.

And the winner is…
Huang [25] pays tribute to Jeffery Hall, Michael Rosbash and Michael Young who were jointly awarded the 2017 Nobel Prize in Physiology or Medicine for the discovery of the circadian clock circuitry.

Review article

Probing respiration at atomic resolution
In this review, Guo et al. [26] describe how recently solved high resolution structures of components of the electron transport chain shed new light on the workings of oxidative respiration.

Original articles

Common dietary fiber may prevent gastric ulcers
In this issue, researchers once again demonstrate the power of plants to treat human ailments. *Plantago ovata* is a medicinal plant native to Western and Southern Asia. The husk and seed of the plant, referred to as psyllium, is an excellent source of dietary fiber, which in addition to relieving constipation, may also protect against damage to gastrointestinal lining [27]. Here, Bagheri et al. [28] test these reported properties in a rat model of gastric ulcers. They find that rats that had been given psyllium for four days before ulcers were chemically induced showed less damage to the intestine and liver than control animals. These findings suggest that psyllium could be used as a supplement to relieve or prevent gastric ulcers.

Risk factors for hip replacement failure
Fractures to the femoral stem remain a challenging problem in total hip arthroplasty, leading to implant failure and need for revision surgery. Here, Chang et al. [29] retrospectively analyze 251 Taiwanese patients undergoing hip replacement to identify risk factors for femoral fractures. They find that small stem size, femoral bone loss after surgery and inadequate medial calcar support were major risk factors for femoral fractures. These findings may help to improve treatment planning and follow-up of patients undergoing total hip arthroplasty.

Conflicts of interest

The author declares no conflict of interests.

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