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Review

Is Alzheimer's disease an inflammasomopathy?

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia in the elderly and, despite the tremendous efforts researchers have put into AD research, there are no effective options for prevention and treatment of the disease. The best way to reach this goal is to clarify the mechanisms involved in the onset and progression of AD. In the last few years the views about the drivers of AD have been changing and nowadays it is believed that neuroinflammation takes center stage in disease pathogenesis. Herein, we provide an overview about the role of neuroinflammation in AD describing the role of microglia and astroglia is this process. Then, we will debate the NLRP3 inflammasome putting the focus on its activation through the canonical, non-canonical and alternative pathways and the triggers involved herein namely endoplasmic reticulum stress, mitochondrial dysfunction, reactive oxygen species and amyloid β peptide. Data supporting the hypothesis that inflammasome-mediated peripheral inflammation may contribute to AD pathology will be presented. Finally, a brief discussion about the therapeutic potential of NLRP3 inflammasome modulation is also provided.

1. Introduction

Alzheimer's disease (AD) constitutes a major public health problem due to an increasingly aged population as consequence of generally improved medical care and demographic changes. However, current available treatments show modest symptomatic efficacy, leaving an unmet medical need for new and more effective therapies. Patients with AD show an impaired ability to perform everyday tasks, and often experience psychiatric, emotional, and personality disturbances (Tarawneh and Holtzman, 2012). At the neuropathological level, AD is characterized by two well-known abnormal protein aggregates that accumulate in the cerebral cortex and hippocampus of the patient's brain: neuritic plaques that are extracellular deposits mainly composed of insoluble amyloid β peptides (Aβ), and neurofibrillary tangles that are intracellular aggregates, mostly consisting by phosphorylated tau, a microtubule associated protein (Jack and Holtzman, 2013). Often diagnosed in people aged ≥ 65 (about 95%), the disease is typically referred to as late-onset, sporadic AD. In contrast to early-onset, familial AD (accounting for 1–5% of all cases), where initial symptoms can be observed between 30 and 65 years of age, occurs due to a familial genetic cause involving mutations in the genes encoding Amyloid-β Protein Precursor (APP) and Presenilins 1 and 2 (PS1 and PS2) proteins (Cardoso et al., 2016).

Since the nineties, the amyloid cascade hypothesis has played the prominent role in explaining the genesis and progression of AD (Hardy and Allsop, 1991; Hardy and Higgins, 1992). It proposes that Aβ is the trigger of AD leading to the formation of the pathological hallmarks of the disease, neuronal cell death, and ultimately dementia. Although familial AD completely fits the amyloid cascade hypothesis, accumulating evidence demonstrates that in the sporadic cases Aβ formation and accumulation result from other events. So, other hypotheses have been put on the table. One of them is the so-called tau hypothesis that postulates that tau is a primary event in AD (Giacobini and Gold, 2013). Indeed, hyperphosphorylated tau, neurofibrillary tangles, and synaptic and neuronal loss are closely associated with memory deficits. This hypothesis has gained attention because it has been confirmed that tau proliferates and propagates between cells and is a trigger for neurodegeneration (Clavaguera et al., 2009, 2013). In fact, both amyloid

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cascade and tau hypotheses consider that Aβ and tau, respectively, form oligomers that are deleterious to neurons and cause mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, neuroinflammation and finally leads to synaptic dysfunction and neuronal loss (Irvine et al., 2008; Gowrishankar et al., 2015). In addition to Aβ and tau hypothesis to explain AD neurodegenerative process, Swerdlow and Khan (2004, 2009) proposed the mitochondrial cascade hypothesis to explain sporadic AD etiopathogenesis. In brief, this hypothesis postulates that inheritance defines an individual's baseline mitochondrial function that is affected by environmental factors determining the speed at which age-associated mitochondrial changes appear, and along with this influence, mitochondria may accumulate damage resulting in both the symptoms and neuropathology found in AD. Several lines of evidence show mitochondrial dysfunction exist independent of Aβ and mitochondrial oxidative stress and redox imbalance occur before Aβ deposition (Cardoso et al., 2016; Swerdlow, 2018).

Neuroinflammation is also implicated in AD etiology, a new vision fueled by the recently discovered inflammatory genes through genome-wide association studies driving neuroinflammation in AD, and examples include loss/reduction of function mutations in the anti-inflammatory/phagocytosis *TREM-2* (triggering receptor expressed on myeloid cells 2) gene; variants of promoter regions of inflammation modulating cytokines interleukin-10 (IL-10) and TNFα (tumor necrosis factor α); loss/reduction of function of the anti-inflammatory/phagocytosis receptor *CD33* gene; and gene variants of the complement receptor 1 (CR1), which may be integral to the phagocytosis of opsonized amyloid oligomers. Neuroinflammation is mainly due to microglial activation but its contribution to disease progression is still not yet understood (Walters et al., 2016). While proper microglial function is essentially required for its scavenging duties, local activation of the brain's innate immune cells also brings about several harmful events, such as secretion of proinflammatory cytokines and reactive oxygen species (ROS) production putting surrounding healthy neurons in danger. Amyloid plaques and neurofibrillary tangles have been both invariably associated with microglia evoked neuroinflammation. A crucial role for NLRP3 inflammasome, which is an important sensor of innate immunity, in Aβ-induced microgliosis and Aβ pathology has been unequivocally demonstrated (Halle et al., 2008; Heneka et al., 2013). More recently, aggregated tau was also found to activate the NLRP3 inflammasome in microglia, and it was demonstrated to exacerbate tau pathology in vivo (Stancu et al., 2019). Despite astrocytes and microglial cells are the main type of cells involved in inflammatory responses in the central nervous system (CNS), neuronal cells can also mount an innate immune response. Neurons express critical Toll/interleukin-1 receptor (TIR) domain-containing adaptors that transduce signals of TLR, regulating the expression of various cytokines. Indeed, TLR 3 and 7, localized in the neuronal endosomal compartment, play a role in neurite outgrowth. It is assumed that the cytokines produced by neurons, in response to pathogen infection or to danger signals, may be just enough to recruit and activate local microglia (Liu et al., 2014; Morales et al., 2014). Furthermore, inflammatory alterations observed in peripheral blood cells are likely to fuel and sustain neuroinflammation in AD. Primed microglial cells become fully activated and attract, by the production of chemokines, peripheral monocytes that can then migrate to the CNS through the blood brain barrier. Monocytes provide assistance to microglia for Aβ clearance and, in turn, the NLRP3 inflammasome is triggered in these cells resulting in the activation of caspase-1 and in the downstream production of IL-1β and IL-18 (Saresella et al., 2016). Preclinical and clinical studies have established that innate immune responses in fact contribute to and drive AD pathogenesis (Guillot-Sestier et al., 2015).

Data from the literature clearly indicate that mitochondrial dysfunction, Aβ oligomers, tau hyperphosphorylation and neuroinflammation are intertwined events and are responsible for AD neurodegenerative process. In this review, we first revise, at a glance, the relevance of neuroinflammation on AD, as well as the cellular players of AD-associated neuroinflammation. Secondly, the mechanisms and the triggers behind NLRP3 inflammasome activation in the context of AD are also reviewed. Finally, the pharmacological intervention on the inflammasome pathway is also highlighted.

2. Neuroinflammation in AD

Although AD has been considered a neurodegenerative disease characterized by extracellular deposits of misfolded Aβ peptides within senile plaques, intracellular aggregates of hyperphosphorylated tau and extensive neuronal loss, recent evidences indicate neuroinflammation as an important component of AD pathology. Indeed, in most cases, following injury to the CNS there is a recruitment of leukocytes to the site of injury and an activation of brain microglia and astrocytes, which are events collectively named neuroinflammation. Accordingly, markers associated to both the innate and adaptive immune system are increased in the brain of AD patients (McGeer et al., 1987; Zotova et al., 2013) and in AD rodent models (Matarin et al., 2015). Using amyloid versus tau mouse models it was shown that immune gene expression correlated tightly with the amyloid pathology whereas synaptic genes correlated negatively with the tau pathology (Matarin et al., 2015). This is in agreement with the observation that in AD patients the Aβ immunotherapy results in a decrease of microglia activation and in a downregulation of inflammatory markers (Zotova et al., 2013). Also, genome-wide association studies (GWAS) identified more than 20 gene variants as risk factors for developing late-onset AD, including genes involved in the inflammatory response, lipid metabolism, and endocytosis (reviewed in Karch and Goate, 2015). Among the immune response related genes, the GWAS identified *CR1*, *CLU* (Harold et al., 2009; Lambert et al., 2009), *CD33*, *MS4A*, *ABCA7*, *EPHA1* (Hollingworth et al., 2011; Naj et al., 2011), *TREM2* (Guerreiro et al., 2013; Jonsson et al., 2013) *TYROBP* (Pottier et al., 2016; Zhang et al., 2013) and *HLA-DRB5/HLA-DRB1* (Lambert et al., 2013). Most of these associated genes are mainly expressed in glial cells (Zhang et al., 2014; reviewed in Arranz and De Strooper, 2019), suggesting a crucial role of these cells in the pathogenesis of AD.

2.1. Cellular players of AD-associated neuroinflammation

2.1.1. Astroglia

Astrocytes are glial cells with key roles in the regulation of neurotransmission and calcium homeostasis as well as in the modulation of synapse formation, maturation and elimination, beyond the supply of nutritional and trophic support to neurons. On the other hand, astrocytes are one of the components of the neurovascular unit contributing to the regulation of the blood-brain barrier (BBB) function. In several CNS disorders astrocytes display morphological alterations that possibly reflect functional changes eventually contributing to the disease pathogenesis. The pathological responses of human astrocytes include astroglial atrophy and reactive astrogliosis. Whereas atrophic astrocytes have a decrease in the cell soma volume and in the number of processes, reactive astrocytes have an increased cell volume, thicker processes and augmented levels of glial fibrillary acidic protein (GFAP) (Arranz and De Strooper, 2019). Both atrophic and reactive astrocytes are detected in the AD brain (Hsu et al., 2018). In *post-mortem* AD brain tissue, reactive astrocytes were observed around senile plaques, near to activated microglia and in regions of neurodegeneration, which may contribute to the inflammatory process through the release of cytokines and other toxic products (Liddelow et al., 2017; Medeiros and LaFerla, 2013;). Remarkably, induced pluripotent stem cells (iPSC)-derived human astrocytes, from both sporadic and familial AD patients, exhibit a pronounced pathological phenotype, with a significantly less complex morphological appearance in vitro compared to control cells (Jones et al., 2017). Animal models of AD also exhibit astrocyte morphological and functional alterations. The astroglial atrophy observed in animal models of AD initiates from early ages and may contribute to the

progressive cognitive deterioration due to the reduction of astrocytic arborisation that possibly affects synaptic connectivity (Kulijewicz-Nawrot et al., 2012; Yeh et al., 2011). Interestingly, whereas astroglial atrophy does not appear to be associated to Aβ plaques, the astrocytes surrounding plaques have a reactive phenotype (Beauquis et al., 2013; Olabarria et al., 2010). Moreover, 12–18 month-old 3xTg-AD mice showed signs of astroglial functional impairment, with a reduction in the number of immunoreactive glutamine synthetase astrocytes in the hippocampus, which is associated with Aβ deposits. This may correlate with the AD-associated dysfunction of the glutamate homeostatic system, possibly underlying the cognitive impairments observed in the disease (Olabarria et al., 2011). Also, in aged APP_{swe}/PS1dE9 AD mice the astrocytes acquire a pro-inflammatory phenotype and simultaneously display a reduced expression of neuronal support and signalling genes, including genes involved in glutamatergic neurotransmission, which are likely to contribute to neuronal dysfunction (Orre et al., 2014). Noteworthy, changes in the expression profile related to the inflammatory phenotype are remarkably comparable in mouse and human AD (Orre et al., 2014).

Beyond the contribution of reactive astrocytes to the inflammatory process in AD, there are some evidences that astrocytes may as well play a role in neurodegeneration. Indeed, in a mouse model it was shown that A1 reactive astrocytes, induced by activated microglia secreting IL-1α, TNFα, and C1q, lost the ability to support neuronal survival and rapidly induce death of neurons and oligodendrocytes. The A1 astrocyte-mediated neurodegeneration is possibly driven by secretion of a soluble neurotoxin but also by releasing multiple complement components that promote synapse dysfunction (Liddelow et al., 2017). Actually A1 astrocytes may up-regulate many classical complement cascade genes (Zamanian et al., 2012), including *C3*, and it was shown that C1q, C3 and the microglia complement receptor CR3 contribute to synapse loss (Hong et al., 2016; Stevens et al., 2007). Interestingly, Aβ can activate the NF-κB pathway in primary astroglial cultures resulting in an increase expression of C3 mRNA, which is consistent with the increased C3 mRNA levels observed in the APP/TTA transgenic mice. Also, both NF-κB and its target C3 are higher in *post-mortem* AD brains (Lian et al., 2015). Of note, astrocyte-derived exosomes from patients with AD have increased concentrations of complement factors, including C3 and C1q, supporting the view that A1 astrocytes may contribute to AD pathogenesis through secretion of complement proteins (Goetzl et al., 2018). The blockade of C3aR rescues cognitive deficits in an AD mouse model pinpointing its potential for AD therapy (Lian et al., 2015). Moreover, in APP/PS1 mice the inhibition of the calcineurin/NFAT pathway, which is involved in astrocyte activation, revealed improved cognition, reduced astrogliosis and lower amyloid levels, highlighting the importance of astroglial inflammation in AD (Furman et al., 2012).

2.1.2. Microglia

Under physiological conditions microglia, which are the resident immune cells of the CNS, have a crucial role in maintaining brain homeostasis and the plasticity of neuronal circuits by regulating the number of functional synapses (Ji et al., 2013). Indeed, microglia promote motor-learning-dependent synapse formation through microglial brain-derived neurotrophic factor (BDNF) signalling (Parkhurst et al., 2013). Furthermore, microglia constantly use highly motile processes to survey the brain for the presence of pathogens but also to detect any sign associated to cell damage. The exogenous signals (pathogen-associated molecular patterns, PAMPs) and self-derived signals (danger-associated molecular patterns, DAMPs) are detected by highly conserved pattern recognition receptors (PRRs). Microglia express a large variety of PRRs, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NOD-like receptors, NLRs), scavenger receptors (SRs) and receptors for advanced glycation end products (RAGEs) (Dansokho and Heneka, 2018). Upon activation of PRRs, distinct signalling cascades elicit microglia activation and the production of inflammatory mediators. In AD microglia can bind soluble Aβ oligomers and fibrils through PRRs, including NLRP3, NLRP1, CD36, CD14, TLR2, RAGE (Fassbender et al., 2004; Halle et al., 2008; Liu et al., 2012; Reed-Geaghan et al., 2009; Stewart et al., 2010; Walter et al., 2007; reviewed in Venegas and Heneka, 2017), which elicits cell activation, production of pro-inflammatory factors such as iNOS, TNF-α, IL-1β and IL-6, and increased expression of the cell adhesion markers CD11b and CD68 (Jana et al., 2008). Also, there are evidences that *in vitro* tau oligomers and neurofibrillary tangles can activate microglia leading as well to the production of NO and IL-6 (Morales et al., 2013). Using different transgenic tau mouse models it was recently shown that factors affecting tau accumulation, phosphorylation and/or aggregation could account for differences in the microglial profile highlighting the need to identify which is the molecular nature of toxic tau species for microglial cells (Romero-Molina et al., 2018). Moreover, several emission tomography (PET) studies correlated *in vivo* microglial activation with cerebral amyloid load and the severity of cognitive deficits (Fan et al., 2015; Hamelin et al., 2016), as well as with both amyloid and tau aggregation (Dani et al., 2018) in MCI and AD patients. These studies support immunohistochemical assays revealing the co-localization of activated microglia with Aβ plaques (Zotova et al., 2013) and tau oligomers (Nilson et al., 2017) in human AD brains.

3. Inflammasome activation in AD

3.1. Inflammasomes: structure, function and activation pathways

Inflammasomes are cytosolic multiprotein complexes that are activated to initiate and sustain the innate immune response (Guo et al., 2015; Walsh et al., 2014). They are classically constituted by three main components: 1) a cytosolic pattern-recognition receptor, NOD-like receptors (NLR); 2) the enzyme caspase 1 and 3) an adaptor protein ASC [apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (CARD)], which facilitates the interaction between the two other former components.

According to the variable amino-terminal domain displayed, there are several subfamilies within the NLR family. The members of the NLRP subfamily carry an N-terminal pyrin domain (PYD), which interacts with the pyrin domain of ASC to bridge the complex to pro-caspase-1, while the NLR subfamily contains a CARD domain that binds directly to pro-caspase-1 (Walsh et al., 2014). Inflammasome assembly induces the autocatalytic cleavage of caspase-1 and processing of the cytokine precursors pro-IL-1β and pro-IL-18 into their mature and bioactive forms IL-1β and IL-18, respectively. These two pro-inflammatory cytokines, which are involved in neuroimmunomodulation, neuroinflammation, and neurodegeneration, can trigger signaling cascades culminating in a type of inflammatory neuronal death termed pyroptosis (Guo et al., 2015; Hanamsagar et al., 2012; He et al., 2016; Walsh et al., 2014).

Focusing on the NLRP3 inflammasome due to the importance garnered in neuroscience, its cytosolic PRR is the NOD-like receptor family pyrin domain-containing 3 (NLRP3). NLRP3 inflammasome is a unique PRR that responds to various activators. There are two well-established pathways for NLRP3 inflammasome activation and an alternative pathway was recently described (Gaidt et al., 2016; He et al., 2016; Walsh et al., 2014).

3.1.1. Canonical inflammasome activation pathway

The canonical inflammasome activation pathway consists in a two-signal model (Guo et al., 2015; Hanamsagar et al., 2012; He et al., 2016; Walsh et al., 2014). The first signal (priming step) is triggered by TLR ligands or endogenous molecules and involves the activation of nuclear factor (NF)-κB or activator protein 1 (AP-1), which upregulate the expression of NLRP3 and other inflammasome components (Bauernfeind et al., 2009; Franchi et al., 2009; Malik and Kanneganti, 2017). The second signal induces the assembly of the inflammasome (activation

step) and is provided by diverse stimuli such as ATP, pore-forming toxins, viral RNA, or particulate matter (He et al., 2016). The fact that NLRP3 inflammasome may be activated by different stimuli suggests that it functions as a general sensor of cellular damage and/or stress (He et al., 2016; Walsh et al., 2014). Currently, the K^+ efflux is pointed out as the most consensual trigger for NLRP3 inflammasome activation (He et al., 2016; Walsh et al., 2014). However, many other physiological events, including endosomal rupture, production of ROS and mitochondrial dysfunction, release of mtDNA or cardiolipin, release of cathepsins into the cytosol after lysosomal destabilization, and alterations in Ca^{2+} homeostasis have also been suggested as potential NLRP3 activating stimuli. As NLRP3 agonists do not induce all the above events, the specific mechanism of NLRP3 activation remains still not fully understood (Guo et al., 2015; He et al., 2016; Walsh et al., 2014).

The assembly of NLRP3 inflammasome includes the oligomerization of NLPR3 proteins as well as the sequestration of ASC protein to form a large protein complex, termed "speck", which further allows the recruitment of pro-caspase 1 into the inflammasome. This recruitment is believed to lead to the auto-proteolytic conversion of pro-caspase 1 into its active form (Guo et al., 2015; He et al., 2016; Walsh et al., 2014).

3.1.2. Noncanonical inflammasome activation pathway

The noncanonical inflammasome activation pathway is induced by the LPS released from Gram-negative bacteria into the cytosol by transfection or infection. Once in the cytosol, LPS binds to caspase-11 in mouse (caspase-4 and caspase-5 in humans) triggering its oligomerization and activation (Guo et al., 2015). This connection is not yet fully understood (He et al., 2016). The active form of caspase-11 induces K^+ efflux through the opening of pannexin-1 channel. As mentioned above, K^+ efflux is considered the most consensual signaling event for NLRP3 activation. The assembly of the NLRP3 inflammasome activates caspase 1 and, subsequently, the secretion of IL-1β and IL-18 (Broz and Dixit, 2016; He et al., 2016). In parallel, the mature form of caspase-11 can induce the cleavage of the GSDMD-N domain of the gasdermin D protein leading to disruption of cellular integrity by forming pores on the membrane, which in turn induces pyroptosis (He et al., 2015, 2016; Kayagaki et al., 2015; Shi et al., 2015). Unlike apoptosis, which is characterized by non-inflammatory phagocytic uptake of membrane-bound apoptotic bodies, pyroptosis is a type of cell death that exhibits rapid plasma-membrane rupture and release of proinflammatory intracellular contents (Bergsbaken et al., 2009). The P2 × 7 purinergic receptors (P2 × 7Rs) are members of the family of ionotropic ATP-gated receptors and when activated by ATP released from the pannexin-1 channel also contribute to pyroptosis induction (He et al., 2016).

3.1.3. Alternative inflammasome activation pathway

Recently, an alternative pathway for the activation of the NLRP3 inflammasome has been proposed. This alternative pathway, which is only activated in human monocytes (Netea et al., 2009; Piccini et al., 2008) in response to LPS, differs from the classical inflammasome activation pathway since it is only induced by TLR4 signaling, without need for a second stimulus (Gaidt et al., 2016; He et al., 2016; Walsh et al., 2014). Additionally, and although the activation of alternative pathway required both ASC and caspase-1, no evidence of ASC “speck” formation or pyroptosis are observed (Gaidt et al., 2016). Concerning the signaling pathway, the K^+ efflux is not required for NLRP3 activation (in contrasts with canonical and non-canonical pathways) and the molecules RIPK1, FAS-associated death domain protein (FADD), and caspase-8 are upregulated downstream of TLR4-TRIF signaling to activate NLRP3 after LPS stimuli (Gaidt et al., 2016).

3.2. Inflammasome triggers in AD

3.2.1. Endoplasmic reticulum (ER) stress

ER stress can be triggered by the accumulation of pathogenic misfolded proteins in the ER lumen or disruption of intracellular Ca^{2+} signaling. To date, three branches of ER stress sensors, which recognize the misfolding of proteins in ER and activate a complex signaling network to generate the unfolded protein response (UPR) have been documented: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE-1), and activating transcription factor 6 (ATF-6) (Ron and Walter, 2007). IRE-1 and PERK both contain cytoplasmic kinase domains known to be activated by homodimerization and autophosphorylation in the presence of ER stressors. In the case of ATF-6, accumulation of unfolded proteins induces ATF-6 transition to the Golgi, where it is cleaved by two transmembrane proteins, Site-1 and Site-2 proteases, which yields a cytoplasmic protein acting as an active transcription factor. Although short-term ER stress could initially activate the UPR to serve adaptive purposes leading to pro-survival transcriptional activities in conditions associated with higher cellular demands and after exposure to a range of pathophysiological insults, prolonged ER stress may become detrimental inducing the major apoptotic pathways (Tsang et al., 2010). Based on results from in vitro systems and AD mouse models, as well as studies in AD brains, the ER stress response has been considered as a potential event involved in AD development (Gerakis and Hetz, 2018).

Numerous studies implicate ER stress and alterations in ER-mitochondria communication mediated by Ca^{2+} and ROS in the pathogenic mechanisms of Aβ (Ferreiro et al., 2006, 2008; Costa et al., 2010, 2012a,b; Resende et al., 2008). Chronic ER stress, which is implicated in AD and other neurodegenerative disorders, can trigger a sterile inflammatory response (Garg et al., 2012). Accordingly, recent findings support that ER stress and the UPR play a prominent role in inflammatory processes leading to synapse failure and memory impairment in AD (Santos and Ferreira, 2017). ER stress-induced UPR signaling is associated with the production of pro-inflammatory molecules such as IL-1β and the three main branches of the UPR were reported to activate the transcription factor NF-κB that mediates crucial pro-inflammatory pathways through the expression of cytokines such as TNFα, IL-1β, IL-6 and IL-8 (reviewed in: Zhang and Kaufman, 2008). The most potent UPR transducers involved in ER stress-induced inflammatory response are IRE1-TRAF2, PERK-eIF2alpha, PERK-GSK-3, ATF6-CREBH, as well as inflammatory caspase-induced signaling pathways (Salminen et al., 2009). Recent studies demonstrate that severe ER stress stimulates the release of extracellular vesicles carrying DAMPs contributing to heighten a systemic inflammatory response (Collett et al., 2018). Interestingly, uncoupling protein 2 (UCP2), which has been demonstrated to regulate ROS production, modulates ER stress and neuroinflammation in astrocytes. Indeed, UCP2 deficiency exacerbated ER stress, cleavage of caspase-12, and aggravated neuroinflammation via the activation of NLRP3 in astrocytes (Lu et al., 2014). In human macrophages, ER stress was shown to activate the NLRP3 inflammasome with subsequent release of the pro-inflammatory cytokine IL-1β and this ER stress-induced proinflammatory signal was demonstrated to require ROS production and K^+ efflux, but to be independent of the classical UPR (Menu et al., 2012). Silver nanoparticles were found to induce different signature ER stress markers in human THP-1 monocytes leading to a rapid ER stress response that triggers pyroptosis and activation of the NLRP3 inflammasome as demonstrated by the processing and increased activity of caspase-1 and secretion of IL-1β and ASC pyroptosome formation (Simard et al., 2015). Furthermore, a significant activation of the NLRP3 inflammasome was observed in LPS-primed monocyte-derived human macrophages treated with the ER stress inducer thapsigargin by inducing generation of non-mitochondrial ROS and lysosomal damage, leading to release of cathepsin B (Shin et al., 2013). Bronner et al., 2015 demonstrated that ER stress-induced mitochondrial dysfunction aids in inflammasome activation. These authors reported that the ER stress sensor IRE1α induces ROS-dependent NLRP3 translocation to mitochondria in tunicamycin (ER stressor)-treated bone-marrow-derived macrophages, which stimulates the caspase-2-Bid mitochondrial damage pathway, leading to release of mitochondrial danger signals that activate the

inflammasome.

ER stress and inflammatory responses are key cellular processes associated with functions of dynamic platforms termed Mitochondria-Associated ER Membranes (MAMs) (reviewed in: Rowland and Voeltz, 2012). These ER-mitochondria contacts provide an excellent scaffold for crosstalk between the ER and mitochondria that is crucial for inter-organelle Ca^{2+} and lipids transmission controlling pro-survival /death pathways and determining cell fate under stressful conditions (van Vliet et al., 2014). Recent studies have shown the critical involvement of contact sites between the ER and mitochondria in regulation of the innate immune system and induction of inflammatory responses (Misawa et al., 2017). The NLRP3-inflammasome is composed of the receptor NLRP3 on the ER side and the adaptor apoptosis-associated speck-like protein containing a CARD on the mitochondrial side that induces caspase-1-dependent maturation of proinflammatory cytokines such as interleukin IL-1β and IL-18 (Song et al., 2017). Mitochondrial outer membrane proteins, namely those involved in ER-mitochondria tethering such as mitofusins, can promote activation of the NLRP3 inflammasome (Ichinohe et al., 2013; Subramanian et al., 2013). Therefore, ER-mitochondria contact sites play key roles in regulation of innate immune responses under stress conditions, such as those occurring in AD. Recently, MAMs have been studied in the context of different age-related disorders such as AD, and compelling evidences support that the metabolic disturbances seen in AD likely arise from increased ER-mitochondrial communication and transfer of stress signals (Area-Gomez et al., 2018).

3.2.2. Mitochondrial dysfunction

Multiple lines of evidence also show that mitochondrial anomalies play a key role in AD. Brains of AD subjects present mitochondrial morphologic alterations (Baloyannis et al., 2004) that precede dendritic degeneration (Saraiva et al., 1985) and synaptic loss (Pickett et al., 2018). The brains of AD subjects also present reduced activity of several mitochondria-localized enzymes, including α-ketoglutarate dehydrogenase (α-KGDH), pyruvate dehydrogenase (PDH) and cytochrome c oxidase (COX) enzymatic complexes, which support AD as a disease of perturbed energy metabolism (Sorbi et al., 1983; Gibson et al., 1988, 1998). In fact, mitochondrial alterations such as decreased COX activity, bioenergetics defects and oxidative stress (Cardoso et al., 2016; Moreira et al., 2007; Pérez et al., 2017) were also observed in platelets and fibroblasts from AD patients suggesting that AD is a systemic disease. Nowadays, it is widely accepted that mitochondrial anomalies that occur in AD include disturbances in oxidative phosphorylation, impaired energy metabolism, excessive generation of reactive oxygen species (ROS), and altered mitochondrial biogenesis, clearance, transport and dynamics (for more details see Silva et al., 2017; Cardoso et al., 2016; Correia et al., 2015, 2016). Indeed, mitochondrial dysfunction, a relevant feature of AD neurodegenerative process, may be directly linked to the activation of innate immunity and promote neuroinflammation (Cardoso and Empadinhas, 2018).

Dysfunctional mitochondria potentiate massive increase in mitochondrial fragmentation (Silva et al., 2013) allowing the release of DAMPs, such as mtDNA, cardiolipin, ATP, mitochondrial transcriptional factor A (TFAM), Formyl-methionine-labeled peptides and cytochrome c (Wilkins et al., 2014), which may signal and activate innate immune responses (Lampron et al., 2013).

One of the pathways of innate immune activation comprises the recognition of the mitochondrial DAMPs by NOD-like receptors, such as the NLRP3 inflammasome. Although NLRP3 is initially associated with the ER membrane, it can be redistributed after activation and associated with mitochondrial membranes. Indeed, mitochondrial ROS have been shown to activate NLRP3 (Hoyt et al., 2017). Data from the literature show that mitochondrial dysfunction inducers, such as rotenone (inhibitor of complex I) and 3-nitropropionic acid (3NP, complex II inhibitor) activate microglia and increase the production of ROS and IL-1β (Gurung et al., 2015; Zhou et al., 2011).

It has been discussed that mitophagy, a vital form of autophagy for selective removal of dysfunctional mitochondria, is a key event that may restrict inflammatory cytokine secretion and directly regulate mitochondrial antigen presentation and to keep the immune system in check (Xu et al., 2019). Indeed, mitochondrial damage is one of the most studied activating stimuli for the NLPR3 pathway. The accumulation of dysfunctional mitochondria leads to the buildup of ROS, increase cytosolic calcium levels and to the release of mtDNA, which results in inflammasome activation (Angajala et al., 2018). Since mtDNA is a danger signal it is recognized by PRR leading to the activation of NF-κB that induces pro-IL-1β and NLRP3 expression (Wilkins et al., 2017). Despite NF-κB is a key activator of NLRP3 inflammasome, it was recently demonstrated that NF-κB-dependent p62/SQSTM1 expression, needed for the elimination of defective poly-ubiquitinated mitochondria through mitophagy, may be an intrinsic regulatory pathway that controls and self-limits the inflammatory response allowing cellular homeostasis (Wilkins et al., 2017).

Given that mitochondrial dysfunction and inflammation are two key hallmarks in AD neurodegenerative process we hypothesize that mitochondrial-driven danger signals could be the initiators of inflammatory responses in AD.

3.2.3. Amyloid- β (Aβ) peptides

The role of neuroinflammation in the etiopathogenesis in AD dates back to 1907, to Alois Alzheimer's original report, which showed a co-localization between activated microglia and Aβ plaques (Alzheimer et al., 1995). We know that various forms of Aβ oligomers and aggregates are detected by different receptors of the innate immune system, such as NLRPs (Minter et al., 2016; Koenigsknecht and Landreth, 2004). Indeed, it has been widely assumed that amyloid proteins such the AD-associated Aβ peptide might be the triggers to activate the NLRP3 inflammasome, which is involved in the activation of inflammatory caspase-1, leading to the cleavage and secretion of inflammatory IL-1β and IL-18 cytokines, finally generating a potent inflammatory response through diverse downstream signaling pathways, leading to neuronal damage. Additionally, several studies have described that Aβ peptides induce an initial inflammatory stimulus, which activates microglia, allowing the maintenance of neuronal plasticity and synaptic connectivity (Chu et al., 2013). The data suggest that the microglia internalize and degrade the Aβ deposits, being involved in its elimination from the brain. However, during the neurodegenerative process, chronic activation of NLRP3 inflammasome triggered by Aβ in microglia contributes to persistent neuroinflammation with the continuous production of pro-inflammatory mediators (He et al., 2016). Aβ has been shown to trigger the release of mature IL-1β via activation of the NLRP3 inflammasome in microglia through lysosomal damage and release of cathepsin B (Halle et al., 2008; Parajuli et al., 2013) and NLRP3 or caspase-1 deficiency were found to substantially attenuate spatial memory impairment and enhance Aβ clearance in AD transgenic mice (Heneka et al., 2013). Interestingly, NLRP3 activation was characterized by ASC speck formation in an immune-activated microglial cell line and required a dual signal to become effective: the phagocytic uptake of Aβ and cathepsin B release after lysosomal disruption (Halle et al., 2008). Additionally, Aβ1-42 stimulation results in an upregulation of NLRP3, caspase 1 and its cleavage products in primary human astrocytes, which was time-dependently mitigated by the endogenous protease inhibitor α1-antitrypsin (Ebrahimi et al., 2018). Accordingly, cultured astrocytes primed with LPS and treated with Aβ showed an ASC-dependent production of IL-1β resulting from inflammasome activation mediated by Aβ phagocytosis and cathepsin B enzymatic activity. Interestingly, downregulation of inflammasome activity increases phagocytosis in astrocytes due to the release of CCL3, sustaining the hypothesis that downregulation of inflammasome activity decreases amyloid load and rescues memory deficits in a mouse model of AD (Couturier et al., 2016). Together, these data suggest that NLRP3 inflammasome activation represents an important and initiating factor in

the inflammatory signaling cascade evoked by fibrillar Aβ, both in vitro and in vivo, thus highlighting a new pathway that could lead to progression of AD and consequently a novel therapeutic target for this disease (Halle et al., 2008; Sheedy et al., 2013). Furthermore, increased NLRP1-mediated caspase-1-dependent pyroptosis was demonstrated to occur in cultured neurons in response to Aβ and NLRP1 or caspase-1 deficiency was found to significantly reduce neuronal pyroptosis and reverse cognitive impairments in APPswe/PS1dE9 mice, supporting the modulation of NLRP1 inflammasome as a promising strategy for AD therapy (Tan et al., 2014).

Recently it was demonstrated that Aβ induced microglia activation and mitochondrial dysfunction associated with ROS production and activation of the NLRP3 inflammasome. Interestingly, upon the attenuation of mitochondrial depolarization it was observed a reduction of mitochondria-derived ROS that suppressed NLRP3 inflammasome-mediated IL-1β secretion (Wang et al., 2017). In accordance, it was demonstrated that inhibition of NLPR3 inflammasome prevented memory loss and decreased Aβ deposition in an AD transgenic mice model (Tan et al., 2013). Terril-Usery and colleagues work, showed that Aβ(1–42) protofibrils induced an inflammatory response in primary microglial cells, inducing the secretion of IL-1β, despite significant intracellular IL-1β accumulation in microglia. These data clearly demonstrate an installation of chronic neuroinflammation (Terrill-Usery et al., 2014).

3.2.4. Reactive oxygen species (ROS)

Several studies suggest that ROS are induced by many NLRP3 inflammasome activators, and elevated ROS are essential for inflammasome formation and activation in response to many exogenous and endogenous stimuli (Tschopp and Schroder, 2010). The notion that ROS are an NLRP3 activator arose when inhibition of NADPH oxidase (NOX)-derived ROS prevented ATP-induced caspase-1 activation and IL-1β production in alveolar macrophages (Cruz et al., 2007). To support this idea, Dostert et al. (2008) observed that knockdown of the p22phox subunit of NOX significantly reduced IL-1β release in THP1 cells when challenged with asbestos and silica. More recently, it was demonstrated that oxidative stress activates NLRP3 via upregulation of cathepsin B activity (Bai et al., 2018).

Chen et al. (2015) found exacerbated cognitive impairment and elevated Aβ levels at 5 months in APP/PS1 mice, an animal model of AD, exposed to paraquat. This study also revealed that paraquat increases mitochondrial oxidative stress causing the activation of neuroinflammasome (Chen et al., 2015). In the same line, Aminzadeh et al. (2018) found that Aβ increases mitochondria and NOX-derived ROS levels activating NLRP3, an effect mediated by the transient receptor potential melastatin 2 (TRPM2) channel.

More studies focused on the involvement of ROS in inflammasome formation and activation in AD are required since this is a poorly explored topic in AD research field.

3.3. Role of peripheral immune cells in inflammasome activation in AD

In addition to the CNS innate immune response that increases the burden of reactive astrocytes and leads to the release of microglia-derived inflammatory cytokines, resulting in a chronic neuroinflammation in cerebral areas involved in AD, peripheral inflammation also plays a pivotal role in AD pathology (Rezai-Zadeh et al., 2011; Nascimento et al., 2014; Dionisio-Santos et al., 2019). Indeed, the risk for cognitive decline in human neurodegenerative diseases, including AD, is increased by systemic inflammation during which primed microglial cells become fully activated thus attracting, by chemokines production, peripheral monocytes that can then migrate to the CNS through the blood brain barrier. In AD patients, these cells are recruited to the CNS, possibly in an attempt to contrast the formation and/or the extension of Aβ plaques (Town et al., 2001, 2005, 2008; Hawkes and McLaurin, 2009; Tan et al., 1999, 2002, 2007; Townsend et al., 2005; Feng et al., 2011; Fiala et al., 2005; Simard et al., 2006; Saresella et al., 2014). Interestingly, the presence of the ApoEε4 allele has been demonstrated to affect the phagocytic efficiency of macrophages derived from peripheral blood monocytes (Jairani et al., 2019). However, in addition to provide assistance to microglial cells for Aβ clearance, CNS infiltrated monocytes, which are the main myeloid cells expressing inflammasomes, can also activate NLRP3 resulting in the activation of caspase-1 and downstream production of IL-1β and IL-18 that will fuel and sustain neuroinflammation (Saresella et al., 2016). Recently, microglial changes upon a peripheral immune challenge in the context of aging and AD was assessed in vivo. Systemic inflammation was shown to promote alterations in microglial morphology and to reduce microglial Aβ clearance in APP/PS1 mice by a NLRP3 inflammasome-mediated mechanism (Tejera et al., 2019). Furthermore, additional studies need to be empowered to elucidate the role of specialized macrophage populations at the CNS borders, which are thought to be involved in the essential exchange between the CNS parenchyma and the periphery (Kierdorf et al., 2019), in the pathogenesis of AD. Recently, an association between altered gut microbiota composition and the peripheral inflammatory state, including increase of *NLRP3* and *IL1β* gene expression, was observed in cognitively impaired elderly individuals with brain amyloidosis (Cattaneo et al., 2017), further supporting the hypothesis that peripheral inflammation evoked by inflammasome activation may contribute to AD pathology.

3.4. Inflammasome modulation as a therapeutic strategy

The modulation of NLRP3 activity has become a focus of exploration in the last years and numerous mediators in the pathway have been pharmacologically modulated, with recent evidence pointing out IL-1β, cathepsins, P2 × 7 receptor and caspase-1 as emerging NLRP3 regulators (White et al., 2017). Currently, the treatments for NLRP3-related diseases comprise biological agents that target IL-1β, namely the neutralizing IL-1β antibody canakinumab, the recombinant IL-1β receptor antagonist anakinra and the soluble decoy IL-1β receptor rilonacept (Ferreira et al., 2017). However, these proteins do not own perfect pharmacokinetic properties and are unlikely to easily cross the blood-brain barrier thus limiting their use on neuroinflammatory-related diseases such as AD. Conversely, IL-1R1 KO mice have cognitive deficits, suggesting that chronic inhibition of IL-1R1 may have detrimental effects in AD (Avital et al., 2003). Targeting IL-1R1 also has the additional drawback of having no effect on caspase-1 dependent pyroptosis. Therefore, microglial death is not abolished, resulting in the release of DAMPS and fewer microglia to perform important functions independent of inflammation.

Hopefully, several in vitro and in vivo pre-clinical studies shed light on potential molecules targeting inflammasome activation in AD. For instance, natural compounds, namely pterostilbene attenuated the in vitro neuroinflammatory response induced by Aβ1-42 in microglia through inhibition of the NLRP3/caspase-1 inflammasome pathway (Li et al., 2018). Also, sulforaphane, an isothiocyanate active component of cruciferous vegetables obtained in high concentrations from broccoli seeds and sprouts, exerts anti-inflammatory effect in human microglia-like cells, through inhibition of cathepsin B- and caspase-1-dependent NLRP3 inflammasome activation induced by mostly Aβ1-42 monomers, an effect that potently reduced excessive secretion of the proinflammatory cytokine interleukin-1β (An et al., 2016). Previous studies also investigated whether astaxanthin (AST) and their synthesized docosahexaenoic-acid-acylated AST diesters (AST-DHA) could delay AD pathogenesis. The findings suggested that AST-DHA attenuated cognitive disorders by reducing pathological features in APP/PS1 mice, namely inflammasome expression (Che et al., 2018). Interestingly, the antimalarial drug artemisinin demonstrated to decrease amyloidogenesis and neuroinflammation in APPswe/PS1dE9 transgenic mice via inhibition of NF-κB and NLRP3 inflammasome activation (Shi et al., 2013). Recently, the neuroprotective effect of *Epimedii Folium* and

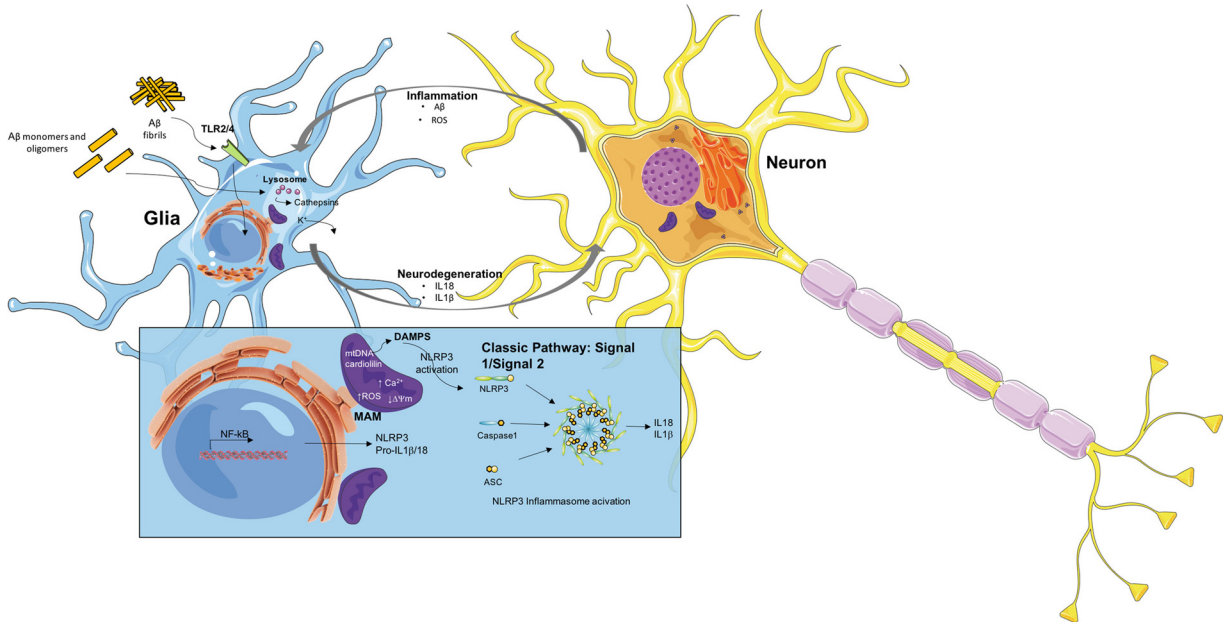

Fig. 1. Major players in NLRP3 activation in Alzheimer's disease. Aβ peptide is closely associated with inflammatory responses in the AD brain. Fibrillar Aβ species are agonists of pattern-recognition receptors, such as TLR 2 and 4, triggering NF-κB activation to upregulate the inflammasome component NLRP3 and pro-interleukins, which are cleaved into their active forms upon assembly of NLRP3, ASC and pro-caspase-1 and subsequent activation of this pro-inflammatory caspase. Furthermore, phagocytosis of soluble Aβ also triggers lysosomal destabilization and consequent cathepsin leakage, leading to inflammasome activation. However, many other DAMPs, including production of ROS, mitochondrial membrane depolarization, release of mtDNA or cardiolipin externalization, as well as alterations in Ca^{2+} homeostasis have also been suggested as potential NLRP3 activating stimuli. Recent evidences support that ER-mitochondria contacts at MAMs are important sites of NLRP3 inflammasome activation. Glial cells are the main cells involved in inflammatory responses in the central nervous system, although neuronal cells can also have a role in the up-regulation of the immune response through the release of danger signals that recruit and activate local microglia. Chronic activation of NLRP3 inflammasome triggered by Aβ contributes to persistent neuroinflammation as evidenced by production and release of pro-inflammatory mediators, which ultimately leads to the neurodegenerative process and neuronal loss. Aβ: amyoid β-peptide; AD: Alzheimer's disease; ASC: Apoptosis-Associated Speck-Like Protein Containing CARD; DAMPs: Danger-Associated Molecular Patterns; ER: Endoplasmic Reticulum; MAMs: Mitochondria-Associated Membranes; mtDNA: mitochondrial DNA; NF-κB: factor nuclear kappa B; NLRP3: nucleotide binding and oligomerization domain–like receptor family pyrin domain-containing 3; TLR; toll-like receptor.

Curculiginis Rhizoma' extracts was investigated using an in vivo mouse model of AD, specifically in rats stereotaxically injected with Aβ1-42 bilaterally into their dorsal hippocampus. The results demonstrated that the protective effect of *Epimedii Folium* and *Curculiginis Rhizoma* was partially achieved through inhibition of the NF-κB/MAPK pathways and NLRP3 inflammasome (Lan et al., 2017). Furthermore, Naoling decoction, a traditional Chinese medicine, restores cognitive function by inhibiting the neuroinflammatory network in a rat model of AD, involving the inhibition of the NF-κB signaling pathway and the ASC-dependent inflammasome in the hippocampus (Xia et al., 2017). Paeoniflorin, one of the major constituents of an herbal medicine derived from *Paeonia lactiflora*, atttenuates amyloidogenesis and the inflammatory responses in a transgenic mouse model of AD, involving inhibitory effects on NLRP3 inflammasome, caspase-1, and IL-1β (Zhang et al., 2015). Interestingly, the ketogenic diet, originally developed for the treatment of epilepsy in non-responder children, is spreading to be used in the treatment of many diseases, including AD. Indeed, β-hydroxybutyrate, the most studied ketone body, has been shown to reduce several pathological hallmarks present on AD, namely the production of ROS, mainly through activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2) and to decrease neuroinflammation by inhibiting NF-κB and NLRP3 inflammasome activation, as well as by inhibiting histone deacetylases (HDACs), improving memory encoding (Pinto et al., 2018). The antioxidant Dl-3-*n*-butylphthalide (Dl-NBP) inhibits NLRP3 Inflammasome and mitigates AD-Like pathology in the transgenic mouse APP/PS1 through Nrf2 activation and suppression of thioredoxin-interacting protein (TXNIP), an endogenous inhibitor of the antioxidant thioredoxin and well known to activate NLRP3 inflammasome (Wang et al., 2019). Coll and collaborators demonstrated that the small molecule named MCC950 inhibits NLRP3 in vivo, in several NLRP3-dependent mouse models, and in ex vivo samples from individuals with cryopyrin-associated periodic syndrome (Coll et al., 2015). More recently, Dempsey and colleagues demonstrated that inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of Aβ and cognitive function in APP/PS1 mice. The authors also demonstrated that activation of the inflammasome contributes to amyloid accumulation and to the deterioration of neuronal function in APP/PS1 mice and prove that blocking assembly of the inflammasome may be a valuable strategy for attenuating changes that negatively impact on neuronal function (Dempsey et al., 2017). More recently, it was also demonstrated that chronic intracerebral administration of MCC950 inhibits exogenously seeded Tau pathology (Stancu et al., 2019). Interestingly, Daniels and colleagues demonstrated that several clinically approved and widely used nonsteroidal anti-inflammatory drugs (NSAIDs) of the fenamate class are effective and selective inhibitors of the NLRP3 inflammasome via inhibition of the volume-regulated anion channel in macrophages, independently of cyclooxygenase enzymes. The authors also demonstrated the therapeutic effects of fenamates using a model of Aβ induced memory loss and a transgenic mouse model of AD. These data suggest that fenamate NSAIDs could be repurposed as NLRP3 inflammasome inhibitors and AD therapeutics (Daniels et al., 2016).

Evidence is building that amyloid mediated NLRP3 inflammasome activation is dependent on the P2 × 7 receptor. This is supported by research demonstrating that pharmacological intervention with P2 × 7 antagonists were found to be therapeutic in a rat amyloid injection model (Sanz et al., 2009), thus suggesting that P2 × 7 inhibition remains an attractive target in AD. As previously stated, amyloid fibrils have been shown to induce phagosomal stress causing NLRP3 activation through a cathepsin B-dependent mechanism. Therefore, targeting

cathepsin B has been successful in animal models of AD by demonstrating that administration of the cathepsin B inhibitor CA074Me is therapeutic in the APP_{Lon} mouse model of AD (Hook et al., 2008).

Targeting the molecular and physiological processing directly involved in inflammasome formation is the optimal approach for limiting the negative effects of IL-1β signaling in AD. Inflammasome specific approaches would have limited side-effects and would not greatly impact the patients' resistance to disease. However, there are currently no drugs which have been conclusively shown to directly inhibit inflammasome formation. Due to the increasing evidences of inflammasome involvement in multiple inflammatory diseases, there is a compelling rationale to develop potent and selective modulators of NLRP3 that could have therapeutic value and to be a useful tool for the further study of inflammasome in human health and disease. In this sense, the development of novel inflammasome inhibitors using screening and structure based molecular modeling techniques to target inflammasome formation could provide a diverse set of tools to further investigate the role of inflammasomes in a range of diseases, including AD.

4. Conclusions

Recent data emerging from animal experimentation, genetics and clinical imaging highlight an intimate and mutual interaction of innate immune mechanisms and AD and it is now clear that neuroinflammation plays a central role in the pathogenesis of this disease. Neuroinflammation is mediated through numerous PRRs including cell surface receptors such as TLR2 and TLR4, as well as cytosolic receptors, of which the NLRP3 inflammasome has been found to be central. Indeed, 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 (Fig. 1). Furthermore, peripheral blood-derived immune cells such as monocytes, which are the main inflammasome-expressing cells, can be recruited into the CNS of AD patients and are thus likely to fuel and sustain neuroinflammation. Therefore, NLRP3 is a very promising novel pharmacological target, which merits further research in the continued endeavour for efficacious therapeutics for AD. However, pharmacological strategies interfering with key parts of the inflammasome (NLRP3, ASC and Caspase-1) in a shotgun manner may also have serious peripheral effects because of the ubiquitous distribution and relevance of inflammasome activation in many cellular events. Therefore, future research should focus on identifying CNS-specific triggers leading to NLRP3 activation in microglia and astrocytes, namely ER stress, mitochondrial dysfunction, ROS and Aβ peptide. As our knowledge expands, the prospect for precise pharmacological targeting of inflammasome will improve and could lead to substantial clinical utility through fine-tuned targeted therapies targeting NLRP3 on AD.

Declaration of Competing Interest

None.

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