Molecular Neurobiology (2019) 56:7741–7753
https://doi.org/10.1007/s12035-019-1638-7

The Role of Neuronal NLRP1 Inflammasome in Alzheimer's Disease: Bringing Neurons into the Neuroinflammation Game

Jeremy Kean Yi Yap[1] · Benjamin Simon Pickard[2] · Elaine Wan Ling Chan[3] · Sook Yee Gan[4]

Received: 15 February 2019 / Accepted: 6 May 2019 / Published online: 20 May 2019

Abstract

The innate immune system and inflammatory response in the brain have critical impacts on the pathogenesis of many neurodegenerative diseases including Alzheimer's disease (AD). In the central nervous system (CNS), the innate immune response is primarily mediated by microglia. However, non-glial cells such as neurons could also partake in inflammatory response independently through inflammasome signalling. The NLR family pyrin domain-containing 1 (NLRP1) inflammasome in the CNS is primarily expressed by pyramidal neurons and oligodendrocytes. NLRP1 is activated in response to amyloid-β (Aβ) aggregates, and its activation subsequently cleaves caspase-1 into its active subunits. The activated caspase-1 proteolytically processes interleukin-1β (IL-1β) and interleukin-18 (IL-18) into maturation whilst co-ordinately triggers caspase-6 which is responsible for apoptosis and axonal degeneration. In addition, caspase-1 activation induces pyroptosis, an inflammatory form of programmed cell death. Studies in murine AD models indicate that the Nlrp1 inflammasome is indeed upregulated in AD and neuronal death is observed leading to cognitive decline. However, the mechanism of NLRP1 inflammasome activation in AD is particularly elusive, given its structural and functional complexities. In this review, we examine the implications of the human NLRP1 inflammasome and its signalling pathways in driving neuroinflammation in AD.

Keywords Alzheimer's disease · Caspase-1 · Interleukin-1β · Interleukin-18 · Neuroinflammation · NLRP1 inflammasome

Introduction

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disease which gradually impairs patients' memory and cognitive functions. It is the most common cause of dementia, accounting for 60–80% of total dementia cases [1]. The clinical symptoms of AD include memory loss, behavioural fluctuations, and difficulty in speech, problem-solving and basic cognitive functions—all of which are attributed to the shrinking of select regions in the brain caused by widespread neuronal loss. As the brain continues to deteriorate, the symptoms worsen, eventually leading to death. At present, there is no available treatment capable of modifying or reversing the progression of AD. Current clinical interventions such as cholinesterase inhibitors (e.g. Donzepil, Rivastigmine and Galantamine) for early to moderate stages of AD, and N-methyl-D-aspartate inhibitors (e.g. Memantine) for late to severe AD, are limited to symptom management and improvement of quality of life [2].

The aetiology of AD has remained elusive ever since the disease was first described. Two well-known pathological hallmarks of AD, namely senile plaques (primarily composed of amyloid-β (Aβ) peptides) and neurofibrillary tangles

✉ Sook Yee Gan
sookyee_gan@imu.edu.my

Jeremy Kean Yi Yap
JEREMY.YAP@student.imu.edu.my

Benjamin Simon Pickard
benjamin.pickard@strath.ac.uk

Elaine Wan Ling Chan
elainechan@imu.edu.my

[1] School of Postgraduate Studies, International Medical University, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

[2] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Hamnett Wing, 161, Cathedral Street, Glasgow G4 0RE, UK

[3] Institute for Research, Development and Innovation, International Medical University, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

[4] Department of Life Sciences, School of Pharmacy, International Medical University, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

(NFTs, primarily composed of tau proteins), have been a major focus in contemporary AD research [3]. To cure AD, however, remains challenging as our knowledge of AD pathophysiology has not yet translated into the development of drugs that target the root cause of the disease. Several drugs designed to reduce Aβ production or aggregation such as rosiglitazone, semagacestat, tarenflurbil, tramiprosate and scyllo-inositol have failed in clinical trials either due to ineffectiveness or severe side effects [4]. As reported in 2018, there are approximately 17 potentially disease-modifying drugs in Phase III clinical trials which include 14 drugs targeting amyloid and one targeting tau [5]. In the wake of the second failure of aducanumab in a recent Phase III clinical trial, we are forced to consider novel approaches for future AD drug development that move beyond the conventional AD pathologies.

In recent years, neuroinflammation has received much attention as a potential driver of neurodegeneration, and its implications for AD are evident in genetic studies, neuroimaging and biopsies of patients, as reviewed in [6, 7]. As inquiries into the role of neuroinflammation in AD gain traction, a type of multiprotein complex known as the inflammasome has garnered much interest for its part in inflammation regulation. Inflammasomes serve as platforms for the recruitment and activation of caspase-1, the de facto executioner of a diverse downstream inflammatory processes including the maturation of two major pro-inflammatory cytokines, interleukin-1β (IL-1β) and interleukin-18 (IL-18) [8]. Several types of inflammasome have been identified within the central nervous system (CNS), of which the best characterized are the absent in melanoma 2 (AIM2), NLR-family pyrin domain-containing 1 (NLRP1), NLRP3 and NLR-family CARD-containing 4 (NLRC4) inflammasomes [9]. Recently, the NLRP1 inflammasome was shown to co-activate with the NLRP3 inflammasome in monocytes of AD patients [10]. In AD brains, an approximately 25- to 30-fold increase in neuronal NLRP1 immunopositivity is observed compared to non-AD brains [11]. As such, we propose that the NLRP1 inflammasome in neurons plays a pivotal role in contributing towards neuroinflammation in AD. In this review, we consolidate the latest findings on the structure and mechanisms of regulation and activation of the NLRP1 inflammasome. Then, we examine potential contribution of the neuronal NLRP1 inflammasome, and its corresponding signalling pathways in AD neurodegeneration.

The Innate Immune System, Inflammation and Inflammasomes in the CNS

The innate immune system acts at the forefront of host defence against infectious pathogens as well as non-infectious harmful stimuli. In the periphery, innate immunity is mediated by immune cells such as mast cells, dendritic cells, macrophages and neutrophils [12, 13]. These immune cells recognize molecules associated with groups of pathogens termed pathogen-associated molecular patterns (PAMPs), or with sterile tissue injuries termed danger-associated molecular patterns (DAMPs) [14]. These signals are recognized through germline-encoded pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), the retinoic acid-inducible gene-I-like receptors (RIG-I-like receptor or RLRs), C-type lectin receptors (CLRs) and the nucleotide oligomerization domain-like receptors (NOD-like receptors or NLRs), as well as a number of DNA-sensing molecules including the pyrin and HIN domain-containing (PYHIN) receptors [15, 16]. When engaged, these receptors function in synergy to promote maturation and secretion of pro-inflammatory cytokines and molecules which result in inflammation and pathogen clearance.

The CNS is separated from the peripheral circulatory system by the blood-brain barrier (BBB), a highly selective semi-permeable membrane barrier which shields the CNS against external injury, toxins and pathogens [17]. In addition, the sanctity of the CNS is maintained by microglia and astrocytes which make up its primary resident immune cells. The roles of these glial cells in immunity are reviewed in [18, 19]. While the primary roles of these cells are to maintain homeostasis and to provide support for neuronal functions, they are capable of eliciting innate immune responses against infections and stimulating inflammation within the CNS, more commonly known as neuroinflammation. Surprisingly, even neurons are shown to be capable of participating in such responses through their expression of PRRs and production of pro-inflammatory cytokines [20, 21]. Although inflammation is intended to be protective in nature, dysregulated inflammation can instead lead to severe tissue damage and even death. In the CNS, neuroinflammation has been implicated in various neurogenerative diseases including AD, Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), as reviewed in [22].

In AD, chronic neuroinflammation is believed to be a possible missing link between neuritic plaques, NFTs and neuronal death [6]. One of the cardinal signs of neuroinflammation in AD is the patients' cytokine profiles. The mRNA expressions of several major cytokines (interleukins, tumour necrosis factor α converting enzyme (TACE), and transforming growth factor β1 (TGFβ1)) are significantly upregulated in the brains of AD patients compared to non-demented controls [23]. Moreover, a meta-analysis has indicated that elevated levels of pro-inflammatory cytokines including tumour necrosis factor α (TNFα), TGFβ1, IL-1β and IL-18 in the peripheral blood of AD patients further substantiate the association between inflammation and AD [24]. Interestingly, this spike in cytokine expression is only observed in late-stage AD with significant cognitive decline, but not in its pre-symptomatic stages, suggesting that neuroinflammation may be a

secondary response to external factors such as Aβ which rapidly escalates with greater amyloid deposition. Moreover, the leaky blood-brain barrier typically observed in the brains of AD patients further encourages influx of toxic molecules, pathogens, peripheral immune cells and pro-inflammatory cytokines which collectively escalate the severity of neuroinflammation [25].

In recent years, a wealth of literature points towards inflammasomes in the CNS as important drivers of AD pathogenesis through caspase-1-mediated neuroinflammatory responses against Aβ [26–29]. Inflammasomes are assembled as clusters of PRRs which recruit caspase-1 via an adaptor protein known as apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). Among the PRRs, only NLRs and PYHINs are capable of forming inflammasomes [30]. The NLRP3 inflammasome expressed in microglia is the most extensively studied of all the inflammasomes, and its roles in AD are well-established [29, 31, 32]. While studies of neuronal inflammasomes are relatively scant, several types, namely AIM2, NLRC4 and NLRP1, have been identified as eliciting similar neuroinflammatory processes [11, 33]. Within neurons, the NLRP1 inflammasome is particularly relevant in AD. Nlrp1-dependent neurotoxicity has been observed in Aβ-treated rat cortical neurons via the activation of caspase-1 and secretion of IL-1β [34]. In human system, NLRP1 inflammasome induces caspase-1 and subsequently caspase-6 activation which consequentially leads to axonal degeneration and neuronal death [11]. These observations allude to NLRP1's contribution towards neurodegeneration in AD (Fig. 1). Furthermore, a cohort study involving Italian AD patients revealed the association of four non-synonymous single nucleotide polymorphisms (SNPs) in the *NLRP1* gene, namely rs2137722 (Arg1322Cys), rs3473379 (Thr995Ile), rs11657747 (Thr878Met) and rs11651595 (Thr246Ser) with the disease [35], although these SNPs were not reported in the recent genome-wide association study (GWAS) meta-analysis of AD [36]. The contradictory results could be due to the differences in the geographic and ethnic background of the participants.

The NLRP1 Inflammasome: Structure and Mechanism of Activation

Although NLRP1 was the first inflammasome to be described, its properties remained particularly enigmatic as studies were hindered by numerous complications such as the uncertainty of its specific ligands and the substantial structural and functional divergence between the human NLRP1 and its murine counterparts [37, 38]. Although found in a diverse mammalian species, the NLRP1 inflammasome has undergone considerable modifications among these species. For example, there are three paralogs which exist in mice, namely *Nlrp1a*, *Nlrp1b*, and *Nlrp1c*, whilst only a single *NLRP1* gene exists in humans (Fig. 2) [39]. Moreover, alternative splicing has resulted in considerable functional variation both within and between species. In humans, there are seven isoforms of NLRP1 known to exist, each with altered protein sequence at the C-terminal region. The specific activators for the NLRP1 inflammasome also vary between the human and rodent orthologues. For example, while it is known that murine Nlrp1b is reactive towards anthrax lethal factor due to the presence of a unique cleavage site located at the N-terminal region [40], human NLRP1 does not produce a similar response. This poses a challenge in accurately modelling human NLRP1, and its related diseases, in animal models.

As a member of the NLR family, the 'canonical' full-length human NLRP1 (1473 amino acids; 165.9 kDa) contains a central NLR which consists of a nucleotide oligomerization domain (NOD) and a leucine-rich repeat (LRR) domain [41]. In common with the other members of the NLRP sub-family, a pyrin domain (PYD) is attached to its N-terminus [42]. Additionally, NLRP1 contains a unique 'function-to-find' (FIIND) domain which is flanked by LRR and caspase recruitment domain (CARD). The post-translational auto-proteolytic cleavage within a region in the FIIND domain is strictly necessary for NLRP1 activation (Fig. 3). Bioinformatic analyses revealed that FIIND is structurally remarkably similar to a combination of two domains namely ZU5 and UPA [43]. Auto-proteolytic cleavage of FIIND results in separated ZU5 and UPA domains which remain non-covalently linked to each other [44]. This cleavage is initiated by deprotonation of Ser^{1213} located within the FIIND domain by a highly conserved distal His^{1186} residue. Incidentally, a SNP near His^{1186} disrupts the cleavage and hence prevents NLRP1 activation.

Unlike other NLRPs including murine Nlrp1, the human NLRP1 simultaneously contains both PYD and CARD within its structure (Fig. 2). These proteins belong to the death domain (DD) superfamily which are protein-protein interaction domains for apoptotic or inflammatory signal transduction [37, 45, 46]. Although the human NLRP1 contains two signal transduction domains, surprisingly the PYD of NLRP1 is dispensable, whereas the CARD appears to be its bona fide effector domain. Crystallization and nuclear magnetic resonance spectroscopy analyses revealed structural distinctions in PYD between NLRP1 and other NLRs [47, 48], with the most conspicuous difference being the lack of a defined α3 helix, one of the six conserved α-helices typical of the DD superfamily, which instead is replaced by a flexible loop. This unique structural feature may be sufficient to modify the function of NLRP1 PYD. In addition to FIIND cleavage, human NLRP1 undergoes N-terminal cleavage which occurs at the unusually long linker region between PYD and NOD, resulting in a severed PYD. Studies have

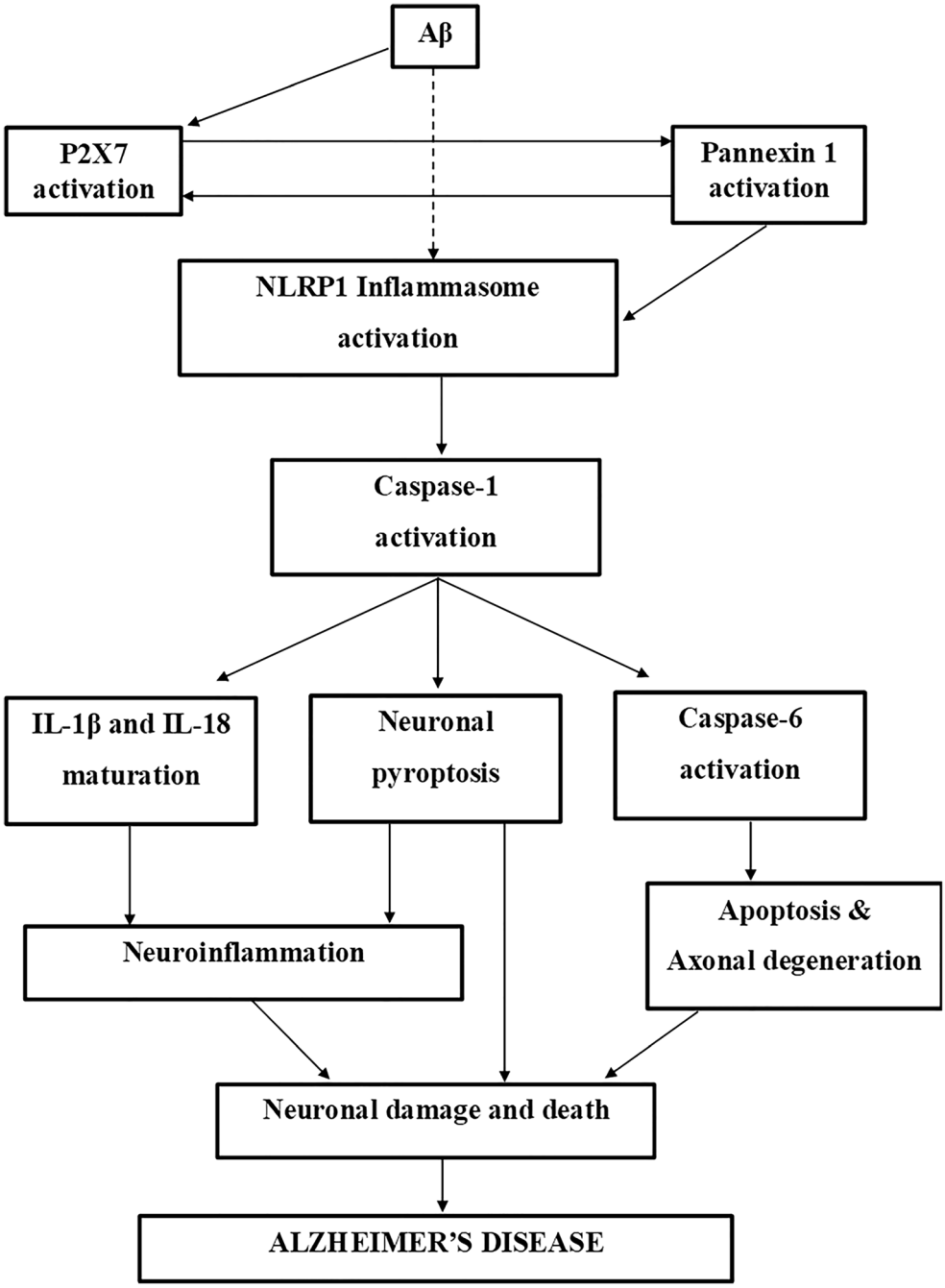

Fig. 1 The activation of NLRP1 inflammasome by AD pathology, most notably by Aβ, ignites a cascade of reactions leading to loss of synapses and functional neurons. As NLRP1 is highly expressed in pyramidal neurons, the cerebral cortex, hippocampus and amygdala are most severely affected, thus leading to the classic manifestation of the clinical pathology of AD

demonstrated that the proteolytic cleavage of NLRP1 N-terminus is a general molecular mechanism for its activation [49, 50]. In a study by Chavarría-Smith et al., a reconstituted human NLRP1 could be activated following an artificial cleavage on the linker sequence even with its PYD replaced with a green fluorescent protein [50]. Interestingly, mouse Nlrp1b lacking a PYD also requires the N-terminal cleavage for its activation [49]. Therefore, it is hypothesized that the N-terminal region of NLRP1 plays an auto-inhibitory role instead of inflammasome signal transduction. Further studies to elucidate the precise role of PYD in human NLRP1 activation are warranted. PYD may participate in an independent process to supplement NLRP1-mediated inflammation.

The N-terminal cleavage of murine Nlrp1b generates a neo-N terminus which is targeted by ubiquitin and subsequently undergoes a proteasome-mediated full-length degradation through the N-end rule pathway. This liberates an active C-terminal fragment with potent inflammatory capacity consisting of the UPA-like domain attached to the CARD [51, 52]. The UPA-CARD fragment assembles into a simpler inflammasome complex with ASC and

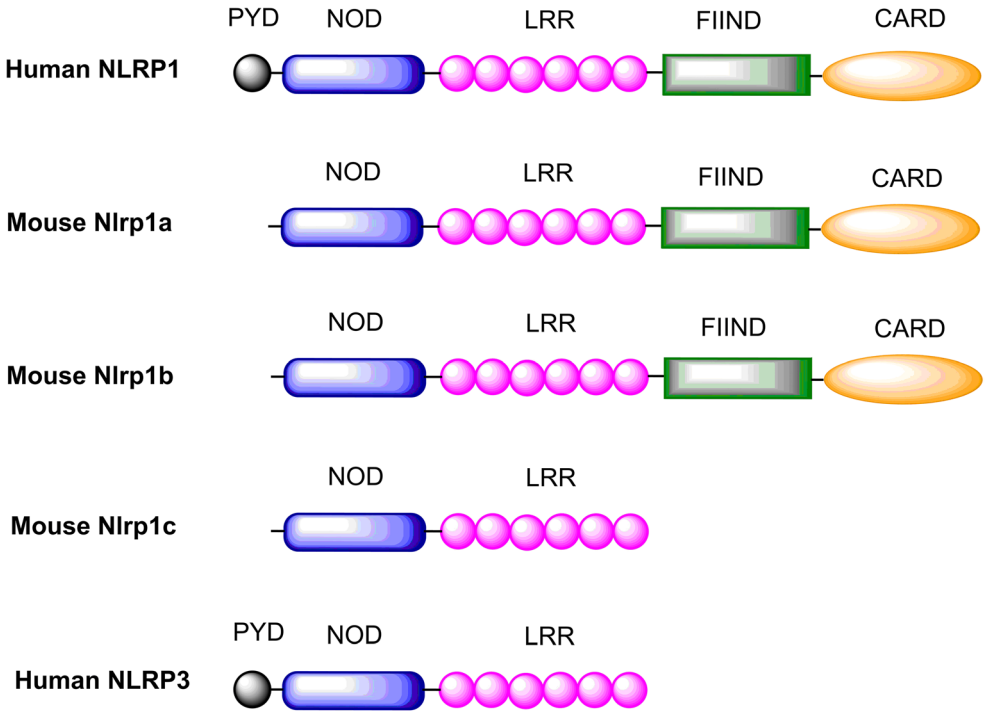

Fig. 2 Structures of NLRs that form inflammasomes. Human NLRP1 is structurally distinct from the three mouse Nlrp1 paralogues, none of which contains a PYD. All (with the exception of mouse Nlrp1c) contain a unique function-to-find domain (FIIND) and a functional CARD at the C-terminus

caspase-1 via CARD-CARD interactions in the absence of NOD (Fig. 4). Unlike murine Nlrp1b, the N-end rule pathway is not necessary for the activation of human NLRP1 [44, 50]. Interestingly, the NOD in the murine Nlrp1b is removed through the N-end rule pathway, but the NOD of human NLRP1 is necessary to form the core of the inflammasome complex. The NOD in human NLRP1 contains Walker-A and Walker-B, two adenosine triphosphate (ATP)-binding motifs which are required for self-oligomerization and inflammasome assembly [53].

Upon activation, NLRP1 initiates a structural conformational shift that allows its oligomerization into the characteristic filamentous star-shaped conformation via clustering among NODs, followed by subsequent ASC speck formation and pro-caspase-1 recruitment resulting in the complete inflammasome complex (Fig. 3). The mechanisms of inflammasome assembly are reviewed in [54, 55]. In most other inflammasomes, the N-terminal PYD interacts with ASC via homotypic PYD-PYD attraction, which in turn recruits pro-caspase-1 (caspase-1 zymogen) via interaction between the CARD of ASC and the CARD of pro-caspase-1. As NLRP1 possesses its own CARD as a primary signal transduction domain, it could theoretically bypass the requirement for ASC in caspase-1 recruitment. Indeed, it was observed that ASC-deleted mouse macrophages were able to produce Nlrp1b-mediated IL-1β and induce pyroptosis in response to anthrax lethal factor without the occurrence of speck formation and caspase-1 auto-proteolysis [56]. However, ASC-driven speck formation could amplify inflammasome signalling by activating sufficient levels of caspase-1 for optimum downstream reactions including production of matured cytokines [57]. It is also noteworthy that in other inflammasomes, the signal transduction domain is located on the N-terminal upstream of NOD. Upon oligomerization, these inflammasomes orientate their PYD or CARD at the core of the complex to create a platform for ASC aggregation and caspase-1 activation. Since the CARD of NLRP1 is located at the C-terminal, the pattern of oligomerization of NLRP1 could differ compared to other inflammasomes. The precise structural mechanism of NLRP1 inflammasome oligomerization is currently undetermined.

Recently, inhibition of dipeptyl peptidase 8 and 9 (DPP8/9) is found to stimulate the activation of Nlrp1b inflammasome [58, 59]. DPP8/9 are intercellular serine peptidases that perform non-reversible N-terminal cleavage on their peptide substrates. Multiple studies have found that DPP8/9 inhibition elicits caspase-1-dependent pyroptosis in both immune and cancer cells, which had led to the development of several small-molecule DPP inhibitors such as Val-boroPro as potential cancer therapeutics [60–62]. In mouse macrophages treated with Val-boroPro, pyroptosis, and concomitantly caspase-1 maturation, ASC speck assembly, and secretion of mature IL-1β and IL-18, were significantly accelerated upon challenge with anthrax lethal factor [59]. On the other hand, DPP9 is shown to suppress human NLRP1 activation by binding to the FIIND domain [63]. These observations suggest that DPP8/9 are important immune suppressor molecules that serve as regulatory checkpoints upstream of inflammasome activity, and their inhibition unleashes NLRP1 for maximum inflammatory potency.

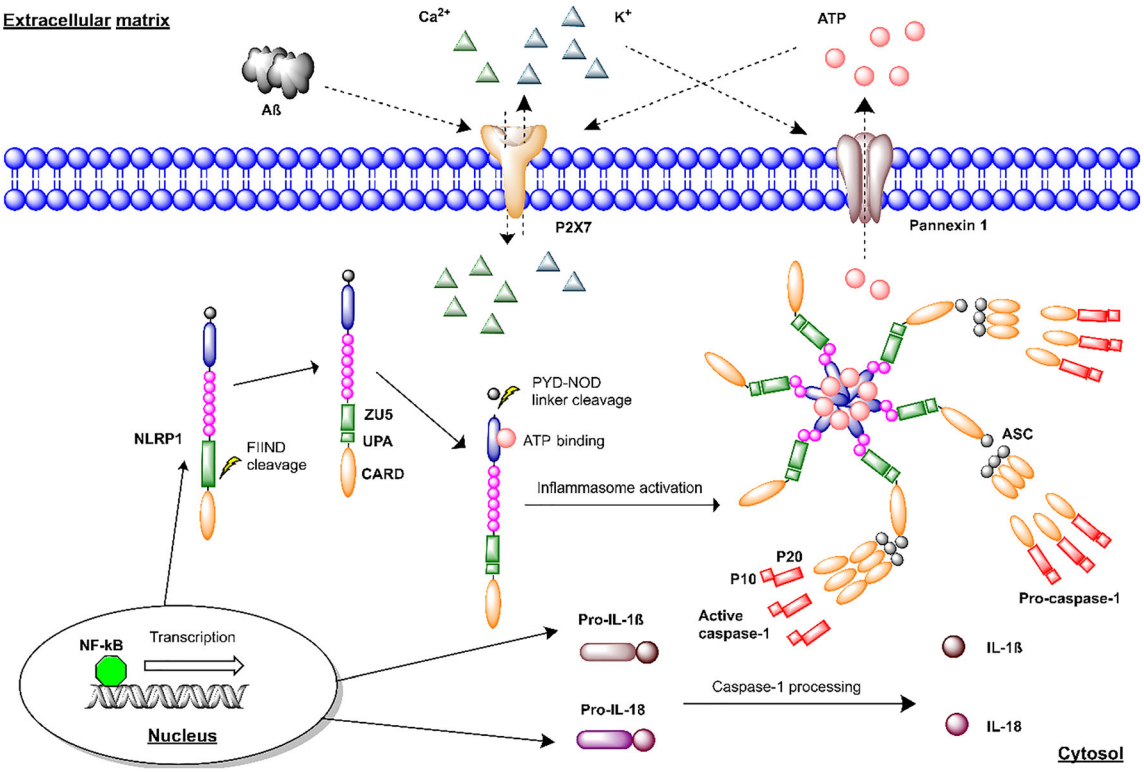

Fig. 3 NLRP1 can be activated by P2X7/pannexin 1 signalling under the influence of Aβ, prompting assembly of the inflammasome. The expression of NLRP1, pro-IL-1β and pro-IL-18 is driven by NF-κB signalling pathways. A region of the FIIND is post-translationally auto-cleaved as a requirement for the subsequent NLRP1 activation. PYD might play an auto-inhibitory role which, when cleaved, activates the NLRP1 to allow inflammasome complex formation. ASC is required to amplify caspase-1 recruitment for optimum downstream inflammasome activities including IL-1β and IL-18 maturation

Aβ Activates NLRP1 Inflammasome via P2X7 Purinoceptor/Pannexin 1 Signalling

Aβ is the product of alternative sequential cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) followed by γ-secretase. The popular but controversial amyloid cascade hypothesis posits that the heavy production and deposition of Aβ peptides into insoluble fibrils and neuritic plaques drive the neurodegenerative process [64]. In fact, the oligomeric forms of Aβ are potentially more neurotoxic compared to their fibrillar counterparts [65]. Aβ oligomers and fibrils are known inducers of neuroinflammation, owing to their ability to potentiate inflammasome activation [26]. A study by Tan et al. provided preliminary evidence that Aβ produced in the brains of AD transgenic mice (APPswe/PS1dE9) indeed activated the Nlrp1 inflammasome leading to neuronal loss, presumably through pyroptosis [34]. These transgenic mice exhibited cognitive and memory deficits compared to wild-type mice. Moreover, Nlrp1-mediated neurotoxicity was also observed in in vitro cultured rat primary neurons challenged with Aβ oligomers. As NLRP1 is primarily expressed in pyramidal neurons and oligodendrocytes (cell types located in the cerebral cortex, the hippocampus and the amygdala), Aβ-induced NLRP1-mediated neurotoxicity could result in destruction of such integral regions of the brain, leading to the brain shrinkage and loss of vital cognitive functions and memory typically observed in AD patients [66]. Importantly, in vivo silencing of Nlrp1 and caspase-1 is able to reduce IL-1β secretion, rescue neurons from cell death and markedly improve spatial learning in APPswe/PS1dE9 mice [34], alluding to the indispensable role of Nlrp1 and caspase-1 in AD neurodegeneration. However, the precise mechanism by which Aβ activates the NLRP1 inflammasome remains to be elucidated.

A series of studies by Orellana et al. indicate that Aβ-induced neuronal death involves P2X7/pannexin 1 interaction [67, 68]. Aβ oligomers are reported to induce ATP leakage in cells and at the same time, cause an overexpression of P2X7 purinergic receptors in both microglia and hippocampal neurons [68, 69]. P2X7 receptors are ATP-gated cation channels which, when stimulated by high concentrations of extracellular ATP (a DAMP typically released in high concentration to the extracellular matrix by injured or inflammatory cells), activate non-selective ionic passages, including potassium (K^+) ion efflux and calcium (Ca^{2+}) influx. Additionally, P2X7 receptors co-activate with pannexin 1, a membrane hemichannel which creates pores to allow

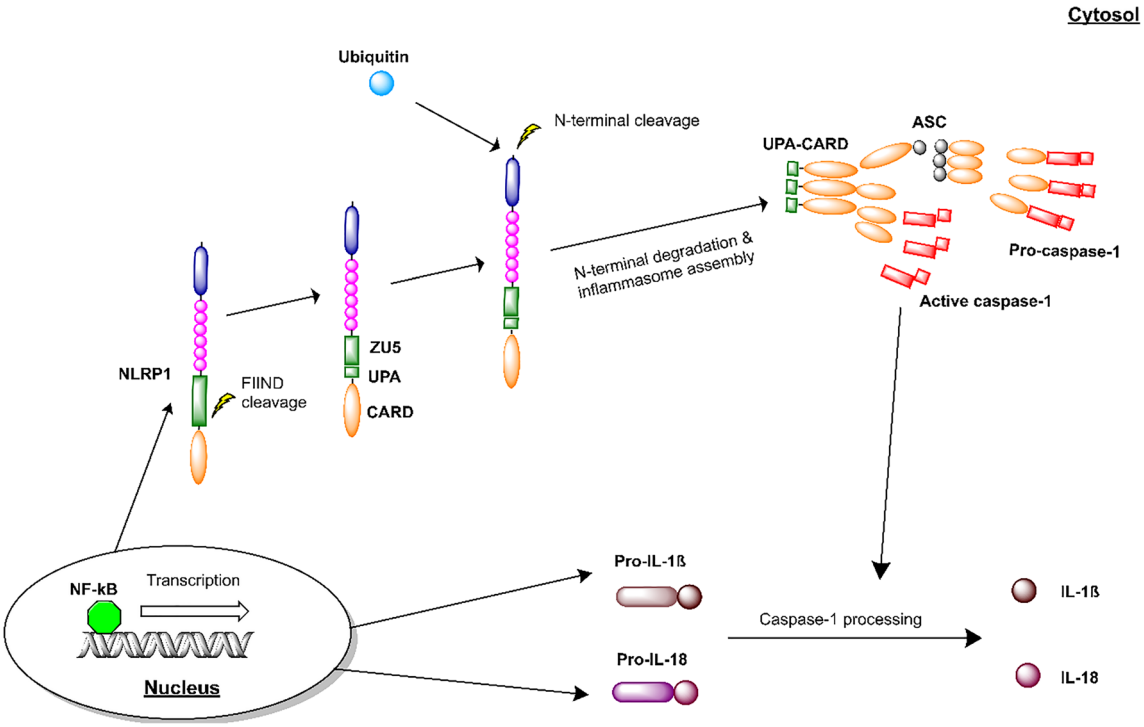

Fig. 4 The activation model of mouse Nlrp1b is characterized by ubiquitin-proteasome degradation post-N-terminal cleavage, liberating an immunoactive C-terminal UPA-CARD fragment. As a consequence of this degradation, mouse Nlrp1b is not capable of forming a complete inflammasome complex like the human NLRP1. Instead, Nlrp1b relies on CARD-CARD interactions for inflammasome-like signalling with the support of ASC

the passage of much larger molecules, most notably ATP and IL-1β [70]. The pannexin 1 channel is activated by high extracellular K^+ ions and effectively establishes a positive feedback activation mechanism with P2X7. More importantly, while the findings by Orellana et al. demonstrated Aβ-induced neuronal death by synaptotoxicity, the K^+/Ca^{2+} imbalance brought about by P2X7/pannexin 1 signalling could also activate inflammasomes, including the NLRP1 inflammasome in neurons (Fig. 3) [71, 72]. P2X7/pannexin 1 activation by elevated extracellular ATP has been shown to stimulate inflammasome activation through the adenosine monophosphate-activated protein kinase (AMPK) signalling pathway [73]. In a separate study on macrophages under hypoxic conditions, a reduced cytosolic ATP content (in addition to high extracellular ATP content) also activated the Nlrp1b inflammasome via AMPK-mediated pathway [74]. In both cases, inflammasome activities were evident in caspase-1 activation and the resultant IL-1β production and cellular pyroptosis.

Implications of NLRP1-Mediated Caspase-1 Activation in AD

Upon NLRP1 inflammasome activation, the recruited pro-caspase-1 cleaves into its p10 and p20 subunits which constitute the active heterodimer caspase (Fig. 3). This initiates a cascade of downstream inflammatory signalling processes such as IL-1β and IL-18 maturation, caspase-6 activation and neuronal death, leading to AD pathology (Fig. 1) [75].

IL-1β and IL-18 Maturation

One of the principal functions of caspase-1 is to process IL-1β and IL-18 to maturity from their respective precursors, pro-IL-1β and pro-IL-18. Both IL-1β and IL-18 belong to the IL-1 family. Although usually recognized as potent pro-inflammatory cytokines, they are, in fact, constitutively expressed in the CNS and are essential for physiological neuromodulation [76]. IL-1β is excessively produced by microglia, astrocytes and neurons in response to brain injury. The intracellular signalling pathways elicited by IL-1β within the CNS are cell type-specific [77]. In glial cells, IL-1β regulates the production and release of inflammatory cytokines (IL-1, IL-6, monocyte chemoattractant protein-1 (MCP-1), and TNFs) through the activation of nuclear factor κB (NF-κB). In hippocampal neurons, IL-1β controls synaptic function by activating the cAMP response element-binding protein (CREB), a transcription factor which plays an integral role in neuronal plasticity and memory formation, via activation of the p38 MAPK (mitogen-activated protein kinase) pathway

but not the MAPK/ERK (extracellular signal-regulated kinases) pathway. Indeed, a controlled level of IL-1β is essential for physiological regulation of neuronal functions and has even been shown to be neuroprotective: IL-1β is reported to decrease Aβ production and ameliorate amyloid burden, possibly through amplification of microglial-mediated amyloid clearance or encouraging non-amyloidogenic processing of APP [78, 79]. On the other hand, aberrantly upregulated levels of IL-1β can result in cognitive impairment and indeed has been implicated in AD [80]. A study on corticol neurons demonstrated that IL-1β suppressed CREB activation by interfering with neurotrophin 3-induced Ras/MAPK/ERK and P13-K/Akt signalling pathways even at a concentration where neuron viability was not compromised [81]. CREB suppression might affect neuronal functionality by interfering with long-term potentiation which affects synaptic plasticity, memory formation and spatial awareness, possibly contributing to symptoms of dementia at early stages of AD including mild cognitive impairment [82]. Despite reducing brain amyloid burden, overexpression of IL-1β can instead encourage tau hyperphosphorylation mediated by p38 MAPK and glycogen synthase kinase 3 β (GSK-3β) signalling pathways [83]. At the same time, IL-1β causes an elevation in neuronal acetylcholinesterase expression and activity which, in hippocampal neurons, is shown to impair excitatory synapses via disruption of neuroligin–neurexin junction and consequentially suppresses synaptic glutaminergic signalling [84, 85].

Like IL-1β, IL-18 is another essential cytokine which is expressed in healthy brain. Physiologically, IL-18 is shown to promote neuronal survivability by increasing the levels of brain-derived neurotrophic factor and the anti-apoptotic protein B cell lymphoma 2 (BCL-2), whilst also inducing the expression of CREB. These processes sufficiently conferred neuroprotection when cortical neurons were challenged with oxygen glucose deprivation [86]. However, IL-18 in AD patients is likewise abnormally upregulated in neurons and glial cells, especially at the frontal lobe where most of the dopamine neurons in the cerebral cortex are located [87]. Unlike IL-1β, increased levels of IL-18 are found to colocalize with both Aβ aggregation and hyperphosphorylated tau. In a study using the SH-SY5Y human neuroblastoma cell line, IL-18 was shown to promote Aβ production and aggregation by upregulating BACE1 and the N-terminal fragment of presenilin 1 [88]. At the same time, IL-18 upregulated kinase activities important for tau phosphorylation, including cyclin-dependent kinase 5 (Cdk5) and GSK-3β [89]. The actual impact of IL-18 in AD susceptibility is currently a subject of debate as multiple case-control studies on two functional polymorphisms in the IL-18 promoter gene (−607 C/A and −137 G/C) have reported conflicting results [90, 91]. In the hope of consolidating these findings, a meta-analysis conducted by Luo et al. revealed that such polymorphisms indeed decrease the risk of AD, particularly in Asian and apolipoprotein-ε4-positive (a significant AD risk gene) population [92]. However, these studies suffer from various limitations such as publication bias and small sample sizes. As with the *NLRP1* gene, the SNPs of IL-18 in AD were not reflected in the recent GWA study [36] possibly due to variation between populations of different ethnicities. As such, larger and more diversified studies on AD and cytokine genetic polymorphisms may be required to evaluate the potential risks that IL-18 confers in AD.

Pyroptosis

Along with cytokine maturation, caspase-1 activation promotes an inflammatory form of programmed cell death known as pyroptosis, characterized by host-mediated poration of the cell membrane which dissipates the cellular ionic gradient, producing a net increase of osmotic pressure, and cell swelling [93]. As opposed to apoptosis, pyroptosis is characterized by membrane rupture causing the release of cytosolic contents, including DAMPs and pro-inflammatory cytokines such as ATP, IL-1β and IL-18 into the extracellular spaces to further perpetuate inflammatory responses. Recent evidence suggests that caspase-1 induces pyroptosis via cleavage of the executioner protein gasdermin D, which is a required component in inflammasome-mediated pyroptosis although it does not participate in IL-1β maturation [94]. Gasdermin D-mediated pyroptosis, however, is required for IL-1β secretion to the extracellular spaces. The activation of gasdermin D is also dependent on its cleavage by caspase-1 at the linker between its N-terminal and C-terminal domains, where the N-terminus of gasdermin D is the effector of pyroptosis and the C-terminus functions as an intramolecular inhibitor when connected to the N-terminus [95]. Pyroptosis is typically observed in macrophages as a result of NLRP3 inflammasome activation. Macrophagic pyroptosis may be beneficial to the host as the released PAMPs are further cleared by surrounding neutrophils [96]. However, pyroptosis in brain cells can be particularly detrimental because it leads to permanent loss of neurons. A study by Tan et al. presumed that Aβ induced Nlrp1-mediated neuronal death via pyroptosis in cultured rat cortical neurons due to the associated caspase-1 activation and IL-1β secretion although the TUNEL assay that was performed did not rule out other forms of cell death such as apoptosis [34]. As such, there are currently no available data that directly associate Aβ with neuronal pyroptosis. It is also not known if gasdermin D is expressed in neurons. Where gasdermin D is not present, NLRP1 activation instead induces cellular apoptosis via caspase-1 cleavage of caspase-3 and caspase-7 [97]. It would be interesting, therefore, to study the effect of Aβ on possible gasdermin D activation in neurons and to evaluate the extent of neuronal pyroptosis that may be involved in AD.

Caspase-6 Activation

Caspase-1 activation in human primary CNS neurons has been demonstrated to activate caspase-6 in an NLRP1-dependent manner [11]. Caspase-6 is a caspase of the apoptosis effector class which is expressed ubiquitously in the brain, including the entorhinal cortex, hippocampus and the striatum [98]. The pathophysiological role of caspase-6 is relatively complex as its function is not limited to apoptosis and does not always induce cell death when activated. Physiologically, caspase-6 plays a vital role in axon pruning during development and has apparent neuroprotective effects against ALS [99]. However, caspase-6 has also been strongly implicated in neurodegenerative diseases including HD and AD [100].

Aberrant caspase-6 activity can be observed at all stages of AD from non-cognitive impaired individuals to cases of very severe AD [101]. The abundance of caspase-6 activity in the entorhinal cortex and hippocampus also correlates inversely with episodic memory assessments, including in non-demented individuals, and is a reliable predictor of a person's risk of developing AD [102]. Caspase-6 processes a range of substrates associated with neurodegenerative diseases including tau, APP, huntingtin, and the presenilins 1 and 2 [103–106]. The presence of active caspase-6 in AD lesions including neuropil threads, neuritic plaques and neurofibrillary tangles suggests that caspase-6 is involved in the production of these pathologies [107]. In fact, caspase-6 is known to facilitate a number of events in early stages of AD which precede Aβ and NFT formation. For example, caspase-6 functions synergistically with caspase-3 in tau Asp^{421} cleavage when stimulated by excessive reactive oxygen species, a sign of mitochondrial dysfunction [108, 109]. Additionally, tau is further cleaved on the N-terminal Asp^{13} by caspase-6, resulting in a compromised cytoskeletal stability that facilitates the formation of tau filament which could be phosphorylated by GSK-3β to produce NFTs [103]. Caspase-6 may also encourage amyloidosis through cleavage of APP at the C terminus in a pathway independent of secretases to generate a 6.5-kDa fragment which could undergo further processing to produce Aβ peptides [104, 110].

Caspase-6 activity may directly compromise neurons independent of Aβ and NFTs, possibly through aberrant apoptosis and axonal degeneration. In a study by LeBlanc et al., transgenic mice free from neuritic plaques and NFTs, but expressing an artificial self-activating form of human caspase-6 in the pyramidal neuron-dense CA1 subfield of the hippocampus, were observed to develop neurodegeneration and memory impairments in an age-dependent manner [111]. As such, the removal of AD pathologies alone without eliminating caspase-6 may be insufficient to halt AD progression. This presents the NLRP1 inflammasome in neurons as an attractive therapeutic target, as both caspase-1-mediated neuroinflammation and caspase-6 activity may be simultaneously disrupted by eliminating the major platform from which they function.

Conclusion and Future Perspectives

The NLRP3 inflammasome in microglia, the resident macrophage of the CNS, has been well-established as a potent driver of neuroinflammation in AD. Here, we propose that the NLRP1 inflammasome activity in neurons is equally paramount in the grand scheme of neuroinflammation in AD. Its capability to provoke a myriad of inflammatory and neurodegenerative pathways within neurons themselves makes NLRP1 a potential therapeutic target for AD intervention. Several studies have identified potential NLRP1 inhibitors that function by preventing ATP-binding and inflammasome complex formation [112]. Although NLRP1 inhibitors are yet to be tested for AD conditions, a recent study has successfully demonstrated that JC-124, an Nlrp3 inhibitor, decreased Aβ deposition and reduced microglia activation in an AD mouse model [113]. Thus, the NLRP1 inhibitors may someday be developed into a new class of anti-neuroinflammatory drugs that can be used in combination with Aβ or NFT-targeting therapies to rescue neurons and hopefully modify disease progression in AD patients. However, there remain many challenges to be solved before such drugs may be developed, as our current knowledge of inflammasome biology, particularly in the context of AD and other neurodegenerative diseases, is still in its adolescence. Given the complexity of the NLRP1 inflammasome and the extreme dissimilarity between its human and mice orthologues, we encourage future studies on neuronal NLRP1 to take advantage of recently developed models derived from human-induced pluripotent stem cells (iPSCs) which would undoubtedly represent the human condition more accurately and at the same time facilitate drug discovery [114–116]. In addition, it would also be beneficial to study the possible relationships between NLRP1 and NLRP3 in the brain. Neuroinflammation is increasingly recognized as a fundamental propagator of neurodegeneration in AD. By understanding precisely how inflammasomes work in the CNS under both physiological and pathological conditions, as well as determining how these inflammasomes can be pharmacologically targeted, we may be one major step closer towards developing a proper cure for AD.

Acknowledgments Funding for this work was from the Fundamental Research Grant Scheme (FRGS/1/2016/SKK08/IMU/03/1) by the Ministry of Higher Education of Malaysia.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Alzheimer's Association (2017) Alzheimer's disease facts and figures. Alzheimers Dement 13(4):325–373. https://doi.org/10.1016/j.jalz.2017.02.001
2. Yiannopoulou KG, Papageorgiou SG (2013) Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord 6(1):19–33
3. Polanco JC, Li C, Bodea LG, Martinez-Marmol R, Meunier FA, Götz J (2018) Amyloid-β and tau complexity - towards improved biomarkers and targeted therapies. Nat Rev Neurol 14(1):22–40. https://doi.org/10.1038/nrneurol.2017.162
4. Salomone S, Caraci F, Leggio GM, Fedotova J, Drago F (2012) New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. Br J Clin Pharmacol 73(4):504–517
5. Cummings J, Lee G, Ritter A, Zhong K (2018) Alzheimer's disease drug development pipeline: 2018. Alzheimer's Dement Transl Res Clin Interv 4:195–214. https://doi.org/10.1016/j.trci.2018.03.009
6. Calsolaro V, Edison P (2016) Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimer's Dement 12(6):719–732. https://doi.org/10.1016/j.jalz.2016.02.010
7. Walters A, Phillips E, Zheng R, Biju M, Kuruvilla T (2016) Evidence for neuroinflammation in Alzheimer's disease. Prog Neurol Psychiatry 20(5):25–31
8. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G (2009) The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nat Immunol 10(3):241–247
9. Walsh JG, Muruve DA, Power C (2014) Inflammasomes in the CNS. Nat Rev Neurosci 15(2):84–97
10. Saresella M, La Rosa F, Piancone F, Zoppis M, Marventano I, Calabrese E et al (2016) The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer's disease. Mol Neurodegener 11:23. https://doi.org/10.1186/s13024-016-0088-1
11. Kaushal V, Dye R, Pakavathkumar P, Foveau B, Flores J, Hyman B et al (2015) Neuronal NLRP1 inflammasome activation of Caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated Caspase-6 activation. Cell Death Differ 22(10):1676–1686
12. Clark R, Kupper T (2005) Old meets new: the interaction between innate and adaptive immunity. J Invest Dermatol 125(4):629–637
13. Newton K, Dixit VM (2012) Signaling in innate immunity and inflammation. Cold Spring Harb Perspect Biol 4(3):a006049
14. Kumar H, Kawai T, Akira S (2011) Pathogen recognition by the innate immune system. Int Rev Immunol 30(1):16–34
15. Takeuchi O, Akira S (2010) Pattern recognition receptors and inflammation. Cell 140(6):805–820. https://doi.org/10.1016/j.cell.2010.01.022
16. Schattgen SA, Fitzgerald KA (2011) The PYHIN protein family as mediators of host defenses. Immunol Rev 243(1):109–118
17. Daneman R, Prat A (2015) The blood-brain barrier. Cold Spring Harb Perspect Biol 7(1):a020412
18. Hauwel M, Furon E, Canova C, Griffiths M, Neal J, Gasque P (2005) Innate (inherent) control of brain infection, brain inflammation and brain repair: the role of microglia, astrocytes, "protective" glial stem cells and stromal ependymal cells. Brain Res Rev 48(2):220–233
19. Griffiths MR, Gasque P, Neal JW (2010) The regulation of the CNS innate immune response is vital for the restoration of tissue homeostasis (repair) after acute brain injury: a brief review. Int J Inflam 2010:151097
20. Ransohoff RM, Brown MA (2012) Innate immunity in the central nervous system. J Clin Invest 122(4):1164–1171
21. Lafon M, Megret F, Lafage M, Prehaud C (2006) The innate immune facet of brain: human neurons express TLR-3 and sense viral dsRNA. J Mol Neurosci 29(3):185–194
22. Frank-Cannon TC, Alto LT, McAlpine FE, Tansey MG (2009) Does neuroinflammation fan the flame in neurodegenerative diseases? Mol Neurodegener 4(1):1–13
23. Morimoto K, Horio J, Satoh H, Sue L, Beach T, Arita S et al (2011) Expression profiles of cytokines in the brains of Alzheimer's disease (AD) patients compared to the brains of non-demented patients with and without increasing AD pathology. J Alzheimers Dis 25(1):59–76
24. Swardfager W, Lanctt K, Rothenburg L, Wong A, Cappell J, Herrmann N (2010) A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 68(10):930–941. https://doi.org/10.1016/j.biopsych.2010.06.012
25. Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Publ Gr 14(3):133–150. https://doi.org/10.1038/nrneurol.2017.188
26. Salminen A, Ojala J, Suuronen T, Kaarniranta K, Kauppinen A (2008) Amyloid-β oligomers set fire to inflammasomes and induce Alzheimer's pathology. J Cell Mol Med 12(6a):2255–2262
27. Gold M, El Khoury J (2015) β-Amyloid, microglia, and the inflammasome in Alzheimer's disease. Semin Immunopathol 37:607–611
28. Dansokho C, Heneka MT (2018) Neuroinflammatory responses in Alzheimer's disease. J Neural Transm 125(5):771–779. https://doi.org/10.1007/s00702-017-1831-7
29. Tan MS, Yu JT, Jiang T, Zhu XC, Tan L (2013) The NLRP3 Inflammasome in Alzheimer's disease. Mol Neurobiol 48(3):875–882. https://doi.org/10.1007/s12035-013-8475-x
30. Davis BK, Wen H, Ting JPY (2011) The Inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 29(1):707–735
31. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A et al (2012) NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 493(7434):674–678
32. Sarlus H, Heneka MT (2017) Microglia in Alzheimer's disease. J Clin Invest 127(9):33–35
33. Adamczak SE, De Rivero Vaccari JP, Dale G, Brand FJ, Nonner D, Bullock M et al (2014) Pyroptotic neuronal cell death mediated by the AIM2 inflammasome. J Cereb Blood Flow Metab 34(4):621–629
34. Tan MS, Tan L, Jiang T, Zhu XC, Wang HF, Jia CD et al (2014) Amyloid-β induces NLRP1-dependent neuronal pyroptosis in models of Alzheimer's disease. Cell Death Dis 5(8):e1382
35. Pontillo A, Catamo E, Arosio B, Mari D, Crovella S (2012) NALP1/NLRP1 genetic variants are associated with Alzheimer disease. Alzheimer Dis Assoc Disord 26(3):277–281
36. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC et al (2019) Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet 51:414–430
37. Martinon F, Burns K, Tschopp J (2002) The Inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. Mol Cell 10(2):417–426

38. Chavarría-Smith J, Vance RE (2015) The NLRP1 inflammasomes. Immunol Rev 265(1):22–34
39. Sastalla I, Crown D, Masters SL, McKenzie A, Leppla SH, Moayeri M (2013) Transcriptional analysis of the three Nlrp1 paralogs in mice. BMC Genomics 14(1):1–10
40. Yu CH, Moecking J, Geyer M, Masters SL (2018) Mechanisms of NLRP1-mediated autoinflammatory disease in humans and mice. J Mol Biol 430(2):142–152. https://doi.org/10.1016/j.jmb.2017.07.012
41. Inohara N, Chamaillard M, McDonald C, Nuñez G (2005) NOD-LRR proteins: role in host-microbial interactions and inflammatory disease. Annu Rev Biochem 74:355–383
42. Kersse K, Bertrand MJM, Lamkanfi M, Vandenabeele P (2011) NOD-like receptors and the innate immune system: coping with danger, damage and death. Cytokine Growth Factor Rev 22(5–6):257–276. https://doi.org/10.1016/j.cytogfr.2011.09.003
43. D'Osualdo A, Weichenberger CX, Wagner RN, Godzik A, Wooley J, Reed JC (2011) CARD8 and NLRP1 undergo autoproteolytic processing through a ZU5-like domain. PLoS One 6(11):e27396
44. Finger JN, Lich JD, Dare LC, Cook MN, Brown KK, Duraiswamis C et al (2012) Autolytic proteolysis within the function to find domain (FIIND) is required for NLRP1 inflammasome activity. J Biol Chem 287(30):25030–25037
45. Maharana J (2018) Elucidating the interfaces involved in CARD-CARD interactions mediated by NLRP1 and Caspase-1 using molecular dynamics simulation. J Mol Graph Model 80:7–14. https://doi.org/10.1016/j.jmgm.2017.12.016
46. Park HH, Lo YC, Lin SC, Wang L, Yang JK, Wu H (2007) The death domain superfamily in intracellular signaling of apoptosis and inflammation. Annu Rev Immunol 25:561–586
47. Hiller S, Kohl A, Fiorito F, Herrmann T, Wider G, Tschopp J et al (2003) NMR structure of the apoptosis- and inflammation-related NALP1 pyrin domain. Structure 11(10):1199–1205
48. Chu LH, Gangopadhyay A, Dorfleutner A, Stehlik C (2015) An updated view on the structure and function of PYRIN domains. Apoptosis 20(2):157–173
49. Chavarría-Smith J, Vance RE (2013) Direct proteolytic cleavage of NLRP1B is necessary and sufficient for Inflammasome activation by Anthrax lethal factor. PLoS Pathog 9(6):e1003452
50. Chavarría-Smith J, Mitchell PS, Ho AM, Daugherty MD, Vance RE (2016) Functional and evolutionary analyses identify proteolysis as a general mechanism for NLRP1 Inflammasome activation. PLoS Pathog 12(12):e1006052
51. Sandstrom A, Mitchell PS, Goers L, Mu EW, Lesser CF, Vance RE (2019) Functional degradation: a mechanism of NLRP1 inflammasome activation by diverse pathogen enzymes. Science 364(6435):eaau1330
52. Chui AJ, Okondo MC, Rao SD, Gai K, Griswold AR, Johnson DC et al (2019) N-terminal degradation activates the NLRP1B inflammasome. Science 364(6435):82–85
53. Faustin B, Lartigue L, Bruey JM, Luciano F, Sergienko E, Bailly-Maitre B et al (2007) Reconstituted NALP1 Inflammasome reveals two-step mechanism of Caspase-1 activation. Mol Cell 25(5):713–724
54. Lu A, Wu H (2015) Structural mechanisms of inflammasome assembly. FEBS J 282(3):435–444
55. Broz P, Dixit VM (2016) Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol 16(7):407–420
56. Van Opdenbosch N, Gurung P, Vande Walle L, Fossoul A, Kanneganti TD, Lamkanfi M (2014) Activation of the NLRP1b inflammasome independently of ASC-mediated caspase-1 autoproteolysis and speck formation. Nat Commun 5:1–14. https://doi.org/10.1038/ncomms4209
57. Dick MS, Sborgi L, Rühl S, Hiller S, Broz P (2016) ASC filament formation serves as a signal amplification mechanism for inflammasomes. Nat Commun 7:11929
58. Okondo MC, Rao SD, Taabazuing CY, Chui AJ, Poplawski SE, Johnson DC et al (2018) Inhibition of Dpp8/9 activates the Nlrp1b inflammasome. Cell Chem Biol 25(3):262–267.e5. https://doi.org/10.1016/j.chembiol.2017.12.013
59. de Vasconcelos NM, Vliegen G, Gonçalves A, De Hert E, Martín-Pérez R, Van Opdenbosch N et al (2019) DPP8/DPP9 inhibition elicits canonical Nlrp1b inflammasome hallmarks in murine macrophages. Life Sci Alliance 2(1):e201900313
60. Walsh MP, Duncan B, Larabee S, Krauss A, Davis JPE, Cui Y et al (2013) Val-BoroPro accelerates T cell priming via modulation of dendritic cell trafficking resulting in complete regression of established murine tumors. PLoS One 8(3):e58860
61. Okondo MC, Johnson DC, Sridharan R, Bin GE, Chui AJ, Wang MS et al (2017) DPP8 and DPP9 inhibition induces pro-caspase-1-dependent monocyte and macrophage pyroptosis. Nat Chem Biol 13(1):46–53. https://doi.org/10.1038/nchembio.2229
62. Johnson DC, Taabazuing CY, Okondo MC, Chui AJ, Rao SD, Brown FC et al (2018) DPP8/DPP9 inhibitor-induced pyroptosis for treatment of acute myeloid leukemia. Nat Med 24(8):1151–1156. https://doi.org/10.1038/s41591-018-0082-y
63. Zhong FL, Tan K-Y, Reversade B, Robinson K, Sobota RM, Reed JC et al (2018) Human DPP9 represses NLRP1 inflammasome and protects against autoinflammatory diseases via both peptidase activity and FIIND domain binding. J Biol Chem 293(49):18864–18878
64. Armstrong R A (2014) A critical analysis of the 'amyloid cascade hypothesis. Folia Neuropathol 3(3):211–225
65. Dahlgren KN, Manelli AM, Blaine Stine W, Baker LK, Krafft GA, Ladu MJ (2002) Oligomeric and fibrillar species of amyloid-β peptides differentially affect neuronal viability. J Biol Chem 277(35):32046–32053
66. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, Martinon F et al (2007) Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. J Histochem Cytochem 55(5):443–452
67. Sáez-Orellana F, Godoy PA, Bastidas CY, Silva-Grecchi T, Guzmán L, Aguayo LG et al (2016) ATP leakage induces P2XR activation and contributes to acute synaptic excitotoxicity induced by soluble oligomers of β-amyloid peptide in hippocampal neurons. Neuropharmacology 100:116–123
68. Sáez-Orellana F, Fuentes-Fuentes MC, Godoy PA, Silva-Grecchi T, Panes JD, Guzmán L et al (2018) P2X receptor overexpression induced by soluble oligomers of amyloid beta peptide potentiates synaptic failure and neuronal dyshomeostasis in cellular models of Alzheimer's disease. Neuropharmacology 128:366–378
69. McLarnon JG, Ryu JK, Walker DG, Choi HB (2006) Upregulated expression of purinergic P2X7 receptor in Alzheimer disease and amyloid-β peptide-treated microglia and in peptide-injected rat hippocampus. J Neuropathol Exp Neurol 65:1090–1097
70. Pelegrin P, Surprenant A (2006) Pannexin-1 mediates large pore formation and interleukin-1β release by the ATP-gated P2X7 receptor. EMBO J 25(21):5071–5082
71. Silverman WR, de Rivero Vaccari JP, Locovei S, Qiu F, Carlsson SK, Scemes E et al (2009) The pannexin 1 channel activates the inflammasome in neurons and astrocytes. J Biol Chem 284(27):18143–18151
72. Yaron JR, Gangaraju S, Rao MY, Kong X, Zhang L, Su F et al (2015) K+ regulates Ca2+ to drive inflammasome signaling: dynamic visualization of ion flux in live cells. Cell Death Dis 6(10):e1954
73. Zha QB, Wei HX, Li CG, Liang YD, Xu LH, Bai WJ et al (2016) ATP-induced inflammasome activation and pyroptosis is

regulated by AMP-activated protein kinase in macrophages. Front Immunol 7:597
74. Liao K-C, Mogridge J (2013) Activation of the Nlrp1b inflammasome by reduction of cytosolic ATP. Infect Immun 81(2):570–579
75. Elliott JM, Rouge L, Wiesmann C, Scheer JM (2009) Crystal structure of procaspase-1 zymogen domain reveals insight into inflammatory caspase autoactivation. J Biol Chem 284(10): 6546–6553
76. Vitkovic L, Bockaert J, Jacque C (2000) "Inflammatory" cytokines: neuromodulators in normal brain? J Neurochem 74(2): 457–471
77. Srinivasan D (2004) Cell type-specific Interleukin-1 signaling in the CNS. J Neurosci 24(29):6482–6488
78. Matousek SB, Ghosh S, Shaftel SS, Kyrkanides S, Olschowka JA, O'Banion MK (2012) Chronic IL-1β-mediated neuroinflammation mitigates amyloid pathology in a mouse model of Alzheimer's disease without inducing overt neurodegeneration. J Neuroimmune Pharmacol 7(1):156–164
79. Tachida Y, Nakagawa K, Saito T, Saido TC, Honda T, Saito Y et al (2008) Interleukin-1β up-regulates TACE to enhance α-cleavage of APP in neurons: resulting decrease in Aβ production. J Neurochem 104(5):1387–1393
80. Forlenza OV, Diniz BS, Talib LL, Mendonça VA, Ojopi EB, Gattaz WF et al (2009) Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord 28:507–512
81. Soiampornkul R, Tong L, Thangnipon W, Balazs R, Cotman CW (2008) Interleukin-1β interferes with signal transduction induced by neurotrophin-3 in cortical neurons. Brain Res 1188(1):189–197
82. Kandel ER (2012) The molecular biology of memory: CAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. Mol Brain 5:14
83. Ghosh S, Wu MD, Shaftel SS, Kyrkanides S, LaFerla FM, Olschowka JA et al (2013) Sustained Interleukin-1 overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model. J Neurosci 33(11):5053–5064
84. Li Y, Liu L, Kang J, Sheng JG, Barger SW, Mrak RE et al (2000) Neuronal-glial interactions mediated by interleukin-1 enhance neuronal acetylcholinesterase activity and mRNA expression. J Neurosci 20(1):149–155
85. Dong H (2004) Excessive expression of acetylcholinesterase impairs glutamatergic synaptogenesis in hippocampal neurons. J Neurosci 24(41):8950–8960
86. Zhou J, Feng PF, Ting LW, Yi FJ, Shang J (2014) Interleukin-18 directly protects cortical neurons by activating PI3K/AKT/NF-κB/CREB pathways. Cytokine 69(1):29–38. https://doi.org/10.1016/j.cyto.2014.05.003
87. Ojala J, Alafuzoff I, Herukka SK, van Groen T, Tanila H, Pirttilä T (2009) Expression of interleukin-18 is increased in the brains of Alzheimer's disease patients. Neurobiol Aging 30(2):198–209
88. Sutinen EM, Pirttilä T, Anderson G, Salminen A, Ojala JO (2012) Pro-inflammatory interleukin-18 increases Alzheimer's disease-associated amyloid-β production in human neuron-like cells. J Neuroinflammation 9:1–14
89. Ojala JO, Sutinen EM, Salminen A, Pirttilä T (2008) Interleukin-18 increases expression of kinases involved in tau phosphorylation in SH-SY5Y neuroblastoma cells. J Neuroimmunol 205(1–2):86–93. https://doi.org/10.1016/j.jneuroim.2008.09.012
90. Yu JT, Tan L, Song JH, Sun YP, Chen W, Miao D et al (2009) Interleukin-18 promoter polymorphisms and risk of late onset Alzheimer's disease. Brain Res 1253(5):169–175. https://doi.org/10.1016/j.brainres.2008.11.083
91. Segat L, Milanese M, Arosio B, Vergani C, Crovella S (2010) Lack of association between Interleukin-18 gene promoter polymorphisms and onset of Alzheimer's disease. Neurobiol Aging 31(1):162–164
92. Luo L, Li K, Wang X (2016) Relationship between the IL-18 gene polymorphisms and Alzheimer's disease: a meta-analysis. Int J Clin Exp Med 9(11):22720–22728
93. Fink SL, Cookson BT (2006) Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages. Cell Microbiol 8(11):1812–1825
94. He WT, Wan H, Hu L, Chen P, Wang X, Huang Z et al (2015) Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Res 25(12):1285–1298. https://doi.org/10.1038/cr.2015.139
95. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H et al (2015) Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 526(7575):660–665
96. Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A et al (2010) Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol 11(12): 1136–1142. https://doi.org/10.1038/ni.1960
97. Taabazuing CY, Okondo MC, Bachovchin DA (2017) Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. Cell Chem Biol 24(4):507–514.e4. https://doi.org/10.1016/j.chembiol.2017.03.009
98. Noël A, Zhou L, Foveau B, Sjöström PJ, LeBlanc AC (2018) Differential susceptibility of striatal, hippocampal and cortical neurons to Caspase-6. Cell Death Differ 25:1319–1335. https://doi.org/10.1038/s41418-017-0043-x
99. Hogg MC, Mitchem MR, König H, Prehn JHM (2016) Caspase 6 has a protective role in SOD1 G93A transgenic mice. BBA - Mol Basis Dis 1862(6):1063–1073. https://doi.org/10.1016/j.bbadis.2016.03.006
100. Wang XJ, Cao Q, Zhang Y, Su XD (2015) Activation and regulation of Caspase-6 and its role in neurodegenerative diseases. Annu Rev Pharmacol Toxicol 55(1):553–572
101. Albrecht S, Bourdeau M, Bennett D, Mufson EJ, Bhattacharjee M, LeBlanc AC (2007) Activation of caspase-6 in aging and mild cognitive impairment. Am J Pathol 170(4):1200–1209
102. Ramcharitar J, Afonso VM, Albrecht S, Bennett DA, LeBlanc AC (2013) Caspase-6 activity predicts lower episodic memory ability in aged individuals. Neurobiol Aging 34(7):1815–1824
103. Horowitz PM (2004) Early N-terminal changes and caspase-6 cleavage of tau in Alzheimer's disease. J Neurosci 24(36):7895–7902
104. Pellegrini L, Passer BJ, Tabaton M, Ganjei JK, D'Adamio L (1999) Alternative, non-secretase processing of Alzheimer's β-amyloid precursor protein during apoptosis by caspase-6 and -8. J Biol Chem 274(30):21011–21016
105. Graham RK, Deng Y, Carroll J, Vaid K, Cowan C, Pouladi MA et al (2010) Cleavage at the 586 amino acid caspase-6 site in mutant huntingtin influences caspase-6 activation in vivo. J Neurosci 30(45):15019–15029
106. Van De Craen M, De Jonghe C, Van Den Brande I, Declercq W, Van Gassen G, Van Criekinge W et al (1999) Identification of caspases that cleave presenilin-1 and presenilin-2: five presenilin-1 (PS1) mutations do not alter the sensitivity of PS1 to caspases. FEBS Lett 445(1):149–154
107. Guo H, Albrecht S, Bourdeau M, Petzke T, Bergeron C, LeBlanc AC (2004) Active caspase-6 and caspase-6-cleaved tau in neuropil threads, neuritic plaques, and neurofibrillary tangles of Alzheimer's disease. Am J Pathol 165(2):523–531. https://doi.org/10.1016/S0002-9440(10)63317-2
108. Rissman RA, Poon WW, Blurton-Jones M, Oddo S, Torp R, Vitek MP et al (2004) Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology. J Clin Invest 114(1):121–130
109. Zhao H, Zhao W, Lok K, Wang Z, Yin M (2014) A synergic role of caspase-6 and caspase-3 in tau truncation at D421 induced by H2O2. Cell Mol Neurobiol 34(3):369–378

110. LeBlanc A, Liu H, Goodyer C, Bergeron C, Hammond J (1999) Caspase-6 role in apoptosis of human neurons, amyloidogenesis, and Alzheimer's disease. J Biol Chem 274(33):23426–23436
111. Leblanc AC, Ramcharitar J, Afonso V, Hamel E, Bennett DA, Pakavathkumar P et al (2014) Caspase-6 activity in the CA1 region of the hippocampus induces age-dependent memory impairment. Cell Death Differ 21(5):696–706. https://doi.org/10.1038/cdd.2013.194
112. Harris PA, Duraiswami C, Fisher DT, Fornwald J, Hoffman SJ, Hofmann G et al (2015) High throughput screening identifies ATP-competitive inhibitors of the NLRP1 inflammasome. Bioorganic Med Chem Lett 25(14):2739–2743. https://doi.org/10.1016/j.bmcl.2015.05.032
113. Yin J, Zhao F, Chojnacki JE, Fulp J, Klein WL, Zhang S et al (2018) NLRP3 Inflammasome inhibitor ameliorates amyloid pathology in a mouse model of Alzheimer's disease. Mol Neurobiol 55(3):1977–1987
114. Jorfi M, D'Avanzo C, Tanzi RE, Kim DY, Irimia D (2018) Human neurospheroid arrays for in vitro studies of Alzheimer's disease. Sci Rep 8(1):2450
115. Gonzalez C, Armijo E, Bravo-Alegria J, Becerra-Calixto A, Mays CE, Soto C (2018) Modeling amyloid beta and tau pathology in human cerebral organoids. Mol Psychiatry 23:2363–2374
116. Park J, Wetzel I, Marriott I, Dréau D, D'Avanzo C, Kim DY et al (2018) A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease. Nat Neurosci 21(7):941–951