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MINI-SYMPOSIUM: Role of the Inflammasome in Brain Pathogenesis: A Potential Therapeutic Target?

Inflammasomes as therapeutic targets for Alzheimer's disease

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Abstract

Alzheimer's disease is the most common form of progressive dementia, typified initially by short term memory deficits which develop into a dramatic global cognitive decline. The classical hall marks of Alzheimer's disease include the accumulation of amyloid oligomers and fibrils, and the intracellular formation of neurofibrillary tangles of hyperphosphorylated tau. It is now clear that inflammation also plays a central role in the pathogenesis of the disease through a number of neurotoxic mechanisms. Microglia are the key immune regulators of the CNS which detect amyloidopathy through cell surface and cytosolic pattern recognition receptors (PRRs) and respond by initiating inflammation through the secretion of cytokines such as interleukin-1β (IL-1β). Inflammasomes, which regulate IL-1β release, are formed following activation of cytosolic PRRs, and using genetic and pharmacological approaches, NLRP3 and NLRP1 inflammasomes have been found to be integral in pathogenic neuroinflammation in animal models of Alzheimer's disease. Therefore, the inflammasomes are very promising novel pharmacological targets which merit further research in the continued endeavor for efficacious therapeutics for Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of progressive dementia representing 60%–80% of dementia cases and affects 26 million people worldwide (7). It is characterized by memory loss and a gradual decline of cognitive function which leads to complete dependence on care, with death occurring an average of 5–7 years from diagnosis (166). Currently there are only symptom modifying interventions for AD which do not alter the progression of the disease (28). Therefore, new treatments are desperately needed (7).

Histological investigation provided the first insights into the underlying causes of AD. Over a century ago Alois Alzheimer described the pathological hall marks of the disease of large insoluble plaques and neurofibrillary tangles (6). The plaques are composed of aggregates of amyloid-β (Aβ) peptide, while neurofibrillary tangles are caused by the accumulation of insoluble filaments of hyper-phosphorylated tau. Subsequent histological studies have identified neuroinflammatory responses by astrocytes and microglia as another characteristic of AD. However, research is on-going into whether these histological markers of the disease represent pathological drivers, unrelated by-products or unsuccessful repair mechanisms.

Neuroimaging and biomarker studies have established that amyloid changes occur prior to tau pathology and this supports the most widely accepted description of the underlying pathology of AD which is the *amyloid cascade hypothesis* (119). This states that AD is caused by disruptions in amyloid processing and/or clearance leading to an accumulation of monomer amyloid peptides which oligomerize into soluble toxic oligomers and insoluble fibrils, the major constitute of plaques (54). This amyloid pathology then interacts with a number processes, including tau physiology and inflammation, to eventually cause neuronal death and cognitive decline (54).

Genetic evidence supports the amyloid hypothesis; mutations in amyloid precursor protein (APP) or amyloid processing enzymes are the only known causes of autosomal dominant inheritable familial AD (12). No mutations in tau have been found to cause AD. However, genome wide association studies have identified a number of other gene variants which confer an increased risk in the development of sporadic AD and these variants have been found to be involved in a variety of physiological processes including lipid transport and autophagy, such as APOE4 (apolipoprotein E4) and PICALM (phosphatidylinositol-binding clathrin assembly protein), respectively reviewed by Tosto *et al* (160). Of interest to this review is that a number of variants of genes involved in regulating innate immune function confer a greater risk of developing AD (58, 128). Examples include loss/reduction of function mutations in the anti-inflammatory/phagocytosis TREM-2 (triggering receptor expressed on myeloid cells 2) gene (52); variants of promoter regions of inflammation modulating cytokines interleukin-10 (IL-10) and TNFα (tumor necrosis factor α) (129); loss/reduction of function of the anti-inflammatory/phagocytosis receptor CD33 gene (20); and gene variants of the complement receptor 1 (CR1), which may be integral to the phagocytosis of opsonized amyloid oligomers (62). The number and range of risk genes that are related

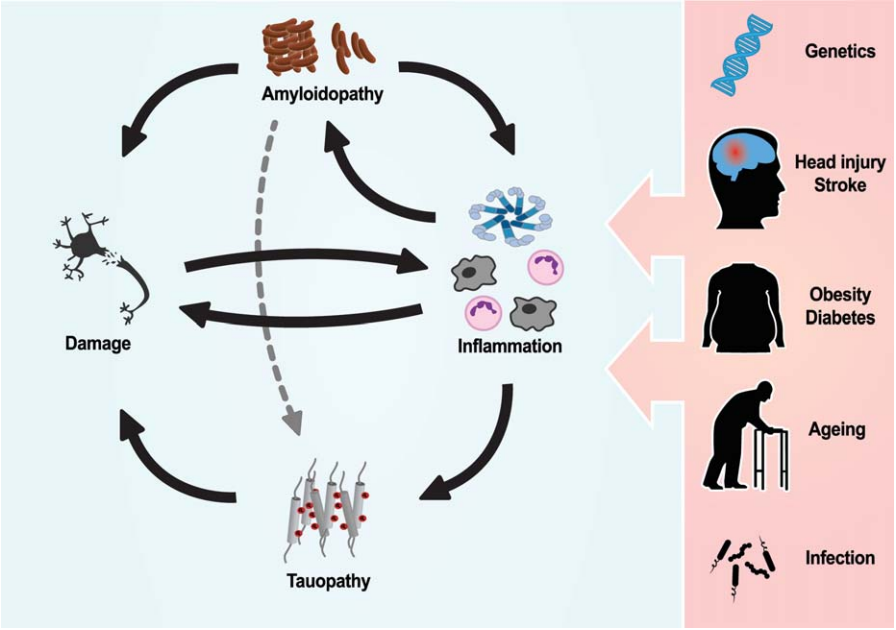

Figure 1. Inflammation has an integral role in the pathogenesis of AD and can be influenced through a number of genetic and environmental factors. Amyloidopathy has been demonstrated to induce neurotoxic inflammation which has been shown to cause and propagate tauopathy. Neuronal damage caused by these processes could result in further inflammation in an unresolved feedback pattern. Many risk factors for AD such as inflammatory gene variants, brain injury, midlife obesity, diabetes, ageing and infection all have an inflammatory component; this supports the critical role inflammation has in AD and highlights the therapeutic potential of targeting inflammation.

to immune function demonstrate the integral role inflammation may play in the pathogenesis of AD.

NEUROINFLAMMATION AND AD

Inflammation is a beneficial immune-vascular response to damage and infection which involves the activation and recruitment of immune cells. This response is regulated by cytokine signaling molecules, of which interleukin-1β (IL-1β) is considered a central member. However, chronic or excessive inflammation can exacerbate tissue damage and contribute to disease. Neuroinflammation is primarily regulated by microglia, the resident immune cells of the brain. These cells make up 10%–15% of the cells of the brain and in a resting state exist in a ramified morphology with long processes which are continually monitoring the extracellular environment for perturbations in homeostasis, tissue damage or infection (124). Upon sensing a change to the extracellular environment, microglia become activated and develop an amoeboid morphology. An activated microglia can act in an anti- or pro-inflammatory manner depending on the stimuli. Anti-inflammatory activated microglia clear debris through phagocytosis, and secrete anti-inflammatory cytokines such as IL-4 and resolution growth factors including brain derived neurotrophic factor (BDNF) (114). A pro-inflammatory activated microglia will release neurotoxic reactive oxygen species (ROS) and inflammatory cytokines, initiating a potentially damaging immune-vascular response (17, 124). Astrocytes are also heavily involved in immune regulation in the brain with continued research supporting growing overlap in astrocyte and microglia function including phagocytosis (68), antigen presentation (31), cytokine secretion (22), ROS production (143) and vascular modulation (23, 149). Histology and PET imaging studies demonstrate that inflammatory phenotypes of astrocytes and microglia are a pathological hallmark of AD (14, 65).

Using traditional histological methods, clusters of activated microglia and astrocytes have been shown to occur in in AD patients (14, 65). These clusters appear in close proximity with amyloid plaques and larger plaques correlate with a greater number of associated microglia, suggesting that amyloid fibrils, or the relatively high concentrations of amyloid oligomers found in the peri-plaque region, are inflammatory (65, 78). Microglia activation can be investigated using PET imaging with radiopharmaceutical tags. Studies using the activated microglia tags [^{11}C](R)-PK11195 and [^{11}C]DAA1106, which recognize the 18 kDa translocator protein (TSPO) present on activated microglia, found that AD patients have elevated levels of activated microglia, and the level of activation correlates with the severity of AD (25, 171, 174). Furthermore, the second generation TSPO ligand [^{11}C]DAA1106 has been used to demonstrate that inflammation is present in people with mild cognitive impairment (MCI) who then go on to develop AD, suggesting that inflammation is chronic and ongoing prior to the onset of AD (171). The correlation between inflammation and AD severity and the presence of inflammation prior to AD onset suggests a causal relationship between inflammation and AD. This is further supported by epidemiological evidence that known risk factors for AD have an inflammatory component including stroke (162), head trauma (104), diabetes (110), mid-life obesity (168), aging (79, 123) and infection (120) (Figure 1).

Mechanisms of inflammation induced neurodegeneration

Inflammation in the brain can cause neuronal dysfunction and death through a number of mechanisms. These can be grouped into the direct and indirect effects of inflammation on neurones. Direct effects are those in which immune cells engage in neurotoxic activities such as the production of digestive enzymes and ROS, and phagocytosis of healthy neurones. The indirect effects of neuroinflammation are caused by astrocytes and microglia not performing their role as homeostasis managing cells which results in neuronal death through perturbations in the intracellular and extracellular environments. Through these mechanisms it has been shown that neuroinflammation alone is enough to cause cognitive deficits and tauopathology; it is particularly interesting that brain regions most affected by AD, such as the hippocampus, are also the most vulnerable regions to neuroinflammation (61, 86).

Perhaps the best characterized mechanism of inflammation induced neurotoxicity is the production of ROS and reactive nitrogen species (RNS) (16, 42). ROS and RNS are highly reactive molecules which can cause auto-catalytic oxidation of phospholipids resulting in the permeabilization of membranes, oxidation of proteins perturbing cellular function and DNA damage leading to disruption of protein production (16, 42). Ultimately, if ROS and RNS production overwhelms the antioxidant mechanisms of the cell, the build-up of oxidative damage will lead to cell death. Amyloid has been shown to induce the production of ROS and RNS in microglia and astrocytes (2, 3, 66). Fibrillary Aβ induces the expression of the ROS producing enzymes nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and inducible nitric oxide synthase (iNOS). These enzymes produce the highly neurotoxic ROS species superoxide and nitric oxide, respectively (127, 161, 167, 169). Microglia cytokine secretion causes the recruitment of peripheral immune cells into the brain including neutrophils which produce the highly neurotoxic ROS hypochlorite (39, 172). In addition to ROS and RNS, neutrophils, microglia and astrocytes all secret neurotoxic proteases including neutrophil elastase, cathepsins and chymotrypsin-like proteases (75, 76, 172). Independent from secreted neurotoxins, microglia induce neuronal death by direct phagocytosis of healthy neurones. Nanomolar concentrations of amyloid monomers, oligomers or fibrils induced microglial phagocytosis of healthy neurones through a membrane phosphatidylserine dependent mechanism (107, 170).

Microglia are essential to the functioning brain. Their role in synapse modulation, microenvironment maintenance and homeostasis is crucial to neuronal function. A seminal article by Parkhurst *et al* (114) demonstrated that depletion of microglia from the cortex of mice caused a significant impairment in learning and memory. Using selective deletion of BDNF from microglia, Parkhurst *et al* demonstrated that it is likely that BDNF production is one of the essential functions of microglia in a healthy brain (114). Microglia treated with amyloid have been shown to dramatically lower the production of BDNF while increasing the production of inflammatory cytokines (60). Additionally, chronically inflamed microglia fail to perform their role of protein uptake and degradation from the extracellular environment and this can lead to the build-up of protein aggregates such as amyloid oligomers and fibrils. This is supported by research demonstrating that chronic inflammation induced by head trauma (26, 67), infection (44), obesity (77, 97) or bacterial toxins (121, 126) accelerates amyloid deposition and memory deficits (112) (Figure 1).

While it appears that amyloid pathology is a causal factor in neuroinflammation in AD, it remains unclear how amyloid is linked to the tau pathology and neurofibrillary tangles (Figure 1). There is growing evidence that neuroinflammation may be one of the critical linking factors (Figure 1). Overexpression of inflammatory cytokines has been shown to increase tau pathology (48). Furthermore, infection and bacterial toxins have been shown to exacerbate tau phosphorylation and aggregation in mouse models of AD and repeated mild head injury alone in wild-type mice is enough to induce AD-like tau pathology (83, 98, 156). There is also evidence that activated microglia cause tau pathology propagation through the secretion of phosphorylated tau in exosomes (8). Interestingly, tau pathology may be causal factor in neuroinflammation induced neurotoxicity with genetic deletion of tau providing protection from inflammatory stimuli in cultured neurones (94). Collectively, this evidence supports a model of AD where amyloid induces sustained inflammation which causes and propagates phosphorylated and aggregated tau species which contributes substantially to neuronal death in AD (Figure 1).

As the primary resident immune cell of the brain, microglia are equipped with a number of cell membrane and cytosolic pattern recognition receptors (PRRs) which initiate the inflammatory phenotype. The cell surface toll-like receptor (TLR) family are a group of structurally similar PRRs expressed in adaptive and innate immune cells, as well as epithelial, endothelial and fibroblast cells. They are traditionally thought of as receptors which recognize pathogen associated molecular patterns (PAMPs) which upon activation initiate a range of responses including cytokine secretion, antigen presentation and proliferation; however it is now clear that several TLRs are integral to the neuroinflammatory response in AD. TLR2 can directly bind amyloid and initiate an inflammatory response through the transcription factor NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) and JNKs (c-Jun N-terminal kinases) (32, 85, 89, 99) (Figure 2). Inhibition of TLR2 has been found to be therapeutic in mouse models of AD (99). TLR4 and its co-receptor CD14, and scavenger receptor A and the Ca^{2+}-activated K^+ channel ($K_{Ca}3.1$) have also been implicated in the detection of amyloid species in the extra-cellular environment (92, 131) (Figure 2). The role of TLR4 signaling in AD pathology is supported by human genetic evidence. A rare variant in the TLR4 gene that causes a reduction in function has been found to dramatically decrease the risk of developing late onset AD (103). Amyloid is also phagocytosed by microglia through binding to the phagocytotic receptor complex that includes CD36, CD47, and α(6)β(1)-integrin (11) (Figure 2). Inside the cell, amyloid may also affect cytosolic PRRs, such as NLRP3 (NLR family, pyrin domain containing 3), to activate inflammatory complexes called inflammasomes (Figure 2*, and see below*). These have been found to be critical in AD associated inflammation through the release of the inflammatory cytokine IL-1β (35, 56) (Figure 2).

Interleukin-1β

There is growing clinical and preclinical evidence that the inflammatory cytokine IL-1β plays a central role in the induction of pathogenic neuroinflammation in AD (24, 148). The release of IL-1β from immune cells facilitates the orchestration of an inflammatory

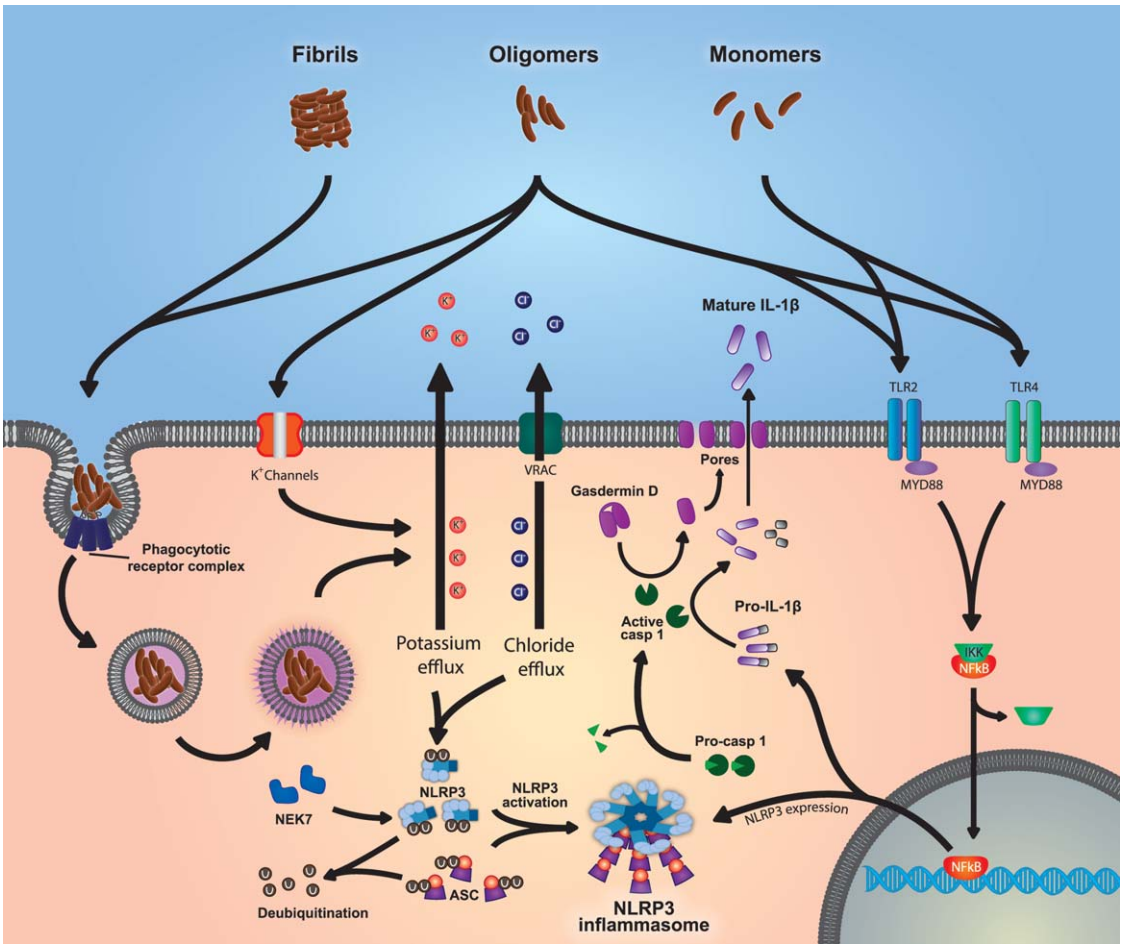

Figure 2. Amyloid oligomers and monomers cause the expression of NLRP3 and proIL-1β through TLR mediated NFκB activation. The NLRP3 inflammasome is then activated by amyloid oligomers and fibrils through phagosomal disruption or cell surface K^+ channels. Both pathways result in K^+ efflux and cell swelling leading to Cl^- efflux through VRAC. This, through an unknown mechanism, leads to deubiquitination of NLRP3 and ASC, and the binding of NEK7 to NLRP3 resulting in NLRP3 inflammasome activation. The NLRP3-ASC speck then recruits and activates caspase-1 which then cleaves gasdermin D and proIL-1β into their active forms. The N-terminus cleavage product of gasdermin D then forms pores in the cell membrane allowing the leaderless IL-1β to leave the cell.

response, mediating the increased expression of adhesion molecules, immune cell infiltration (165), and the production of further inflammatory cytokines (38). Because of the central role of IL-1β in coordinating inflammatory responses it is regulated at multiple biological check points: expression, maturation, and secretion (142). IL-1β is expressed as an inactive precursor, proIL-1β, which is mediated through a NFκB-dependent mechanism downstream of cell surface PRRs or IL-1 receptor 1 (IL-1R1) (157). For example, a well characterized method of inducing proIL-1β expression is the activation of TLR4 by lipopolysaccharide (LPS) (27). ProIL-1β is biologically inactive requiring proteolytic cleavage into its mature form which is mediated by caspase-1, a pro-inflammatory cysteine aspartate-specific protease. Alongside IL-1β cleavage caspase-1 has additional essential roles, previously reviewed by Denes *et al* (36), of note: cleavage of proIL-18 and initiating the inflammatory form of cell death, pyroptosis (Figure 2). During pyroptosis, gasdermin D is cleaved by caspase 1 and the N-terminal fragment associates with the cell membrane facilitating membrane permeabilization, cell death and IL-1β (and IL-18) release (74, 145). Once cleaved, IL-1β is secreted from cells through a non-conventional pathway, bypassing the Golgi-ER network, and has been demonstrated to be secreted by several mechanisms, including: the shedding of micro-vesicles and cell membrane permeabilization. Secretion of IL-1β from cells has not been fully elucidated, however it is largely accepted that the mode of secretion engaged by cells is a continuum dependent upon the strength stimulus, reviewed by Lopez-Castejon and Brough (90). However, caspase-1 is produced in cells as an inactive zymogen, procaspase-1, and requires proximity-induced self-cleavage for activation. Homotypic interactions between death domains motifs between proteins facilitate the oligomerization of large multimeric protein structures which act as platforms to concentrate caspase-1 and catalyze auto-activation (81, 82, 132).

Inflammasomes—protein scaffolds for caspase-1 activation

The large protein complexes which facilitate caspase-1 activation are referred to as "inflammasomes" and are largely comprised of

three core components: an inflammasome sensor molecule, an adaptor protein, apoptosis-associated speck-like protein containing a CARD (ASC), and caspase-1 (82, 142). Inflammasome sensing molecules are intracellular PRRs which sense inflammatory stimuli and oligomerise with ASC via pyrin (PYD) death domains. This initial ASC seeding triggers rapid recruitment of ASC dimers to form large protein specks (82). Subsequently, interactions between caspase activation and recruitment domains (CARD) present in ASC and procaspase-1 recruit caspase-1 to the inflammasome and initiate self-cleavage (43, 125). Multiple sensor molecules have been identified which trigger inflammasome oligomerization, all maintaining a common basic organization but varying in formation, structure and activation.

The majority of inflammasome sensors that have been identified contain a NOD-like receptor (NLR) domain, characterized by three distinct entities: a common NACHT domain; a leucine rich repeats (LRRs) domain and one or both death domains, PYD or CARD mediating ASC/caspase-1 interaction (96). The first inflammasome to be identified was the NLRP1 (NOD-, LRR- and pyrin domain-containing 1) followed by the identification of additional NLR containing inflammasomes, including: NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4 (NOD-, LRR- and CARD-containing 4) (82) which are activated in response to a broad range of molecular signals. For example, it has been demonstrated that murine NLRP1, NLRP7 and NLRC4 are activated in response to: anthrax toxin (19), bacterial LPS (74) and cytosolic flagellin (1), respectively. Another inflammasome, absent in melanoma 2 (AIM2), has been identified which contain a sensor molecule that contains a pyrin and HIN domain-containing protein (PYHIN) domain (21). The HIN region has been shown to bind directly to cytosolic DNA to facilitate inflammasome formation and caspase-1 activation. The identification and characterization of these inflammasome structures, their specific activators and independent mechanisms of activation demonstrates the immense complexity of the innate immune system and its ability to detect and respond to danger signals.

NLRP3 inflammasome

Canonical NLRP3 activation. The most extensively studied inflammasome is the NLRP3 inflammasome and has been strongly implicated in AD pathology (57). Despite being well studied the mechanisms underpinning NLRP3 activation have not been fully elucidated. Canonical NLRP3 activation, similar to IL-1β maturation, requires two independent signals: (i) an initial NF-κB activating signal to upregulate NLRP3 expression (13) and (ii) an additional activating signal which initiates a conformational change in NLRP3 and drives inflammasome assembly. Whilst a diverse range of molecules have been demonstrated to activate NLRP3, the molecular pathways which lead to its activation are incompletely understood. Various models of activation have been hypothesized, including: (i) formation of pores in the membrane and subsequent K^+ efflux (45, 118); (ii) lysosomal rupture and release of cathepsins into the cytosol (64); (iii) mitochondrial dysfunction and the production of ROS (147) and (iv) post translational modifications, including deubiquitination (70, 91). In a landmark article, Muñoz-Planillo *et al* (105) were able to demonstrate that the proposed hypotheses for NLRP3 activation converge on K^+ efflux, leading to the acceptance of its pivotal role in triggering NLRP3 activation. Recent studies have also illustrated that volume regulated anion channels (VRAC) and subsequent Cl^- efflux are also vital for inflammasome activation (35). Another landmark discovery in the field of NLRP3 activation is the identification of NEK7 (NIMA-related kinase 7) as an essential upstream regulator of NLRP3 (Figure 2). Two groups independently demonstrated NEK7 directly interacting with NLRP3 and that this interaction is essential for ASC recruitment and inflammasome activation (141, 144). It is evident that the activation and regulation of NLRP3 is a rapidly expanding field and new discoveries are constantly being made identifying novel molecular pathways involved in its regulation (Figure 2).

A diverse range of activators have been identified including pathogenic, environmental and sterile molecules. Pathogenic activators which activate NLRP3, range across the microbial spectrum including: viruses, fungi and pore forming toxins produced from bacteria, including nigericin produced from *Streptomyces hygroscopicus* (117). Environmental pollutants, such as silica and asbestos (40), can also activate the inflammasome. Notably, NLRP3 inflammasome is activated to a diverse range of endogenous danger signals and consequently is implicated in the pathology of sterile inflammatory diseases. Sterile activators of NLRP3 can be largely grouped into two main categories: (i) molecules released from dying cells and (ii) extracellular particulates. An example of the former includes the release of ATP into the extracellular milieu from dying cells, which activates P2X7 ATP-gated ion channels causing K^+ efflux and NLRP3 activation (95). The latter encompasses large sterile particulate matter, including crystals of monosodium urate and calcium pyrophosphate dihydrate, central to gout and pseudogout pathology, respectively, and cholesterol crystals, involved in atherosclerosis (41). Moreover, Halle *et al* (53) identified fibrillary Aβ as an NLRP3 activator. Other sterile activators of the inflammasome that have been identified include elevated extracellular glucose (173), zinc deficiency (154) and changes in osmolality (30).

Non-canonical NLRP3 activation. In addition to the canonical activation pathway, a non-canonical pathway of activation has been identified. This pathway describes murine caspase-11 or its human orthologues, caspase-4 and caspase-5 dependent NLRP3 activation, IL-1β release and pyroptotic cell death in response to intra-cellular Gram-negative bacteria. The non-canonical pathway was first described by Kayagaki *et al* (73), where they demonstrated NLRP3 activation by pathogen stimuli was caspase-11 dependent yet caspase-11 was not required for canonical NLRP3 inflammasome activation. It has since been discovered that intracellular LPS is the molecule which activates caspase-11 through binding to caspase-11 CARD domain and triggering oligomerization and activation (146). Further research elucidated K^+ efflux as the trigger for NLRP3 activation in the non-canonical pathway, identifying the point in which canonical and non-canonical pathways converge (134). More recently, a novel pathway of activation has been described in human monocytes, the alternative pathway. Gaidt *et al* (46) discovered a novel pathway in human monocytes which leads to NLRP3 activation in response to LPS. Notably, activation via this pathway is independent of many of the hallmark features of canonical activation including K^+ efflux and pyroptosis, and is mediated by a TLR-4/caspase-8 dependent pathway. Despite the identification and characterization of multiple inflammasomes adopting complex

independent regulatory systems the end point remains unified: caspase-1 activation and IL-1β (and IL-18) maturation.

The role of IL-1β and IL-18 in AD

Elevated IL-1β levels in AD brains has been reported as early as 1989, and subsequent research has established a distinct role for IL-1β in AD pathology (51). There is increased IL-1β expression in microglia which cluster around amyloid plaques in the APP_{Swe}/PS1deltaE9 (APP/PS1) mouse model of AD (148), and mice lacking IL-1 receptor antagonist, an endogenous IL-1 receptor 1 blocker, have increased microglial activation and neuronal damage after intracerebroventricular Aβ injection (34). Evidence also suggests that IL-1β can directly affect both the amyloidgenesis and tauopathy that is central to AD pathogenesis. It has been shown that IL-1β can upregulate APP and Aβ production in astrocytes (15) and can induce tau phosphorylation via the MAPK-p38 pathway to form neurofibrillary tangles (50). Alongside IL-1β, IL-18 has been implicated in AD pathology; brains have increased mRNA and protein levels of IL-18 that co-localize with peri-plaque neurones, astrocytes and microglia in human AD tissue (108). Preclinical studies have also demonstrated a link between IL-18 and amyloidopathy and tauopathy. IL-18 has been shown to upregulate components of the γ-secretase complex accelerating Aβ production (155), and to elevate proteins associated with the hyperphosphorylation of tau, such as, glycogen synthase kinase 3β and cyclin dependent kinase-5, in SH-SY5Y neuroblastoma cells (109). Additionally, genetic analysis has identified polymorphisms in the IL-18 promoter region to be associated with an increased risk in developing sporadic late onset AD in specific populations (18). Combined this research has shown that IL-1β and IL-18 have a pivotal role in AD and has thus provoked further research focusing on the molecular entities upstream of IL-1β and IL-18, investigating how inflammasome dysregulation may contribute to AD.

Inflammasome activation in AD

Following the discovery that fibrillar Aβ can activate NLRP3 (53), further research has identified that all amyloid species, monomers, oligomers and fibrils, have effects on NLRP3 expression and activation (Figure 2). A seminal article published by Heneka *et al* (56) directly implicated NLRP3 activation in AD pathology. Heneka showed that APP/PS1/$NLRP3^{-/-}$ and APP/PS1/caspase-$1^{-/-}$ mice have reduced neuroinflammation, decreased amyloid burden and notably were protected from AD associated memory deficits. Interestingly, the reduced amyloid burden was found not to be because of a decrease in APP processing but rather an increase in phagocytic activity from microglia. This suggests that activated NLRP3 contributes to AD pathogenesis two-fold: generating toxic IL-1β and propagating neuroinflammation, whilst impeding Aβ clearance resulting in plaque build-up (49). Furthermore, research which crossed $ASC^{-/-}$ mice with the $APP_{Swe,Flor,Lon}$, PSEN1, M146L, L286V (5xFAD) mouse model of AD found that 5xFAD/$ASC^{+/-}$ mice had reduced amyloid burden, increased astrocytic phagocytic activity and reduced memory deficits compared with the 5xFAD controls (33). The role of NLRP3 in AD has been further acknowledged in clinical studies, alongside a further inflammasome, NLRP1. Seresella *et al* (139) investigated gene expression and inflammasome activation in monocytes from patients diagnosed with severe AD, mild AD and MCI. NLRP3 and NLRP1 inflammasome components were upregulated compared with age matched healthy controls and there was an augmented response to LPS and Aβ stimulation. An additional mechanism in which NLRP3 can contribute to AD pathogenesis is in response to dying neurones releasing ATP. The release of ATP can activate P2X7 receptors on microglia to activate NLRP3 and consequently exacerbate inflammation and damage (59). Furthermore, there is evidence of P2X7 receptor upregulation in both preclinical and clinical AD research (100).

Unlike NLRP3 which is highly expressed in microglia, NLRP1 is mainly expressed in neurones (80) and its proposed role in AD pathogenesis is largely associated with neuronal death and axonal degeneration, although its exact role is not clearly defined. Tan *et al* (159) found that NLRP1 levels are upregulated in APP/PS1 mice and went on to show *in vitro* that silencing of NLRP1 reduced Aβ-induced pyroptotic cell death. They also showed that silencing NLRP1 and caspase-1 in APP/PS1 mice reduced cell death in the cortex and hippocampus, and improved spatial learning and memory in these animals. Therefore, proposing a role of NLRP1 in AD pathology via neuronal pyroptotic cell death, synaptic loss and subsequent cognitive decline. However, Kaushal *et al* (72) identified a novel NLRP1/caspase-1/caspase-6 pathway, demonstrating that activation of NLRP1 mediates caspase-1 activation which: (i) cleaves IL-1β, (ii) activates caspase-6 and subsequent caspase-6 associated axonal degeneration and, (iii) increases the ratio of $Aβ_{42}$ to total Aβ proteins. Despite proposing different hypotheses both groups have identified an important role for NLRP1 activation in neurones and axonal degeneration in AD, further highlighting an area of interest to elucidate its exact role. It is important to note there are fundamental differences in NLRP1 between mice and humans. Rodents express three paralogous NLRP1 genes where as humans only express one, and there are structural differences in the death domains (163). Furthermore, a genetic association between NLRP1 and AD has been proposed because of the identification of four non-synonymous polymorphisms in the NLRP1 gene which confer an increased risk for the development of AD (122).

A role for the NLRC4 inflammasome in AD pathology has been identified in response to the fatty acid palmitate in astrocytes. Lui *et al* (87) demonstrates that NLRC4 is activated and IL-1β is secreted in palmitate treated primary astrocyte cultures, and furthermore NLRC4 and ASC are upregulated in AD brains. Lui *et al* (87) also showed that conditioned media from palmitate treated astrocytes increases the expression of BACE-1 and production of $Aβ_{42}$ in neurones. This is of significant interest because fatty acid metabolism has been identified as a risk factor for AD development (113) and there is a higher fatty acid content in AD brain compared with healthy controls (135).

TARGETING THE INFLAMMASOME FOR AD

The processes involved in IL-1β secretion and signaling can be pharmacologically targeted at a number of locations in the pathway [reviewed by Baldwin *et al* (10)]. Recently, our group were the first to successfully pharmacologically target the NLRP3 inflammasome in animal models of AD (35). We screened NSAIDs for activity on NLRP3 activation *in vitro* and found that the fenamate subclass

selectively inhibited NLRP3 inflammasome formation. The target was established to be the inhibition of the membrane ion channel VRAC. Treatment with the fenamate mefenamic acid was then found to abate memory deficits seen in a rat amyloid oligomer injection model and APP_{Swe}, $PS1_{M146V}$ and tau_{P301L} (3xTgAD) mouse model of AD (35). Previous research has shown that mefenamic acid can reduce amyloid toxicity in neuronal cultures and abate memory deficits in rats infused with amyloid monomers (69). Furthermore, the fenamate tolfenamic acid, which is structurally very similar to mefenamic acid, has been found to be therapeutic in the APP_{Swe} R1.40 mouse model of AD, lowering plaque burden, tau pathology and cognitive deficits (4, 152, 153). It was proposed that tolfenamic acid was therapeutic through the inhibition of the gene regulator specificity protein 1 (SP1). However, similar therapeutic effects in similar animal models of AD were seen solely from the genetic deletion of the NLRP3 inflammasome and the inflammasome adapter molecule ASC, suggesting that inhibitory activity of fenamates on NLRP3 activation could exclusively explain their efficacy (33, 53, 56). Collectively, this evidence demonstrates that through NLRP3 inhibition and other potential mechanisms, fenamates have been found to be therapeutic in four animal models of AD and are therefore a promising potential therapeutic in AD.

Pharmacologically inhibiting cell surface receptors which induce IL-1β expression may prove difficult in AD because of the diversity of the receptors involved. TLR2, TLR4, CD36 and IL-1R1, have all been implicated in AD associated neuroinflammation. Therefore, a polypharmacy approach would be required, increasing the potential of off-target effects, as discussed below. Downstream of these receptors is the intracellular adaptor molecule MyD88, which is essential for TLR2, TLR4 and IL-1R signaling and may therefore be a promising target in AD. Genetic deletion of MyD88 has been found to reduce plaque load and abate neuroinflammation in the APP/PS1 mouse model of AD (84). However, MyD88 remains a controversial target for AD with further studies showing that $MyD88^{-/+}$ mice having accelerated AD pathology and memory deficits in the APP/PS1 mouse model (102). This may be because of the MyD88 receptor family being integral to the beneficial phagocytotic response by microglia (47, 102, 133). The MyD88 receptor family induce transcriptional changes through transcription regulator of NFκB, however, targeting NFκB in AD is unlikely to be successful because of the broad range of processes and genes that NFκB regulates (111). For example NFκB expression and activation is upregulated during synaptic activity and this has been shown to be essential for long-term potentiation (LTP), an essential process in learning and memory (5, 101). An additional problem for targeting TLRs, MyD88 and NFκB in AD is that these proteins are essential for host response to infection and therefore the chronic inhibition needed to treat AD may render the patient susceptible to infection (88, 130, 137, 158). Conversely, the NLRP3 inflammasome is primarily activated by sterile stimuli. Furthermore, the minimal effect of genetic deletion of NRLP3 on infection has led to the proposal that inflammasomes are largely redundant in vertebrate adapted pathogens (93). This suggests that chronic inhibition of inflammasomes, particularly the NLRP3 inflammasome, would not greatly affect the susceptibility of patients to infection, making inflammasomes an excellent target for AD.

There are multiple cell pathways that act as the secondary stimulus in inflammasome activation and these may provide an attractive target for pharmacological intervention in AD. The P2X7 receptor is activated by extracellular ATP which is released upon cell death and leads to NLRP3 inflammasome stimulation via K^+ efflux. Evidence is building that amyloid mediated NLRP3 inflammasome activation is dependent on the P2X7 receptor (115, 138). This is supported by research which demonstrated that pharmacological intervention with P2X7 antagonists were found to be therapeutic in a rat amyloid injection model (138). Yet again there is an issue with off target effects because of the P2X7 receptor having a range of functions on a range of cell types including neurones, astrocytes and oligodendrocytes. However, evidence is building that activation of the P2X7 receptor is pathologically elevated in AD in multiple cell types which leads to amyloidogenic APP processing. This suggests that P2X7 inhibition remains an attractive target in AD with multiple therapeutic mechanisms (37, 150).

Phagosomal stress causes the release of cathepsin B into the cytosol where it activates the NLRP3 inflammasome. Amyloid fibrils have been shown to induce phagosomal stress causing NLRP3 activation through a cathepsin B dependent mechanism. There is evidence that cathepsin B's role in NLRP3 activation involves both the prototypical NLRP3 activation stimulus of K^+ efflux (53, 105) as well as the cathepsin B dependent degradation of NLRP10 which acts as an inhibitor of NLRP3 activation (106). Targeting cathepsin B has been successful in animal models of AD with research demonstrating that administration of the cathepsin B inhibitor CA074Me is therapeutic in the APP_{Lon} mouse model of AD (63). However, there is evidence that cathepsins play an important role in amyloid degradation (164), therefore further research is required to evaluate the potential of cathepsins as a putative therapeutic target in AD.

Downstream from inflammasome activation there are a number of potential therapeutic targets including caspase-1 activation and signaling at the IL-1R1 receptor. Neither, caspase-1 or IL-1R1 have been pharmacologically targeted in animal models of AD. However, genetic deletion of caspase-1 has been shown to increase amyloid phagocytosis in isolated microglia and reduce neuroinflammation following striatal amyloid injections in mice (53, 56). Therefore, there is some evidence that this approach is worth pursuing. Conversely, evidence for IL-1R1 antagonists as therapeutic in AD does not appear promising. IL-1R1 KO mice have cognitive deficits, suggesting that chronic inhibition of IL-1R1 may have detrimental effects in AD (9). Possible causes for the cognitive effects of IL-1R1 inhibition include: (i) the need for low levels of IL-1 signaling to promote phagocytosis of extracellular debris (9), (ii) the critical role of neuronal IL-1R1 signaling in LTP induction (136) and (iii) the role of IL-1 signaling in synapse formation through IL1RAPL1 (interleukin-1-receptor accessory protein like 1) mediated JNK activation pathway (116). Targeting IL-1R1 also has the additional drawback of having no effect on caspase-1 dependent pyroptosis. Therefore, there will continue to be microglial death, resulting in the release of damaging cell contents, and fewer microglia to perform important functions independent of inflammation. Because of these limitations, inhibition of IL-1R1 is not the preferred therapeutic strategy of inflammasome dependent AD pathology.

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. Several approaches could be taken in drug design including: (i) inhibiting NLRP3-NEK7 binding (55), possibly by targeting NEK7 phosphorylation (144); (ii) targeting NLRP3 ubiquitination status by augmenting specific ubiquitin ligases activity or blocking deubiquitinases (70, 91), although this approach may have potential off target effects because of the many roles of the ubiquitin system; (iii) inhibiting the phosphorylation of the NLRP3 protein (151); (iv) or targeting the PRR-ASC, ASC-ASC or ASC-caspase interaction sites directly (140). Currently, there are existing inflammasome inhibiting drugs available where the mechanism of action has not fully been elucidated and may involve targeting the processes mentioned above or an unknown regulatory system of inflammasome formation. The drugs include: (i) 3,4-methylenedioxy-β-nitrostyrene (MNS) which has been shown to alter cysteines on the NLRP3 protein itself and this may alter NLRP3-NEK7, NLRP3-NLRP3 or NLRP3-ASC associations; (ii) MCC950 (CP-456773) is also a potent inhibitor of NLRP3 activation whose mechanism of action has been shown to be down stream of potassium efflux but does not alter NLRP3-ASC or ASC-ASC binding, possibly implicating NLRP3-NEK7, NLRP3-NLRP3, ubiquitination or phosphorylation as potential mechanisms of action (29). There are continuing efforts to develop novel inflammasome inhibitors using screening and structure based molecular modeling techniques to target inflammasome formation and these will provide a diverse set of tools to further investigate the role of inflammasomes in a range of diseases including AD.

CONCLUSION

It is now clear that inflammation plays a fundamental role in the pathophysiology of AD. Neuroinflammation in AD is mediated through a number of 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. Consequently, inflammasomes are an attractive therapeutic target for AD and have multiple points in the activation pathway which can be inhibited. Because of non-specific effects and complicated interactions with AD pathology targets upstream of inflammasome formation, such as TLR4 and cathepsin B, may not be preferable as a chronic pharmacological intervention strategy required for AD. Similarly, targeting IL-1R1 may have negative effects of cognition and AD progression because of the essential role of basal IL-1 signaling in brain parenchyma maintenance. However, the NLRP3 inflammasome is an attractive pharmacological target as inhibition would specifically abate pathological inflammation without altering basal microglia function or leaving the patient overly susceptible to infection. No drugs have currently been established to directly bind and inhibit the NLRP3 inflammasome, however, the essential processes for NLRP3 activation of VRAC activation has been targeted using currently indicated fenamate NSAIDs and these were found to be therapeutic in four separate animal models of AD (35, 68, 152). However, fenamate NSAIDs are also COX inhibitors and potentially have other effects on APP expression and cleavage (71). The challenge for the field now is to develop non-toxic and specific inflammasome inhibitors to fully elucidate the therapeutic potential of targeting this pathway in AD.

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