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Innate Immunity Fights Alzheimer's Disease

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Abstract

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 pre-clinical mouse models provide supportive evidence. This concept represents an important step toward innate immune targeted therapy to combat AD.

Keywords

amyloid; apolipoprotein E; immunotherapy; interleukin-10; microglia; phagocytosis

1. The central role of cerebral innate immunity in Alzheimer's disease

Alzheimer's disease (AD) currently affects more than 5 million Americans, and newly diagnosed cases are expected to reach 10–15 million in the U.S.A. by 2050 [1], highlighting the major impact of the disease on public health. AD is characterized by intracellular neurofibrillary tangles (comprised of misfolded tau protein), extracellular amyloid-β (Aβ) 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 a number of 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 resultant adverse events [3,4]. An alternative strategy that is gaining momentum is targeting the other side of the 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 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 pro-inflammatory 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 association studies (GWAS) have identified a cluster of AD risk alleles belonging to core innate immune pathways [3,4,11]. A common phenotype linking these risk alleles is modulation of phagocytosis [12–15]. Consequently, regulation of inflammation and the cerebral innate immune response have become major areas 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) and 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 CSF [25–27].

While pro-inflammatory mediators have garnered the most attention in this regard, the cardinal anti-inflammatory regulators transforming growth factor-beta 1 (TGF-β1) [28] and interleukin-10 (IL-10) [25] are also elevated in human AD, raising a possible 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], those authors did not relate *IL10* polymorphism to IL-10 activity in AD patients. This is important, because CNS IL-10 abundance is increased in 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 down-regulation 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 putative contribution of IL-10 signaling in the context of AD. Indeed, new studies show that inhibiting IL-10/STAT3 signaling dramatically mitigates Alzheimer-like pathology [37], while brain overexpression of *Il10* produces complementary effects [43]. This has 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.

2. Interleukin-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 pro-inflammatory cytokines [45,46].

In the central nervous system, IL-10 expression is increased in response to major neurological diseases including stroke, multiple sclerosis, meningitis, and AD [47]. Increased IL-10 abundance in AD patients' sera and brains has been reported [25,48], and we recently showed that all canonical IL-10 pathway signaling elements (*i.e.*, IL-10R1 and downstream JAK1, phospho-JAK1 (pJAK1), STAT3, phospho-STAT3 and SOCS3) are overly abundant in AD hippocampi compared to age-matched, non-demented controls [37]. These results led us to hypothesize that elevated IL-10 signaling in the AD brain blocks physiological innate immune recognition, phagocytosis, and clearance of cerebral β-amyloid.

To test this hypothesis, effects of IL-10 modulation were independently examined in three different mouse models (TgCRND8, Tg2576 and APP/PS1) exhibiting cortical and hippocampal Aβ plaques, gliosis, synaptic deficits, and associated cognitive impairment. Cerebral *Il10* overexpression using adeno-associated virus in TgCRND8 and Tg2576 mice exacerbated Aβ plaque number and size [43], while deletion of *Il10* reduced the severity of cerebral amyloid angiopathy and amyloidosis in APP/PS1 mice [37]. In neither experimental scenario did changes in IL-10 abundance affect APP metabolism or Aβ production; suggesting that IL-10-dependent alteration of cerebral amyloid deposition is owed to Aβ clearance [37,43]. Further support came from *in vitro* evidence showing that the IL-10/STAT3 pathway modulates microglial Aβ phagocytosis. Specifically, recombinant IL-10 treatment of primary microglial cultures promoted nuclear translocation of downstream STAT3 [37] and decreased phagocytosis of Aβ40 [43] and Aβ42 microaggregates [37].

However, IL-10 had no effect on Aβ40 or Aβ42 astrocytic uptake [43]. Importantly, genetic ablation of *Il10* or *Stat3* in microglial cultures increased Aβ42 uptake into phagolysosomes [37].

Essential validation of these observations came from *in vivo* experiments, where *Il10* deficient APP/PS1 mice presented increased astrocytosis and reactive microglia [37]. Specifically, β-amyloid plaques, which appeared more diffuse than typical dense-cored plaques, were associated with greater numbers of monocytes compared with *Il10* sufficient APP/PS1 mice [37]. Cell number was not the only monocyte phenotype that *Il10* deficiency modified; intriguingly, mononuclear phagocytes infiltrating Aβ deposits expressed CD68 (a cell surface, phagolysosomal and endosomal marker) [49]. These striking results suggest that *Il10* deficient monocytes are prone to penetrate β-amyloid plaques and to phagocytose Aβ deposits [37]. Finally, cutting-edge quantitative three-dimensional *in silico* modeling (q3DISM) allowed us to quantitate Aβ phagocytosis *in vivo* (Figure 1). Results from this line of investigation confirm that *Il10* deficient monocytes are more efficient Aβ phagocytes versus *Il10* sufficient cells. Altogether, these data suggest that 1) endogenous overproduction of IL-10 causes defective innate immune Aβ phagocytosis leading to plaque build-up, and 2) inhibition of the IL-10/STAT3 pathway returns the system to homeostasis; thereby enabling cerebral Aβ clearance.

3. Beneficial effects of blocking IL-10/STAT3 signaling in the context of Alzheimer's disease

A key question is whether the effects of IL-10 modulation are restricted to cerebral amyloidosis or more broadly impact Alzheimer-like pathology. The first hint of this came from *Il10* overexpression, which decreased synaptic protein abundance and worsened cognitive impairment [43]; whereas *Il10* deletion led to stabilization of synaptic health and mitigated behavioral deficits [37]. These important findings indicate that the specific innate immune activation profile is of utmost importance for determining damaging vs. beneficial responses [10,41,50–52]. If left unchecked–or if overly repressed–cerebral innate immunity can perpetrate neuronal damage (directly or via Aβ); but if controlled, the system can be harnessed to clear the brain of damaging Aβ species without coming at the cost of bystander neuronal injury.

The notion that monocyte activation states are clearly divided between a pro-inflammatory M1 phenotype and a pro-phagocytic M2 phenotype has become obsolete [9,10,50]. Rather, microglia can assume a continuum of activation states characterized by expression of intersecting markers [10,53]. This concept was corroborated by analysis of *Il10* dependent inflammatory genes via RNAseq [37] or NanoString [43]. In transgenic mouse models of cerebral amyloidosis, genes that were altered by *Il10* overexpression or *Il10* deficiency were further interrogated for immune-related function(s) [37,43]. Gene pathways were largely overlapping between these two opposing manipulations, and were responsible for: phagocytosis, chemoattraction/chemokine signaling, innate immune regulation (*e.g.*, toll-like receptor signaling), inflammation and the acute phase response (*e.g.*, LXR/RXR pathway), Aβ interaction, dendritic cell maturation and T cell activation, the protein complement system, communication between innate and adaptive immune cells, and IL-10

signaling itself (Figure 2). In both reports, mononuclear phagocyte activation state was neither absolutely M1 nor M2; rather, unique activation phenotypes fell within the continuum between M1 and M2 extremes [10,37,43]. Importantly, *Il10* deficient APP/PS1 animals exhibited polarization of microglial activation away from a traditional M2 state but had increased phagocytic capacity, confirming–yet again–how the M1/M2 dichotomy is not a useful classification system [10,37,50,52].

4. Intersection between IL-10 and apolipoprotein E pathways

Of the differentially expressed genes identified by large-scale expression profiling in *Il10* targeted cerebral amyloidosis mouse models, one hit stood out: apolipoprotein E *(Apoe)* [37,43]. This is because the ε4 allele of *APOE* is the strongest genetic susceptibility factor for human AD. Strikingly, *Il10* overexpression increases cerebral *Apoe* mRNA abundance [43], while *Il10* deficiency reduces *Apoe* expression [37] in mouse models. These findings are particularly interesting, because human ApoE isoform-specifically regulates Aβ metabolism, aggregation, deposition and clearance [54,55], and cerebral vasotonus [56]. Knocking in human *APOE4* into mouse models of cerebral amyloidosis exacerbates microglial inflammation and Aβ deposition [57], while *APOE2* promotes clearance of preexisting deposits [58].

Remarkably, cerebral *Il10* overexpression increases murine APOE association with insoluble amyloid and promotes direct ApoE- Aβ interaction that inhibits phagocytosis of the complex [43]. Additionally, treatment of microglial cultures with Aβ bound to human ApoE isoforms reveals isoform-specific reduction of Aβ phagocytosis (E4 > E3 > E2) [37]. These results are particularly significant in light of previous studies showing ApoE isoform-dependent enhanced Aβ oligomerization and fibril stabilization [59–62], and Aβ clearance by glial cells can be negatively affected by ApoE-Aβ association [63]. Strikingly, this result mirrors the well-established relative risk of ApoE for human AD (E4 > E3 > E2) [64]. Importantly, *Il10* deficiency rescues impaired Aβ phagocytosis by ApoE3 [37]. Altogether, these results provide the basis for mechanistic intersection between IL-10 signaling and the greatest genetic risk factor for LOAD: *APOE*.

5. Conclusions

In this Opinion, we have illustrated the complex interplay between anti-inflammatory factors and AD pathoetiology. Specifically, evidence is presented that innate immunity is pathologically repressed by anti-inflammatory factors in the AD brain; obviating β-amyloid plaque phagocytosis and clearance. Specifically, elevated IL-10 signaling in the context of cerebral amyloidosis promotes a pathological form of cerebral innate immunity that licenses ApoE-Aβ binding and reduces Aβ clearance by mononuclear phagocytes. Therefore, IL-10 acts via dual mechanisms to promote cerebral amyloidosis–on the one hand, by retarding Aβ phagocytosis, and on the other, by promoting ApoE-Aβ co-deposition (Figure 3).

Modulating IL-10/STAT3 signaling has proven effective in other therapeutic settings [65,66], and rebalancing cerebral innate immunity to promote beneficial neuroinflammation may be more efficacious than anti-inflammatory therapy for AD. However, several key issues need to be explored before moving forward and enlisting the innate immune system to

clear Aβ as a therapeutic modality (see Outstanding Questions). First and foremost, whether activated monocytes in AD patients' brains arise from infiltrating peripheral macrophages or expansion of resident microglia remains unknown. As discussed above, in late stages of AD (*i.e.*, after amyloidosis is established) microglia are inefficient Aβ phagocytes [5,7]. However, several studies have shown that peripheral macrophages infiltrating the brain in mouse models of cerebral amyloidosis home to amyloid plaques and effectively clear Aβ [40,67,68]. To therapeutically target innate immunity in AD, it is therefore crucial to delineate the relative contribution(s) of central vs. peripheral mononuclear cells. Pan-inhibition of IL-10 signaling would not be judicious, because IL-10 is critically important to militate against peripheral inflammatory diseases (*e.g.*, rheumathoid arthritis, psoriasis, and Crohn's disease). Yet, it deserves mentioning that IL-10-based therapeutics have already proven effective in aging populations [69]. The observation that IL-10 can modulate ApoE-Aβ interaction is original, and has major implications for therapeutic strategies. A deeper understanding of the intersecting points between IL-10 and ApoE in the context of AD is needed. It is important to note that genetic blockade of both major anti-inflammatory pathways: TGF-β-Smad 2/3 [40] and IL-10/STAT3 [37], results in an innate immune shift towards cerebral amyloid clearance. This exciting new research focus on blocking anti-inflammatory pathways is eventually expected to lead to safe and effective AD treatment.

Outstanding Questions

- Do activated monocytes in AD patients' brains arise from infiltrating peripheral macrophages or expansion of resident microglia? Is it possible to specifically target peripheral monocytes or CNS microglia in LOAD?
- Are hematogenous monocytes more efficient Aβ phagocytes than brain-resident microglia? If so, what is the molecular mechanism for this important difference?
- What is the mechanism underlying increased LOAD risk incurred by the polymorphic *IL10* allele? Does the *IL10* polymorphism affect IL-10 signaling independently of its action on reducing IL-10 expression?
- Does IL-10 retard monocyte clearance of Aβ/β-amyloid, and therefore contribute to amyloid deposition in AD? What inflammatory genes does IL-10 signaling directly alter to influence monocyte Aβ phagocytosis and clearance?
- Can we determine more specific therapeutic targets that are downstream of the IL-10 pathway? At what stage would blocking IL-10 signaling be most effective against LOAD?
- How does IL-10 modulate ApoE-Aβ interaction, and does association of ApoE with lipids influence formation of this complex? Do lipids impact ApoE isoform-specific alteration of Aβ phagocytosis?
- Does *Il10* deletion mitigate Alzheimer-like pathology in *Apoe*-deficient mice, or in chimeric mice expressing human ApoE2, ApoE3, or ApoE4? Answering this important question could pave the way to understand the specific role(s) of

ApoE isoforms in *Il10* deficient mouse models of cerebral amyloidosis, and in the human disease.

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Trends Box

- 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 Alzheimer-like pathology, while brain overexpression of *Il10* 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.

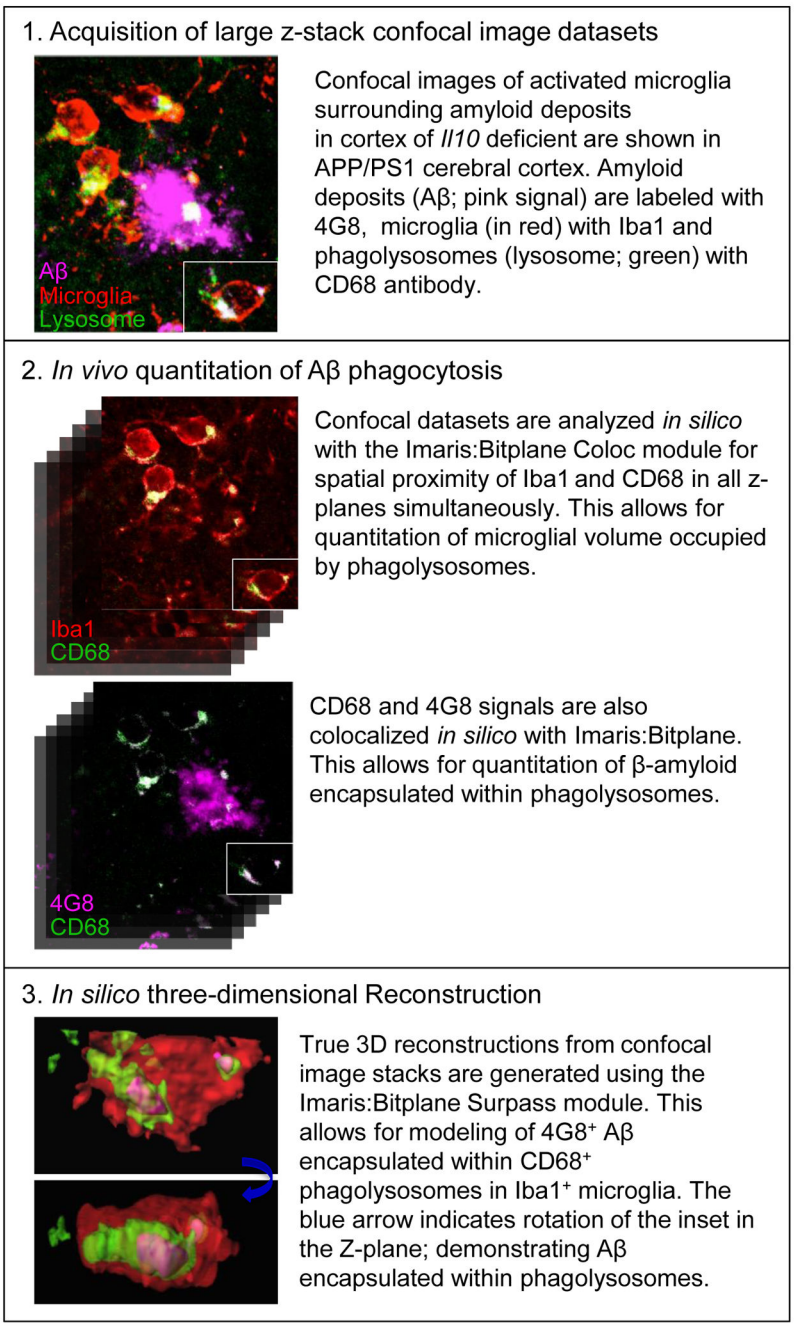

Figure 1. Methodology for quantitative 3D *in silico* modeling (q3DISM) of Aβ phagocytosis

This multi-stage q3DISM technique is depicted. This cutting-edge technology allows for true 3D quantitation of Aβ phagocytosis *in vivo* by mononuclear phagocytes.

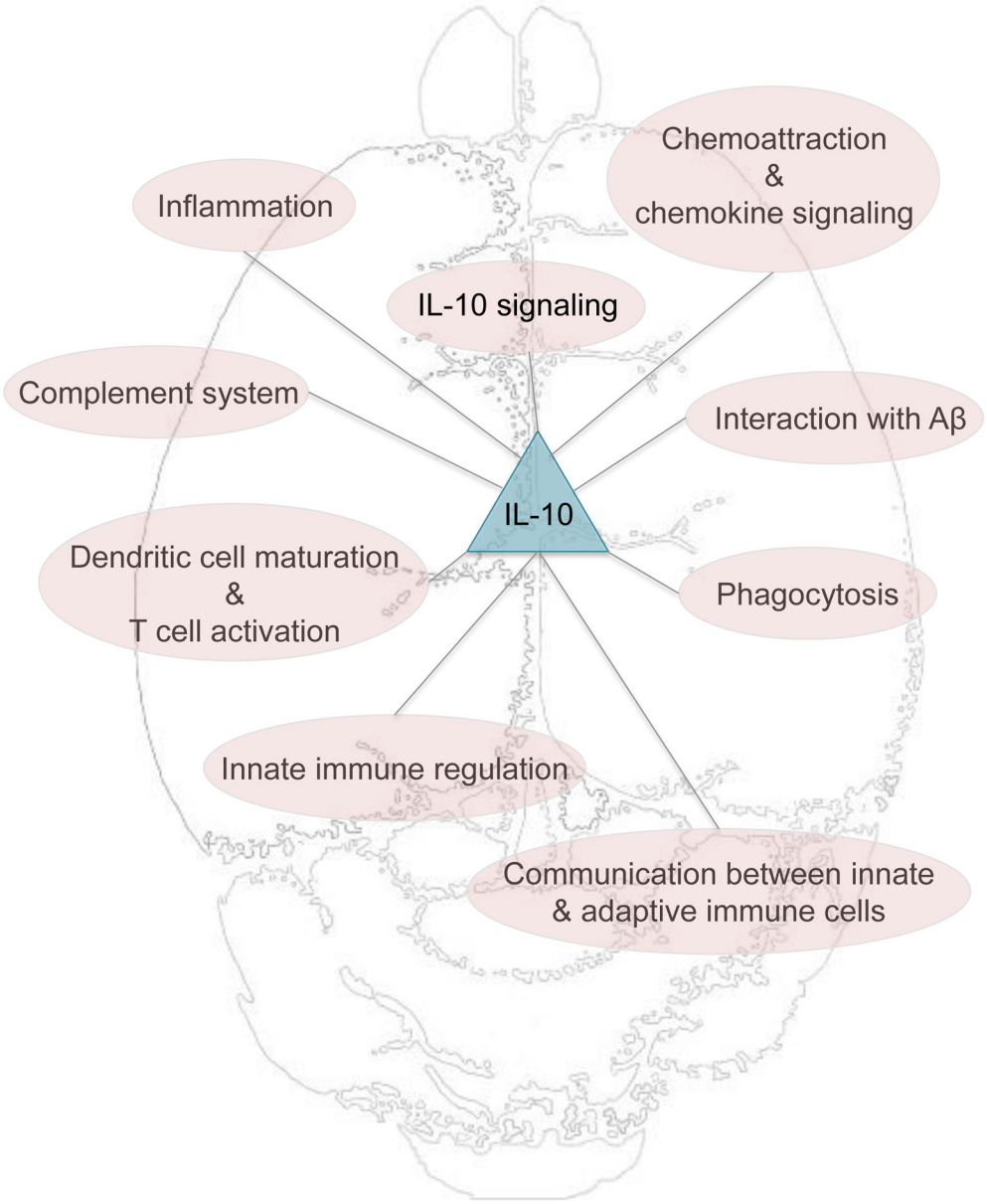

Figure 2. *Il10* dependent neuroinflammatory gene profiles in mouse models of cerebral amyloidosis

The diagram shows the broad categories of major gene groups affected by experimental targeting of *Il10* (overexpression or genetic ablation) according to transcriptomics published in [32–33].

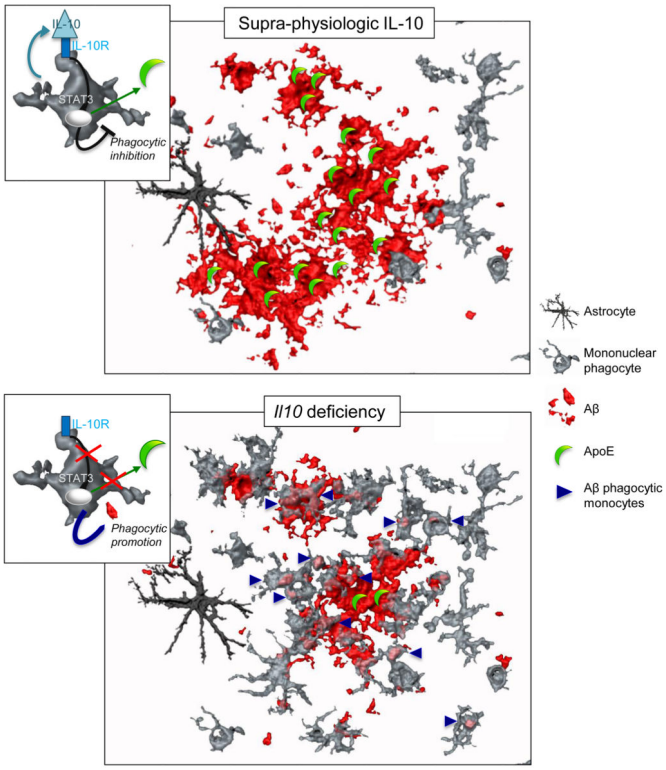

Figure 3. Proposed model for the impact of IL-10 on Aβ clearance by mononuclear phagocytes

The top panel depicts effects of supra-physiologic IL-10; present in AD brains and in mouse models of cerebral amyloidosis. IL-10/STAT3 pathway activation reduces monocyte Aβ phagocytosis. Concomitantly, ApoE expression is increased and clusters in Aβ deposits, retarding Aβ clearance. The lower panel illustrates effects of *Il10* ablation in mouse models of cerebral amyloidosis. Microglial phagocytic capacity is enhanced and ApoE expression, reduced, enabling Aβ clearance by mononuclear phagocytes.