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Impact of the CD40-CD40L Dyad in Alzheimer's Disease

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Abstract

As the number of elderly individuals rises, Alzheimer's disease (AD), marked by amyloid-β deposition, neurofibrillary tangle formation, and low-level neuroinflammation, is expected to lead to an ever-worsening socioeconomic burden. AD pathoetiologic mechanisms are believed to involve chronic microglial activation. This phenomenon is associated with increased expression of membrane-bound CD40 with its cognate ligand, CD40 ligand (CD40L), as well as increased circulating levels of soluble forms of CD40 (sCD40) and CD40L (sCD40L). Here, we review the role of this inflammatory dyad in the pathogenesis of AD. In addition, we examine potential therapeutic strategies such as statins, flavonoids, and human umbilical cord blood transplantation, all of which have been shown to modulate CD40-CD40L interaction in mouse models of AD. Importantly, therapeutic approaches focusing on CD40-CD40L dyad regulation, either alone or in combination with amyloid-β immunotherapy, may provide for a safe and effective AD prophylaxis or treatment in the near future.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia among the elderly affecting an estimated 5.2 million Americans in 2008 alone, a number that is expected to more than double in decades to come [1]. Age remains the most apparent risk factor for developing AD, as the prevalence for the disease begins to mount at age 65 and plateaus at 50% around age 85–90 [2–4]. However, both the prevalence and incidence of AD are expected to rise as diagnosis of the disease improves and general medicine prolongs longevity. At present, the annual economic impact of AD on the American people is estimated to exceed 100 billion dollars. Undoubtedly, the public health challenge is significant.

AD is pathologically distinguished from other forms of dementia by the presence of both extraneuronal β-amyloid plaques and intraneuronal neurofibrillary tangles. Common pathological features of this chronic neurodegenerative disease also include neuronal injury and low-level, chronic neuroinflammation characterized by activated glial cells. While the "amyloid cascade" hypothesis proposes that the central pathoetiologic mechanism of AD involves the dysmetabolism and deposition of amyloid-β peptides (Aβ) as senile plaques, there

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are a growing number of reports supporting the notion of neuroinflammation as a disease-perpetrating event [5]. The most compelling data come from epidemiologic studies showing that exposure to non-steroidal anti-inflammatory drugs (NSAIDs) is inversely associated with risk for AD [6–8]. While the only randomized controlled primary prevention trial with NSAIDs initially reported a positive association with risk for AD with an early follow-up period [9], Breitner and colleagues recently presented data from this trial suggesting that NSAIDs actually reduced risk for AD when the follow-up period was extended. Furthermore, the investigation of the role of neuroinflammation in AD has uncovered the importance of glial activation in disease progression. In particular, the activation of microglia, the resident immune cells of the central nervous system (CNS), is believed to significantly contribute to the pathoetiology of AD.

Essential to microglial activation is the stimulatory signal from CD40 ligation. CD40 is a 45- to 50-kDa type I integral membrane glycoprotein and a member of the tumor necrosis factor receptor superfamily. Studies originally identified CD40 on B lymphocytes, where it was shown to mediate T cell-dependent B cell activation and differentiation. It is found on most immune and some non-immune cells including macrophages, dendritic cells, endothelial cells, smooth muscle cells, and B cells, as well as astrocytes and microglia [5,10–15]. Membrane-bound CD40 and its cognate CD40 ligand (CD40L–also known as CD154), a trimeric 33-kDa type II membrane glycoprotein, play a critical role in microglial phenotypic transformation from a ramified (resting), to an activated macrophage morphology [16] and enhance surface expression of inflammatory markers [17,18].

Accordingly, these cell surface molecules have been reported to augment neuroinflammation and reduce clearance of Aβ from the brain. CD40L also occurs in a soluble, secreted form (sCD40L) that retains the ability to bind and activate membrane-bound CD40 [19,20]. Further, CD40 can also be secreted as a soluble form (sCD40), which may serve to neutralize CD40L [21]. Clearly, CD40 and CD40L are key immunoregulatory molecules as they provide co-stimulatory input to cells from both the innate and adaptive arms of the immune system, substantiating the importance of this duet in the neuroinflammatory component of AD. In this article, we review the implications of this inflammatory dyad for the pathogenesis, diagnosis, and potential treatment of AD.

THE CD40-CD40L DYAD AND NEUROINFLAMMATION IN AD

Over the past two decades, our understanding of AD pathophysiology has greatly expanded, and proponents of the amyloid cascade hypothesis have revised it accordingly. However, one general concept has remained constant – that Aβ peptides are neurotoxic. Notably, a continuous inflammatory cycle exists in the AD brain marked by chronic, low-level secretion of pro-inflammatory cytokines and acute-phase reactants around Aβ plaques. The term “reactive gliosis” has been used to describe this inflammatory cycle wherein glial cells, including microglia and astrocytes, undergo various phenotypic changes indicative of activation. Aβ peptides (both $_{1–40}$ and $_{1–42}$ isoforms) have traditionally been regarded as potent activators of microglia, and numerous research articles demonstrate neuronal damage by means of this unrestrained inflammatory response [22], which often involves the cytokines tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), as well as nitric oxide [23–27]. Importantly, microglia have long been considered to elicit these neuroinflammatory reactions *via* the CD40-CD40L dyad [23,28].

In support of this CD40-CD40L neuroinflammatory pathway, we and others have demonstrated that microglia are only modestly activated by Aβ exposure *in vitro* and that co-stimulation with IFN-γ or CD40L synergistically enhances this activation by upregulation of CD40 expression and ligation, respectively [22,29–35]. Specifically, when cultured microglia are co-

administered Aβ peptide and IFN-γ or CD40L in the presence of primary neurons, microglia secrete appreciably high levels of TNF-α, resulting in neuronal injury [28,36]. In addition, CD40L treatment of cultured human microglia has been reported to disturb the expression of genes regulating amyloid precursor protein (APP) processing and tau phosphorylation (a process contributing to neurofibrillary tangle formation) [37]. As *in vivo* validation of this pathway, we found that disruption of CD40-CD40L signaling (*via* CD40L deficiency) in mice carrying human "Swedish" mutant APP (APPsw, increases the production of Aβ) results in significantly less microgliosis and tau hyperphosphorylation in these animals [36]. Furthermore we have demonstrated that PSAPP AD model mice genetically deficient in CD40L exhibit decreased astrocytosis and microgliosis, which is associated with diminished Aβ levels and β-amyloid plaque load. Treatment of PSAPP mice (bigenic AD mice expressing mutant human presenilin-1 and APPsw) with CD40L-depleting antibody also caused marked attenuation of Aβ/β-amyloid pathology, which was associated with decreased amyloidogenic processing of APP and increased circulating levels of Aβ. Moreover, in neuroblastoma cells overexpressing wild-type human APP, the CD40–CD40L interaction resulted in amyloidogenic APP processing. These studies are key because they demonstrate that blocking CD40-CD40L interaction by genetic or pharmacologic means mitigates β-amyloid plaque deposits in multiple models of AD. Indeed, this work is salient because we can draw the conclusion that CD40L-induced microgliosis is indeed a pathogenic form of microglial activation in the context of AD-like pathology [36].

Similar to our studies above, Todd Roach and colleagues [35] showed that PSAPP mice given a regimen of anti-CD40L antibody (commencing at an age when initial Aβ deposition occurs) exhibited superior spatial as well as non-spatial memory compared to non-treatment control animals. Furthermore, Laporte and colleagues [33] demonstrated that APPsw mice deficient for CD40 experience reduced reactive gliosis (microgliosis and astrocytosis) and cerebral Aβ burden compared to CD40-sufficient littermates. Altogether, these studies suggest that CD40-CD40L interaction is essential for neuroinflammatory responses and, in particular, microglial activation, which may significantly contribute to AD pathogenesis.

Perhaps the most convincing clinical evidence of the role of CD40-CD40L signaling in inflammatory AD-like neurodegeneration comes from clinical studies demonstrating a mild increase of circulating sCD40L in mild cognitive impairment (MCI), which likely represents a prodrome to AD as it is positively associated with increased risk of AD incidence and rapid cognitive decline [35,38]. This clinical association between sCD40L and AD is also strengthened by evidence of sCD40L engagement of CD40 on endothelial cells resulting in various pro-inflammatory responses, including expression of adhesion molecules and tissue factors, release of cytokines/chemokines and expression of vessel-remodeling metalloproteinases [29,31,38]. Interaction between CD40L and CD40 activates various signaling cascades *via* the tumor necrosis factor receptor-associated factor family members [12,21,39–42]. As sCD40L also negatively affects re-endothelizing functions of endothelial cells [43], it has even further potential to interfere with microcirculation. Thus taken together, the soluble or membrane-bound CD40L and CD40 on smooth muscle and endothelial cells seem to work in concert with Aβ peptides to promote a feed-forward, self-perpetuating inflammatory cascade in both the vascular wall and brain parenchyma which, in turn, may initiate AD pathogenesis and/or propagate its progression [40,44].

Aβ-induced CD40 is incorporated into the cell membrane at constitutively low levels on vascular smooth muscle and endothelial cells [5,45,46]. Therefore, not surprisingly, the risk relationship between sCD40L and AD mirrors the positive correlation between sCD40L levels and vascular disease. This is because endothelial cells are a key component of the blood-brain barrier, suggesting that there could be alterations of this physiological unit under conditions of increased sCD40L expression or function. Accordingly, we previously demonstrated that

Aβ increases both CD40 mRNA transcription and CD40 protein expression in cultured human vascular endothelial cells within 48 hours of exposure [47–49]. These findings further suggest that factors that increase the risk of developing vascular disease also increase the risk for AD [45,49]. In fact, cerebral perfusion abnormalities are even seen in the earliest phases of AD [50,51]. This is not surprising, as the majority (>95%) of circulating CD40L exists in platelets [52]. CD40L is rapidly translocated to the platelet surface after stimulation and is then cleaved, generating sCD40L over a period of minutes to hours [53]. Taken together, these data suggest CD40-sCD40L/CD40L dyad is a central mediator of both vascular and AD.

In contrast to their role as elicitors of neuronal damage, a number of studies have suggested a neuroprotective role for microglia in AD [54]. The theories of neuroprotection or neurotoxicity regarding microglia are not mutually exclusive, however. Activated microglia augment Aβ clearance and Aβ vaccination [55–57] or recruitment of bone marrow-derived microglia [58, 59] can result in neuroprotection. Moreover, the low-density lipoprotein-related protein receptors on microglia may promote the export of soluble Aβ from the brain. However, these same receptors on neurons have also been found to increase intraneuronal uptake and toxicity of Aβ [60]. Similarly, carrier proteins such as apolipoprotein E, apolipoprotein J, and α2-macroglobulin can transport Aβ either to microglia, promoting Aβ clearance, or to neurons, promoting neurodegeneration [61].

Additional data confirming microglia-associated neuroprotection comes from studies demonstrating the attenuation of microgliosis with concomitant secretion of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 [62]. Indeed, just as IL-1β can activate neurotoxic effects of microglia, IL-4 and other anti-inflammatory cytokines promote an alternate activation state of microglia [63]. Microglia, much like peripheral macrophages, consist of a heterogeneous population of effector-type cells. Accordingly, several subsets of microglia have been characterized by differential expression of alloantigen molecules; primarily CD40 and = major histocompatibility complex class II, during establishment of cell lines [64–66]. The putative anti-inflammatory, neuroprotective subset of microglia or Th2-responsive cells are induced by IL-4, reduction of CD40 expression, and various other anti-inflammatory cytokines [10]. Such Th2-type microglia are distinct from Th1-type (characterized by pro-inflammatory cytokine production) in terms of the expression of at least two cell surface molecules: Th2-microglia express no CD40 and/or low CD86, both of which are expressed by antigen presenting cells to function in communication with $CD4^+$ Th cells. However, further differentiation of Th1 and Th2-responsive microglia may be necessary [64–66]. Nevertheless, in order to mitigate the chronic inflammatory cycle that exists in AD, it may be necessary to promote these Th2-type (anti-inflammatory cytokine producing) microglial responses as opposed to Th1-type responses. Indeed, a current popular hypothesis we and other have suggested is that transitioning from Th1- to Th2-type responses may not only suppress neuroinflammation, but also enhance Aβ clearance and neuroprotective mechanisms [67].

However, it should be noted that a recent study employing TgCRND8 and APPsw AD model mice suggests the converse, that Th1-type responses may be beneficial. IL-6 is a well-established pro-inflammatory cytokine, which is elevated in AD patients. Interestingly, Chakrabarty and colleagues [68] found that murine IL-6 expression resulted in extensive reactive gliosis that concurrently reduced amyloid burden in TgCRND8 mice. This reduction was accompanied by up-regulation of glial phagocytic markers *in vivo*. Murine IL-6 also enhanced microglia-mediated phagocytosis of Aβ aggregates *in vitro*. Importantly, murine IL-6-induced neuroinflammation had no effect on APP processing in TgCRND8 and had no effect on APP processing or steady-state levels of Aβ in young APPsw mice, suggesting that murine IL-6-mediated gliosis may be beneficial early in the disease process by potentially enhancing clearance of β-amyloid [67,69].

CD40 AS A BIOMARKER FOR AD

CD40 protein induction on microglia and vascular endothelial cells occurs in the presence of low doses of soluble forms of Aβ, suggesting that microgliosis may occur early in disease progression, prior to Aβ deposition [68]. For this reason, a number of studies have examined levels of gliosis-associated cytokines present in the cerebrospinal fluid (CSF) of patients with AD, in an attempt to identify objective, quantitative markers of this neuropsychiatric illness. Unfortunately, these types of studies have been plagued by problems, as data from the literature about intrathecal or circulating cytokine levels are often discordant. One explanation for this discordance is the nature of cytokines in general, which are characterized by short half-lives and signaling that occurs mainly in autocrine or paracrine fashions. Additionally, cytokines may be buffered by soluble receptors in the periphery, further confounding results. Furthermore, cytokines released in the CNS may act in similar manners across neurological disorders, amplifying certain neuropathological events. Thus, no specific defined cytokine release pattern in the circulation or CSF has as yet been identified for AD.

The pattern of expression of both CD40 and CD40L has been reported to be altered in the brains of AD patients as well as in several animal models of AD [45]. Recently, sCD40L was quantified at baseline in 136 subjects with MCI and 30 age-matched controls. Of the MCI patients, sixty of the 136 cases converted to AD (MCI-AD) during a follow-up period of 4–7 years. It was found that baseline levels of sCD40, but not sCD40L, were elevated in MCI-AD cases compared to age-matched controls. Furthermore, MCI patients who were cognitively stable or developed vascular dementia during follow-up did not have significantly increased levels of sCD40 or sCD40L compared to controls. The levels of sCD40 correlated with decreased baseline performance on mini-mental state examination in both controls and plasma levels of sCD40 correlated with the levels of soluble amyloid precursor protein-α and -β (sAPP-α and sAPP-β) in CSF [70,71]. An earlier study (73 AD patients compared to 102 controls) found sCD40 and sCD40L are increased in AD which in turn, correlated positively $A\beta_{1–40}$ and $A\beta_{1–42}$, respectively. When they combined sCD40, sCD40L, Aβ and apolipoprotein E for a diagnostic predictor of AD, they found that this panel had high sensitivity and specificity (>90%) [28]. The consistent findings in the above studies make a compelling case for using both sCD40 and sCD40L as plasma biomarkers of AD; however, it should be noted that these measures would likely need to be combined with others in order to attain the requisite sensitivity, specificity, and predictive value to be useful biomarkers [see ref. 72 for a review].

CD40-CD40L TARGETED AD THERAPEUTIC STRATEGIES

Statins

Statins belong to a class of drugs that inhibit the activity of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. For that reason, statins have been prescribed primarily for the purposes of lowering cholesterol levels. By inhbiting HMG-CoA reductase, these compounds not only decrease cholesterol synthesis, but also increase synthesis of low-density lipoprotein receptors, resulting in an increased clearance of low-density lipoprotein from the bloodstream [29]. Interestingly, some epidemiological studies, although preliminary, suggest that statin administration might be protective against the development of AD [73–75].

In light of these studies, we examined how statins may mechanistically afford protection against AD. We initially found that lovastatin suppresses IFN-γ-induced CD40 expression. Additionally, lovastatin markedly inhibits IFN-γ intracellular signaling. Furthermore, lovastatin suppressed TNF-α, interleukin IL-1β and IL-6 production promoted either by IFN-γ or by Aβ peptide challenge in the presence of CD40 stimulation. Moreover, data revealed that lovastatin markedly attenuates CD40-mediated inhibition of microglial phagocytosis of

Aβ peptide, causing a deficit in amyloid clearance from the brain [76]. Importantly, in a small clinical pilot study, patients with mild to moderate AD who were administered 80 mg atorvastatin daily over 1 year experienced a significant clinical improvement [77]. As sCD40L is involved in both activation of microglia and induction of vascular inflammation, this clinical benefit could be secondary not only to cholesterol-dependent reduction of vascular risk factors, but also because of reduced Aβ deposition in brain parenchyma, as demonstrated in our experimental models [78] and by others, as well [77]. Additionally the lipid-independent anti-inflammatory properties of statins [79], including reduction of circulating sCD40L levels in different clinical conditions [80] may have also led to this outcome.

Flavonoids

While several anti-inflammatory drugs have been found to prevent microglial-mediated inflammation, their underlying mechanisms remain unclear and the search for more effective practical compounds continues. Recent research has focused on the analysis of flavonoids, which epidemiological studies suggest are beneficial agents that militate against neurodegeneration and aging [81]. Flavonoids, a group of phenolic phytochemicals, are common in vascular plants and are abundant in particular spices, vegetables, and fruits. They are considered important constituents in the human diet, although their daily intake varies with dietary habits [82]. Several medicinal properties have been ascribed to flavonoids, notably anti-oxidant [83,84], anti-carcinogenic [84,85], and anti-inflammatory activity [86]. One such flavonoid, apigenin, and its phase I metabolite, luteolin, have been found to reduce CD40 and CD40L expression on dendritic cells and basophils, respectively. Previous research has also shown apigenin's ability to inhibit pro-inflammatory cytokine production by monocytes, macrophages, and microglia and further substantiates this compound as a versatile immunomodulator [87].

In a recent study, we investigated the potential anti-inflammatory effects and mechanisms of the flavonoids, apigenin and luteolin, in cultured microglia. Both apigenin and luteolin significantly reduced CD40 expression in N9 and murine-derived primary microglia cell lines induced by IFN-γ. This reduction was paralleled by significant decreases in the release of the pro-inflammatory cytokines IL-6 and TNF-α by microglia. Furthermore, we demonstrated that apigenin and luteolin treatments achieve these reductions through inactivation of the signal transducer and activator of transcription-1 signaling pathway, which plays a central role in IFN-γ-induced microglial CD40 expression [88,89]. In this manner, flavonoids may prove to be effective modulators of CD40-CD40L interactions and consequently effective therapeutics for AD-like neurodegeneration [90].

Human Umbilical Cord Blood Cell Transplantion

A major clinical challenge is finding a suitable cell source for the regeneration of damaged tissues. Human umbilical cord blood cells (HUCBCs) have unique immunomodulatory potential. In addition to fulfilling the function of tissue reconstruction, the immune properties of HUCBCs are advantageous for clinical applications where an anti-inflammatory, Th2 response is therapeutic. Previous work has indicated that HUCBCs may be immune-privileged cells as the surface antigen expression characteristics of the cells may enable them to avoid rejection or induction of graft versus host disease. Previous analysis has demonstrated HUCBCs do not express = major histocompatibility complex class II molecules or CD40 required for Th1-cell activation thought to be responsible for both transplant rejection and AD progression [91,92]. Also, HUCBCs do not elicit a proliferative response of allogeneic peripheral bone marrow cells during coculture *in vitro* [93]. Thus, an additional potential anti-CD40 treatment is human umbilical cord blood cell transplantion.

Previous experiments in our laboratory have shown they alter Alzheimer-like pathology after infusion into the PSAPP mouse model. Specifically, we observed marked reductions in Aβ levels/β-amyloid plaques and associated astrocytosis following multiple low-dose infusions of HUCBCs. HUCBC infusions also reduced cerebral vascular Aβ deposits in the APPsw mouse model. All of these effects were associated with suppression of the CD40-CD40L interaction, as evidenced by decreased circulating and brain sCD40L, elevated systemic immunoglobulin M levels, attenuated CD40L-induced inflammatory responses, and reduced surface expression of CD40 on microglia. Importantly, deficiency in CD40 abolishes the effect of HUCBCs on elevated plasma Aβ levels. Moreover, microglia isolated from HUCBC-infused PSAPP mice demonstrated increased phagocytosis of Aβ. Furthermore, sera from HUCBC-infused PSAPP mice significantly increased microglial phagocytosis of the Aβ peptide while inhibiting IFN-γ-induced microglial CD40 expression. Increased microglial phagocytic activity in this scenario was inhibited by addition of recombinant CD40L protein [94–96]. While the findings above testament of the beneficial effects of human umbilical cord blood cell transplantion, it is important to note that to date the exact mechanism(s) of action that confer these reductions in amyloidosis coincident with CD40 dyad modulation has yet to be established. For review of the various theories the reader is referred to Kostrzewa and Segura-Aguilar [97].

Aβ VACCINATION

Immunization with Aβ peptide efficiently reduces amyloid plaque load and memory impairment in transgenic mouse models of AD. Active Aβ “immunotherapy” has also yielded favorable results in a subset of AD patients. However, a small percentage of patients developed severe aseptic meningoencephalitis associated with brain inflammation and infiltration of T cells. We recently demonstrated genetic or pharmacologic interruption of the CD40-CD40L dyad enhances $A\beta_{1–42}$ immunization efficacy to reduce cerebral amyloidosis in the APPsw and PSAPP mouse models of AD. Potentially deleterious pro-inflammatory immune responses seen in the previous Elan/Wyeth AN-1792 trial, cerebral amyloid angiopathy and cerebral microhemorrhage, were reduced or absent in these combined approaches. Furthermore, pharmacologic blockade of CD40L decreased T-cell neurotoxicity to Aβ-producing neurons. Further reduction of cerebral amyloidosis in Aβ-immunized PSAPP mice completely deficient for CD40 occurred in the absence of Aβ immunoglobulin G antibodies or efflux of Aβ from brain to blood, but was rather correlated with anti-inflammatory cytokine profiles and reduced plasma sCD40L. These results suggest that CD40-CD40L dyad blockade promotes anti-inflammatory cellular immune responses, likely resulting in promotion of microglial phagocytic activity and Aβ clearance without generation of neurotoxic Aβ-reactive T-cells. Thus, combined approaches of Aβ immunotherapy and CD40-CD40L dyad blockade may provide for a safer and more effective Aβ vaccine in the future [97–100].

CONCLUDING REMARKS

Neuroinflammation is a complex process that employs signaling pathways crucial to the dynamic interplay between glial cells and neurons, which is required to maintain neural health. Complete abolishment of CD40-CD40L interactions between microglia, astrocytes, and neurons may prove to be hazardous, as we have previously shown that ligation of CD40 protected neuronal cells from nerve growth factor-β or serum withdrawal-induced injury and promoted differentiation [101]. For this reason, modulation specifically directed toward neuroinflammatory reactions in CNS would appear to be a preferable way to treat neurodegenerative disease. In this regard, we have summarized such neuroinflammatory events, as well as biomarker correlates, in AD that may be ameliorated by immunotherapy, including statin and flavonoid treatment, Aβ vaccination, and human umbilical cord blood cell transplantion (Fig. 1). Importantly, modulation of the CD40-CD40L dyad is central to this immunotherapy for AD.

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ABBREVIATIONS

Aβ	Amyloid beta/beta amyloid
AD	Alzheimer's disease
APP	Amyloid precursor protein
CNS	Central nervous system
CSF	Cerebrospinal fluid
CD40L	CD40 ligand
HUCBCs	Human umbilical cord blood cells
IFN	Interferon
IL	Interleukin
MCI	Mild cognitive impairment
NSAIDs	Non-steriodal anti-inflammatory drugs
sCD40	Soluble CD40
sCD40L	Soluble CD40 ligand
Th	T helper cell
TNF	Tumor necrosis factor

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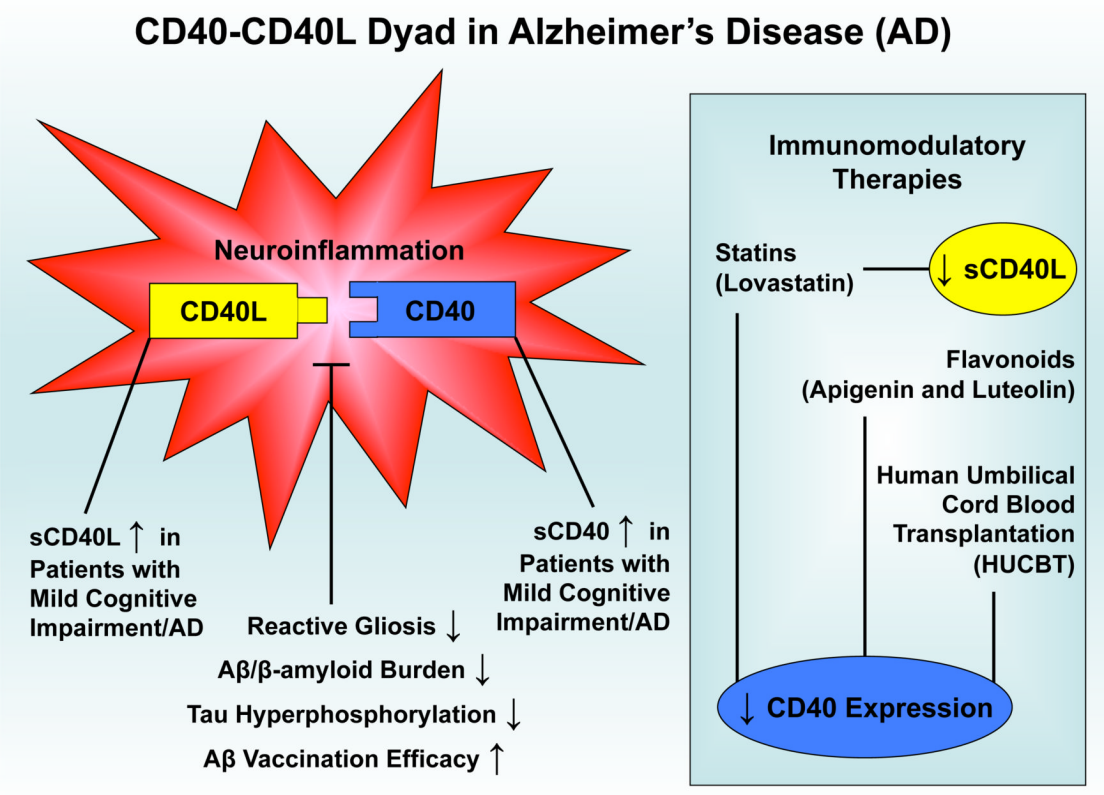

Fig. 1.
Model for CD40-CD40L inflammatory dyad in the pathogenesis and potential treatment of AD. See text for references.