Targeting the Inflammasome: A cure for Alzheimer's disease?

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Alzheimer's disease is the most common neurodegenerative disease in the world. Despite years of intense research, its pathogenesis remains quite controversial. Many different explanations have been proposed to describe its onset, the most established of which is the β-amyloid hypothesis. This hypothesis proposes that the disease is primarily caused by the formation of β-amyloid plaques in the brain. The presence of these plaques, it is suggested, ultimately leads to neuroinflammation, tau aggregation and, eventually, neuronal death and the often-cited neurocognitive sequelae observed in Alzheimer's patients. However, recent evidence suggests neuroinflammation may in fact be a root cause of the disease as opposed to acting as an eventual or coincidental manifestation. More specifically, it has been found that the activation of inflammasomes in microglia (the brains immune cells) contributes to the production of proinflammatory cytokines which then potentiates the neuroinflammatory response, with other downstream affects including increased β-amyloid plaque build-up, tau aggregation and a loss in cognitive function. Therefore, more and more studies are suggesting that neuroinflammation - and particularly the inflammasome - could be targeted therapeutically to prevent and treat Alzheimer's disease in patients.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world affecting more than 5 million people over the age of 65. It is often characterised clinically by a decline in cognitive function, worsening performance in the arenas of learning and memory and a battery of other, related behavioural issues (Anand et al., 2014). To date, while a proportion of patients are able to alleviate symptoms somewhat, an AD cure remains elusive. It is often believed that to identify novel therapeutic targets in the treatment of AD patients, both the macroscopic and molecular pathogenesis of the disease must be clearly understood.

This has been the subject of challenging research for many years and has culminated in the proposal of many hypotheses. This profound explanatory list includes the β-amyloid hypothesis, the cholinergic hypothesis, the tau tangle hypothesis, and the inflammatory hypothesis (Kurz & Perneczky, 2011) – with some crossover between ideas. Although the official pathogenesis of the disease remains controversial, it has been generally accepted that amyloid plaques and neurofibrillary tangles (NFTs) are the key features contributing to the pathogenesis of the disease (Ramirez-Bermudez, 2012) – especially given that these features are present in the autopsied brains of AD patients (Buée et al., 2000). Amyloid plaques are deposits of β-amyloid protein (Aβ) in the brain. Aβ is produced by neurons from amyloid precursor protein (APP) present in their membrane. APP is cleaved by enzymes, β-secretase and γ-secretase, to form Aβ in the extracellular matrix. NFTs on the other hand are composed of helical, hyperphosphorylated tau proteins. Over time NFTs destabilise axonal transport in neurons (Roberson et al., 2007; Shipton et al., 2011; Vossel et al., 2010) and result in interruptions in synaptic transmission, neural and synaptic loss, and ultimately leads to cognitive defects (Anand et al., 2014).

Although the Aβ hypothesis is widely accepted as the root cause of AD, certain experimental evidence calls the role of Aβ into question. It is interesting to note that while low levels of Aβ are found in all aged brains, only some individuals go on to develop AD (Lesné et al., 2013). Furthermore, while the experimental concentration of Aβ needed to simulate the toxicity observed in the AD brain have been found to be in the micromolar range (Forloni et al., 1993; May et al., 1992; Yankner et al., 1989), the concentrations of Aβ actually found in the brain of AD patients is in the much lower picomolar concentration (Brody et al., 2008; Steinerman et al., 2008; Xia et al., 2009). This is

complicated by the in vitro studies examining induced pluripotent stem cell (iPSC) neurons from AD patients, which found that neuronal Aβ production was inconsistent between patients (Israel et al., 2012; Kondo et al., 2013). Furthermore, there is evidence to suggest that targeting the Aβ plaque alone is not enough to prevent the disease from occurring (Pimplikar, 2009; Sala Frigerio & De Strooper, 2016). Therefore the question remains: is Aβ synthesis and deposition an adequate explanation of what is causing the AD neurodegenerative cascade? It would seem, from the new studies being published, that there must be other factors causing or coinciding with Aβ synthesis in the AD brain.

The level of inflammation present in the AD brain has been significantly overlooked or has been considered secondary in nature and importance. However, a number of groups have proposed that inflammation - in the presence of Aβ - results in plaque neurotoxicity (McGeer & McGeer, 2013). Studies have shown that patients using non-steroidal anti-inflammatory drugs (NSAIDs), if started early enough, have up to a six-fold sparing effect in the context of AD (McGeer et al., 1990). Similar evidence has supported and further developed the inflammatory hypothesis, which now states that it is the inflammatory environment in the brain that drives the pathogenesis of AD. Inflammation is complicit with Aβ in causing AD rather than appearing as an eventual by-product of plaque overload (Heppner et al., 2015). However, neither the Aβ hypothesis nor the inflammatory hypothesis can be taken alone. Both must be considered in order to properly propagate further research into AD.

It is supported that Aβ, found in all aged brains, can lead to inflammation. Recent research showed inflammasome activation is heavily involved in the neuroinflammatory response. Aβ can directly, and indirectly through reactive oxygen species (ROS), activate the inflammasome – thereby causing its oligomerization into a large protein complex that catalyses an intracellular caspase cascade (Parajuli et al., 2013; Saresella et al., 2016). Activating the caspase cascade results in proinflammatory mediator production – specifically IL-1β and IL-18 (Halle et al., 2008). These cytokines ultimately potentiate Aβ production by affecting the enzyme β-secretase (increasing its activity) (Sastre et al., 2008). This marks the entry of the effected brain tissue into a proinflammatory-Aβ cycle (Figure 2b).

Aβ plaques are thought to increase tau aggregation (Braak & Braak, 1991), leading to neuronal degeneration and death. Unfortunately, there is a lack of clear experimental evidence explaining how Aβ causes tau aggregation. However since Aβ plaque exacerbates inflammation, it is often believed that the higher proportion of pro-inflammatory mediators present may upregulate tau, resulting in its aggregation (McGeer & McGeer, 2013). Once tau aggregates are formed, they are self-sustaining. Therefore, targeting inflammation could be critical in decreasing or preventing tau aggregation and, subsequently, neuronal death in AD. Since it has been shown that microglial inflammasomes are activated in AD in the context of neuroinflammation (Saresella et al., 2016), the inflammasome therefore stands out as a potential novel therapeutic target in the treatment of AD.

This review aims to outline the connection between inflammasome activation in the brain and the pathogenesis of AD, as well as discuss the inflammasome is a potential therapeutic target to both prevent and treat AD.

What is the inflammasome?

Inflammasomes are protein complexes that amplify the innate immune responses to certain stressors, which can involve the production of pro-inflammatory mediators or the induction of an inflammation-related form of cell death. Inflammasomes are particularly useful in protecting us against pathogens and in preventing persistent infections (Guo et al., 2015). In the brain, they are expressed and activated in microglial cells (Greter et al., 2015). The inflammasomes are activated through pattern recognition receptors (PRRs). PRRs can either be NOD-like receptors (NLRs), nucleotide-binding domains (NBDs), or absent in melanoma 2 (AIM2)-like receptors (ALRs) (Takeuchi & Akira, 2010). The best studied inflammasome, and most relevant to AD, is the NLRP3 inflammasome, which can be activated by a wide range of stimuli (Sutterwala et al., 2014).

All NLRs are found as inactive monomers intracellularly (Sutterwala et al., 2014). They

Figures

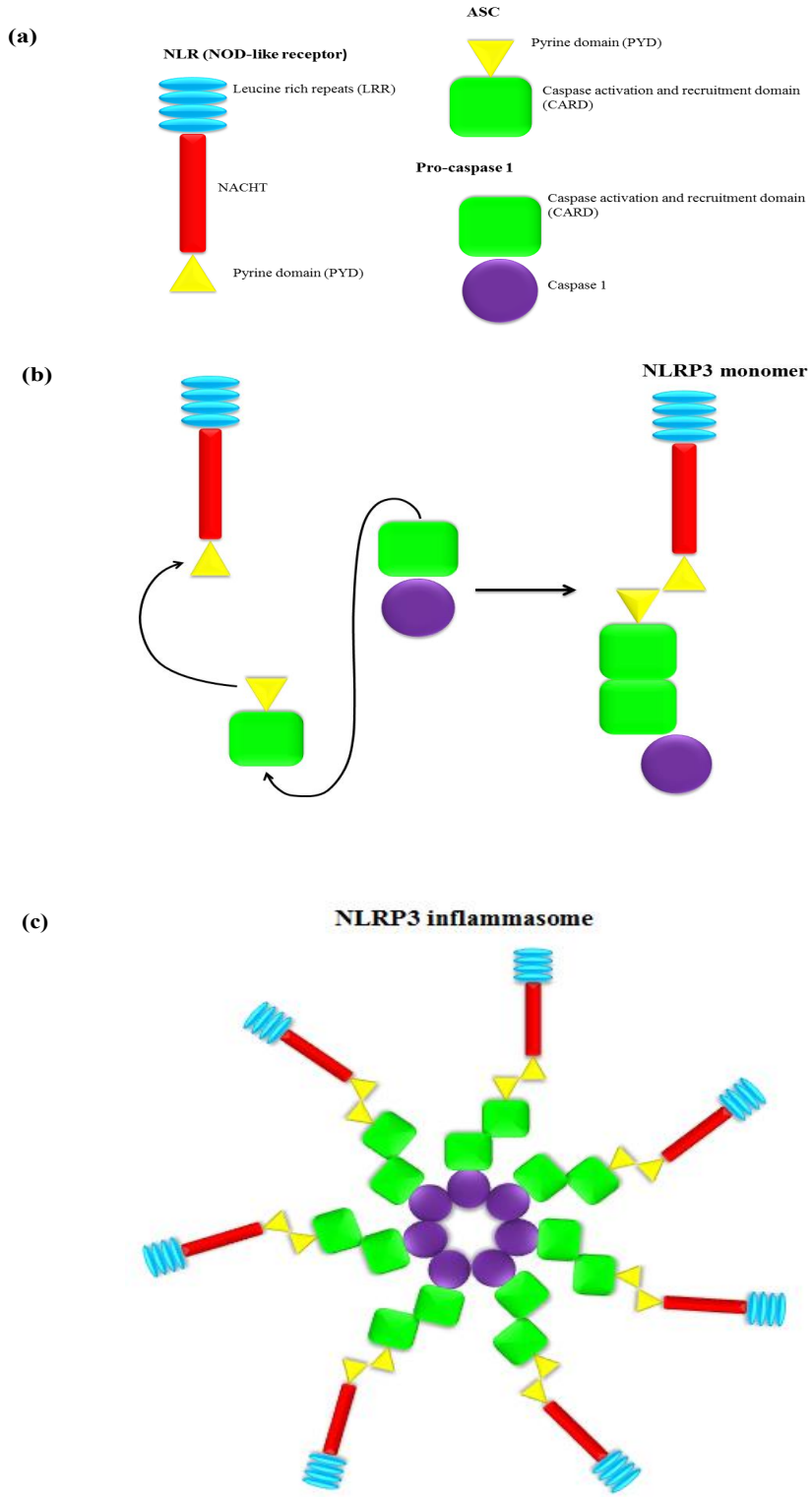


Figure 1. The components and formation of the NLRP3 inflammasome. (a) The protein complexes that make up a single monomer of the NLRP3 inflammasome, and the important domains found in each complex that allow for protein-protein interaction. (b) The structure of oligomerised NLRP3 monomer. (c) Seven NLRP3 monomer bind to form the cyclical structure of the NLRP3 inflammasome.

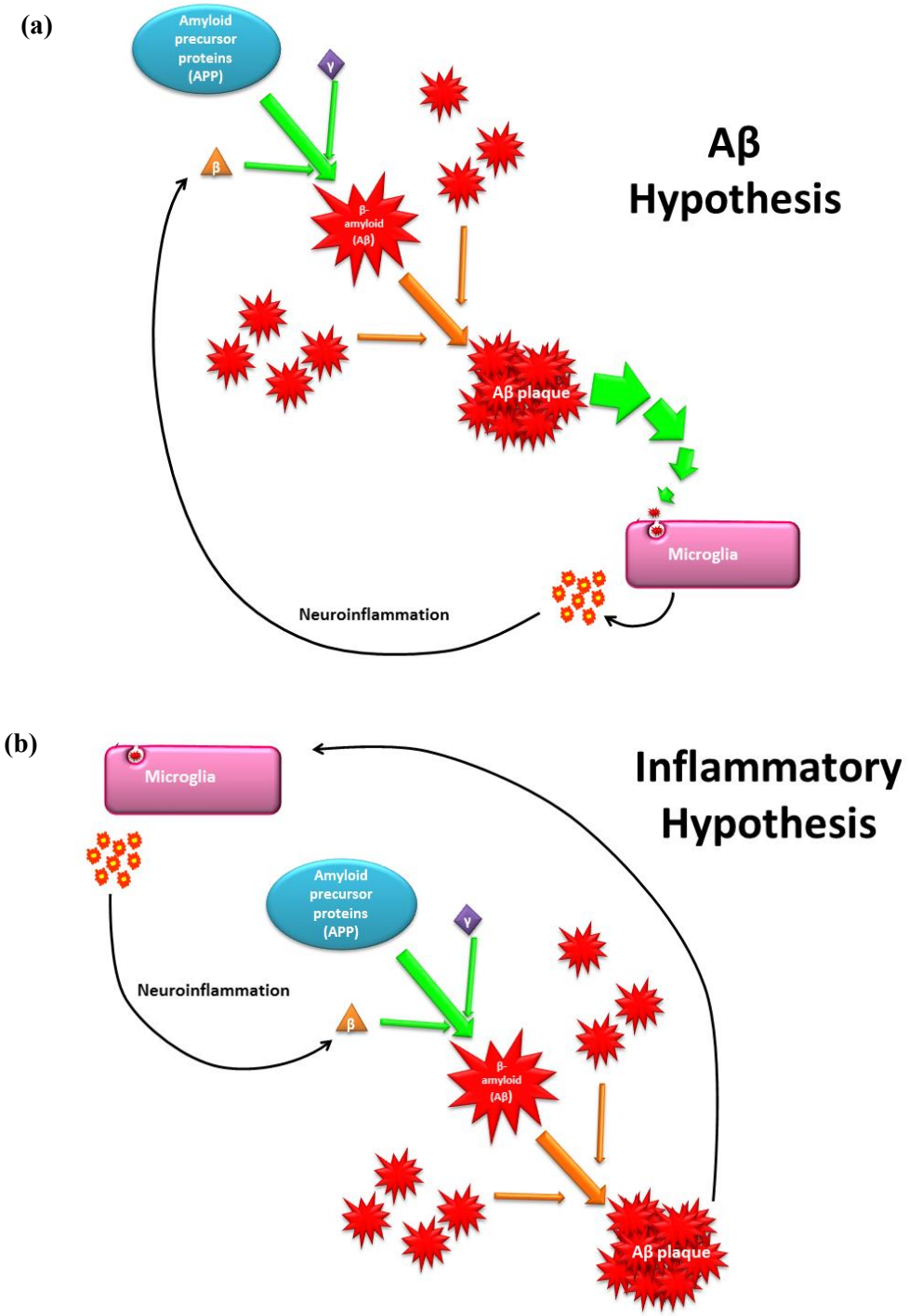
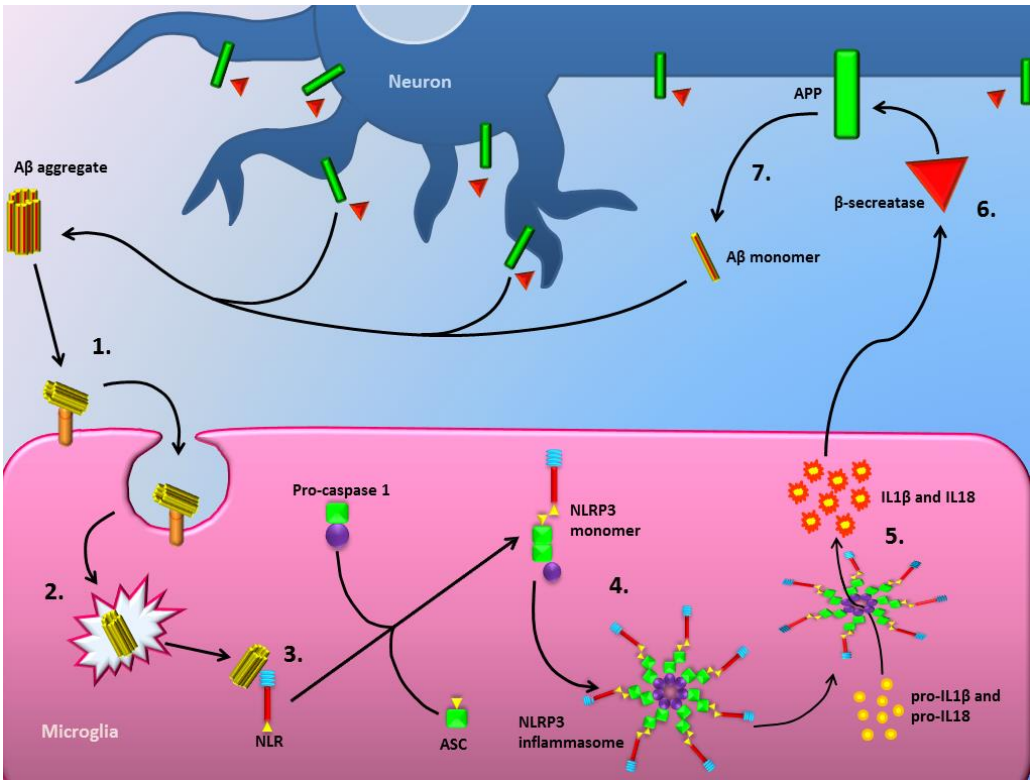


Figure 2. The Aβ hypothesis compared with the inflammatory hypothesis. (a) Sporadic cleavage of APP by β-secretase and γ-secretase leads to the production Aβ. Aβ aggregation occurs spontaneously, forming Aβ plaques. The Aβ plaques are phagocytosed by microglia, which become activated and produce proinflammatory cytokines. These cytokines act on the β-secretase enzyme, upregulating its activity and increasing APP cleavage and Aβ formation. (b) Naturally present Aβ or other PAMPs/DAMPs are phagocytosed by microglia. Microglia become activated and produce proinflammatory cytokines. These cytokines act on the β-secretase enzyme, upregulating its activity and increasing APP cleavage and Aβ formation. Aβ aggregation occurs forming Aβ plaques.

(a)



(b)

Figure 3. (a) Schematic of the inflammatory hypothesis. (b) Steps to the inflammatory hypothesis

consist of leucine rich repeat domains, a NACHT domain, and a pyrine domain (PYD) (Figure 1a). When an NLR becomes activated, it binds to an adaptor protein, called apoptosis-associated speck-like protein containing a CARD domain (ASC). ASC is composed of a PYD and caspase activation and recruitment domain (CARD) (Figure 1a). The binding of the NLR to the ASC is called oligomerisation. NLR binds ASC through PYD-PYD interactions (Cai et al., 2014; Lu et al., 2014). The CARD of ASC brings protein monomers of pro-caspase 1 into close proximity and ASC binds pro-caspase 1 through CARD-CARD interactions. When all components are bound, this structure is called a NLRP3 monomer (Figure 1b). Seven NLRP3 monomers form the NLRP3 inflammasome ring structure (Figure 1c). The inflammasome initiates pro-caspase 1 self-cleavage, producing active caspase 1 (Guo et al., 2015).

Caspase 1 is an enzyme that activates many cellular processes. It proteolytically cleaves proteins such as proIL-1β and proIL-18 into active IL-1β and IL-18, and it amplifies immune responses (Agostini et al., 2004; Bryant & Fitzgerald, 2009; Halle et al., 2008; Horvath et al., 2011; Kanneganti et al., 2006; Lamkanfi & Dixit, 2014; Mariathasan et al., 2006; Martinon et al., 2004; Martinon et al., 2009; Martinon & Tschopp, 2004; Wen et al., 2013). These proinflammatory mediators are found in high concentrations in the brains of AD patients (Saresella et al., 2016). Activation of the inflammasome can lead to proinflammatory cell death, called pyroptosis (Lamkanfi & Dixit, 2012; Strowig et al., 2012). Pyroptosis leads to the release of the intracellular cytokines into the extracellular matrix. These cytokines interact with β-secretase, upregulating it activity, and leading to increased APP cleavage and Aβ production. More Aβ production and aggregation results in further microglial and inflammasome activation, and creates a pro-inflammatory cycle, as seen in AD (Strowig et al., 2012) (Figure 2b). Another component released from pyrotosed cells is the ASC protein. This protein is responsible for cell-cell communications and amplifying the activated inflammasome signal i.e. when cell death occurs through inflammasome activation, ASC specks build up extracellularly, maintaining IL-1β production in the extracellular fluid. ASC is also taken up by microglia, resulting in lysosomal damage and more inflammasome IL-1β production. Essentially, minimal signals that only activate a few NLRs can be amplified to cause large multicellular responses mediated by ASC (Baroja-Mazo et al., 2014; Franklin et al., 2014). This ASC protein could be a potential therapeutic target for AD, in order to reduce neuroinflammation. As Aβ plaque in the brain of AD patients is in such low concentration (Brody et al., 2008; Steinerman et al., 2008; Xia et al., 2009), it may only directly activate a few microglia and inflammasomes. However, through IL-1β, IL-18, and extracellular ASC, the inflammatory signal could be amplified and spread, causing huge neuroinflammation, resulting in more plaque build-up, and further exacerbate the disease.

In terms of NLRP3 inflammasome activation, the signalling cascade has yet to be defined. However, agonists which activate the NLRP3 inflammasome are well known, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), ion gradient changes across cell, ROS (Abais et al., 2015), cytokines, and, in the case of AD, Aβ (Halle et al., 2008). Engulfed PAMPs and DAMPs can enter the cytosol through lysosomal rupturing. The release of lysosomal contents intracellularly results in NLRP3 inflammasome assembly and activation. The lysosome contains phagocytosed particles, such as Aβ, ROS (Zhou et al., 2011), and cathepsin B (Hornung et al., 2008). Cathepsin B is an important component of the lysosome, which has been linked to AD pathogenesis, making it a possible target in AD.

The inflammatory hypothesis

Neuroinflammation in AD is not a new concept, and was proposed almost two decades ago (McGeer et al., 1996; Rogers et al., 1996; Stewart et al., 1997; Verri et al., 2012; Yao et al., 2009). It was established that there was increased Aβ plaque build-up in the AD brain, and that these plaques were surrounded by microglia trying to phagocytose the plaques (Simard et al., 2006). These microglia simultaneously produced pro-inflammatory cytokines, such as IL-1β and IL-18 (Zhu et al., 1999). Therefore, it was deduced that increased inflammation in the brain was a consequence of Aβ plaque, and further exacerbated the condition.

Although neuroinflammation has been known about for years, the inflammatory hypothesis is a

relatively new idea (Zotova et al., 2010). While the Aβ hypothesis states that Aβ plaque build-up is the cause of neuroinflammation and tau aggregation (Figure 2a), the inflammatory hypothesis suggests that inflammation may actually precede Aβ plaque build-up, and drive the pathogenesis of the disease itself (Miller et al., 2013; Zhang et al., 2013) (Figure 2b,3). It has been claimed numerous times that Aβ plaque deposits are what activate microglia, and cause the neuroinflammation. However, recent studies show increased microglial dysfunction in severe AD brains compared to healthy controls (Krabbe et al., 2013). It is thought that chronic activation of microglia in the early stages of AD, due to the neuroinflammatory environment naturally found in aged brains, overwhelms the microglial response. This dysfunction reduces Aβ clearance and promotes further Aβ plaque deposition. It has been found that inhibiting neuroinflammation through downregulation of the NLRP3 inflammasome leads to decreased Aβ deposition in AD (Heneka, Carson, et al., 2015; Heneka, Golenbock, et al., 2015; Heneka et al., 2014; Heneka et al., 2013; Tan et al., 2013).

The inflammatory hypothesis is further supported by more studies, which demonstrate that increased chronic inflammation through TLR and inflammasome activation initiated the deposition of Aβ plaques in wild type (WT) mouse models, as well as exacerbated Aβ plaques in the AD mouse model (Krstic et al., 2012). Other studies have suggested that increased peripheral inflammation in AD patients damages the blood brain barrier (BBB), causing a more rapid decline in cognitive function (Holmes et al., 2009; Perry et al., 2007). The inflammatory milieu impairs synaptic transmission (Camacho-Arroyo et al., 2009; Hein & O'Banion, 2009; McAfoose & Baune, 2009; Rao et al., 2012), and results in a large cognitive decline, as seen in AD with chronic peripheral immune system activation.

Despite convincing evidence, the inflammatory hypothesis has been overlooked in favour of the Aβ hypothesis. However, despite evidence favouring one hypothesis over another, both hypotheses must be considered in order to ameliorate the disease. The question is how neuroinflammation can be targeted specifically to protect the brain from degeneration? There have been promising results with the use of NSAIDs, with many epidemiological studies suggesting that long term use could protect against AD development (Stewart et al., 1997; Vlad et al., 2008). However, another prospective clinical trial on mild AD patients showed that NSAID treatment had very little effect on AD pathogenesis (Martin et al., 2008). Although results using NSAIDs were found to be inconsistent, these trials have started investigating the possibility of inflammation leading to and exacerbating AD.

Through current emerging literature, it seems as though the inflammasome plays a huge role in neuroinflammation in AD. Targeting the complex itself could be a more specific way of lowering inflammation and disease progression. A direct link between the NLRP3 inflammasome and AD was demonstrated in in vivo mouse models, by knocking out NLRP3 and caspase-1. These mice showed decreased AD-related pathogenesis, less neuroinflammation, reduced Aβ plaque deposits, and less cognitive impairment than the control WT mice (Heneka et al., 2013). Another recent study also showed an increased expression of caspase-1 in AD brains compared to healthy controls, again, denoting the importance of the inflammasome in the pathogenesis of the disease. Collectively, studies have pointed to the importance of the inflammasome in AD and how it could potentially be therapeutically targeted to treat and prevent the pathogenesis of the disease. Inhibiting the NLRP3 inflammasome activation would decrease Aβ plaque deposition (Heneka, Carson, et al., 2015; Heneka, Golenbock, et al., 2015; Heneka et al., 2014; Heneka et al., 2013; Tan et al., 2013), decrease the level of proinflammatory cytokines in the brain (Schroder & Tschopp, 2010), and prevent tau aggregation and neuronal dysfunction and death.

However, despite growing evidence for the inflammatory hypothesis, many studies still suggest that inflammasome activation is secondary to Aβ plaque deposition, through Aβ-mediated ROS production and oxidative damage (Kurz & Perneczky, 2011), and Aβ targeting alone will be enough to cure AD. ROS can go on to activate the inflammasome, exacerbating Aβ production, and worsening the disease. IL-1β, as well as other proinflammatory cytokines, such as TNF-α and IFN-γ produced by the inflammasome, stimulate

astrocyte and neurons to produce more Aβ oligomers, stimulating further dispersal of Aβ (Dal Prà et al., 2015) (Figure 3). It is clear that although Aβ plaque deposition is an important target for therapies, both Aβ and inflammation are key mediators in the pathogenesis of AD, and both should be considered in the aim of finding a therapeutic agent that can prevent and treat the disease pathogenesis. So far many clinical trials targeting the Aβ hypothesis have failed (Aisen et al., 2011; Doody et al., 2013; Karran & Hardy, 2014; Karran et al., 2011; Siemers et al., 2016), so new approaches are needed if we are to potentially wipe-out AD.

Current and future therapeutics

Currently, the only pharmacological treatments available for AD are three cholinesterase inhibitors (CIs), donepezil, rivastigmine, and galantamine, and one N-methyl-D-aspartate (NMDA) inhibitor, memantine. The CIs are used to treat mild-moderate AD and prevent the breakdown of acetylcholine at relevant synapses. They counteract the loss of cholinergic neurons due to poor synaptic function that characterises the disease, and attempt to decrease the rapid deterioration in memory and cognitive function (Bartus et al., 1982; Cummings & Back, 1998). The NMDA antagonist, memantine, is used for patients with moderate-severe AD, and attempts to protect neurons from excitotoxicity and preserve neuronal function (Yiannopoulou & Papageorgiou, 2013).

The problem with the current available treatments is that they are only symptom modifying interventions; they do not slow its progression or target the root cause of the disease (Citron, 2010). In order to definitively cure AD, therapeutic agents must specifically target the underlying pathophysiology of the disease.

To date, major pharmaceutical companies have run clinical trials for new therapies which aim to decrease Aβ plaque load in the AD brain (Scarpini et al., 2011; Yiannopoulou & Papageorgiou, 2013). The mechanisms of action of these therapies have involved either inhibiting the proteases producing Aβ e.g. semagacestat (Doody et al., 2013), decreasing Aβ aggregation, e.g., tramiprosate (Aisen et al., 2011), or favouring Aβ clearance by immunotherapy, e.g., solanezumab (Siemers et al., 2016). However, studies have shown, it may not be enough to target plaque deposits alone (Pimplikar, 2009). Previous animal model data suggests that targeting inflammation through the inflammasome could be used in combination with Aβ inhibitors to completely prevent the development of AD (Hook et al., 2008). Addressing both the Aβ hypothesis and the inflammatory hypothesis together could be the key to treating and preventing the disease.

The NLRP3 inflammasome has been shown to initiate Aβ plaque deposition (Krstic et al., 2012). It is activated by Aβ plaque (Halle et al., 2008), and is upregulated in AD (Saresella et al., 2016). Many aspects of the NLRP3 inflammasome could be targeted in order to reduce neuroinflammation, and therefore prevent exacerbation or onset of AD. Studies have suggested that inhibiting the deubiquination of the inflammasome prevents its activation (Juliana et al., 2012; Py et al., 2013). Deubiquination is a key step in the priming of the NLRP3 inflammasome, needed for its response against a stimulus (Guo et al., 2015). There is also increasing evidence that inhibiting caspase-8 would prevent priming and activation of the inflammasome (Allam et al., 2014; Ganesan et al., 2014; Gurung et al., 2014), and processing of pro-IL-1β.

The surface receptor CD36 on microglia was found to be responsible for the uptake of Aβ intracellularly, and results in NLRP3 inflammasome activation, exposing another potential target (Guo et al., 2015; Sheedy et al., 2013). As activation is due to Aβ plaque causing lysosomal rupture and the release of cathepsin B intracellularly (Halle et al., 2008); there has been a study carried out that showed that the inhibition of cathepsin B improved the memory deficits in AD significantly, and simultaneously decreased Aβ plaque deposit load in the AD brain in vivo (Hook et al., 2008). This finding could be a huge step towards not only preventing neuroinflammation, Aβ build-up, and cognitive dysfunction, but perhaps could repair damage caused by AD itself.

As discussed above, it was recently discovered that ASC, a major component of the inflammasome, is released from dying cells (Bryan et al., 2009; Franklin et al., 2014; Huang et al., 2009). This can lead to cleavage of extracellular pro-IL-1β and can activate caspase-1 in the microglia that phagocytose the ASC specks. The phosphorylation of ASC is a key checkpoint in speck formation, so targeting the

kinases, Syk and JNK, could be used to therapeutically neutralise the ASC, ultimately decreasing neuroinflammation and Aβ plaque (Hara et al., 2013).

As the inflammasomes role in AD pathogenesis is a relatively new concept, to date there have been no clinical trials targeting this protein complex directly. However, trials targeting the inflammasome and its products have been carried out for other diseases, such as atherosclerosis, metabolic syndrome, and age-related macular degeneration (Ozaki et al., 2015). Currently, the best therapy seems to be inhibition of the inflammasome product IL-1β. Antibodies specifically targeting IL-1β, such as canakinumab, are available for rheumatoid arthritis. These antibodies may also be useful for AD (Moll & Kuemmerle-Deschner, 2013). In terms of inhibiting inflammasome components, some drugs have been identified and investigated. These include parthenolide and pralnacasan (caspase-1 inhibitors) (Dinarello et al., 2012; Heinrich et al., 1998), and a cysteinyl leukotriene receptor antagonist acting as an ASC inhibitor. The latter molecule has prevented the oligomerisation of ASC and NLR in certain models of disease (Coll et al., 2011).

These newer, more specific therapeutic molecules have not been tested in any AD clinical trials so far. However, their existence opens doors for future clinical trials, and eventually, one or more of them could be available for the treatment of AD in the clinic.

Conclusion

For years, it was thought that curing Alzheimer's disease could only involve the targeting and clearing of Aβ plaque deposits. However, new studies have demonstrated that Aβ plaques alone are not sufficient to cause AD and thus their clearance may not be sufficient to cure it. Nowadays, an increasing number of groups are attempting to more accurately dissect the disease's multifaceted pathogenesis. To date, the therapeutic agents used to treat Alzheimer's disease have been quite non-specific and aim to alleviate disease symptoms rather than the mechanisms underlying its onset. More exact targeting of molecular components in the AD inflammatory cascade is needed. Only recently has the importance of inflammasome activation in AD been elucidated and importantly, it seems to play a role in the initiation of Aβ plaque deposition in the brain. This highlights the therapeutic potential of the inflammasome in AD. With time and effort, inflammasome modulators may be integrated into routine clinical practice alongside existing therapies and could facilitate the eradication of the disease entirely.

Take home points:

- Alzheimer's disease is the most common neurodegenerative disease in the world, affecting over 5 million above the age of 65.
- The current AD treatments only modify symptoms of the disease - they do not target the root cause.
- For years, it has been assumed that β-amyloid plaque deposition in the brain is what causes the pathogenesis of AD, but recent clinical trials targeting and eliminating these plaques have shown poor results.
- Recent studies suggest that inflammation could play a key role in AD pathogenesis.
- The inflammasome complex has been found to be upregulated in the brains of AD patients, and is responsible for the production of proinflammatory cytokines. The presence of these mediators is associated with increased β-amyloid plaque deposition, increased tau aggregation, and increased neuronal death.
- Therapeutically modulating the inflammasome may be the key to ameliorating and preventing AD, and could wipe the disease out entirely.

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