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Is Alzheimer's Associated Amyloid Beta an Innate Immune Protein

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Abstract

There is now abundant evidence that chronic inflammation in the brain is central to the pathogenesis of Alzheimer's disease (AD) and that this is precipitated through accumulation of amyloid beta ($A\beta$) peptides. In this review, we first outline this evidence and how specific receptors on microglia and monocyte/macrophages determine whether extracellular $A\beta$ peptides can be cleared through non-inflammatory phagocytosis or instead result in pro-inflammatory cytokine generation. Most efforts of treatment for AD so far have focused on reduction of $A\beta$ levels (in particular neurotoxic oligomers of $A\beta_{1-42}$) in the brain. Recent findings suggest an alternative approach in which pro-inflammatory responses to $A\beta$ peptides are targeted to reduce injury. Most recently evidence has come to light that $A\beta$ peptides resemble antimicrobial peptides which are part of the innate defense system against infection. Such peptides act both by directly inactivating pathogens, but also by modulating responses of innate immune cells, including phagocytes. Indeed, $A\beta$ peptides, particularly $A\beta_{1-42}$, do inhibit a range of potential pathogens, including bacteria, fungi, and viruses. Coupling this with evidence linking chronic viral, bacterial, or fungal infection to AD suggests that production of $A\beta$ peptides in the brain is part of an innate immune response which might normally be beneficial, but which leads to harm when it is chronic or uncontrolled. This suggests that discovery of the original possibly infectious (or other inflammatory) stimulus for $A\beta$ production would allow early intervention to prevent development of AD.

Keywords: Inflammasome, TREM2, Microglia, antimicrobial peptide

1. Introduction

A β accumulation is believed to contribute strongly to the pathogenesis of AD, although the actual physiological function and reason for accumulation of A β in the brain are not known. A β is a fragment of the larger β amyloid precursor protein (APP) which is a transmembrane protein which can be broken down by various proteases into a variety of fragments, including extracellular and intracellular fragments and the peptide fragments A β 1-42 and A β 1-40 which are composed partly of the extracellular and partly of the transmembrane domain of APP. A β 1-40 is more abundant than A β 1-42, but A β 1-42 is the more amyloidogenic and neurotoxic species [1–3]. The neurotoxicity of A β 1-42 has been shown to depend on the ability of this peptide to form unstable oligomers (pentamers mainly), whereas the protofibrils or fibrils formed from the peptide are less neurotoxic. Recent studies are at last starting to elucidate why accumulation of A β , especially the 1–42 form leads to brain injury. These studies focus on the role of A β as a trigger of inflammation and emphasize its interaction with glial cells in the brain. A vicious cycle appears to occur in which A β peptides activate glial and other phagocytic cells which in turn impairs the ability of these cells to clear A β peptides and plaques from the brain. The reasons for production of A β in the brain in the first place are less clear. Recent findings that A β peptides function as antibacterial and antimicrobial peptides have given rise to the hypothesis that production of A β peptides may have evolved as part of the innate host defense system.

I. Evidence for a link between chronic inflammation and AD—At the outset, it is important to distinguish between early onset AD and late onset AD. Both forms of AD are strongly linked to excess accumulation of A β in plaques in the brain; however, the causes of A β accumulation may differ. In the case of early onset disease, there is a link to actual mutations in the A β gene or in genes involved in proteolytic processing of the precursor protein to form A β peptides. The most commonly used mouse model, the APP-PS1 model, of AD is based on over-expression of A β peptides in the brain in a similar manner. Late onset AD appears mainly to result from impaired clearance of A β peptides (rather than increased production per se) and is linked to polymorphisms of several genes as outlined below. There is strong and growing evidence for a link between chronic inflammation and the development of both forms of AD and some other dementing illnesses. We refer the reader to several recent excellent reviews for in depth consideration this topic [4–6]. A link between inflammation and AD has long been suspected in part based on clinical findings (e.g., the apparent protective effect of long-term non-steroidal anti-inflammatory use against development of sporadic AD) [7, 8]. In addition, pathological studies have shown evidence of inflammation surrounding neuritic plaques in AD. Complement factors, clusters of activated microglia and cytokines has been found in and near A β plaques [5, 9]. These findings of inflammation were also noted as early events in the brains of patients with AD. Expression of genes associated with inflammation in brain is increased in aging, and this effect is accentuated in patients with AD [10, 11].

II. Microglia and monocyte/macrophages as pivotal cells in mediating clearance or inflammatory responses to A β peptides—Microglia are resident phagocytic cells in the brain that plays a key role in maintaining the health of neurons and responding to sterile or infectious

injury. Evidence is now converging from genome-wide association studies (GWAS), in vitro cell biologic experiments and mouse models of excess A β accumulation, that microglia and to an extent recruited blood monocyte macrophages, are critical in mediating either protective clearance of A β or damage through inflammatory activation by A β peptides.

A. GWAS studies—The first gene to show strong linkage to development of AD was the $\epsilon 4$ variant of apolipoprotein E (APOE). Although APOE is mainly known for its ability to regulate cholesterol and lipid transport, the APOE $\epsilon 4$ allele is linked to accumulation of A β in plaques in humans and mouse models [12]. In addition, there is evidence that APOE $\epsilon 4$ may be linked to inflammatory responses in the brain through interaction with receptors on microglia [13]. For instance, crossing APOE $\epsilon 4$ over-expressing mice with APP/PS1 mice results in worsening inflammatory responses to lipopolysaccharide (LPS) as compared to APP/PS1 mice over-expressing APOE $\epsilon 3$ [7]. Other proteins which modulate lipid metabolism, for instance surfactant protein D, have innate immune activity as well [14]. Of interest, surfactant protein D has also been linked to dementia [15]. Several other gene variants which are primarily expressed on microglia or other myeloid cells have been linked to AD. The most prominent of these is the triggering receptor expressed on myeloid cells 2 (TREM2) [6, 16–18]. This receptor mediates phagocytic activity and cytokine responses of myeloid cells and polymorphic forms of this receptor are linked to development of late onset AD with an effect size similar to APOE $\epsilon 4$. Similar polymorphisms of the complement receptor CR-1 and an additional myeloid cell receptor, CD33, have been linked to development of AD [19, 20]. The contributions of these and other myeloid receptors to accumulation of A β and neuronal injury are now being elucidated through in vivo and in vitro studies.

B. Cell biology and mouse model studies—There is abundant evidence that accumulation of A β 1-42 itself activates microglia and monocyte macrophages through binding to various receptors on these cells, either directly or through binding to other proteins (e.g., complement). A key hypothesis which brings together the various studies is that the ability of microglia to ingest A β 1-42, or to degrade it through proteolysis is protective, whereas production of pro-inflammatory cytokines (e.g., TNF, IL-1 or IL-18) in response to A β 1-42 is harmful. Microglia and macrophages can have a variety of phenotypes, with two major categories being the M1 and M2 phenotypes. The M1 phenotype is associated with pro-inflammatory cytokine generation as well as production of nitric oxide or superoxide radicals. In contrast, the M2 phenotype (presumably the more beneficial phenotype in the context of A β accumulation) is associated with enhanced phagocytosis and reduced pro-inflammatory signaling. Given the sensitive nature of the brains and neurons, clearance of pathogens, harmful proteins, or cellular debris ideally would proceed with minimal inflammation. The beneficial or harmful effects of various myeloid receptors have been categorized according to whether they mediate either M1 or M2 like activities [5, 21].

Microglial scavenger receptors—Receptors shown to promote phagocytosis and non-inflammatory clearance of A β 1-42 include the scavenger receptors SR-A or Scara-A [22, 23]. In contrast, CD36, which is another scavenger receptor, appears to mediate pro-inflammatory responses to A β 1-42 [24, 25]. Crossing of APP/PS1 with mice-lacking SR-A leads to greater A β accumulation and worsened survival, whereas crossing with mice-lacking CD36 causes

reduced brain cytokine production and A β accumulation and improved survival. CD33 is another receptor that is involved in uptake of A β peptides by microglia. CD33 is over-expressed in microglia of humans with AD and the CD33 mutations that were found to be protective vs AD caused decreased expression of CD33 [19, 26]. Crossing of mice-lacking CD33 with APP/PS1 mice leads to reduced A β peptide accumulation and plaque burden [19]. In vitro studies showed that CD33 actually reduces A β 1-42 uptake by microglial cells.

Triggering receptor expressed on myeloid cells 2 (TREM2)—TREM2 has a more complex role in that it can mediate either phagocytic clearance or pro-inflammatory cytokine responses by myeloid cells [6]. Like CD33, it is highly expressed in microglia and monocytes in the brain. In particular, it is highly expressed in microglia surrounding amyloid plaques in APP/PS1 mice [16]. In one study using this mouse model, deletion of TREM2 reduced inflammatory pathology in the brain [27]. In contrast, in another study, over-expression of TREM2 in these mice improved pathology [28]. The GWAS studies suggest that polymorphisms associated with decreased TREM2 production increase risk of development of AD or other neurodegenerative diseases [16]. Based on this, it has been postulated that loss of TREM2 impairs non-inflammatory phagocytic clearance of A β peptides or of damaged neurons. TREM2 is well described as a phagocytic receptor for bacteria. Further studies will be needed to understand the complex role of TREM2 in AD. Of interest, two recent studies provide potential links between the contributions of APOE ϵ 4 and TREM2 to inflammation in AD. APOE was shown to bind to wild-type (but not mutant) TREM2 [29] and the APOE ϵ 4 variant has distinctive effects (as compared to other APOE subtypes) in modulating microglial prostaglandin production and TREM2 expression [30].

Complement and complement receptors—The complement receptor CR-1 also appears to have a complex role in AD [20]. CR-1 is the receptor for complement factors C3b and C4b. A β can activate the complement cascade and bind to C3b. This in turn leads to binding of A β peptides to CR-1. CR-1 is expressed on myeloid cells and erythrocytes. In the case of erythrocytes, it serves to mediate clearance of complement bound proteins or organisms from the circulation. There is some evidence that this may promote clearance of A β outside the brain [31]. CR-1 also mediates phagocytosis of complement bound proteins and pathogens by phagocytes. A β can activate the complement system via the alternative pathway. This could conceivably lead to increased inflammation in the brain. However, it has been found that C3 deficiency or inhibition of complement worsens A β accumulation and neurodegeneration in mice [32]. These findings suggest that the complement activation may overall be beneficial vs AD. A possible explanation for the role of CR-1 is that the polymorphism most tightly linked to increased risk for AD (CR1-S) has an increased C3b/C4b binding site and that CR-1 actually acts to inhibit further activation of the complement cascade after binding to C3b/C4b [20].

Toll like receptors—Toll-like receptors (TLRs) and the associated adaptor protein also have been found to mediate phagocyte activation by A β [24, 33–37]. Once again the exact role of TLRs in AD pathology is unclear. A simplistic hypothesis would assume that TLR activation should worsen AD pathology; however, there is also evidence that the reverse may be true [33, 38]. Of interest, IL-10 which is predominantly an anti-inflammatory cytokine has been found to have adverse effects in AD mouse models [39].

Inflammasomes—Another important line of evidence relates to the role of nucleotide-binding domain leucine-rich repeat containing 3 (NLRP3) inflammasomes in AD [4, 40, 41]. Inflammasomes are multi-molecular complexes in phagocytic cells which mediate production of the pro-inflammatory cytokines IL-1 and IL-18 through the action of caspase 1 and induction of an inflammatory form of cell death called pyroptosis [42, 43]. Inflammasomes are involved in phagocyte mediated host defense against various pathogens. In the case of bacteria, the inflammasomes are activated by pathogen-associated molecular patterns (or PAMPs), like LPS. Increasingly, however, inflammasomes have been implicated in various inflammatory states triggered by self molecules termed damage-associated molecular patterns or DAMPs. NLRP3 inflammasomes activation has been linked to inflammatory bowel diseases, celiac disease, gout, multiple sclerosis, and type II diabetes mellitus. It appears that NLRP3 inflammasomes also mediate chronic inflammatory responses to A β peptides. NLRP3 inflammasomes are one subtype among a variety of inflammasomes. **Figure 1** illustrates the potential mechanism of assembly and activation of NLRP3 inflammasomes by A β peptides. A β peptides appear to act as a DAMP. As noted, two signals are required for activation, both of which could be triggered by A β peptides. The NLRP3 inflammasome complex consists of oligomeric assemblies of the NLRP3 protein, the apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) protein and caspase 1. Crossing of mice lacking caspase 1 or NLRP3 with APP/PS1 mice results in increased clearance of A β peptides and plaques, reduced neurodegeneration and a skewing of microglia to the M2 phenotype. Pro-inflammatory signaling in response to A β peptides mediated through inflammasomes appears to lead to a vicious cycle in which microglia acquire and M1 phenotype and cause increasing injury and decreased A β clearance [21].

Chemokines—Chemokines and their receptors also appear to modulate A β -related pathology. The chemokine CXCL10 is expressed at high levels in AD brain. Deletion or inhibition of the receptor for this and other CXCL chemokines (CXCR3) increased microglial uptake of A β in vitro and in vivo [44]. Deletion of CXCR1 had a similar effect [45]. These findings imply that these chemokines worsen the inflammatory effects which lead to increased injury or impaired clearance of A β . An active area of investigation as well is the role of recruited monocyte macrophages to AD pathology or A β clearance. Deletion of the monocyte receptor CCR2 in mice reduces monocyte recruitment and increases amyloid pathology in APP/PS1 mice [46], indicating that these cells play a role in clearance. Similarly CCR5 deletion increased A β deposition and neurological loss [47]. Other cytokines, like IL-12, are linked to exacerbation of AD as is activation of oxidant production by microglia [48–50].

C. Epidemiological studies—Life-style or other factors which are known to increase AD incidence also may mediate their effects through chronic inflammation. Examples include obesity, lack of exercise, peri-odontitis, or diabetes [5]. Overall these studies lend strong support to the hypothesis that the innate immune system, and specifically, resident or recruited phagocytic cells play a pivotal role in determining the balance between protective A β clearance or damaging A β peptide-induced inflammation.

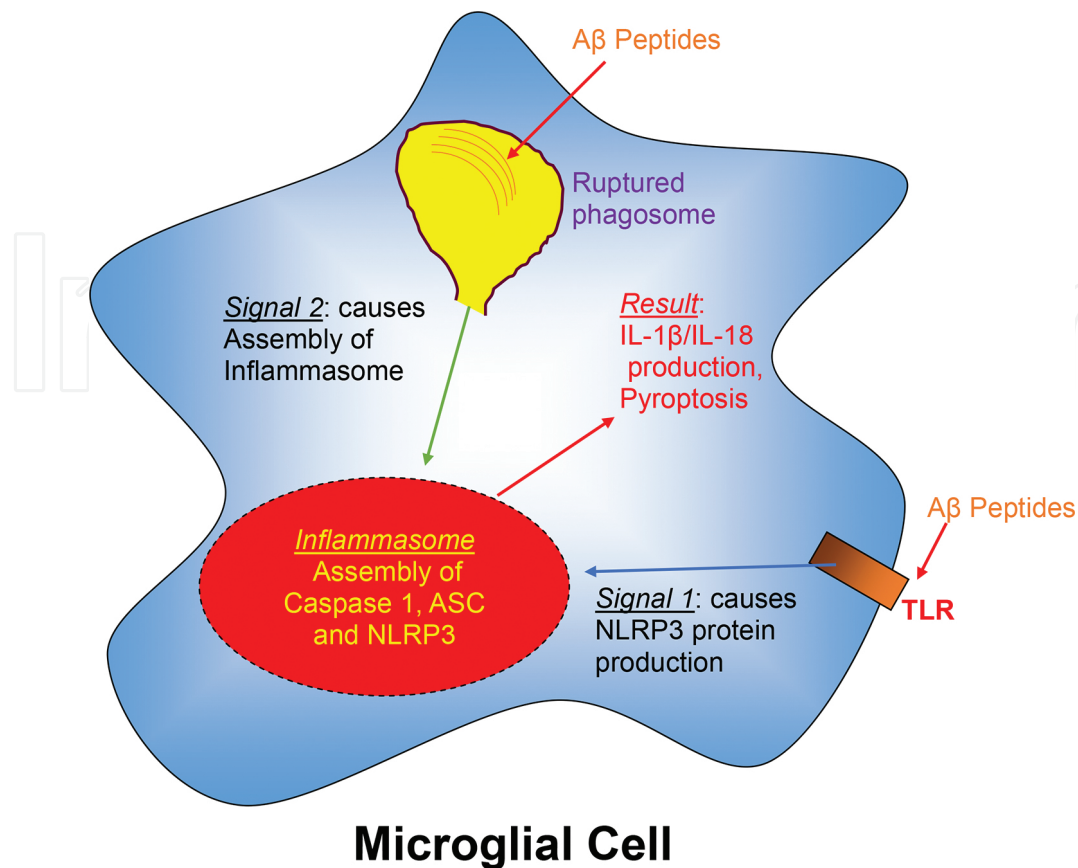


Figure 1. Microglial NLRP3 inflammasome activation by A β oligomers—the NLRP3 inflammasome can be activated by various PAMPs or DAMPs. A β oligomers can be considered as a DAMP which leads to NLRP3 activation in microglia. To induce NLRP3 activation, there needs to be at least two signals. The first signal causes increased production of the NLRP3 protein, and the second signal induces assembly of the multimolecular inflammasome complex. Other proteins involved in this complex include ASC and caspase 1. Activation of caspase 1 results in cleavage of pro-IL-1 β and pro-IL-18 to form active IL-1 β and IL-18. An additional effect of inflammasome activation is induction of a form of cell death caused pyroptosis. The result is a significant induction of local inflammation but also impairment of microglial phagocytosis, reducing further clearance of A β . The exact triggers of signal 1 and 2 are have not been fully elucidated. Since A β can trigger TLR activation, it is possible that this provides signal 1. In the case of some bacteria, rupture of phagosomes appears to provide signal 2, possibly by release of cathepsin B. We speculate that this could be involved in NLRP3 inflammasome activation by A β . Other possible mediators of the second signal include reactive oxygen species release or activation of plasma membrane ion channels.

III. What is the physiological stimulus for A β production?—Thus far most of the studies we, we have discussed consider the downstream effects of A β accumulation on inflammation or cellular dysfunction. For early onset AD, and for the APP/PS1 mice, increased A β accumulation is the result of alterations of the A β protein itself or of the enzymes involved in cleavage of the precursor protein. It is unclear, however, what triggers A β production under normal circumstances or in late onset AD. Attempts to directly reduce A β levels through the use of antibodies against A β peptides have not been highly successful, although it is possible that use in earlier stages of the disease (prior to major cognitive impairment) may be beneficial. There is also hope that intervention to reduce inflammatory response to A β may be beneficial, although here again it may be necessary to act early in the course of disease since the inflammatory phenotype seems to precede clinical AD.

If it was possible to determine the initial causes for A β accumulation in the brain, this might provide another approach to early intervention. One hypothesis is that infection initiates or sustains the process of A β accumulation. Excess accumulation of A β has been linked to Human Immunodeficiency Virus-related dementia [51, 52], and the virus can cause A β accumulation in vitro as well [53, 54]. Similarly Herpes Simplex Virus (HSV) induced encephalitis, and HSV infection in vitro is associated with A β accumulation [55–59], again implying that viruses may be a stimulus of A β production or impaired clearance. These findings suggest that viruses that infect the brain could be triggers for accumulation of A β , perhaps as part of an aberrant or sustained innate immune response. Antibodies to Cytomegalovirus, Epstein Barr Virus, or Human Herpes Virus 6 (HHV6) have also been associated with AD [60, 61] in some studies. In contrast, another study showed no link between AD and antibodies to HHV6 [62]. A variety of studies have also linked bacterial infection, including with chlamydia to development of AD [63, 64]. Of great interest, recent studies found fungal forms and sequences in brains of AD patients but not in controls [65–67]. Of course of a causal connection between these infections and AD is far from proven.

IV. A β peptides as antimicrobial agents—An alternative hypothesis to explain A β peptide and ultimately plaque production is that it is part of a host defense response to infectious or traumatic injury. A β peptides resemble some anti-microbial peptides or AMPs in their structure [68, 69]. A β peptides are similar to the porcine AMP, protegrin, in ability to form channels in membrane structures which is believed to be one of the anti-bacterial and anti-fungal mechanisms of AMPs. Recently, Soscia et al. demonstrated antibacterial and antifungal activity for A β peptides [70]. In addition, this study showed that A β isolated from the brain of AD patients had antimicrobial activity and that incubation of these brain-derived samples with antibodies to A β ablated the antimicrobial activity. More recently, we demonstrated that A β peptides also have antiviral activity using influenza A virus as a model [71]. In our study and that of Soscia et al., A β 1-42 was found to have greater antimicrobial or antiviral activity than A β 1-40. We demonstrated that A β 1-42, but not A β 1-40, caused viral aggregation which appears to contribute to its antiviral effects. This implies a possible connection between the ability of A β 1-42 to assemble into oligomers and its antiviral activity, since this peptide has a greater propensity to form oligomers and fibrils than A β 1-40.

The finding that A β peptides, especially, A β 1-42 act like other cationic antimicrobial peptides may also explain its ability to activate phagocytic cells. AMPs have direct antimicrobial and antiviral activities but they also trigger recruitment and activation of immune cells [34, 36, 72]. We also recently showed that A β 1-42 modulates responses of neutrophils and monocytes to the influenza virus [71]. A β 1-42 increased neutrophil uptake of influenza A virus and potentiated neutrophil respiratory burst and neutrophil extracellular trap (NET) formation in response to the virus. A β 1-42 also reduced inflammatory cytokine production triggered by influenza virus in monocytes. The opsonizing activity of A β 1-42 was again not replicated with A β 1-40. More recently, we found that A β peptides can increase neutrophil uptake of bacteria as well (unpublished data). Overall, these studies lend support to the hypothesis that A β peptides serve a host defense role and that chronic infectious or inflammatory stimuli may result in an aberrant prolongation of what normally would be a helpful response.

2. Conclusions

There is now abundant evidence from a variety of sources that AD is characterized by a chronic inflammatory response in the brain. The key elements in this process include the ability of A β peptides, especially A β 1-42, to directly activate phagocytic cells, most notably microglia and, to a lesser extent, monocyte/macrophages. **Figure 2** summarizes the microglial receptors, cytokines, and signaling mechanisms known to be linked to responses to A β peptides. These phagocytic cells are at the cross-roads of innate immune responses in the brain, and they appear to play a pivotal role in determining whether the response to A β peptide accumulation is non-inflammatory phagocytosis or pro-inflammatory cytokine production. One conclusion from these studies is that inhibition of pro-inflammatory responses early in the evolution of A β related pathology could be protective. For example, inhibition of inflammasome activation has been proposed as an approach to treatment. One dilemma is that there is not a simple correlation between processes normally thought of as pro-inflammatory and reduction of neuronal injury in AD models. As prime examples, activation of the complement system or of toll-like receptor pathways appears to be protective in some studies. In addition, the role of TREM2, while clearly important, is not as simply as initially expected. The recent findings that A β peptides (especially A β 1-42) function like other AMPs suggest that A β peptides may play a beneficial physiological role in vivo and may actually be part of an innate immune response to infection. If this is so then discovery of underlying infectious triggers of AD might provide a different modality of treatment.

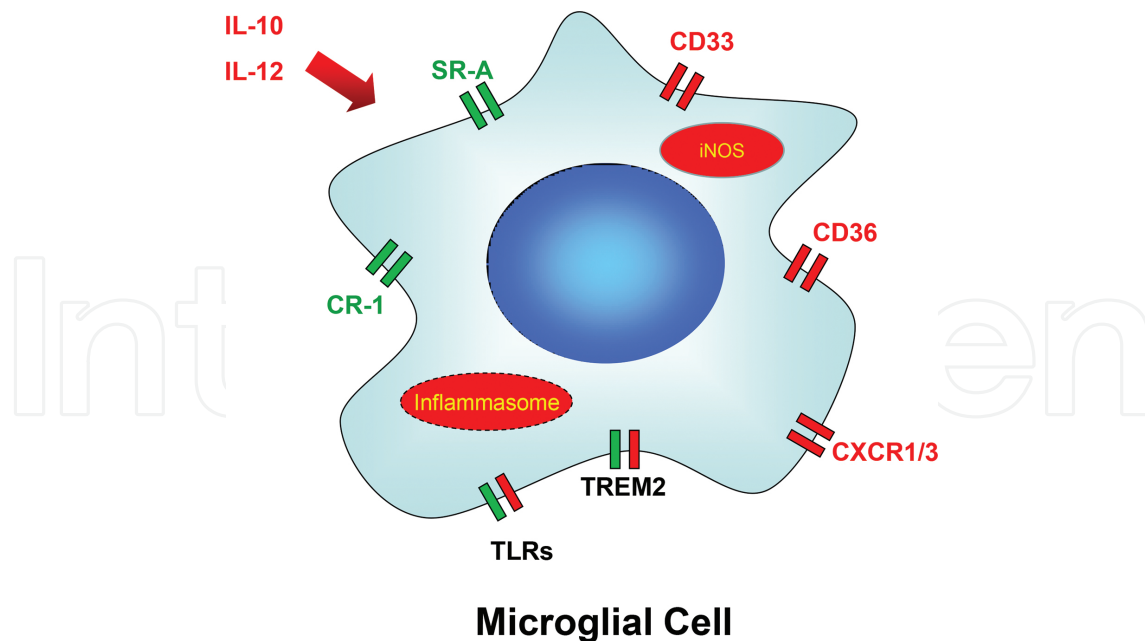


Figure 2. Microglial receptors and signaling pathways that are involved in response to A β —receptors, signaling pathways or extracellular cytokines shown to promote neuronal injury are shown in red, whereas those shown in green are protective vs neuronal injury or progression of AD like pathology. Receptors shown in as a mixture of green and red have been found to have both beneficial or adverse effects in various studies.

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