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Review

The role of the immune system in Alzheimer disease: Etiology and treatment

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ABSTRACT

The immune system is now considered a major factor in Alzheimer Disease (AD). This review seeks to demonstrate how various aspects of the immune system, both in the brain and peripherally, interact to contribute to AD. We highlight classical nervous system immune components, such as complement and microglia, as well as novel aspects of the peripheral immune system that can influence disease, such as monocytes and lymphocytes. By detailing the roles of various immune cells in AD, we summarize an emerging perspective for disease etiology and future therapeutic targets.

1. Introduction

The immune system is composed of an army of cells whose duty is to protect us from invasion by external pathogens. Hidden behind the walls of the blood brain barrier, the central nervous system (CNS) was previously thought to act independently in protecting the brain from disease. Mounting evidence has erased this ideology and demonstrated that dysfunction in the immune system may be a primary factor in neurodegenerative disease, such as Alzheimer Disease (AD).

In AD, patients are characterized by the pathological accumulation of toxic proteins in the brain such as amyloid-beta peptide (Aβ) and tau, with eventual cognitive decline and death (Hardy and Selkoe, 2002; Schöll et al., 2016). Neuropathological examination of AD patients identifies dense protein aggregates comprising extracellular Aβ plaques and intracellular neurofibrillary tangles. Tau is a microtubule-associated protein that plays an important role in Aβ toxicity and brain levels correlate strongly with the cognitive decline seen in AD patients (Brier et al., 2016; Götz et al., 2001; Schöll et al., 2016). However, tau is proposed to be downstream of Aβ in AD pathogenesis and, as such, this review will focus on the Aβ peptide as the initiating pathological factor in AD (Hardy and Selkoe, 2002; Roberson et al., 2007). Accumulation of Aβ peptide occurs both intracellularly and extracellularly and can aggregate to form insoluble plaques (LaFerla et al., 2007). This accumulation is thought to be one of the initiating events and occurs partially through dysfunction of clearance pathways (Mawuenyega et al., 2010; Potter et al., 2013). The Aβ peptide is produced from sequential cleavage of the transmembrane amyloid precursor protein by β- and γ-secretase, and can range in length from 36 to 43 amino acids (Vassar et al., 1999). Of these various forms, the most abundant are Aβ40 and Aβ42, with the latter being more potent in seeding amyloid formation (Jarrett et al., 1993). Once produced, the Aβ peptide can form oligomers which inhibit long-term potentiation and mediate Aβ toxicity (Ahmed et al., 2010; Walsh et al., 2002). For decades, therapies have been developed that directly target Aβ production or aggregation, however, all have failed to slow disease progression (Cummings et al., 2014). Several factors may have hindered the effectiveness of these potential therapeutics. For example, a phase 3 trial of semagacestat, a general γ-secretase inhibitor, was halted due to associations with worsening cognitive function and skin cancer development (Doody et al., 2013). However, this toxicity might have resulted from the non-specific inhibition of Notch signalling, highlighting the need for more specific drug candidates (De Strooper, 2014). Furthermore, lack of drug entry to the brain, timing of intervention, and level of amyloid load in enrolled patients are all factors considered to potentially affect clinical trial success (Selkoe, 2011). Therefore, Aβ remains a strong candidate as a therapeutic target however the failure of multiple therapeutic trials suggests the need to consider other targets as well (Cummings et al., 2014).

In this regard, the immune system has emerged as a key player in disease etiology and pathogenesis. In this review, we highlight novel discoveries featuring the role of both central and peripheral immune systems in clearing Aβ peptide and how immune dysfunction may contribute to AD etiology. Specifically, we will focus on immune contributors comprising complement, microglia, and peripheral immune cells including monocytes and lymphocytes. We will not discuss other immune contributors, including toll-like receptors or the contribution

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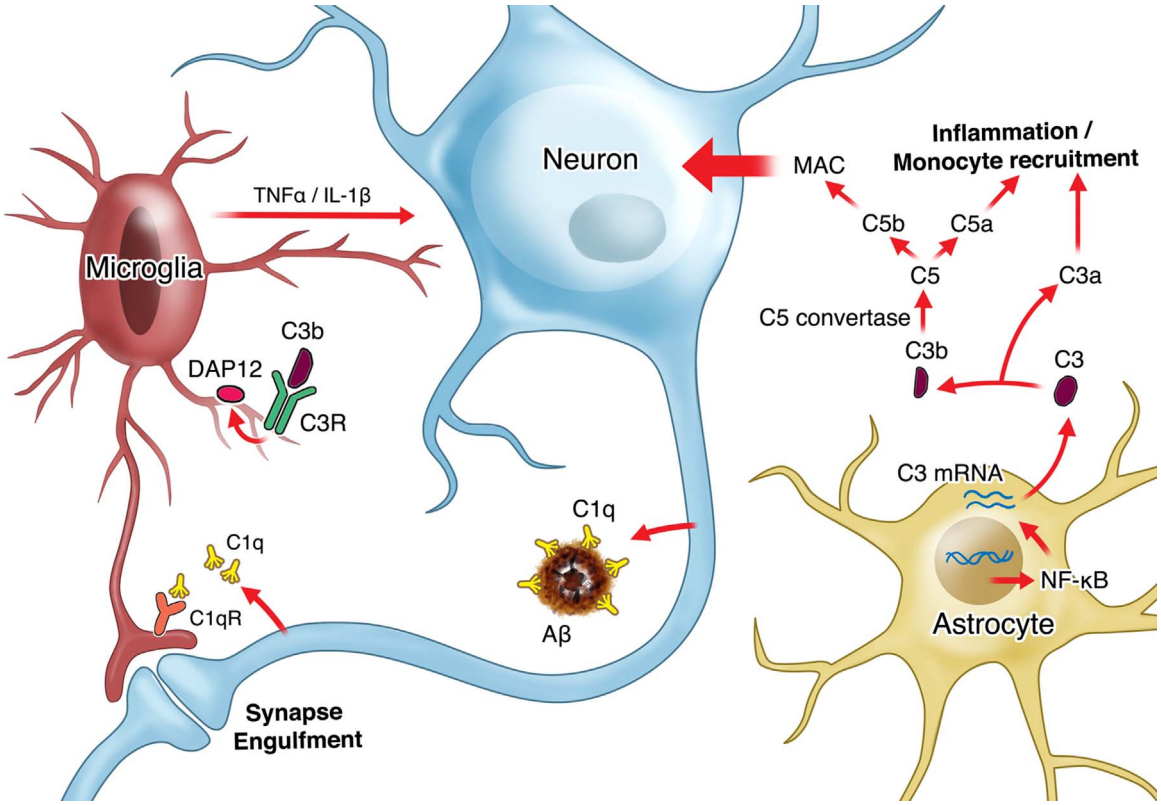

Fig. 1. Cellular Mechanisms of Complement Activation and Inflammation in Alzheimer Disease. During AD, toxic amyloid-beta (Aβ) species accumulate to form insoluble plaques. This results in complement activation, including C1q secreted by neurons and C3 produced by astrocytes. C1q can bind directly to Aβ as well as activate its respective receptor, C1qR, on microglia. Activation of C1qR results in synaptic pruning and phagocytosis by microglia. In astrocytes, inflammatory signalling initiated by the transcription factor NF-κB leads to production of C3 mRNA and protein. Once secreted, C3 is activated through cleavage into C3b and C3a, which lead to formation of the membrane attack complex (MAC) complex and inflammation/monocyte recruitment, respectively. C3b can also activate the C3 receptor (C3R) on microglia, leading to DAP12 activation and inflammatory signalling.

of other brain cell types, such as astrocytes, as they have previously been reviewed in depth (De Strooper and Karran, 2016; Su et al., 2016). Together, this research illustrates a comprehensive model of immune system involvement in AD, thus offering novel insights and potential therapeutic targets.

2. Complement: overwhelming the enemy

Complement proteins form part of the innate immune system that function as a first line of defense to maintain homeostasis. Complement activation can occur through either the classical, alternative, or lectin pathways (Emmerling et al., 2000; Sarma and Ward, 2012). These pathways differ based on their mode of activation, where: antibody bound to antigen or a solid surface activates the classical pathway; mannose moieties on bacteria activate the lectin pathway; and spontaneous hydrolysis of the complement protein C3 or binding of C3b to microbes activates the alternative pathway (Joshua et al., 2006; Wyss-Coray and Rogers, 2012). All these pathways lead to formation of a C3 convertase that hydrolyzes C3 into effector C3a and C3b molecules (Fig. 1). C3a is a potent anaphylatoxin that regulates further immune responses such as inflammation, while C3b opsonizes targets and promotes formation of the membrane attack complex (MAC, formed from C5b-C9) (Emmerling et al., 2000). The effector complement products carry out additional functions through cell surface receptor binding, important for this review to lymphocytes and to neurons (Arakelyan et al., 2011; Hazrati et al., 2012). One such receptor is complement receptor 1 (CR1), of which the CR1-S allele has been linked to an increased risk of AD (Lambert et al., 2009).

2.1. Harms of complement

In the healthy brain, astrocytes and neurons produce complement proteins that are essential for synaptic pruning and neural circuit maintenance (Fig. 1; Bahrini et al., 2015; Emmerling et al., 2000; Levi-Strauss and Mallat, 1987; Schafer et al., 2012). In AD, there is evidence that the complement pathway is up-regulated and results in neuronal atrophy. Initial studies in AD patients demonstrated *in vivo* activation of C1q (classical pathway) by the Aβ peptide (Rogers et al., 1992). C1q was found to be tightly associated with Aβ plaques and caused surrounding neuronal atrophy through microglial engulfment (Hong et al., 2016; McGeer et al., 1989; Rogers et al., 1992). In AD mice, C1q associates with synapses prior to noticeable plaque deposition, suggesting early activation in disease (Hong et al., 2016). Furthermore, inhibiting the C1q pathway (using either antibody treatment or gene knockout) in wild-type mice reduced synapse loss after oligomeric-Aβ injection. These results suggest that inhibiting C1q activation during the prodromal phase of disease may prove effective in preventing cognitive decline, via a reduction of synapse pruning (Jack et al., 2013; Schöll et al., 2016). However, C1q presents greater challenges as a therapeutic target compared to current complement targets (see 1.2.3 Complement-Targeted Therapy). One reason is due to its physiological function in clearing apoptotic cells, where individuals with a C1q deficiency also have high penetrance of lupus (Macedo and Isaac, 2016). Thus, specifically disrupting C1q in the brain may prove more promising.

In addition to C1q, the C3 protein has emerged as another important complement protein in AD (Lian et al., 2015). Knock-out of C3 (downstream to C1q activation) partially rescued synapse loss in the APP/PS1 AD model at both young (4 month) and older (16 month) time points (Hong et al., 2016; Shi et al., 2017). However, lack of C3 did significantly increase Aβ load suggesting part of the plaque toxicity is