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Immunity and Alzheimer's disease: immunological perspectives on the development of novel therapies

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Alzheimer's disease (AD) is the most common neurodegenerative disorder among older people. However, no cure or disease-modifying treatments are currently available, and the molecular and cellular mechanisms responsible for the etiology of AD remain under debate. Recent studies suggest that the immune system has a crucial role in AD pathogenesis and, thus, immunotherapy might be a promising new treatment. Here, we review the roles of the immune system in AD pathogenesis as well as recent developments in immunotherapy for AD. Furthermore, we hypothesize that age-related immune dysregulation, which might be a consequence of the age-associated chronic inflammation known as 'inflammaging', significantly contributes to AD pathogenesis. Finally, we propose various immunological mechanisms for the development of safe and effective therapies for AD.

AD is the most common neurodegenerative disease in older people. Accumulation of the amyloid beta (Aβ) protein in Aβ deposits and intracellular neurofibrillary tangles (NFT) in the brain are pathopneumonic. However, the exact mechanism of AD remains unclear, although accumulating evidence suggests a close association between the immune system and AD. Aging is the strongest risk factor for developing AD, putatively in part as a result of chronic inflammation during aging, known as 'inflammaging' [1]. Studies in recent years focused on developing effective therapies for AD have been largely immune based. Active and passive immunotherapies targeting Aβ have long been regarded as promising strategies towards Aβ clearance and cognitive protection [2]. However, immunotherapy has yet to be translated to the clinic successfully, partly owing to various immune-related adverse effects. Thus, clarification of the immunological mechanisms involved in the disease and treatment is required.

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Systemic inflammation

Inflammation in AD, specifically in the form of microglial activation, has been considered to be involved in disease pathogenesis [3,4]. That being said, inflammation can be salutary or deleterious. There are four traditional cardinal signs of inflammation: redness, swelling, heat, and pain, with a fifth sign, loss of function, also being added. Typically, this process is restorative in response to an injury or infection. Recently, the term 'inflammaging' was coined to characterize a widely accepted paradigm that aging is accompanied by a low-grade chronic upregulation of certain inflammatory responses that are not regenerative [1,5–8]. Specifically, this inflammaging differs significantly from the traditional five cardinal features of acute inflammation in that it is a low-grade, controlled, asymptomatic, chronic, and systemic state of inflammation [1]. This systemic inflammatory response is evidenced by increased serum levels of pro-inflammatory cytokines [interleukin (IL)-6, IL-15, and IL-8)] and other inflammatory biomarkers, such as coagulation factors [7]. The end result of this cycle is a chronic and systemic pro-inflammatory state where both

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tissue-damaging and -healing mechanisms operate simultaneously. Over decades, these opposing forces are likely to be crucial perpetrators of aging and age-related diseases, leading to an accumulation of subtle tissue damage. Several routes by which a systemic inflammatory response might communicate with the central nervous system (CNS) have been illustrated in recent years [9,10]. In the brain, exposure of microglial cells to systemic inflammatory signals is hypothesized to lead to a phenotypic switch of the former from their normal quiescent state to an activated state [11].

Inflammaging contributes to amyloidosis and vice versa in a feed-forward cycle [1]. Fibrillar Aβ species promote inflammation in the brain by activating the innate immune system [12–14], and intracellular oligomeric Aβ species also induce microglia activation and neuroinflammation [15]. Neuroinflammation in the brain might participate in tau-mediated neurodegeneration [16], which itself promotes the development of senile plaques.

During the early stages of AD, transient microglia activation might be beneficial by phagocytizing Aβ. Furthermore, it has been shown that there is a significant correlation between activation of microglia and reduction of plaque levels [17]. However, this is a double-edged sword: upon activation, microglia exhibit upregulated surface molecules, such as CD14 and major histocompatibility complex (MHC) molecules, pro-inflammatory cytokines, and their corresponding receptors profile, which might be the drivers of the local secretion of complement components and subsequent neuronal degeneration [18].

Complement system and its regulators

As integral components of amyloid plaques and cerebral vascular amyloid in AD brains, complement proteins have dual roles in disease pathogenesis and progression (Fig. 1a) [19]. Levels of mRNA for complement proteins, especially C1q and C9, are upregulated in the affected areas of AD brains [20]. Direct binding of fibrillar Aβ40 and Aβ42 to C3 and the globular heads of C1q activates both the alternative pathway and classical pathway *in vitro* [21]. Interactions between Aβ and C1q lead to increased amyloid aggregation, which additionally activates the complement system in AD brains [21]. The interactions referred to above trigger the covalent binding between C3b and Aβ, and subsequent

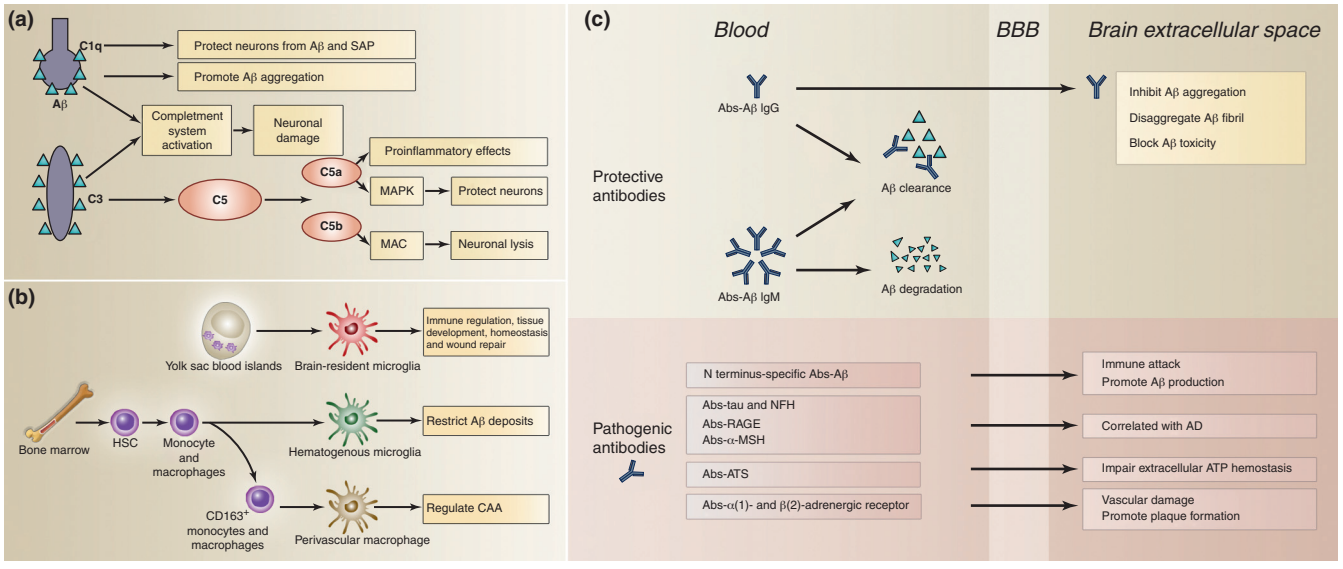

FIGURE 1

(a) Roles of complement system in Alzheimer's disease (AD). Complement proteins have dual roles in the pathogenesis of AD. Direct binding of fibrillar Aβ to C3 and the globular heads of C1q activates both the alternative pathway and classical pathway. Interactions between Aβ and C1q increase amyloid aggregation, which additionally activates the complement system in AD brains. Covalent binding of C3b and Aβ induces subsequent cleavage of C5 into two fragments, the inflammatory factor C5a (which exerts proinflammatory effects and activates MAPK) and MAC formation mediator C5b (which induces neuronal lysis). Neurons are particularly susceptible to complement-mediated death owing to their low-level expression of CRegs. (b) Roles of microglia in AD. Microglia functions depend on two factors; subclass and activation state. Microglia in AD have three subclasses: brain-resident microglia, hematogenous microglia, and perivascular macrophages. Resident microglia originate from progenitors in the embryonic yolk sac. Hematogenous microglia originate from monocytes and/or macrophages in the bone marrow. Perivascular macrophages originate from $CD163^{+}$ monocytes and/or macrophages in the bone marrow. Resident microglia have some basic functions, such as maintaining hemostasis of the brain and wound repair. Hematogenous microglia have important roles in restricting Aβ deposition, whereas perivascular macrophages regulate CAA. Microglia have two activation states in AD: classical activation (proinflammatory) and alternative activation (anti-inflammatory). Each microglia population has its activation state, thus making it hard to clarify the complexity of microglia functions in AD. (c) Antibody profiles in AD. Brain-reactive antibodies include pathogenic antibodies and protective antibodies. The latter include Abs-Aβ and Abs-CAPS. Abs-Aβ are present in both IgG and IgM forms. In the periphery, these antibodies are responsible for Aβ binding and clearance. A class of catalytic IgMs has the capacity to induce Aβ degradation. Antibody-mediated peripheral clearance of Aβ induces its efflux from the brain, where Abs-Aβ inhibit Aβ aggregation, disaggregate Aβ fibrils, and block Aβ toxicity. Pathogenic antibodies include N terminus-specific Abs-Aβ, Abs-tau/NFH, Abs-RAGE, Abs-α-MSH, Abs-ATS, Abs-α(1)-adrenergic and β(2)-adrenergic receptors. *Abbreviations*: Aβ, amyloid β; Ab, antibody; ATS, ATP synthase; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; CAPS, cross-linked Aβ protein species; CReg, complement regulator; Ig, immunoglobulin; MAC, membrane-attack complex; MAPK, mitogen-activated protein kinase; α-MSH, α-melanocyte-stimulating hormone; NFH, heavy neurofilaments; RAGE, receptor of advanced glycation endproducts.