Chapter 7

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 (Aβ) peptides. In this review, we first outline this evidence and how specific receptors on microglia and monocyte/macrophages determine whether extracellular Aβ 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 Aβ levels (in particular neurotoxic oligomers of Aβ1-42) in the brain. Recent findings suggest an alternative approach in which pro-inflammatory responses to Aβ peptides are targeted to reduce injury. Most recently evidence has come to light that Aβ 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, Aβ peptides, particularly Aβ1-42, do inhibit a range of potential pathogens, including bacteria, fungi, and viruses. Coupling this with evidence linking chronic viral, bacteria, or fungal infection to AD suggests that production of Aβ 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 Aβ production would allow early intervention to prevent development of AD.

Keywords: Inflammasome, TREM2, Microglia, antimicrobial peptide

1. Introduction

Aβ accumulation is believed to contribute strongly to the pathogenesis of AD, although the actual physiological function and reason for accumulation of Aβ in the brain are not known. Aβ 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 Aβ1-42 and Aβ1-40 which are composed partly of the extracellular and partly of the transmembrane domain of APP. Aβ1-40 is more abundant than Aβ1-42, but Aβ1-42 is the more amyloidogenic and neurotoxic species [1–3]. The neurotoxicity of Aβ1-42 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 Aβ, especially the 1–42 form leads to brain injury. These studies focus on the role of Aβ as a trigger of inflammation and emphasize its interaction with glial cells in the brain. A vicious cycle appears to occur in which Aβ peptides activate glial and other phagocytic cells which in turn impairs the ability of these cells to clear Aβ peptides and plaques from the brain. The reasons for production of Aβ in the brain in the first place are less clear. Recent findings that Aβ peptides function as antibacterial and antimicrobial peptides have given rise to the hypothesis that production of Aβ 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 Aβ in plaques in the brain; however, the causes of Aβ accumulation may differ. In the case of early onset disease, there is a link to actual mutations in the Aβ gene or in genes involved in proteolytic processing of the precursor protein to form Aβ peptides. The most commonly used mouse model, the APP-PS1 model, of AD is based on over-expression of Aβ peptides in the brain in a similar manner. Late onset AD appears mainly to result from impaired clearance of Aβ 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 Aβ 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 Aβ 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

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

A. GWAS studies—The first gene to show strong linkage to development of AD was the ε4 variant of apolipoprotein E (APOE). Although APOE is mainly known for its ability to regulate cholesterol and lipid transport, the APOEε4 allele is linked to accumulation of Aβ in plaques in humans and mouse models [12]. In addition, there is evidence that APOEε4 may be linked to inflammatory responses in the brain through interaction with receptors on microglia [13]. For instance, crossing APOEε4 over-expressing mice with APP/PS1 mice results in worsening inflammatory responses to lipopolysaccharide (LPS) as compared to APP/PS1 mice over-expressing APOEε3 [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 APOEε4. 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 Aβ 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 Aβ1-42 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 Aβ1-42, 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 Aβ1-42 is harmful. Microglia and macrophages can have a variety of phenotypes, with two major categories being the MI and M2 phenotypes. The MI 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 Aβ 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 Aβ1-42 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 Aβ1-42 [24, 25]. Crossing of APP/PS1 with mice-lacking SR-A leads to greater Aβ accumulation and worsened survival, whereas crossing with mice-lacking CD36 causes

reduced brain cytokine production and Aβ accumulation and improved survival. CD33 is another receptor that is involved in uptake of Aβ 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 Aβ peptide accumulation and plaque burden [19]. In vitro studies showed that CD33 actually reduces Aβ1-42 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 neuro-degenerative diseases [16]. Based on this, it has been postulated that loss of TREM2 impairs non-inflammatory phagocytic clearance of Aβ 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 APOEε4 and TREM2 to inflammation in AD. APOE was shown to bind to wild-type (but not mutant) TREM2 [29] and the APOEε4 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. Aβ can activate the complement cascade and bind to C3b. This in turn leads to binding of Aβ 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 Aβ outside the brain [31]. CR-1 also mediates phagocytosis of complement bound proteins and pathogens by phagocytes. Aβ 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 Aβ accumulation and neurodegeneration in mice [32]. These finding 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 Aβ [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].

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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 Aβ 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 Aβ peptides. Aβ peptides appear to act as a DAMP. As noted, two signals are required for activation, both of which could be triggered by Aβ 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 Aβ peptides and plaques, reduced neurodegeneration and a skewing of microglia to the M2 phenotype. Pro-inflammatory signaling in response to Aβ peptides mediated through inflammasomes appears to lead to a vicious cycle in which microglia acquire and M1 phenotype and cause increasing injury and decreased Aβ clearance [21].

Chemokines—Chemokines and their receptors also appear to modulate Aβ-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 Aβ 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 Aβ. An active area of investigation as well is the role of recruited monocyte macrophages to AD pathology or Aβ 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 Aβ 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 Aβ clearance or damaging Aβ peptide-induced inflammation.

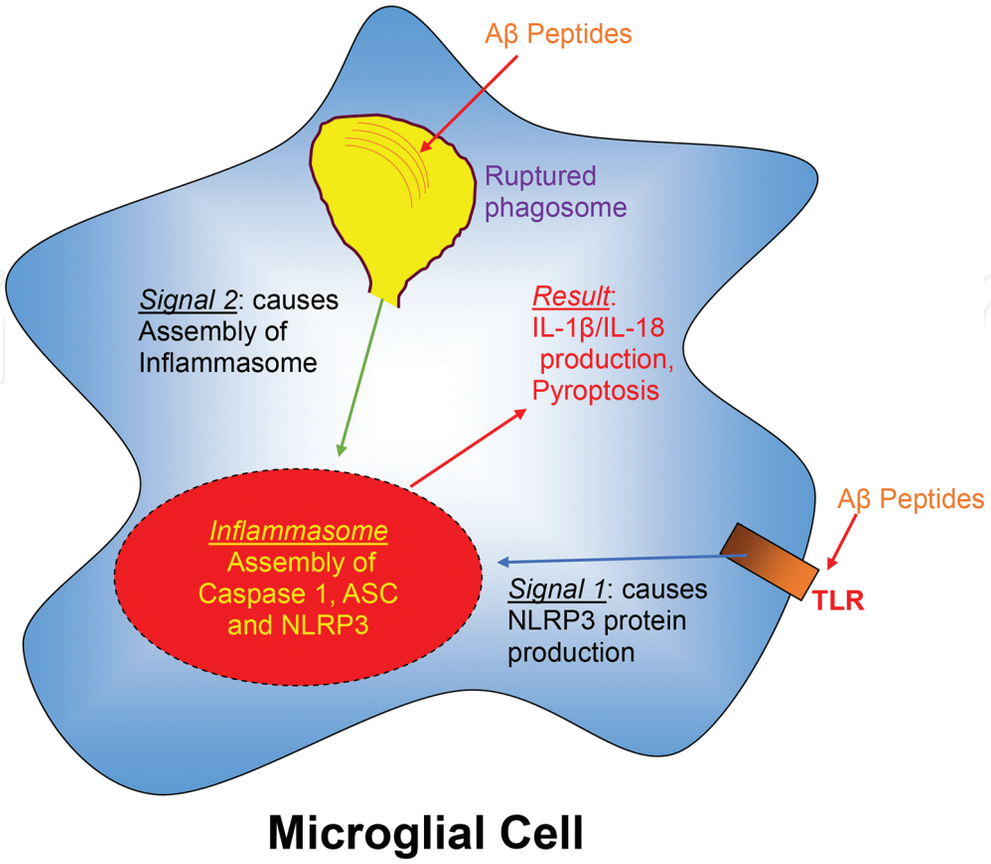

Figure 1. Microglial NLRP3 inflammasome activation by Aβ oligomers—the NLRP3 inflammasome can be activated by various PAMPs or DAMPS. Aβ oligomers can be considered as a DAMP which leads to NLRP3 activation in microglia. To induce NLRP3 activation, there needs to be at least two signals. The first signal 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-1β and pro-IL-18 to form active IL-1β 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 Aβ. The exact triggers of signal 1 and 2 are have not been fully elucidated. Since Aβ 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 Aβ. 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 Aβ production?—Thus far most of the studies we, we have discussed consider the downstream effects of Aβ accumulation on inflammation or cellular dysfunction. For early onset AD, and for the APP/PS1 mice, increased Aβ accumulation is the result of alterations of the Aβ protein itself or of the enzymes involved in cleavage of the precursor protein. It is unclear, however, what triggers Aβ production under normal circumstances or in late onset AD. Attempts to directly reduce Aβ levels through the use of antibodies against Aβ 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 Aβ 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.

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If it was possible to determine the initial causes for Aβ accumulation in the brain, this might provide another approach to early intervention. One hypothesis is that infection initiates or sustains the process of Aβ accumulation. Excess accumulation of Aβ has been linked to Human Immunodeficiency Virus-related dementia [51, 52], and the virus can cause Aβ accumulation in vitro as well [53, 54]. Similarly Herpes Simplex Virus (HSV) induced encephalitis, and HSV infection in vitro is associated with Aβ accumulation [55–59], again implying that viruses may be a stimulus of Aβ production or impaired clearance. These findings suggest that viruses that infect the brain could be triggers for accumulation of Aβ, 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. Aβ peptides as antimicrobial agents—An alternative hypothesis to explain Aβ peptide and ultimately plaque production is that it is part of a host defense response to infectious or traumatic injury. Aβ peptides resemble some anti-microbial peptides or AMPs in their structure [68, 69]. Aβ 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 Aβ peptides [70]. In addition, this study showed that Aβ isolated from the brain of AD patients had antimicrobial activity and that incubation of these brain-derived samples with antibodies to Aβ ablated the antimicrobial activity. More recently, we demonstrated that Aβ peptides also have antiviral activity using influenza A virus as a model [71]. In our study and that of Soscia et al., Aβ1-42 was found to have greater antimicrobial or antiviral activity than Aβ1-40. We demonstrated that Aβ1-42, but not Aβ1-40, caused viral aggregation which appears to contribute to its antiviral effects. This implies a possible connection between the ability of Aβ1-42 to assemble into oligomers and its antiviral activity, since this peptide has a greater propensity to form oligomers and fibrils than Aβ1-40.

The finding that Aβ peptides, especially, Aβ1-42 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 Aβ1-42 modulates responses of neutrophils and monocytes to the influenza virus [71]. Aβ1-42 increased neutrophil uptake of influenza A virus and potentiated neutrophil respiratory burst and neutrophil extracellular trap (NET) formation in response to the virus. Aβ1-42 also reduced inflammatory cytokine production triggered by influenza virus in monocytes. The opsonizing activity of Aβ1-42 was again not replicated with Aβ1-40. More recently, we found that Aβ peptides can increase neutrophil uptake of bacteria as well (unpublished data). Overall, these studies lend support to the hypothesis that Aβ 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 Aβ peptides, especially Aβ1-42, 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 Aβ 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 Aβ 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 Aβ 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 Aβ peptides (especially Aβ1-42) function like other AMPs suggest that Aβ 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.

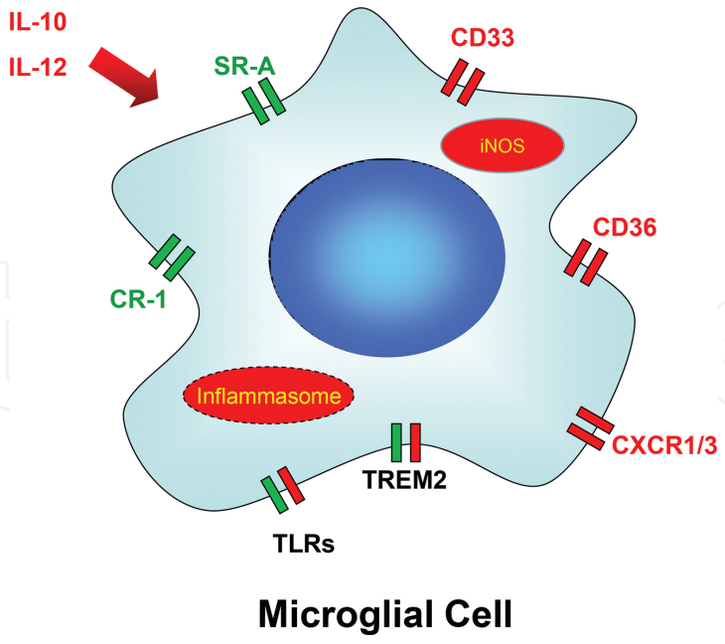

Figure 2. Microglial receptors and signaling pathways that are involved in response to Aβ—receptors, signaling pathways or extracellular cytokines shown to promote neuronal injury are shown in red, whereas those shown in green are protective vs neuronal injury or progression of AD like pathology. Receptors 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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References

[1] Dahlgren KN, Manelli AM, Stine WB, Jr., Baker LK, Krafft GA, LaDu MJ. Oligomeric and fibrillar species of amyloid-beta peptides differentially affect neuronal viability. J Biol Chem. 2002;277(35):32046–53. PubMed PMID: 12058030.

[2] Masters CL, Selkoe DJ. Biochemistry of amyloid beta-protein and amyloid deposits in Alzheimer disease. Cold Spring Harbor Perspect Med. 2012;2(6):a006262. doi:10.1101/cshperspect.a006262. PubMed PMID: 22675658; PubMed Central PMCID: PMC3367542.

[3] Selkoe DJ. Biochemistry and molecular biology of amyloid beta-protein and the mechanism of Alzheimer's disease. Handb Clin Neurol. 2008;89:245–60. doi:10.1016/S0072-9752(07)01223-7. PubMed PMID: 18631749.

[4] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013;493(7434):674–8. doi:10.1038/nature11729. PubMed PMID: 23254930; PubMed Central PMCID: PMC3812809.

[5] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388–405. doi: 10.1016/S1474-4422(15)70016-5. PubMed PMID: 25792098.

[6] Hickman SE, El Khoury J. TREM2 and the neuroimmunology of Alzheimer's disease. Biochem Pharmacol. 2014;88(4):495–8. doi:10.1016/j.bcp.2013.11.021. PubMed PMID: 24355566; PubMed Central PMCID: PMC3972304.

[7] Burton A. NSAIDS and Alzheimer's disease: it's only Rock and Rho. Lancet Neurol. 2004;3(1):6. PubMed PMID: 14700055.

[8] Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature. 2001;414(6860):212–6. doi:10.1038/35102591. PubMed PMID: 11700559.

[9] Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, et al. Complement activation by beta-amyloid in Alzheimer disease. Proc Natl Acad Sci USA. 1992;89(21): 10016–20. PubMed PMID: 1438191; PubMed Central PMCID: PMC50268.

[10] Barrientos RM, Kitt MM, Watkins LR, Maier SF. Neuroinflammation in the normal aging hippocampus. Neuroscience. 2015;309:84–99. doi:10.1016/j.neuroscience. 2015.03.007. PubMed PMID: 25772789; PubMed Central PMCID: PMC4567963.

[11] Jiang T, Yu JT, Zhu XC, Tan MS, Gu LZ, Zhang YD, et al. Triggering receptor expressed on myeloid cells 2 knockdown exacerbates aging-related neuroinflammation and cognitive deficiency in senescence-accelerated mouse prone 8 mice. Neurobiol Aging. 2014;35(6):1243–51. doi:10.1016/j.neurobiolaging.2013.11.026. PubMed PMID: 24368090.

[12] Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106–18. doi:10.1038/nrneurol. 2012.263. PubMed PMID: 23296339; PubMed Central PMCID: PMC3726719.

[13] Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. Cold Spring Harbor Perspect Med. 2012;2(3):a006312. doi:10.1101/cshperspect.a006312. PubMed PMID: 22393530; PubMed Central PMCID: PMC3282491.

[14] Hartshorn KL. Role of surfactant protein A and D (SP-A and SP-D) in human antiviral host defense. Front Biosci (Schol Ed). 2010;2:527–46. PubMed PMID: 20036966.

[15] Nybo M, Andersen K, Sorensen GL, Lolk A, Kragh-Sorensen P, Holmskov U. Serum surfactant protein D is correlated to development of dementia and augmented mortality. Clin Immunol. 2007;123(3):333–7. PubMed PMID: 17449329.

[16] Neumann H, Daly MJ. Variant TREM2 as risk factor for Alzheimer's disease. N Engl J Med. 2013;368(2):182–4. doi:10.1056/NEJMe1213157. PubMed PMID: 23151315.

[17] Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. 2013;368(2): 107–16. doi:10.1056/NEJMoa1211103. PubMed PMID: 23150908; PubMed Central PMCID: PMC3677583.

[18] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, et al. TREM2 variants in Alzheimer's disease. N Engl J Med. 2013;368(2):117–27. doi:10.1056/NEJMoa1211851. PubMed PMID: 23150934; PubMed Central PMCID: PMC3631573.

[19] Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K, et al. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron. 2013;78(4):631–43. doi:10.1016/j.neuron.2013.04.014. PubMed PMID: 23623698; PubMed Central PMCID: PMC3706457.

[20] Brouwers N, Van Cauwenberghe C, Engelborghs S, Lambert JC, Bettens K, Le Bastard N, et al. Alzheimer risk associated with a copy number variation in the complement

receptor 1 increasing C3b/C4b binding sites. Mol Psychiatry. 2012;17(2):223–33. doi: 10.1038/mp.2011.24. PubMed PMID: 21403675; PubMed Central PMCID: PMC3265835.

[21] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nat Immunol. 2015;16(3):229–36. doi:10.1038/ni.3102. PubMed PMID: 25689443.

[22] Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, Puckett L, et al. Scara1 deficiency impairs clearance of soluble amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. Nat Commun. 2013;4:2030. doi: 10.1038/ncomms3030. PubMed PMID: 23799536; PubMed Central PMCID: PMC3702268.

[23] Wilkinson K, El Khoury J. Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int J Alzheimer's Dis. 2012;2012:489456. doi: 10.1155/2012/489456. PubMed PMID: 22666621; PubMed Central PMCID: PMC3362056.

[24] Stewart CR, Stuart LM, Wilkinson K, van Gils JM, Deng J, Halle A, et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol. 2010;11(2):155–61. doi:10.1038/ni.1836. PubMed PMID: 20037584; PubMed Central PMCID: PMC2809046.

[25] Coraci IS, Husemann J, Berman JW, Hulette C, Dufour JH, Campanella GK, et al. CD36, a class B scavenger receptor, is expressed on microglia in Alzheimer's disease brains and can mediate production of reactive oxygen species in response to beta-amyloid fibrils. Am J Pathol. 2002;160(1):101–12. PubMed PMID: 11786404; PubMed Central PMCID: PMC1867121.

[26] Carlin AF, Chang YC, Areschoug T, Lindahl G, Hurtado-Ziola N, King CC, et al. Group B Streptococcus suppression of phagocyte functions by protein-mediated engagement of human Siglec-5. J Exp Med. 2009;206(8):1691–9. PubMed PMID: 19596804.

[27] Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. J Exp Med. 2015;212(3):287–95. doi:10.1084/jem.20142322. PubMed PMID: 25732305; PubMed Central PMCID: PMC4354365.

[28] Jiang T, Tan L, Zhu XC, Zhang QQ, Cao L, Tan MS, et al. Upregulation of TREM2 ameliorates neuropathology and rescues spatial cognitive impairment in a transgenic mouse model of Alzheimer's disease. Neuropsychopharmacology. 2014;39(13):2949–62. doi:10.1038/npp.2014.164. PubMed PMID: 25047746; PubMed Central PMCID: PMC4229581.

[29] Atagi Y, Liu CC, Painter MM, Chen XF, Verbeeck C, Zheng H, et al. Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J Biol Chem. 2015;290(43):26043–50. doi:10.1074/jbc.M115.679043. PubMed PMID: 26374899; PubMed Central PMCID: PMC4646257.

[30] Li X, Montine KS, Keene CD, Montine TJ. Different mechanisms of apolipoprotein E isoform-dependent modulation of prostaglandin E2 production and triggering receptor expressed on myeloid cells 2 (TREM2) expression after innate immune activation of microglia. FASEB J. 2015;29(5):1754–62. doi:10.1096/fj.14-262683. PubMed PMID: 25593125; PubMed Central PMCID: PMC4415020.

[31] Rogers J, Li R, Mastroeni D, Grover A, Leonard B, Ahern G, et al. Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. Neurobiol Aging. 2006;27(12):1733–9. doi:10.1016/j.neurobiolaging.2005.09.043. PubMed PMID: 16290270.

[32] Wyss-Coray T, Yan F, Lin AH, Lambris JD, Alexander JJ, Quigg RJ, et al. Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. Proc Natl Acad Sci USA. 2002;99(16):10837–42. doi:10.1073/pnas.162350199. PubMed PMID: 12119423; PubMed Central PMCID: PMC125059.

[33] Michaud JP, Richard KL, Rivest S. MyD88-adaptor protein acts as a preventive mechanism for memory deficits in a mouse model of Alzheimer's disease. Mol Neurodegener. 2011;6(1):5. doi:10.1186/1750-1326-6-5. PubMed PMID: 21235801; PubMed Central PMCID: PMC3030527.

[34] Jana M, Palencia CA, Pahan K. Fibrillar amyloid-beta peptides activate microglia via TLR2: implications for Alzheimer's disease. J Immunol. 2008;181(10):7254–62. PubMed PMID: 18981147.

[35] Tang SC, Lathia JD, Selvaraj PK, Jo DG, Mughal MR, Cheng A, et al. Toll-like receptor-4 mediates neuronal apoptosis induced by amyloid beta-peptide and the membrane lipid peroxidation product 4-hydroxynonenal. Exp Neurol. 2008;213(1):114–21. PubMed PMID: 18586243.

[36] Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid beta 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. J Neurosci. 2008;28(22):5784–93. PubMed PMID: 18509040.

[37] Chen K, Iribarren P, Hu J, Chen J, Gong W, Cho EH, et al. Activation of Toll-like receptor 2 on microglia promotes cell uptake of Alzheimer disease-associated amyloid beta peptide. J Biol Chem. 2006;281(6):3651–9. PubMed PMID: 16339765.

[38] Michaud JP, Halle M, Lampron A, Theriault P, Prefontaine P, Filali M, et al. Toll-like receptor 4 stimulation with the detoxified ligand monophosphoryl lipid A improves Alzheimer's disease-related pathology. Proc Natl Acad Sci USA. 2013;110(5):1941–6. doi:10.1073/pnas.1215165110. PubMed PMID: 23322736; PubMed Central PMCID: PMC3562771.

[39] Michaud JP, Rivest S. Anti–inflammatory signaling in microglia exacerbates Alzheimer's disease-related pathology. Neuron. 2015;85(3):450–2. doi:10.1016/j.neuron.2015.01.021. PubMed PMID: 25654250.

[40] Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhelawon B, Carpenter SB, et al. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. Nat Immunol. 2013;14(8):812–20. doi:10.1038/ni.2639. PubMed PMID: 23812099; PubMed Central PMCID: PMC3720827.

[41] Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol. 2008;9(8):857–65. doi:10.1038/ni.1636. PubMed PMID: 18604209; PubMed Central PMCID: PMC3101478.

[42] Gold M, El Khoury J. beta-amyloid, microglia, and the inflammasome in Alzheimer's disease. Semin Immunopathol. 2015;37(6):607–11. doi:10.1007/s00281-015-0518-0. PubMed PMID: 26251237; PubMed Central PMCID: PMC4618770.

[43] Lamkanfi M, Dixit VM. Inflammasomes and their roles in health and disease. Annu Rev Cell Dev Biol. 2012;28:137–61. PubMed PMID: 22974247.

[44] Krauthausen M, Kummer MP, Zimmermann J, Reyes-Irisarri E, Terwel D, Bulic B, et al. CXCR3 promotes plaque formation and behavioral deficits in an Alzheimer's disease model. J Clin Invest. 2015;125(1):365–78. doi:10.1172/JCI66771. PubMed PMID: 25500888; PubMed Central PMCID: PMC4382235.

[45] Fuhrmann M, Bittner T, Jung CK, Burgold S, Page RM, Mitteregger G, et al. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. Nat Neurosci. 2010;13(4):411–3. doi:10.1038/nn.2511. PubMed PMID: 20305648; PubMed Central PMCID: PMC4072212.

[46] Hickman SE, El Khoury J. Mechanisms of mononuclear phagocyte recruitment in Alzheimer's disease. CNS Neurol Disord Drug Targets. 2010;9(2):168–73. PubMed PMID: 20205643; PubMed Central PMCID: PMC3684802.

[47] Lee YK, Kwak DH, Oh KW, Nam SY, Lee BJ, Yun YW, et al. CCR5 deficiency induces astrocyte activation, Abeta deposit and impaired memory function. Neurobiol Learn Memory. 2009;92(3):356–63. doi:10.1016/j.nlm.2009.04.003. PubMed PMID: 19394434.

[48] Vom Berg J, Prokop S, Miller KR, Obst J, Kalin RE, Lopategui-Cabezas I, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. Nat Med. 2012;18(12):1812–9. doi:10.1038/nm.2965. PubMed PMID: 23178247.

[49] Huang TC, Lu KT, Wo YY, Wu YJ, Yang YL. Resveratrol protects rats from Abeta-induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation. PLoS One. 2011;6(12):e29102. doi:10.1371/journal.pone.0029102. PubMed PMID: 22220203; PubMed Central PMCID: PMC3248406.

[50] Medeiros R, Prediger RD, Passos GF, Pandolfo P, Duarte FS, Franco JL, et al. Connecting TNF-alpha signaling pathways to iNOS expression in a mouse model of Alzheimer's disease: relevance for the behavioral and synaptic deficits induced by amyloid beta

protein. J Neurosci. 2007;27(20):5394–404. doi:10.1523/JNEUROSCI.5047-06.2007. PubMed PMID: 17507561.

[51] Zhang J, Liu J, Katafiasz B, Fox H, Xiong H. HIV-1 gp120-induced axonal injury detected by accumulation of beta-amyloid precursor protein in adult rat corpus callosum. J Neuroimmune Pharmacol. 2011;6(4):650–7. PubMed PMID: 21286834.

[52] Andras IE, Eum SY, Toborek M. Lipid rafts and functional caveolae regulate HIV-induced amyloid beta accumulation in brain endothelial cells. Biochem Biophys Res Commun. 2012;421(2):177–83. PubMed PMID: 22490665.

[53] Lan X, Kiyota T, Hanamsagar R, Huang Y, Andrews S, Peng H, et al. The effect of HIV protease inhibitors on amyloid-beta peptide degradation and synthesis in human cells and Alzheimer's disease animal model. J Neuroimmune Pharmacol. 2012;7(2):412–23. doi:10.1007/s11481-011-9304-5. PubMed PMID: 21826404; PubMed Central PMCID: PMC3223330.

[54] Lan X, Xu J, Kiyota T, Peng H, Zheng JC, Ikezu T. HIV-1 reduces Abeta-degrading enzymatic activities in primary human mononuclear phagocytes. J Immunol. 186(12): 6925–32. PubMed PMID: 21551363.

[55] Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett. 2007;429(2–3):95–100. PubMed PMID: 17980964.

[56] Wozniak MA, Frost AL, Preston CM, Itzhaki RF. Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1. PLoS One. 2011;6(10):e25152. PubMed PMID: 22003387.

[57] De Chiara G, Marcocci ME, Civitelli L, Argnani R, Piacentini R, Ripoli C, et al. APP processing induced by herpes simplex virus type 1 (HSV-1) yields several APP fragments in human and rat neuronal cells. PLoS One. 2010;5(11):e13989. PubMed PMID: 21085580.

[58] Lukiw WJ, Cui JG, Yuan LY, Bhattacharjee PS, Corkern M, Clement C, et al. Acyclovir or Abeta42 peptides attenuate HSV-1-induced miRNA-146a levels in human primary brain cells. Neuroreport. 2010;21(14):922–7. PubMed PMID: 20683212.

[59] Piacentini R, Civitelli L, Ripoli C, Marcocci ME, De Chiara G, Garaci E, et al. HSV-1 promotes Ca2+ -mediated APP phosphorylation and Abeta accumulation in rat cortical neurons. Neurobiol Aging. 2010;32(12):2323 e13–26. PubMed PMID: 20674092.

[60] Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA, et al. Virological and immunological characteristics of human cytomegalovirus infection associated with Alzheimer disease. J Infect Dis. 2013;208(4):564–72. PubMed PMID: 23661800.

[61] Carbone I, Lazzarotto T, Ianni M, Porcellini E, Forti P, Masliah E, et al. Herpes virus in Alzheimer's disease: relation to progression of the disease. Neurobiol Aging. 2013;35(1): 122–9. PubMed PMID: 23916950.

[62] Agostini S, Mancuso R, Baglio F, Cabinio M, Hernis A, Guerini FR, et al. Lack of evidence for a role of HHV-6 in the pathogenesis of Alzheimer's disease. J Alzheimers Dis. 2015;49(1):229–35. doi:10.3233/JAD-150464. PubMed PMID: 26444787.

[63] Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. BMC Neurosci. 2010;11:121. doi:10.1186/1471-2202-11-121. PubMed PMID: 20863379; PubMed Central PMCID: PMC2949767.

[64] Gerard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, et al. Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. FEMS Immunol Med Microbiol. 2006;48(3):355–66. doi:10.1111/j.1574-695X.2006.00154.x. PubMed PMID: 17052268.

[65] Pisa D, Alonso R, Rabano A, Rodal I, Carrasco L. Different brain regions are infected with Fungi in Alzheimer's disease. Sci Rep. 2015;5:15015. doi:10.1038/srep15015. PubMed PMID: 26468932; PubMed Central PMCID: PMC4606562.

[66] Alonso R, Pisa D, Rabano A, Rodal I, Carrasco L. Cerebrospinal fluid from Alzheimer's disease patients contains fungal proteins and DNA. J Alzheimers Dis. 2015;47(4): 873–6. doi:10.3233/JAD-150382. PubMed PMID: 26401766.

[67] Alonso R, Pisa D, Rabano A, Carrasco L. Alzheimer's disease and disseminated mycoses. Eur J Clin Microbiol Infect Dis. 2014;33(7):1125–32. doi:10.1007/s10096-013-2045-z. PubMed PMID: 24452965.

[68] Kagan BL, Jang H, Capone R, Teran Arce F, Ramachandran S, Lal R, et al. Antimicrobial properties of amyloid peptides. Mol Pharm. 2012;9(4):708–17. PubMed PMID: 22081976.

[69] Jang H, Ma B, Lal R, Nussinov R. Models of toxic beta-sheet channels of protegrin-1 suggest a common subunit organization motif shared with toxic alzheimer beta-amyloid ion channels. Biophys J. 2008;95(10):4631–42. PubMed PMID: 18708452.

[70] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One. 2010;5(3):e9505. PubMed PMID: 20209079.

[71] White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, et al. Alzheimer's associated beta-amyloid protein inhibits influenza A virus and modulates viral interactions with phagocytes. PLoS One. 2014;9(7):e101364. doi:10.1371/journal.pone.0101364. PubMed PMID: 24988208; PubMed Central PMCID: PMC4079246.

[72] Oppenheim JJ, Yang D. Alarmins: chemotactic activators of immune responses. Curr Opin Immunol. 2005;17(4):359–65. PubMed PMID: 15955682.

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