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-β production and fibrillation in the pathogenesis of Alzheimer’s disease (AD). However, the pathological pathways from amyloid-β 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-β oligomers and fibrils and their cellular effects can activate the innate immunity defence and induce inflammatory and apoptotic responses in human brain. Amyloid-β 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-1β and IL-18 cytokines. Interestingly, recent observations have demonstrated that amyloid-β 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-β 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-β oligomers and fibrils in the pathogenesis of AD. However, pathological pathways from the amyloid-β 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-β oligomers (ADDLs), especially those consisting of Aβ1–42, in the pathogenesis of AD [2, 3]. ADDLs form trimeric and tetrameric oligomers which are stable and target, e.g. synapses to cause...
signalling, interact with nicotinic receptors, alter K⁺ acetylcholine synthesis and release, impair muscarinic M1 receptor
abilities for cholinergic therapies. A large body of literature shows
detail the deficiencies of cholinergic functions in AD and the pos-
tion during the early-phase of AD. Giacobini [10] has reviewed in
brain cholinergic neurons are particularly vulnerable to degenera-
tional, either directly or via muscarinic and nicotinic cholinergic
receptors [7–9]. It has been known for some time that basal fore-
brain cholinergic neurons are particularly vulnerable to degenera-
tion during the early-phase of AD. Giacobini [10] has reviewed in
detail the deficiencies of cholinergic functions in AD and the poss-
ibilities for cholinergic therapies. A large body of literature shows
that amyloid-β peptides can impair cholinergic neurotransmission
at many levels [7–9]. For example, amyloid-β 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 amy-
loid-β oligomers [e.g. 11, 12]. In conjunction with novel discoveries
on the regulation of innate immunity, it has been recognized that
amyloid-β oligomers and fibrils can induce self-defence, inflam-
atory 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 neuroprotec-
tive T lymphocytes [15] or they may enhance amyloid-β uptake and clearance by microglia [16].

In brain, there are several PRR systems which recognize both
pathogen- and damage-associated molecular patterns. Inflamma-
somes, a multiprotein complex containing nucleotide-binding
oligomerization domain (NOD)-like receptors and inflammatory
caspases, are the danger sensing receptors which specifically trig-
ger the secretion of IL-1β and IL-18 cytokines [17, see below]. Interestingly, studies on AD have revealed that IL-1β 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 amy-
loid-β1–42 peptides induce a stronger IL-1β response in microglia
isolated from brain autopsies of AD patients than in the cells of
normal individuals [21]. Oligomeric amyloid-β peptides are also
more potent in their ability to induce IL-1β secretion than fibrillar peptides [22]. In transgenic Alzheimer mice, intense IL-1β expres-
sion was observed in the reactive astrocytes surrounding amyloid-
β 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 Levy body
pathologies by increasing MAPK-p38 activation and τ-hyperphos-
phorylation in rat cortical neurons [e.g. 24]. Shaftel et al. [25]
observed that sustained overexpression of IL-1β in the hippocam-
pus of transgenic mice induced chronic neuroinflammation but,
progressively, 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 amy-
loid-β formation [26].

In conclusion, it seems that until now there has been one piece
missing in the AD puzzle linking amyloid-β oligomers, IL-1β secre-
tion and loss of cholinergic cells. This missing piece could be the
inflammasomes since IL-1β 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-1β
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 pat-
terns as a self-defence mechanism for danger signals [27–30, see
above]. During the last 2 years, the general aspects of inflamma-
some 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) adap-
tor 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 bac-
terial flagellin [29]. The activation of NALP1, and especially
NALP3 inflammasomes is more diverse. Inflammasome activa-
tion can be initiated by a plethora of pathogenic peptides, such
as muramyldipeptides, 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 activa-
tion, NLR interacts with the adapter protein which in the case of
NALP1 and NALP3 is ASC (apoptosis-associated speck-like pro-
tein containing caspase-recruitment domain [CARD] and pyrin
domain (PYD) domains) [28]. Through its CARD, ASC incorpo-
rates 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-1β 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-1β and IL-18 which are stored in cells. Increased
expression of IL-1β 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-β [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 inflammasomes proteins is usually something else, such as pyroptosis or pyroptosis, rather than apoptosis [34, 35]. Pyroptosis and pyroptosis 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-1β 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-1β 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-1β, 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, gramicidin, 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-1β 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-1β 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-1β 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) apotosome formation and caspase maturation [44]. Interestingly, the pro-apoptotic...
APAFA-1 protein is structurally very similar to NOD-like receptors, containing a CARD motif for the recruitment of caspase-9 [34]. Apoptosomes formed by APAFA-1 factors and caspase-9 the activation of caspase-6 in human neurons and, importantly, caspase-1 can cleave and activate the pro-caspase-6 in human neurons [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 \( \tau \)-protein [58].

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-18 and IL-18 cytokines. As described above, the expressions of caspase-1, IL-18 and IL-18 appear to be significantly increased not only in specimens from patients with AD, but also in amyloid-\( \beta \)-treated neurons and transgenic Alzheimer mice [e.g. 18–20, 23, 53]. Caspase-1 substrates, with the exception of pro-IL-18 and pro-IL-18, are not well defined. Shao et al. [54] have screened the capase-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, gyceraldehyde-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 \( \tau \)-protein [58].

**Alzheimer's pathology: downstream from the inflammasomes**

Is there any role for inflammasomes in Alzheimer's pathology? There are many papers indicating that amyloid-\( \beta \) 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-\( \beta \) [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-\( \beta \) 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-\( \beta \). \( K^+ \) 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-\( \beta \) ion channels' which are pores in the membranes formed by the amyloid-\( \beta \) 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-\( \beta \) oligomers and fibrils (Fig. 1).

**Amyloid-\( \beta \) 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-\( \beta \) 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-\( \beta \) also induced caspase-1 activation and IL-18 secretion from microglia [52]. Subsequently, IL-18 activated the secretion of several pro-inflammatory and chemotactic mediators (Fig. 1). Moreover, Halle et al. [52] demonstrated using different knock-out mice that amyloid-\( \beta \) fibrils could induce IL-1 pro-inflammatory pathway also in vivo by triggering inflammasomes and caspase-1 activation.
Interestingly, Guo et al. [58] observed that active caspase-6 and caspase-6-cleaved τ-protein were present in neuropil threads, neuritic plaques, and neurofibrillary 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-1β and IL-18 can switch on local inflammatory processes in brain. The effects of IL-18 signalling, however, are highly cell-type specific [59]. In glial cells, IL-18 can induce cytokine production via NF-κB signalling, whereas in neurons, IL-18 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-18 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-1β and IL-18, can affect synaptic plasticity and inhibit long-term potentiation and subsequently learning and memory [62]. In rat hippocampus, amyloid-β activates JNK (c-Jun N-terminal kinase) via IL-1β 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-β peptide production and their oligomerization, fibrillation and aggregation to neuritic plaques form the major pathogenic cascade in AD. Amyloid-β 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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