Alzheimer’s disease (AD), dementia and cognitive impairment in later life are commonly associated with a mixed set of pathologies, which are frequently accompanied by local and systemic inflammation. Conflicting observations have made understanding the relative importance of innate and adaptive immune processes difficult in such pathologies. However, clinical trials using immunization, monoclonal antibodies or anti-inflammatory medication have produced disappointing results in treating AD [1]. This suggests a need to change focus. Recent data suggest that monocytes and microglia, the main innate immune defense of the CNS, may aid the clearance of β-amyloid (Aβ) deposits in the brain by recruiting macrophages to the affected areas. This may represent a novel strategy for intervention.

Dementia, especially in later life, is typically a complex phenotype with a spectrum of pathological changes, which together result in a progressive loss of neurons and axons, notably producing atrophy, especially in the cortex and hippocampus [2]. The major processes underlying this include AD-like pathology, which itself is characterized by an accumulation of Aβ deposits and neurofibrillary tangles. In addition, vascular lesions and Lewy bodies also occur [2]. Across this spectrum, local and systemic inflammation is a common accompaniment. Which of these processes are causal in humans is still very unclear. In recent years, there has been increasing evidence for neuroinflammation having a causative role in cognitive impairment [3]. Acute inflammatory responses to Aβ, pathogens or brain injury are damaging to local tissues, as activated microglia secrete a range of cytokines and damaging agents such as nitric oxide and reactive-oxygen species. Neuronal death would follow if the acute response continued, but a range of anti-inflammatory, neuroprotective and growth factors are also secreted by microglia, which result in the regeneration of damaged neurons and the curbing of the acute response [4].

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Alzheimer’s pathology: should peripheral monocytes and CCR2 take center stage?

“Increased CCR2 expression in the cognitively impaired may be due to an increased demand for macrophage-mediated clearance of β-amyloid, caused by impaired phagocytosis by microglia and also the self-perpetuating nature of the pro-inflammatory state of aging.”

“...bone marrow-derived microglia have a greater ability to clear β-amyloid deposits compared with brain-based microglia... Therefore, microglia may be key to understanding the contribution of neuroinflammation to cognitive impairment...”
Dysfunction of this process is proposed to be a major causative factor in cognitive decline, as persistent proinflammatory signals would result in irreversible neuronal death.

Epidemiological studies have gone some way in linking both local (the brain) and systemic inflammation [4]. Evidence suggests that circulating inflammatory biomarkers such as C-reactive protein are associated with increased risk of impairment and also decreased cerebral volume [5]. However, the causal implications remain uncertain. Intervening in the immune system with a view to modifying brain or systemic inflammation, and thereby the course of AD, has been a popular strategy, with a variety of trials, including immunization with Aβ42 [6] and the use of monoclonal antibodies against Aβ [7]. In addition, nonsteroidal and other anti-inflammatory medications have been studied, also with mixed results [8]. This may be partially explained by the observation that some individuals may have been taking such medications to combat the effects of an already activated immune system. Therefore, attributing any improvement to either the anti-inflammatory system or the drugs in question is difficult. Unfortunately, these strategies have so far yielded limited success in patients with established pathology. In response to this, some researchers have suggested that using these approaches before or at the start of the development of dementia would be more productive [9]. In addition, it could also be that a change in focus within the immune system would help for at least some types of presentation.

Macrophages play a key role in both the innate and adaptive immune systems. Macrophages originate from hematopoietic stem cells and migrate toward body tissues, where they differentiate into tissue-resident macrophages such as Langerhans cells in the epidermis, osteoclasts in the bone, Kupffer cells in the liver and microglia in the brain [10]. This differentiation is regulated by specific cytokines and other signaling pathways. Differentiated macrophages are involved in the destruction of infectious agents and tumor cells by phagocytosis, triggering inflammatory responses, presenting digested peptides/antigens to T lymphocytes and tissue repair (including that in the brain). Simard et al. have reported that bone marrow-derived microglia have a greater ability to clear Aβ deposits compared with brain-based microglia [11,12]. Therefore, microglia may be key to understanding the contribution of neuroinflammation to cognitive impairment – this has recently been reviewed by several authors [11–14].

The ability of monocytes to differentiate is essential for normal functioning. Studies in mice, and more recently in humans, have shown that monocytes in aged individuals have impaired phagocytosis and are associated with increased TNFα production [15]. Altered activation of monocytes with age may, therefore, directly contribute to neuronal degradation, as microglia are extremely sensitive to extracellular cues when surveying the brain tissue in search of pathogens and cellular debris (such as Aβ) [16,17]. Early-life exposures and other (genetic/epigenetic) factors influence monocyte senescence later in life, thus contributing to disease [18]. Activation, targeting and differentiation of monocytes is directed by a range of chemokines and chemokine receptors. One such molecule is CCR2, which stimulates monocyte migration and differentiation when a ligand is bound. CCL2, also known as MCP-1, is secreted by astrocytes (brain support cells) and resident microglia to attract monocytes (excluding neutrophils) to sites of action, following signals such as Aβ deposits or damaged neurons. CCL2 secretion is also implicated in autoimmune diseases and atherosclerosis, suggesting that dysfunctional monocyte differentiation (i.e., impaired phagocytosis and increased pro-inflammatory activity) may be key to several aging phenotypes.

Recent mouse models have also shown the critical importance of microglia in maintaining cognitive function. CCR2-deficient AD-like mice have impaired microglial accumulation and display an accelerated Alzheimer’s disease-like phenotype [19]. In other mouse models of AD, CCR2+ microglia are protective of cognitive impairment [20] and alleviate disease progression when transplanted into CCR2-deficient mice [21]. These studies indicate the importance of normal microglia functioning and migration in the maintenance of cognitive function, yet the whole story is still to be elucidated.

Mouse models of AD are regarded with caution, not least because Aβ-producing mouse models show little neuronal death, the major feature of AD in humans. Could CCL2-sensitive macrophages be key in humans? Human evidence is inherently harder to obtain due to low accessibility to the tissue of interest. We recently explored gene expression in peripheral blood
mononuclear cells in a group of nearly 700 community-living older adults [22]. In a genome-wide expression screen of 16,571 expressed transcripts, CCR2 expression emerged as the principal marker associated with cognitive function (Mini Mental State Examination scores) in older adults [22]. Individuals who scored lower on the cognitive performance tests expressed higher levels of CCR2. Interestingly, CCR2 expression was also positively associated with the AD ApoE ε4 risk haplotype.

Increased CCR2 expression in the cognitively impaired may be due to an increased demand for macrophage-mediated clearance of Aβ, caused by impaired phagocytosis by microglia and also the self-perpetuating nature of the pro-inflammatory state of aging. The fact that this association is observed in peripheral cells, not those residing in the brain itself, is consistent with CCR2 only being expressed by circulating monocytes and lymphocytes, and not by resident microglia of the brain [23]. CCR2 expression may increase in response to CCL2 because monocytes still respond, migrate and secrete inflammatory chemokines, but are not able to successfully differentiate and phagocytose Aβ. Westin et al. have reported that CCL2 levels in the cerebrospinal fluid of a subgroup of patients with prodromal AD were correlated with faster cognitive decline [24]. In this study, levels of CCL2 in cerebrospinal fluid were combined with measures of tau, phosphorylated tau and Aβ42 to predict future conversion to AD and the rate of cognitive decline in patients.

These findings, if independently replicated, suggest that peripheral macrophage functioning may be a productive avenue to explore in preventing or controlling Aβ and, perhaps, human AD pathology. Being peripheral, accessibility issues are reduced and interventions to improve macrophage migration and effectiveness in the brain may be feasible. Possible hurdles are likely to include the many maturation pathways of peripheral macrophages in diverse tissues. Nevertheless, these studies provide new insight into the precise nature of the immune deficits and responses in dementia, and a better understanding of these mechanisms is likely to be a prerequisite to specifically tailoring treatment.

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