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Opinion

Innate Immunity Fights Alzheimer's Disease

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Alzheimer's disease (AD) is the most common age-related dementia. Pathognomonic accumulation of cerebral β-amyloid plaques likely results from imbalanced production and removal of amyloid-β (Aβ) peptides. In AD, innate immune cells lose their ability to restrict cerebral Aβ accumulation. At least in principle, mononuclear phagocytes can be enlisted to clear Aβ/β-amyloid from the brain. While the classical focus has been on dampening neuroinflammation in the context of AD, we hypothesize that rebalancing cerebral innate immunity by inhibiting actions of key anti-inflammatory cytokines returns the brain to a physiological state. Recent experiments demonstrating beneficial effects of blocking anti-inflammatory cytokine signaling in preclinical mouse models provide supportive evidence. This concept represents an important step toward innate immune-targeted therapy to combat AD.

Trends

Recent GWAS have identified a cluster of AD risk alleles belonging to core innate immune pathways that modulate phagocytosis.

Functional polymorphism within the *IL10* gene has been linked to increased risk for LOAD in certain populations, and IL-10 signaling is abnormally elevated in AD patient sera and brains.

Inhibiting IL-10/STAT3 signaling dramatically mitigates AD-like pathology, while brain overexpression of IL-10 aggravates Aβ deposition in mouse models of cerebral amyloidosis.

Elevated IL-10 signaling reduces Aβ clearance by mononuclear phagocytes and licenses ApoE–Aβ binding.

IL-10/STAT3 pathway blockade enhances microglial Aβ phagocytic activity and decreases ApoE expression, thereby mitigating ApoE–Aβ binding that retards Aβ phagocytosis.

Blocking anti-inflammatory mediators represents a promising future treatment approach for AD.

The Central Role of Cerebral Innate Immunity in AD

AD currently affects more than 5 million in the USA, and newly diagnosed cases in this country are expected to reach 10–15 million by 2050 [1], highlighting the major impact of the disease on public health. AD is characterized by intracellular neurofibrillary tangles (composed of misfolded tau protein), extracellular β-amyloid accumulation (consisting of β-pleated sheet conformers of insoluble Aβ peptides), and neuroinflammation, earmarked by reactive astrocytes and brain-resident monocytes (microglia) surrounding β-amyloid deposits [2]. While several preventative and therapeutic strategies are being pursued, an effective treatment for AD does not yet exist.

A widely accepted theory of AD pathogenesis holds that imbalanced production versus clearance of Aβ peptides precipitates disease. In recent decades, the major therapeutic approach has been aimed at reducing cerebral Aβ production. Specifically, drugs have been designed to inhibit the β- and γ-secretases responsible for Aβ production from amyloid precursor protein (APP) endoproteolysis. However, the secretases cleave a variety of other substrates, and lack of specificity has been implicated in adverse events [3,4]. An alternative strategy that is gaining momentum is targeting the other side of this equation: Aβ clearance. This concept is rooted in the notion that failure of the innate immune system to clear Aβ, rather than overproduction of the peptides, is likely to be the etiologic culprit in sporadic AD [5]. Indeed, extensive microglial recruitment to plaques in human AD is accompanied by very little, if any, Aβ phagocytosis [5,6], and occurs with increased production of proinflammatory cytokines that associate with cognitive decline [7]. A parsimonious conclusion from these findings is that innate immune cells (including both CNS-resident microglia and peripheral mononuclear phagocytes) lose their physiologic ability to restrict cerebral Aβ accumulation and switch into a pathological state [2,7–10]. It remains unclear at what stage, and to what degree, a switch from 'good' to 'bad' microglia occurs, and whether this is reversible.

The most common form of the disease, sporadic or late-onset AD (LOAD), has a complex etiology that includes genetic, environmental, and lifestyle risk factors. Recent genome-wide

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association studies (GWAS) have identified a cluster of AD risk alleles belonging to core innate immune pathways [11]. A common phenotype linking these risk alleles is modulation of phagocytosis [12–15]. Consequently, the regulation of inflammation and the cerebral innate immune response has become a major area of interest, both in terms of understanding AD etiology and for developing new therapeutic approaches. However, inconsistent results reported for non-steroidal anti-inflammatory drugs (NSAIDs) in AD prevention [16–19] imply that a more 'surgical' approach targeting select immune pathways is needed. However, refining therapeutic targets has been difficult. This is because activated microglia express a multitude of inflammatory cytokine and chemokine receptors in the context of AD-like pathology [20–24], and myriad cytokines and chemokines have been detected in AD patient brains and cerebrospinal fluid (CSF) [25–27].

While proinflammatory mediators have garnered the most attention in this regard, the cardinal anti-inflammatory regulators transforming growth factor-β1 (TGF-β1) [28] and interleukin-10 (IL-10) [25] are also elevated in human AD, raising a putative pathogenic role for these cytokines. Further, a functional polymorphism within the *IL10* gene has been linked to increased risk for LOAD in some [29–32], but not all populations [33–35]. While an initial report suggested that the *IL10* AD risk allele was associated with reduced IL-10 expression in healthy control plasma [32], these authors did not relate *IL10* polymorphism to IL-10 activity in AD patients. This is important because CNS IL-10 abundance is increased in several neurological diseases including stroke, multiple sclerosis, meningitis, and AD [36]. Further, we and others have shown that the IL-10 signaling pathway is abnormally elevated in AD patient sera and brains [25,37]. The earlier conclusion that IL-10 downregulation is a risk factor for AD is at odds with recent integrative genomic evidence showing increased IL-10 signaling in AD brains [38,39]. Clearly, further work is necessary to understand the *IL10* allele–AD risk relationship.

Contrary to the notion that all forms of inflammation are deleterious in the context of AD, awareness is being raised to the concept that blocking immunosuppressive pathways can be beneficial. In this regard, we demonstrated that TGF-β–Smad 2/3 signaling inhibition in peripheral macrophages caused brain infiltration of these cells and restriction of cerebral β-amyloidosis. Genetic blockade of the TGF-β signaling pathway led to dramatically elevated central and peripheral IL-10 abundance [40–42], prompting investigation into the possible contribution of IL-10 signaling in the context of AD. Indeed, new studies show that inhibiting IL-10/STAT3 signaling dramatically mitigates AD-like pathology [37], while brain overexpression of *Il10* produces complementary effects [43]. These lines of evidence have led us to theorize that 'rebalancing' activation of the innate immune system, as opposed to shutting it off completely, represents a novel AD therapeutic approach.

IL-10 signaling Suppresses Cerebral β-Amyloid Clearance

IL-10 is a prototypical anti-inflammatory cytokine that is produced by and regulates activation of T cells, dendritic cells, peripheral macrophages, and CNS-resident microglia [44,45]. Signaling is elicited by binding of IL-10 to its cognate receptor (IL-10R), which triggers phosphorylation of Janus kinase 1 (JAK1) that, in turn, phosphorylates signal transducer and activator of transcription 3 (STAT3). STAT3 homodimerizes and translocates to the nucleus, where it transactivates genes including suppressor of cytokine signaling 3 (SOCS3). SOCS3 is then phosphorylated by Src family kinases and interacts with receptors for inflammatory cytokines, targeting them for ubiquitin-mediated degradation. Activation of the IL-10 pathway referees essential functions of monocytes including phagocytosis, cytokine production, expression of costimulators, and antigen presentation. The *modus operandi* of this cytokine is to suppress overly-exuberant inflammatory responses by blocking the action of proinflammatory cytokines [45,46].