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REVIEW

β-amyloid, microglia, and the inflammasome in Alzheimer's disease

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Abstract There is extensive evidence that accumulation of mononuclear phagocytes including microglial cells, monocytes, and macrophages at sites of β-amyloid (Aβ) deposition in the brain is an important pathological feature of Alzheimer's disease (AD) and related animal models, and the concentration of these cells clustered around Aβ deposits is several folds higher than in neighboring areas of the brain [1–5]. Microglial cells phagocytose and clear debris, pathogens, and toxins, but they can also be activated to produce inflammatory cytokines, chemokines, and neurotoxins [6]. Over the past decade, the roles of microglial cells in AD have begun to be clarified, and we proposed that these cells play a dichotomous role in the pathogenesis of AD [4, 6–11]. Microglial cells are able to clear soluble and fibrillar Aβ, but continued interactions of these cells with Aβ can lead to an inflammatory response resulting in neurotoxicity. Inflammasomes are inducible high molecular weight protein complexes that are involved in many inflammatory pathological processes. Recently, Aβ was found to activate the NLRP3 inflammasome in microglial cells in vitro and in vivo thereby defining a novel pathway that could lead to progression of AD [12–14]. In this manuscript, we review possible steps leading to Aβ-induced inflammasome activation and discuss how this could contribute to the pathogenesis of AD.

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Function of microglial cells in the brain

Five to twelve percent of all cells in the brain are microglial cells, depending on the brain region [15]. Because of their immunomodulatory function, they are considered the resident macrophages of the brain. Using direct RNA sequencing, our group found important differences in gene expression between microglial cells and peripheral monocytes and macrophages [16]. However, in spite of these differences, microglial cells share a myeloid origin and several similarities in their receptor repertoire with peripheral monocytes and macrophages. All three cell types also share the ability to activate several inflammatory pathways in response to injurious stimuli.

In general, microglial cells constantly sense and screen the environment with their processes. They are able to adopt an amoeboid shape, migrate to the location of an injury, and become activated [17]. Activated microglial cells are found in states of infection and trauma but also in neurodegenerative diseases like Parkinson disease, prion disease, and AD. Elevated levels of pro-inflammatory mediators have been found in all of these conditions [18–20]. The production of such mediators including cytokines, chemokines, reactive oxygen species, and nitrogen monoxide [9, 21] helps to attract more microglial cells and possibly peripheral monocytes and ultimately could lead to the removal of pathogens and other toxic stimuli.

Microglia and Aβ

Microglial cells, monocytes, and macrophages express receptors that promote phagocytosis of Aβ, and intracellular Aβ

deposits have been observed in mononuclear phagocytes in AD brains. These cells also express Aβ degrading enzymes further contributing to Aβ clearance. In mouse models of AD, we found that uptake of Aβ is mediated via the class A scavenger receptor Scara1, and deficiency in this receptor is associated with increased mortality and Aβ accumulation in these mice [8, 10] further supporting the paradigm that these cells play a neuroprotective role by promoting Aβ phagocytosis, degradation, and clearance. On the other hand, we also found that the interaction of Aβ with a receptor complex that includes the pattern recognition receptor CD36 and a heterodimer composed of the Toll-like receptors (TLR) 4 and 6, is required for activation of microglial cells and the production of inflammatory cytokines, chemokines, and neurotoxins [9, 11]. Following Aβ binding to this receptor complex, intracellular signaling leads to the translocation of nuclear factor κB (NFκB) from the cytoplasm into the nucleus [22] but also activation of cAMP/protein kinase A/phosphorylated cAMP response element binding protein (CREB) [23] resulting in the transcription of several pro-inflammatory cytokines, NO-Synthase, and cyclooxygenase-2 [24, 25]. Recently, an alternative intracellular signaling pathway that is downstream from Aβ binding came into focus: the activation of the NLRP3 inflammasome [13, 14].

The NLRP3 inflammasome

Inflammasomes are inducible high molecular weight protein complexes that were described first by Martinon et al. in 2002 [26]. Four different inflammasomes and their activators have been well characterized so far: NLRP1 [27], NLRP3 [28], NLRC4 [29], and AIM2 [30]. The NLRP3 inflammasome in particular seems to be involved in many pathological mechanisms, since it is activated by several microbes [31, 32], urate crystals [33], cholesterol crystals [34], and soluble and aggregated Aβ [12]. The NLRP3 inflammasome is an intracellular protein complex consisting of the sensor protein NLRP3, the adaptor protein apoptosis-associated speck-like protein containing a caspase activating and recruitment domain (ASC) and pro caspase-1. Assembly and activation of this complex leads to the cleavage of pro caspase-1 to active caspase-1 (Fig. 1). Active caspase-1 in turn cleaves and thereby activates pro-inflammatory cytokines of the IL-1β family. IL-1β is synthesized as an inactive precursor and undergoes posttranslational modifications to become an active cytokine [35]. IL-1β is a very potent pyrogenic cytokine and therefore its production and release has to be tightly controlled. In the central nervous system, IL-1β seems to impact long-term potentiation and synaptic plasticity in the hippocampus where memory is consolidated [36].

Two steps are necessary to activate the NLRP3 inflammasome: the first step involves "priming" of the inflammasome, and is the result of disinhibition and nuclear translocation of NF-kB which leads to the transcription of NLRP3 itself and pro IL-1β, both prerequisites for the actual activation of the inflammasome [37, 38]. Many signaling pathways induced by a plethora of stimuli converge in the activation of NF-kB—the most prominent stimuli being LPS that signals via TLR4/CD14 [39]. A much faster way to make NLRP3 available is the deubiquitination of NLRP3 which is suggested to be dependent on mitochondrial ROS activity [40]. The second step of NLRP3 activation is the oligomerization of NLRP3 and the assembly with ASC and pro caspase-1. NLRP3 has been shown to sense putative ligands with its C-terminal leucine-rich repeats and self-oligomerizes via its nucleotide binding domain NACHT [41]. Upon oligomerization, ASC joins the complex and recruits caspase-1 via its caspase recruitment and activating domain (CARD) [42]. In addition, data from murine macrophages indicate that ASC specks can transmit inflammasome activation from cell-to-cell in a prion-like manner [43, 44].

Because inflammasome activation is involved in many pathological processes, attention has been shifting lately to understanding mechanisms of inflammasome regulation. Yan et al. found that dopamine serves as an endogenous inhibitor of the NLRP3 inflammasome [45]. This dopamine effect may be mediated via dopamine receptor 1 which is expressed on many subsets of immune cells including microglial cells [46]. The proposed underlying mechanism of NLRP3 inhibition in this context is ubiquitination and autophagy-mediated degradation of NLRP3 mediated by increased levels of cAMP as described earlier by Lee et al. [47]. In addition, to such endogenous regulatory pathways, Coll et al. characterized a very specific NLRP3 small inhibitor [48]. MCC950, a diarylsulfonylurea-containing compound, blocked NLRP3 inflammasome activation induced by ATP, Nigericin, and urate crystals in vitro in human and murine macrophages and delayed the onset and slowed the progression of experimental autoimmune encephalitis, an in vivo mouse model of multiple sclerosis. This inhibitor could be used to study the suitability of NLRP3 as a therapeutic target in many diseases.

The NLRP3 inflammasome in AD

Elevated levels of IL-1β, an endproduct of inflammasome activation, have been reported in brains of AD patients as far back as 1989 [49]. It took nearly three decades to identify a potential pathway that could explain such elevated levels, when Aβ was identified as an inflammasome activator [12]. Halle et al. proposed that phagocytosis of Aβ is the first step in NLRP3 inflammasome activation. Such activation required priming of bone-marrow-derived macrophages and microglia with interferon-γ or LPS before uptake of Aβ fibrils. Inhibition of phagocytosis with cytochalasin D abrogated inflammasome activation by Aβ fibrils. Following their

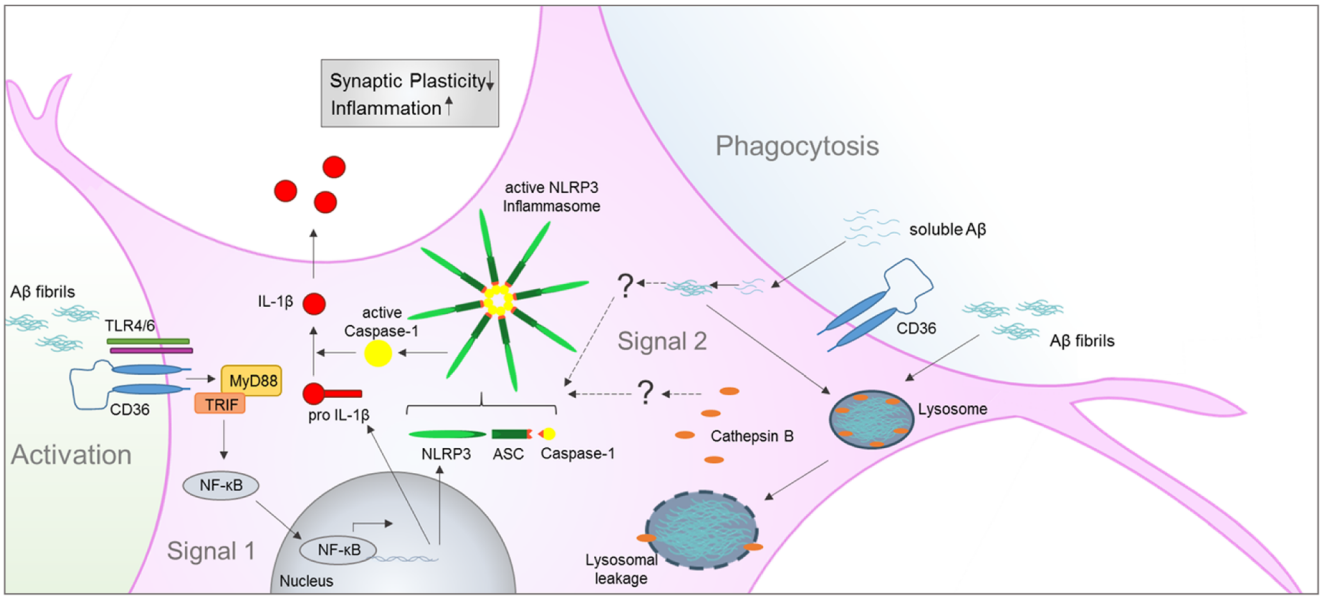

Fig. 1 Activation of the NLRP3 inflammasome by Aβ. Both soluble and fibrillar Aβ can contribute to inflammasome activation. Aβ fibrils cause activation of microglial cells and therefore provide signal 1 via NF-κB transcription of NLRP3 and pro IL-1β. Signal 2 can either be provided by intracellular aggregation of soluble Aβ or by lysosomal rupture through phagocytosed Aβ fibrils. Both events lead to the formation of the active NLRP3 inflammasome. Active Caspase-1 finally cleaves pro IL-1β to active IL-1β which is released into the extracellular space

phagocytosis, Aβ fibrils localize in intracellular lysosomes, compromising the membrane of these lysosomes and leading to the release cathepsin B, a lysosomal proteolytic enzyme, into the cytosol, thereby activating the inflammasome (Fig. 1). The mechanisms by which cathepsin B activates the inflammasome and whether this phenomenon occurs in AD patients or AD animal models is not clear. Data from Aβ treated rat primary microglial cells suggest an inhibitory role for NLRP10 in this context [50]. NLRP10 inhibits the formation of the NLRP3 inflammasome by interacting with ASC. Upon treatment with a cocktail of aggregated Aβ1-42 and Aβ1-40, NLRP10 is degraded, probably by cathepsins, allowing the NLRP3 inflammasome protein complex to be formed.

Sheedy et al. suggested that the pattern recognition receptor CD36 is a possible receptor for soluble Aβ that conveys the signal from Aβ to the inflammasome in the aforementioned two-step manner [14]. CD36 seems to be responsible for priming of the cells through activation of the receptor complex CD36/TLR4/6, subsequent translocation of NF-κB to the nucleus and transcription of NLRP3 and pro IL-1β (Fig. 1). The mechanism by which soluble Aβ leads to the assembly of the NLRP3 inflammasome is not fully understood. Sheedy et al. show intracellular formation of Aβ fibrils and lysosomal location after 3 h of treatment with soluble Aβ, but they did not determine lysosomal integrity or the levels of cathepsin B. Aβ treatment of cells obtained from *CD36*$^{-/-}$ mice or pretreatment with Congo red that interferes with the formation of β-sheets, reduces IL-1β secretion. However, in this study, murine bone-marrow-derived macrophages were used and not immune cells isolated from the brain.

In 2013 Heneka et al. showed enhanced caspase-1 activation in human brains from patients suffering from mild cognitive impairment and AD. They also found that NLRP3 or Caspase-1 deficiency in mice that carry mutations associated with familial AD (APP/PS1) were associated with improvements in cognitive decline [13]. In addition, APP/PS1/*Nlrp3*$^{-/-}$ mice had reduced hippocampal and cortical Aβ deposition, although the processing and expression of the amyloid precursor protein was not affected. Using methoxy-XO4, a fluorescent molecule that binds Aβ with high affinity, injected intraperitoneally into adult APP/PS1/ *Nlrp3*$^{-/-}$ and APP/PS1/*Casp1*$^{-/-}$ mice, the authors showed a twofold increase in Aβ phagocytosis by microglial cells from these mice compared to APP/PS1 mice. This finding suggests that NLRP3 inflammasome activation reduces phagocytosis of Aβ by microglial cells. NLRP3 activation could therefore contribute to the pathogenesis of AD via two processes. First, it can regulate production of IL-1β and possibly neurotoxins causing neuronal degeneration. Second, it can reduce Aβ clearance leading to enhanced deposition, thereby creating a self-perpetuating loop that culminated in AD progression.

A second pathway that might contribute to inflammasome activation in AD brains involves extracellular ATP and the purinergic receptor P2X7. Extracellular ATP may be released by dying or degenerating neurons and activates P2X7 [28, 51]. P2X7, which is expressed on microglia [16], in turn activates the NLRP3 inflammasome [28, 51]. Interestingly, P2X7 expression is increased in human AD brains [52]. Based on

these reports, it is possible that signaling via P2X7 provides a second mechanism for NLRP3 inflammasome activation in addition to Aβ-induced signaling [53].

Open questions and caveats

Because microglial cells are the resident mononuclear phagocytes of the CNS, most published studies refer to Aβ-associated mononuclear phagocytes as microglia. Work done in animal models of Aβ deposition suggested that in addition to microglia, some Aβ-associated mononuclear phagocytes are blood or bone-marrow-derived monocytes [54, 55]. Our own work using the Tg2576 mouse model of Aβ deposition supported the possibility that blood-borne monocytes accumulate in the brains of these mice as the disease progresses [8]. Indeed, we observed a significant increase in $CD11b^{+}/CD45^{hi}$ cells (believed to be monocytes based on their high expression of CD45 [56, 57]) in Tg2576 animals compared to non-Tg controls. We also found that accumulation of $CD11b^{+}/CD45^{hi}$ cells is significantly impaired in Tg2576 mice deficient in the chemokine receptor Ccr2 [8], a major chemokine receptor highly expressed on monocytes [58] but not on resident microglia [16]. This was later confirmed by Naert and colleagues [59]. More recent reports showed that cells expressing monocyte markers are associated with plaques in two transgenic models of Aβ deposition [60] and that adoptively transferred monocytes home in to these plaques [61]. Furthermore, while CD36 is expressed in microglial cells, its level of expression on peripheral monocytes and macrophages is more than 100-fold higher than in microglial cells [16]. These studies raise the possibility that Aβ-induced CD36-dependent inflammasome activation in AD may occur not only in microglia but also in peripheral blood monocytes recruited to the brain.

Conclusion

The NLRP3 inflammasome appears to play an important role in the pathogenesis and progression of AD making an attractive target for therapeutic intervention. However, interfering with key parts of the inflammasome (NLRP3, ASC, and Caspase-1) in a shotgun manner as a therapeutic approach may also have serious systemic effects because of the ubiquitous distribution and importance of inflammasome activation in many peripheral processes. Future research should focus on identifying CNS-specific pathways leading to inflammasome activation, including possible additional receptors or endogenous cell-specific inhibitors.

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Conflict of interest The authors declare that they have no competing interests.

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