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Amyloid-β oligomers set fire to inflammasomes and induce Alzheimer's pathology

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Abstract

Genetic and molecular studies have confirmed the central role of amyloid-ß production and fibrillation in the pathogenesis of Alzheimer's disease (AD). However, the pathological pathways from amyloid-ß peptide oligomerization to the major pathological hallmarks of AD, such as neurofibrillary tangles, inflammation and loss of cholinergic neurons, are largely unknown. The innate immunity defence system utilizes pattern recognition receptors to respond to a variety of danger- and pathogen-associated molecular structures. Amyloid-ß oligomers and fibrils and their cellular effects can activate the innate immunity defence and induce inflammatory and apoptotic responses in human brain. Amyloid-ß oligomers can interfere with many aspects of neuronal membrane functions and can evoke potassium (K^+) efflux from neurons. A low K^+ concentration is a potent activator for the NALP1 inflammasomes, which then stimulate caspase-1 to cleave the proforms of IL-1ß and IL-18 cytokines. Interestingly, recent observations have demonstrated that amyloid-ß fibrils can activate NALP3 inflammasomes *via* the lysosomal damage in mouse microglia. We will review here the activation mechanisms of NALP inflammasomes in neurons and microglia and several downstream effects in brain demonstrating that toxic amyloid-ß oligomers and fibrils can light a fire in inflammasomes and induce Alzheimer's pathology.

Keywords: apoptosis • inflammasome • innate immunity • neurodegeneration • NLR • review

Introduction

The neuropathology of Alzheimer's disease (AD) was discovered by Alois Alzheimer over a century ago and the amyloid hypothesis was proposed twenty years ago [1] but the molecular pathogenesis still needs to be clarified. In particular, this is important in drug discovery process. Genetic and molecular studies have confirmed the central role of amyloid-ß oligomers and fibrils in the pathogenesis of AD. However, pathological pathways from the amyloid-ß peptides to the major pathological hallmarks of AD, such as neurofibrillary tangles, inflammation and loss of cholinergic neurons, are largely unknown.

Recent studies have revealed the toxic role of soluble amyloid-ß oligomers (ADDLs), especially those consisting of Aß1–42, in the pathogenesis of AD [2, 3]. ADDLs form trimeric and tetrameric oligomers which are stable and target, *e.g.* synapses to cause

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synaptic dysfunction and ultimately the loss of synaptic integrity. Interestingly, ADDLs accumulate into lipid rafts along with τ-protein; this recruitment seems to be regulated by Fyn kinase [4]. Furthermore, it has been claimed that ADDLs activate the N-methyl D-aspartate (NMDA) receptors and induce oxidative stress in hippocampal neurons [5]. This effect can be blocked by memantine which indicates that calcium influx may be involved in the process. The structural interactions of ADDLs with neuronal membrane need to be clarified but several studies have led to the pore-forming hypothesis, *i.e.* oligomers can create an ion channel in membrane, the so-called Aß channel, which can mediate ion fluxes [6].

Amyloid-ß peptides seem to target cholinergic neurons in particular, either directly or *via* muscarinic and nicotinic cholinergic receptors [7–9]. It has been known for some time that basal forebrain cholinergic neurons are particularly vulnerable to degeneration during the early-phase of AD. Giacobini [10] has reviewed in detail the deficiencies of cholinergic functions in AD and the possibilities for cholinergic therapies. A large body of literature shows that amyloid-ß peptides can impair cholinergic neurotransmission at many levels [7–9]. For example, amyloid-ß peptides reduce acetylcholine synthesis and release, impair muscarinic M1 receptor signalling, interact with nicotinic receptors, alter K^+ currents and inhibit long-term potentiation which can cause cognitive deficits and ultimately lead to the death of cholinergic neurons during the later phases of AD.

AD-associated inflammation has been generally considered as a secondary response to the pathological lesions evoked by amyloid-ß oligomers [*e.g.* 11, 12]. In conjunction with novel discoveries on the regulation of innate immunity, it has been recognized that amyloid-ß oligomers and fibrils can induce self-defence, inflammatory responses *via* pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) [13, 14]. However, TLRs might have also neuroprotective effects, *e.g. via* recruitment of neuroprotective T lymphocytes [15] or they may enhance amyloid-ß uptake and clearance by microglia [16].

In brain, there are several PRR systems which recognize both pathogen- and damage-associated molecular patterns. Inflammasomes, a multiprotein complex containing nucleotide-binding oligomerization domain (NOD)-like receptors and inflammatory caspases, are the danger sensing receptors which specifically trigger the secretion of IL-1ß and IL-18 cytokines [17, see below]. Interestingly, studies on AD have revealed that IL-1ß and IL-18 are the cytokines which display major up-regulation in AD patients, both in brain and plasma [*e.g.* 18–20]. Furthermore, fibrillar amyloid-$ß_{1–42}$ peptides induce a stronger IL-1ß response in microglia isolated from brain autopsies of AD patients than in the cells of normal individuals [21]. Oligomeric amyloid-ß peptides are also more potent in their ability to induce IL-1ß secretion than fibrillar peptides [22]. In transgenic Alzheimer mice, intense IL-1ß expression was observed in the reactive astrocytes surrounding amyloid-ß deposits [23]. The staining was already present during a very early stage of plaque development. Cell culture studies have shown that IL-1 cytokines can enhance Alzheimer and Lewy body pathologies by increasing MAPK-p38 activation and τ-hyperphosphorylation in rat cortical neurons [*e.g.* 24]. Shaftel *et al.* [25] observed that sustained overexpression of IL-1ß in the hippocampus of transgenic mice induced chronic neuroinflammation but, surprisingly, reduced amyloid plaque formation in transgenic Alzheimer mice. This could be due to the induction of TNF-α converting enzyme (TACE), an α-secretase, which decreases amyloid-ß formation [26].

In conclusion, it seems that until now there has been one piece missing in the AD puzzle linking amyloid-ß oligomers, IL-1ß secretion and loss of cholinergic cells. This missing piece could be the inflammasomes since IL-1ß secretion is critically dependent on the activation of inflammasomes and apoptotic/pyroptotic cell death is a hallmark of inflammasomal function [27].

Inflammasomes: platforms for pro-IL-1ß processing and cell death

Inflammasomes are intracellular multiprotein systems which are activated, *e.g.* by pathogen-associated molecular patterns as a host-defence reaction or by damage-associated molecular patterns as a self-defence mechanism for danger signals [27–30, see above]. During the last 2 years, the general aspects of inflammasome assembly, structure, and function have been extensively reviewed [*e.g.* 28–30]. Inflammasomes contain (*i*) NOD-like receptor (NLR) recognizing danger signals and ligands, (*ii*) adaptor protein recruiting the effector proteins to the complex and (*iii*) inflammatory caspases as effectors [28]. According to their NLR part, inflammasomes can be divided into several types. To date, the best characterized are the inflammasomes containing NACHT-LRR-PYD containing protein 1 (NALP1), NALP3 or ICE-protease-activating factor (IPAF) [28, 29].

The speciality of IPAF inflammasome is the activation by bacterial flagellin [29]. The activation of NALP1, and especially NALP3 inflammasomes is more diverse. Inflammasome activation can be initiated by a plethora of pathogenic peptides, such as muramyl dipeptides, and bacterial toxins and viral RNA, and, interestingly, also by a variety of inherent danger signals, like a low intracellular K^+ concentration due to K^+ efflux [31] or uric acid crystals in gout [32, see below]. Leucine-rich repeats in NLRs probably play a role in ligand sensing [28]. After activation, NLR interacts with the adapter protein which in the case of NALP1 and NALP3 is ASC (apoptosis-associated speck-like protein containing caspase-recruitment domain [CARD] and pyrin domain (PYD) domains) [28]. Through its CARD, ASC incorporates caspase(s) to the inflammasome [28, 29]. Caspase-1 is the principal caspase found in human inflammasomes. The crucial function of the activated caspase-1 is to cleave the precursors of pro-inflammatory cytokines, such as IL-1ß and IL-18 to mature and active cytokines which are secreted from cells. It should be noticed that inflammasomes only induce the processing and release of IL-1ß and IL-18 which are stored in cells. Increased expression of IL-1ß and IL-18 normally requires the activation of TLRs or cytokine signalling.

Caspase-5 is another pro-inflammatory cysteine protease which may also be recruited to the inflammasome complex. It probably enhances the cleavage of pro-IL-1β by caspase-1 [27, 28]. Caspase-4 is also included in human inflammatory caspases [28] although its presence in inflammasomes has not been verified. It is worth noting that endoplasmic stress can activate caspase-4 and induce apoptotic cell death, *e.g.* in neurons exposed to amyloid-ß [33].

Inflammasome proteins and even the functional machinery of inflammasomes have been linked to cell death in several cell types [34]. However, the type of cell death associated with the inflammasome proteins is usually something else, such as pyroptosis or pyronecrosis, rather than apoptosis [34, 35]. Pyroptosis and pyronecrosis differ from each other, *e.g.* by activating factors and the dependence of caspase-1 [34]. On the other hand, they share similar morphological features, *i.e.* loss of plasma membrane integrity and lack of chromatin condensation, which also resemble necrosis [34, 35]. As an interesting example of the involvement of inflammasome proteins with cell death, K^+ efflux has been shown to evoke inflammatory cell death *via* pyroptosis along with IL-1ß maturation and secretion [35].

NALP1 inflammasomes in neurons

Kummer *et al.* [36] have screened the expression patterns of NALP1 and NALP3 in human tissues. NALP1 and NALP3 proteins exhibited different expression profiles in human tissues, NALP1 being more generally expressed than NALP3. NALP1 protein was highly expressed in cells of the immune system, *e.g.* in T and B cells and dendritic cells. In brain, NALP1 protein was present at high levels in pyramidal neurons and oligodendrocytes but not in astrocytes or microglia. NALP1 protein is also expressed in the neurons of normal rat spinal cord, localized mainly in cytoplasm [37]. Neurons also express ASC and caspase-1 suggesting that the components of NALP1-type inflammasomes are present in neurons [37].

In spinal cord, a contusion injury has been shown to induce inflammatory response with the increased expression and processing of pro-IL-1ß and pro-IL-18 [37]. The expression of ASC was increased and caspase-1 was activated suggesting that trauma triggered inflammasome system. In normal state, the anti-apoptotic XIAP (X-linked inhibitor of apoptosis) protein is a part of inflammasome complex, but after a trauma, XIAP becomes cleaved [37]. In an immunohistochemical study, the immunostaining of NALP1 and ASC was highly increased after trauma and intense patchy staining was present in neuronal soma near plasma membrane. Furthermore, injection of anti-ASC neutralizing antibodies after trauma significantly reduced the activation and processing of IL-1ß, IL-18 and caspase-1, indicating that inflammasomal signalling was inhibited [37]. ASC neutralization also reduced the spinal cord lesion volume and improved the movement recovery after trauma which highlights the role of inflammasomes in spinal cord trauma.

Potassium efflux activates NALPs: mechanism in Alzheimer's disease?

Inflammasomes can be activated by microbial pathogens but also by endogenous danger signals [27–29]. It is known that several microbial toxins, such as nigericin, gramacidin, maitotoxin and α-toxin activate inflammasomes [27, 28]. Furthermore, extracellular ATP, reactive oxygen species, monosodium urate crystals, calcium pyrophosphate dihydrate depositions and some detergents can activate inflammasomes and caspase-1 [29]. Recently, Fernandes-Alnemri *et al.* [34] and Petrilli *et al.* [31] were able to identify a common mechanism for these very different inducers. These workers convincingly demonstrated that the efflux of K^+ and low intracellular K^+ concentration can activate caspase-1. Petrilli *et al.* [31] showed that low K^+ can activate NALP3 and NALP1 to recruit ASC and caspase-1 into the inflammasome complex. IPAF inflammasomes were not affected by lowering of K^+ concentration. K^+ efflux can be induced either by causing pores in plasma membrane, such as microbial toxins [39], or by activating K^+ efflux *via* channels, such as ATP *via* P2X7 channel [40]. Neuronal cell culture experiments have demonstrated that increasing the K^+ efflux with valinomycin can trigger the activation of caspase-1 and increase the secretion of IL-1ß also in cultured spinal cord neurons [37]. In rat cerebellar granule neurons, withdrawal of serum/K^+ from medium highly increased the expression of NALP1 and NALP5 proteins [38].

Fernandes-Alnemri *et al.* [35] observed that a low intracellular K^+ concentration can dramatically increase the dimerization of ASC adapter molecules and subsequently these dimers oligomerize to form supramolecular structures called pyroptosomes. These ASC aggregates recruit and activate caspase-1 enzymes which cleave pro-IL-1ß and pro-IL-18 cytokines but also cause cellular injuries, a process which is named pyroptosis (see above). It is noteworthy that these studies highlight that intracellular K^+ concentration can regulate the activation of inflammasomes and hence trigger larger inflammatory responses *via* IL-1ß and IL-18. On the other hand, the activation of caspase-1 *via* the K^+ regulation can play a broader cellular role, since Gurcel *et al.* [39] have demonstrated that caspase-1 can activate sterol regulatory element binding proteins which are central regulators of membrane biogenesis, and support cellular survival. It seems that the degree of K^+ efflux or, more generally, the intracellular concentration of K^+ is the key regulator in sensing cellular danger and making the life and death decisions.

A low intracellular K^+ concentration due to K^+ efflux has a critical role in apoptosis of several cell types and different apoptosis models [*e.g.* 41–43]. Activation of K^+ channels, either in plasma membrane or in inner mitochondrial membrane, represents the primary cause of cell shrinkage, caspase activation, and ultimately, apoptotic cell death. Apoptosis can be suppressed by K^+ channel blockers or by increasing extracellular K^+ concentration. It is well known that the intracellular concentration of K^+ regulates the apoptotic protease-activating factor 1 (APAF-1) apoptosome formation and caspase maturation [44]. Interestingly, the pro-apoptotic

APAF-1 protein is structurally very similar to NOD-like receptors, containing a CARD motif for the recruitment of caspase-9 [34]. Apoptosomes formed by APAF-1 factors and caspase-9 trigger apoptosis but in contrast, inflammasomes including NALPs, ASC and caspase-1 evoke both inflammation and cell death *via* pyroptosis [34, see above]. It seems that it is the intracellular K^+ concentration that critically regulates the assembly of these cellular demise machines.

Is there any role for inflammasomes in Alzheimer's pathology? There are many papers indicating that amyloid-ß oligomers can disturb the function of K^+ channels and decrease intracellular K^+ concentration [*e.g.* 45–47] suggesting that K^+ channels could play a role in the pathogenesis of AD [46, 47–49]. Cholinergic neurons and the cell line SN56 are especially sensitive to any increase in the outward K^+ currents and cell death induced by amyloid-ß [46]. Neuronal death can be prevented by increasing the extracellular K^+ concentration or by blocking K^+ channels with tetraethylammonium [46, 47].

Recently, Pannaccione *et al.* [48] have observed that amyloid-ß peptides can increase the expression and activity of the voltage-gated potassium channel, Kv3.4, along with the accessory subunit MinK-related peptide 2. Interestingly, Angulo *et al.* [49] have demonstrated that the expression of the Kv3.4 channel subunit can be up-regulated in the early stages of AD and this phenomenon also occurs in transgenic mice displaying Alzheimer's pathology. These results indicate that the functional potentiation of Kv3.4 channels may expose neurons to toxic effects of amyloid-ß. K^+ efflux can also be caused by the activation of the complement system and the formation of terminal membrane attack complexes which can disrupt the neuronal surface membrane. Complement system is known to be activated in AD [50]. In addition, K^+ efflux can be caused by 'amyloid-ß ion channels' which are pores in the membranes formed by the amyloid-ß oligomers [6, see above]. However, type of the cell death was generally interpreted as apoptotic and the mechanism to be Ca^{2+}-induced death due to simultaneous Ca^{2+} influx. Currently, it is known that K^+ efflux and the subsequent low level of intracellular K^+ concentration can activate the inflammasomes. This provides a novel interpretation to explain why inflammatory responses and cholinergic cell death are induced by amyloid-ß oligomers and fibrils (Fig. 1).

Amyloid-ß fibrils activate NALP3 inflammasomes in microglia

Urate and silica crystals as well as calcium pyrophosphate dihydrate depositions can activate inflammasomes [29, 51]. Hornung *et al.* [51] have demonstrated that the phagocytosis of silica crystals and aluminium salts can induce the activation of NALP3 inflammasomes in phagocytes. Several experiments confirmed that the activation of NALP3 inflammasomes is dependent on lysosomal destabilization and damage caused by silica crystals. Inhibition of cathepsin B activity impaired NALP3 activation suggesting that cathepsin B is involved in the NALP3 activation process. NALP3 activation was also induced by crystal-independent rupture of lysosomes which indicates that lysosomal damage is an endogenous danger signals for NALP3 inflammasomes [51].

Interestingly, Halle *et al.* [52] recently demonstrated that the phagocytosis of fibrillar amyloid-ß activates NALP3 inflammasomes in mouse microglia. The activation of NALP3 was dependent on lysosomal damage and cathepsin B release [52], as was observed earlier in the crystal-induced NALP3 activation (see above). NALP3 activation by fibrillar amyloid-ß also induced caspase-1 activation and IL-1ß secretion from microglia [52]. Subsequently, IL-1ß activated the secretion of several pro-inflammatory and chemotactic mediators (Fig. 1). Moreover, Halle *et al.* [52] demonstrated using different knockout mice that amyloid-ß fibrils could induce IL-1 pro-inflammatory pathway also *in vivo* by triggering inflammasomes and caspase-1 activation.

Alzheimer's pathology: downstream from the inflammasomes

In order to confirm that the activation of inflammasomes can lead to Alzheimer's pathology, we need to understand the pathogenetic processes induced by the activation of inflammatory caspases in neurons, and the signalling pathways and responses of secreted IL-1ß and IL-18 cytokines. As described above, the expressions of caspase-1, IL-1ß and IL-18 appear to be significantly increased not only in specimens from patients with AD, but also in amyloid-ß treated neurons and transgenic Alzheimer mice [*e.g.* 18–20, 23, 53]. Caspase-1 substrates, with the exception of pro-IL-1ß and pro-IL-18, are not well defined. Shao *et al.* [54] have screened the caspase-1 digestome to identify caspase target proteins. Surprisingly, along with some chaperones and cytoskeletal proteins, they identified many proteins including in the glycolytic pathway, such as aldolase, glyceraldehyde-3-phosphate dehydrogenase and pyruvate kinase. Metabolic insufficiency in AD has also been verified using gene expression profiling [55]. This connection between inflammasomal activation and metabolic impairment seems to represent a novel mechanism as a way of inducing cell death, either *via* apoptosis or pyroptosis (see above).

Several studies have attempted to reveal the connection between caspase-1 and apoptotic effector caspases. It seems that caspase-6 represents the link between inflammatory caspases and apoptotic caspase cascades [56]. Caspase-6 is highly expressed in human neurons and, importantly, caspase-1 can cleave and activate the pro-caspase-6 in human neurons [56]. Caspase-6 can be involved in several ways with AD, *e.g.* caspase-6 can cleave both amyloid precursor protein [57] and τ-protein [58].

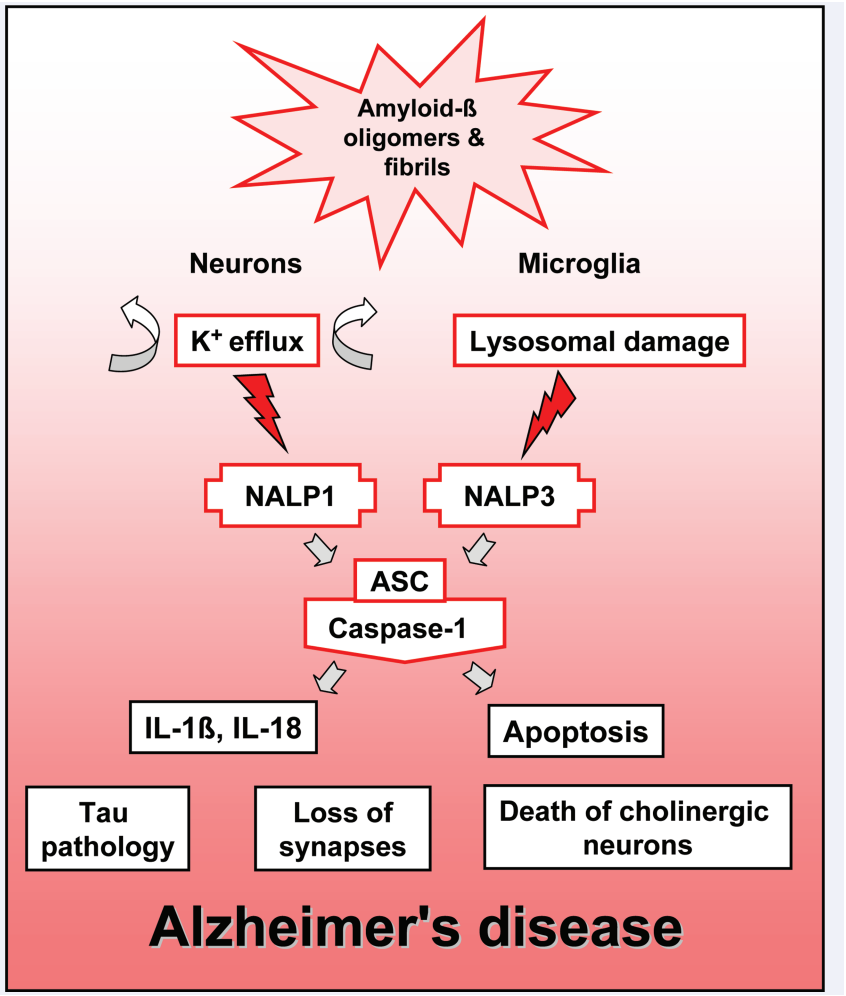

Fig. 1 A hypothetical model on the pathogenesis of Alzheimer's disease indicating that toxic amyloid-ß oligomers and fibrils can set fire to neuronal NALP1 inflammasomes *via* K^+ efflux and microglial NALP3 inflammasomes *via* lysosomal damage and through these danger signals induce Alzheimer's pathology.

Interestingly, Guo *et al.* [58] observed that active caspase-6 and caspase-6-cleaved τ-protein were present in neuropil threads, neuritic plaques, and neurofibrillar tangles in AD. This functional link between caspase-1 and caspase-6 seems to connect the activation of inflammasomes to apoptotic cell death and Alzheimer's pathology.

Secreted, mature IL-1ß and IL-18 can switch on local inflammatory processes in brain. The effects of IL-1ß signalling, however, are highly cell-type specific [59]. In glial cells, IL-1ß can induce cytokine production *via* NF-κB signalling, whereas in neurons, IL-1ß activates the MAPK-p38 signalling pathway *via* type 1 IL-1 receptors [59]. MAPK-p38 pathway is one of the major signalling cascades involved in inflammatory responses and MAPK-p38 is activated at early stages in AD [60]. Immunoreactivity is mainly located in hippocampal neurons exhibiting neurofibrillar tangles but not in the tangles themselves. Several studies have demonstrated that IL-1ß can induce the phosphorylation of τ-protein and hence mediate the formation of neurofibrillary tangles [*e.g.* 24, 61].

In addition to the τ-pathology, pro-inflammatory cytokines, especially IL-1ß and IL-18, can affect synaptic plasticity and inhibit long-term potentiation and subsequently learning and memory [62]. In rat hippocampus, amyloid-ß activates JNK (c-Jun N-terminal kinase) *via* IL-1ß and induces the expression of pro-apoptotic Bax, the release of cytochrome c to cytosol and cleavage of PARP (poly-ADP-ribose polymerase), all of which are typical characteristics of apoptosis [63].

Conclusions

NALP-dependent inflammasomes are the primary PRRs sensing endogenous danger signals [29]. Amyloid-ß peptide production and their oligomerization, fibrillation and aggregation to neuritic plaques form the major pathogenic cascade in AD. Amyloid-ß oligomerization and fibrillation occur *via* distinct intermediates,

such as short oligomers, protofibrils and polymorphic fibrils, prior to the formation of amyloid aggregates or plaques. Recent observations clearly show that soluble oligomers (ADDLs) are the most toxic amyloid-ß species [2, 3] and therefore potent danger signals to activate inflammasomes. However, several factors affect the fibrillation process as well as the toxicity of intermediates. For instance, the ratio of Aß40 and Aß42 peptides present affects the fibrillogenesis and neuronal toxicity [64]. Lipids can affect the fibrillation but also revert inert amyloid-ß fibrils to neurotoxic protofibrils [65]. Furthermore, the accumulation of amyloid-ß oligomers in intraneuronal compartments seems to be a major risk factor for Alzheimer pathology [66]. Recently, Parvathy *et al.* [67] demonstrated that amyloid-ß oligomers and fibrils, but not protofibrils, induced IL-1α expression in primary microglia, although all forms of amyloid-ß were taken up by microglia. Ultimately, comparison of the studies involving amyloid-ß is quite challenging since the exact conformation of amyloid-ß has not generally been characterized, and the reproducible assembly of amyloid-ß oligomers and fibrils seems to be difficult.

In conclusion, innate immunity system of brain can recognize toxic amyloid-ß oligomers and fibrils as danger signals and activate NALP-dependent inflammasomes, probably *via* K^+ efflux in neurons and *via* lysosomal damage in microglia. These toxic initiation signals light a fire in inflammasomes, which can subsequently evoke hallmarks of AD *via* caspase cascades and inflammatory response (Fig. 1).

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