Ageing Research Reviews 88 (2023) 101954

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

The central role of the NLRP3 inflammasome pathway in the pathogenesis of age-related diseases in the eye and the brain

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ARTICLE INFO

Keywords:
Inflammasome
Dementia
Age-related macular degeneration
Glaucoma
Cataract
Inflammaging

ABSTRACT

With increasing age, structural changes occur in the eye and brain. Neuronal death, inflammation, vascular disruption, and microglial activation are among many of the pathological changes that can occur during ageing. Furthermore, ageing individuals are at increased risk of developing neurodegenerative diseases in these organs, including Alzheimer's disease (AD), Parkinson's disease (PD), glaucoma and age-related macular degeneration (AMD). Although these diseases pose a significant global public health burden, current treatment options focus on slowing disease progression and symptomatic control rather than targeting underlying causes. Interestingly, recent investigations have proposed an analogous aetiology between age-related diseases in the eye and brain, where a process of chronic low-grade inflammation is implicated. Studies have suggested that patients with AD or PD are also associated with an increased risk of AMD, glaucoma, and cataracts. Moreover, pathognomonic amyloid-β and α-synuclein aggregates, which accumulate in AD and PD, respectively, can be found in ocular parenchyma. In terms of a common molecular pathway that underpins these diseases, the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome is thought to play a vital role in the manifestation of all these diseases. This review summarises the current evidence regarding cellular and molecular changes in the brain and eye with age, similarities between ocular and cerebral age-related diseases, and the role of the NLRP3 inflammasome as a critical mediator of disease propagation in the eye and the brain during ageing.

1. Introduction

1.1. Epidemiology of age-related diseases: brain and the eye

Ageing is a natural phenomenon which affects an organism's health span and longevity at different rates. Age-related studies have shown that improvement in longevity, particularly in humans, is based on an individual's genetics, social and economic factors such as income, education, employment, access to healthcare, community safety, and lifestyle choices (I'Feiffer, 1970; Palmore, 1969). However, new emerging views in the biomedical research field suggest that ageing is associated with the predisposition of older individuals to many diseases (Knapowski et al., 2002). Particularly within the central nervous system, recent studies have presented that chronic cumulative inflammation, a phenomenon described as inflammaging, is causative in various neuro-degenerative diseases of the eye and brain, such as Alzheimer's disease

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https://doi.org/10.1016/j.arr.2023.101954
Received 14 February 2023; Received in revised form 8 May 2023; Accepted 12 May 2023
Available online 13 May 2023

(AD) and Parkinson's disease (PD), glaucoma and age-related macular degeneration (AMD) (Kauppinen et al., 2012; Lue et al., 2001; Mao et al., 2017b).

Furthermore, the global health burden of these diseases is immense. AD and other dementias affect over 43 million people worldwide and contribute to over 28 million disability-adjusted life years annually (Nichols et al., 2019). Similarly, AMD is the leading cause of blindness globally in individuals over 50 years (Fleckenstein et al., 2021). Given the burden these age-related diseases pose to the health system, there is an urgent need for alternative treatments and therapies to inhibit the underlying upstream drivers of age-related disease, particularly in the brain and the eye.

1.2. Cellular and molecular changes in the brain with age

Inflammaging has been thought to accelerate age-related diseases and is responsible for various changes observed within the brain and the eye during ageing. Particularly within the brain, the effects of ageing are multifaceted. With ageing, neuronal connectivity and strength decrease (Onoda et al., 2012). Studies have demonstrated that there may be a decrease of up to 5% in brain mass and volume per decade after the age of 40 years (Svennerholm et al., 1997).

At the cellular level, the ageing process also affects the connectivity and neuromodulatory control of the brain. Previous investigations have highlighted that neurotransmitters such as acetylcholine, dopamine, serotonin, glutamate and GABA, which modulate synaptic plasticity in the hippocampus, may decrease in concentration with age, causing a reduction in neuroplasticity, leading to cognitive impairment (Mahncke et al., 2006). Specifically, dopamine levels, dopaminergic neuron populations, and dopamine receptors decline with age, which has been thought to contribute to cerebral pathology and cognitive impairment (Mukherjee et al., 2002; Nyberg and Bäckman, 2004). Furthermore, the function and activities of microglia cells and astrocytes within the brain are pathologically altered with age (Chinta et al., 2015). Microglia derived from older individuals exhibit pathological alterations in their cellular structure, including de-ramification, shortening, twisting and breakdown of cellular processes (Streit, 2004; Streit et al., 2004). Dystrophy of microglia with increasing age causes them to become activated and secrete cytokines, chemokines, growth factors, and complement proteins which induce inflammation and cellular death (Wyss-Coray and Rogers, 2012).

Consequently, the ageing process contributes to the disruption of the brain's cerebrovasculature, specifically the blood-brain barrier (BBB). The BBB is the primary interface between the blood and the neural environment. However, the BBB becomes more permeable with increasing age and exhibits structural impairment. There may be a loss of endothelial cells and pericytes, contributing to reduced barrier integrity (Erickson and Banks, 2019; Yang et al., 2017). This leads to the accumulation of neurotoxic substances, increased immune cell infiltration and propagation of chronic inflammation, which leads to degeneration and death of neurons and glia (Erickson and Banks, 2019; Stranahan et al., 2016; Yang et al., 2017). Consistent with this, increased BBB permeability was reported in individuals diagnosed with AD and PD (Erickson and Banks, 2019; Farrall and Wardlaw, 2009).

1.3. Cellular and molecular changes in the eye with age

The eyes similarly undergo numerous structural, cellular, and molecular changes with age. For example, the lens becomes increasingly rigid and thickened with age, resulting in cataracts and presbyopia (Cavallotti et al., 2004). Like trends in the brain, studies have identified that nerve terminal density and volume in retinal layers are diminished in older individuals in both mice models and humans (Demirkaya et al., 2013; Ito et al., 2020; Samuel et al., 2011). Notably, the ganglion cell layer (GCL) and the inner plexiform layer (IPL) are the most susceptible to thinning with age.

On a cellular level, decreased retinal pigmented epithelium (RPE) cell, photoreceptor, and ganglion cell populations are observed with age. There is prominent loss and disorganization of cells in the nerve fibre layer (NFL), inner nuclear layer (INL) and outer nuclear layer (ONL), which manifests as thinning of the retina (Matsumoto et al., 2009; Mugisho et al., 2019a). Interestingly, the RPE also degenerates during ageing, primarily due to the accumulation of oxidative and inflammatory damage (Tisi et al., 2021). Over time, the RPE becomes incapable of regulating biological waste products, metabolites and organelles, which accumulate in the Bruch's membrane and manifest as drusen (Tisi et al., 2021).

During ageing, there is also increased retinal gliosis, where glial cells such as Müller cells, proliferate and become activated (Bringmann et al., 2006; Ly et al., 2011; Sorrentino et al., 2016; Telegina et al., 2018). Chronic gliosis causes exacerbation of damage to the retinal vasculature, where studies have indicated that this may result in increased neovascularisation, which is linked to AMD and diabetic retinopathy (DR) (Bringmann et al., 2006; Ly et al., 2011; Sorrentino et al., 2016; Telegina et al., 2018).

With increasing age, damage to the blood-retinal barrier (BRB) can also occur (Campbell and Humphries, 2013). Like findings in the brain with the BBB, studies have indicated that over time, the blood vessels forming the BRB may thin and reduce in integrity, which causes the BRB to become leakier (Chen et al., 2019; Tisi et al., 2021). These changes allow for an increased influx of neurotoxic substances into the retina, which contributes to inflammation and cellular death (Chen et al., 2019). Interestingly, studies have indicated that this may be primarily mediated by chronic low-grade inflammation in the retina, suggesting an 'inflammaging' process in the eyes as well (Chan-Ling et al., 2007; Lee et al., 2021).

This process does not appear to be restricted to the retina. Age-related changes are also observed in the cornea, iris, lens and vitreous. Within the cornea, age-related dystrophic changes have been shown to occur in the epithelium, stroma and endothelium, manifesting as corneal dystrophies and endothelial cell failure (Roh et al., 2013). Furthermore, studies have indicated that age-related cataractogenesis may be linked to reactive oxygen species (ROS) production, pyroptosis and raised levels of proinflammatory cytokines (Jin et al., 2018; Periyasamy and Shinohara, 2017). Similarly, the vitreous degenerates with age and can exhibit increased levels of inflammatory cytokines during neovascular AMD, while there is increased expression of genes associated with inflammation in iris tissue during age-related exfoliation syndrome (Hirbo et al., 2023; Minaker et al., 2021). These suggest an inflammatory aetiology for age-related ocular diseases.

1.4. Inflammaging in the brain and eye

Inflammation is an essential biological response induced by the immune system to protect against harmful stimuli such as pathogens and other irritants and mediate the repair of damaged tissues (Lawrence and Gilroy, 2007). Although inflammation is beneficial in the acute setting, it may become detrimental and damaging when chronic inflammation is established. With increasing age, immune and inflammatory pathway dysregulation occurs in the CNS, including the brain and the eye. This process of age-related immune dysregulation, which results in low-grade sterile chronic inflammation, is known as 'inflammaging' (Fulop et al., 2018).

Age-related diseases in the eye and brain share a common inflammatory aetiology. Studies have indicated that the pathological changes observed within the brain in AD, PD, cerebral small vessel disease, BBB dysfunction and other neurodegenerative diseases are linked to chronic low-grade inflammatory processes that increase in propensity with age (Calabrese et al., 2018; Li et al., 2020; Mészáros et al., 2020; Onyango et al., 2021). Within the eye, the formation of cataracts, corneal dystrophies, AMD, and DR have all also been associated with inflammation (Fernandes et al., 2019; Forrester et al., 2020; Gallenga et al., 2014; Jin

et al., 2018; Periyasamy and Shinohara, 2017). The causes of inflammaging are diverse and numerous, including accumulation of extracellular debris, cellular senescence and age-related alterations in the immune system over time. However, an extensively studied mediator of inflammaging that is of great interest in the literature is the activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome (Yerramothu et al., 2018).

2. What is the inflammasome?

2.1. NLRP3 inflammasome

The innate immune system is responsible for host defence from the invasion of microorganisms and foreign molecules; however, it has also been thought to play a crucial role in the initiation and propagation of sterile inflammation. The assembly of multimeric nucleotide-binding and oligomerization domain-like receptors-apoptosis-associated speck-like protein-caspase-1 (NLR-ASC-Caspase-1) inflammasome complexes, the subsequent autolytic cleavage of caspase-1, and the synthesis and release of proinflammatory cytokines are thought to mediate sterile inflammation (Kelley et al., 2019). While there are over 20 various NLR genes in humans, the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome is the most extensively studied inflammasome and is thought to play a crucial role in chronic ocular and CNS diseases (Ulevitch, 2004). Other less-extensively studied inflammasomes that contribute to chronic inflammation exist as well, such as the AIM2 inflammasome, NLRP1 and NLRC4 inflammasome (Davis et al., 2011; Kesavardhana and Kanneganti, 2017).

The NLRP3 inflammasome is usually located within the cytosol of innate immune and non-immune cells in the CNS, including microglia, dendritic cells, macrophages, astrocytes, retinal pigment epithelium (RPE) cells and endothelial cells, and typically assumes an autoinhibited state prior to activation (Zangiabadi and Abdul-Sater, 2022). The activation of the NLRP3 inflammasome is generally a two-step process containing a priming and an activation phase (Mugisho and Green, 2022).

2.2. Priming

The priming signal is initiated through pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), which bind to pattern recognition receptors (PRRs) such as TLRs on cell surfaces and causes upregulation and activation of the NF-κB pathway (Mugisho and Green, 2022). NF-κB is translocated into the cell nucleus, and transcription of NLRP3 protein and inactive proinflammatory cytokines such as pro-IL-1β and pro-IL-18 are increased (Mugisho and Green, 2022). Examples of PAMPs include bacterial toxins and surface proteins, and viral RNA. DAMPs, on the other hand, may include ROS, nuclear or cytoplasmic proteins from cells and crystalline structures such as urate (Mugisho et al., 2018). Following translation, the assembly of NLRP3 inflammasome complexes is regulated by several complex post-translational modifications, including ubiquitination, phosphorylation, acetylation, SUMOylation, and nitrosylation which are comprehensively discussed in a review by McKee and Coll (McKee and Coll, 2020; Paik et al., 2021).

2.3. Activation

Following priming and upregulation of NLRP3 gene expression, an activation signal is necessary to allow the NLRP3 inflammasome to assemble and function. Such activation signals include extracellular ATP, potassium, calcium, mitochondrial dysfunction and lysosomal destabilisation (Gao et al., 2015; Swanson et al., 2019). Concentrations of these signals are primarily influenced by the micro-inflammatory environment surrounding the cell (Mugisho and Green, 2022). In the presence of an activation signal, NLRP3 oligomerizes with pro-caspase-1 and ASC to create a multimeric and functional inflammasome complex (Gao et al., 2015). Inflammasome assembly allows for the formation of a scaffold for autocatalytic cleavage of pro-caspase-1 into active cleaved caspase-1. Following this, caspase-1 can fully function and cleave pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18. These are secreted into the extracellular space and contribute to inflammation (Kelley et al., 2019). Activation of caspase-1 also contributes to the cleavage of Gasdermin D, which forms pores in the cell membrane contributing to cell death known as pyroptosis (Kelley et al., 2019). Autocrine feedback of inflammatory cytokines and pyroptotic cell death results in the release of intracellular contents into the extracellular matrix to be recognized as DAMPs by other cells, further contributes to the production and release of inflammatory cytokines. This forms a basis for the development and perpetuation of chronic inflammatory disease (Mugisho and Green, 2022; Mugisho et al., 2018).

2.4. Consequences of IL-1β and IL-18 secretion

In the acute phase of inflammation, increased secretion of IL-1β recruits immune cells to affected tissues and promotes the differentiation of immune cells into their activated and mature forms (Yazdi and Ghoreschi, 2016). However, this increases the secretion of other proinflammatory cytokines, such as IL-6 and TNF-α, which induces apoptosis and aberrant activation of immune cells in tissue (Zhang and An, 2007). In particular, excess IL-1β secretion may mediate cellular death within ocular and neural tissues (Guadagno et al., 2015; Ozen et al., 2020; Wooff et al., 2019; Yazdi and Ghoreschi, 2016). Within the CNS, microglia and glial cells also become activated under this proinflammatory environment and proliferate, resulting in further tissue damage (Buffo et al., 2008; Muzio et al., 2021). IL-18, on the other hand, causes increased development of Th1 cells and stimulates dendritic cells and macrophages in an autocrine or paracrine manner to induce increased secretion of other proinflammatory cytokines (Członkowska and Kurkowska-Jastrzębska, 2011; Muzio et al., 2021; Vecchié et al., 2021; Zhang and An, 2007). Furthermore, IL-18 has been shown to stimulate the upregulation of vascular endothelial growth factor (VEGF) in synovial and tumour tissues, which increases neovascularisation and vessel leakage (Volin and Koch, 2011). IL-18 may also directly influence macrophage polarisation and alteration, which can lead to excessive angiogenesis (Kobori et al., 2018). In agreement with this, several studies suggest that elevated concentrations of IL-1β and IL-18 are associated with ageing (Ferrucci et al., 2005; Gangemi et al., 2003; Porcher et al., 2021).

2.5. Role of connexins

Connexins are key proteins comprising gap junctions and hemichannels, which help cells communicate with adjacent cells or the extracellular space. However, under pathological conditions, recent studies have shown that connexin43 hemichannels contribute to NLRP3-mediated inflammation and perpetuate inflammatory cytokine release (Zeitz and Smyth, 2023). Under normal physiological conditions, connexin43 hemichannels are typically closed. However, connexin43 hemichannels may become abnormally opened during cellular stress and inflammation and contribute to the release of ATP into the extracellular space (Danesh-Meyer et al., 2016; Mugisho et al., 2019b). ATP is an activator of the NLRP3 inflammasome, and connexin43 hemichannel-mediated ATP release has been shown to play a vital role in the propagation of chronic inflammation through inflammasome activation (Mugisho et al., 2018). Several studies have supported and investigated this phenomenon, where increased connexin43 protein expression was correlated with increases in markers of inflammation such as activation of microglia, astrogliosis and increases in proinflammatory cytokine concentrations in models of various CNS cells (Maatouk et al., 2019; Orellana et al., 2010; Yi et al., 2016), including

RPE cells (Kuo et al., 2020; Mao et al., 2017a; O'Carroll et al., 2013).

Furthermore, other studies have suggested that increased extracellular ATP concentrations through pathologically open connexin43 hemichannels may stimulate the P2X7 receptor (Mugisho and Green, 2022; Savio et al., 2018). This can increase non-selective pore formation, allowing free passage of ions such as Ca^{2+}, Na^{+} influx and K^{+} efflux, which can also cause and perpetuate inflammasome activation (Savio et al., 2018).

3. Inflammasome activation in age-related brain diseases

The role of the NLRP3 inflammasome has been well-described in the CNS, particularly within the brain. Senescent cells, proteins, endogenous metabolic danger signals, mitochondrial impairment, and lysosomal destabilisation, accumulate in the brain parenchyma with time (Hu et al., 2019; Nixon, 2020), resulting in aberrant inflammasome activation and chronic cerebral inflammation. Mejias et al. demonstrated this, where inflammasome components such as caspase-1, ASC and IL-1β were upregulated in the hippocampus of aged mice compared to young mice (Hu et al., 2019; Mejias et al., 2018). Levels of pyroptosome formation were also increased, indicative of more significant levels of inflammatory cell death (Mejias et al., 2018). Interestingly, this trend was also consistent with that identified in humans, where individuals over 45 years of age were found to have higher serum levels of ASC and IL-18, indicating that the inflammasome may contribute to a systemic inflammatory process during ageing (Mejias et al., 2018).

Several neural cell lines have been identified to demonstrate inflammasome activation, including astrocytes, neurons, and oligodendrocytes (Adamczak et al., 2014; L'Homme et al., 2013; McKenzie et al., 2018; Zhu et al., 2018). Notably, ageing is associated with more astrocytes developing a pro-inflammatory phenotype, which may be partly mediated by NLRP3 activation (Clarke et al., 2018; She et al., 2022). However, microglia are the most widely studied cell type linked to increased cerebral inflammasome activation (Hu et al., 2019). Previous investigations by Youm et al. demonstrated that ablation of *Nlrp3* in mice resulted in reduced microglial activation, IL-1β release and levels of tissue necrosis factor (Youm et al., 2013). Conversely, microglia become more senescent with age and express higher levels of NLRP3 than young microglia (Youm et al., 2013). Taken together, this may suggest that with increasing age, inflammation is amplified, and the status of inflammaging is mediated by increases in NLRP3 activation, prominently observed in microglia (Gustin et al., 2015) (Fig. 1).

3.1. Inflammasome activation in mild cognitive impairment

The idea that neuroinflammation is linked to cognitive decline has been well supported by various studies in rodents, humans, and other species (Dik et al., 2005; Gemma et al., 2005; Holden et al., 2008; Magaki et al., 2007; van den Kommer et al., 2012; Wan et al., 2007). Specifically, increased NLRP3 activation is associated with poorer memory and cognitive performance in wild-type mice compared to *Nlrp3*$^{-/-}$ mice, and this is partly mediated by IL-1β (Youm et al., 2013). In another investigation, specific inhibition of caspase-1 by Ac-YVAD-cmk in mice also prevented age-related cognitive impairment in mice during exposure to isoflurane, suggesting that the inflammasome plays a role in cognitive decline (Wang et al., 2018). At the same time, increased inflammasome activation is associated with reduced life span and increased mortality (Furman et al., 2017).

In a case-control study of 33 humans with mild cognitive impairment, mRNA and protein levels of NLRP3, caspase-1, and IL-1β were significantly elevated relative to healthy controls (Rui et al., 2021). Furthermore, IL-1β levels in the serum of patients with mild cognitive impairment were associated with poorer cognitive test scores on the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) as well (Rui et al., 2021). Inflammasome activation has also been suggested to play a role in perpetuating cognitive impairment secondary to organic diseases of the brain, such as multiple sclerosis. Hou et al. showed that in the late stages of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, NLRP3 inflammasome components were increased in the cerebral tissue of mice alongside the development of cognitive impairment (Hou et al., 2020). Remarkably, through the activity of IL-18, the NLRP3 inflammasome was found to induce astrocyte conversion to an A1 phenotype, where several neurotoxic genes may be expressed (Hou et al., 2020). With relevance to this, other studies have also shown that normal ageing induces the conversion of astrocytes to an A1-like phenotype, and that A1 astrocytes contribute to cognitive dysfunction alongside amplifying inflammation (Clarke et al., 2018; Reid and Kuipers, 2021; Zhang et al., 2020). Indeed Hou et al. showed that the inhibition of NLRP3 by MCC950 reversed cellular pathological markers of neuroinflammation and also ameliorated cognitive impairment in these mice, suggesting that inflammasome activation plays a key role in

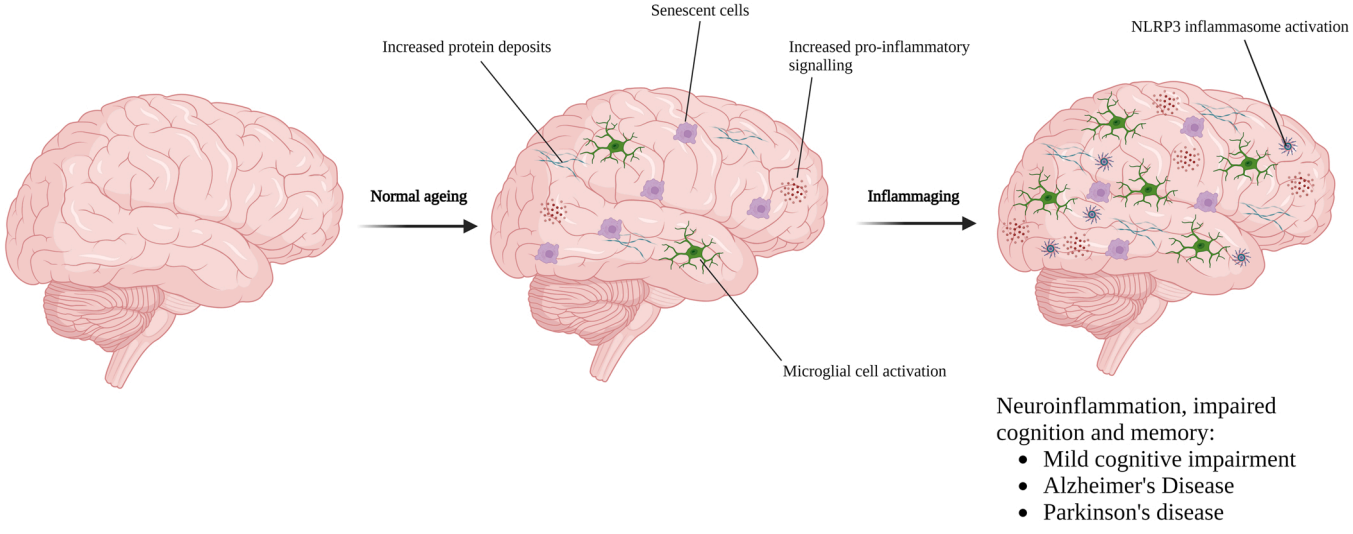

Fig. 1. Illustrative diagram showing age-related changes in brain parenchyma, which perpetuate pathological inflammation and neurocognitive disease. With increasing age, cellular senescence, microglial cell activation, and protein deposition occur. This triggers NLRP3 inflammasome activation and the process of 'inflammaging', where cognitive impairment and chronic neuroinflammation may occur. These inflammatory changes precipitate the development of mild cognitive impairment, Alzheimer's disease, and Parkinson's disease. Figure created with BioRender.com.

functional disturbances and immune dysregulation of the brain during mild cognitive impairment (Hou et al., 2020).

3.2. Inflammasome activation in Alzheimer's disease

AD is the most common neurogenerative disease associated with age (Weller and Budson, 2018). AD is characterized by the gradual decline in memory and cognitive function with age, where extracellular amyloid-β (Aβ) plaque deposition is a pathological hallmark. However, previous studies have shown that the deposition of Aβ peptide in neural parenchyma can activate the inflammasome, particularly in CNS microglia (Halle et al., 2008; Heneka et al., 2015). Specifically, Parajuli et al. showed that in LPS-primed microglia, IL-1β secretion is significantly increased by amyloid-β in an NLRP3 and caspase-1-dependent manner (Parajuli et al., 2013). This has been similarly proven in HEK293T cells and human peripheral mononuclear cells, where oligomers of amyloid-β activated the inflammasome and induced IL-1β production (Nakanishi et al., 2018).

In human brains with AD, elevated cleaved caspase-1 is found in brain lysates from the frontal cortex and the hippocampus and within peripheral blood mononuclear cells (Heneka et al., 2013; Saresella et al., 2016). This pattern is similarly observed in mouse models of AD, where APP/PS1 mice express increased levels of cortical amyloid-β deposition. Genetic deletion of genes encoding either caspase-1 or NLRP3 reduced parenchymal amyloid deposition, improved memory and diminished neuroinflammation (Han et al., 2020; Heneka et al., 2013).

Remarkably, other investigations have shown that NLRP3 inflammasome activation might exacerbate amyloid-β pathology through IL-1β, where injection of ASC specks results in the spreading of amyloid pathology and is reversed by co-application of anti-ASC antibody (Hu et al., 2019; Venegas et al., 2017). These findings have been similar in the case of tau protein, where tau-mediated inflammasome activation can exacerbate further tau deposition (Stancu et al., 2019). Other inflammasomes, such as NLRP1 and AIM2, have also demonstrated similar roles in AD, where activation plays a role in AD exacerbation while inhibition may result in disease amelioration (Choubey, 2019; Li et al., 2023). The consequences of inflammasome activation in this context may be severe, with a vicious cycle of inflammasome-mediated cytokine production, inflammation and neurofibrillary protein aggregation, which results in the clinical deficits of AD, such as reduced synaptic plasticity, learning and memory (Heneka et al., 2015; Heneka et al., 2013; Pickering and O'Connor, 2007; Salminen et al., 2008).

3.3. Inflammasome activation in Parkinson's disease

PD is a neurogenerative disorder characterized by the loss of dopaminergic neurons within the brain, associated with an intra-neuronal build-up of cytotoxic α-synuclein aggregates in the substantia nigra pars compacta (SNc) with increasing age (Przedborski, 2017). Pathological hallmarks of PD include extensive neuroinflammation, build-up of aggregated misfolded α-synuclein known as Lewy Bodies, and mitochondrial dysfunction (Moore et al., 2005; Phani et al., 2012). In particular, a neuroinflammatory process similar to inflammaging is also implicated in PD (More et al., 2013).

Studies of PD models have indicated that in early disease pathogenesis, previously quiescent microglia are pathologically activated in an uncontrolled fashion. Post-mortem studies of PD brains have identified significant activation of microglial cell expression of HLA-DR, mainly within the SNc (McGeer et al., 1988). Furthermore, other studies have shown that these activated microglia express elevated levels of inflammatory cytokines such as TNF-α, IL-6, and IL-1β (De Lella Ezcurra et al., 2010; Karpenko et al., 2018). One particular study by Imamura et al. demonstrated that serum levels of IL-1β and IL-6 are elevated in patients with PD. Analysis of brain tissue from these human patients revealed an accumulation of MHC class-II positive activated microglia in the hippocampus of PD brains and upregulation of IL-1β and IL-6 mRNA within the neocortex (Imamura et al., 2005). Other studies have replicated these findings, indicating an inflammatory aetiology involving microglia and cytokines (Boyko et al., 2017; Cebrián et al., 2014; De Lella Ezcurra et al., 2010; McGeer et al., 1988; Phani et al., 2012).

The NLRP3 inflammasome has also been found to be activated in models of PD through the effect of α-synuclein. In peripheral blood mononuclear cells, fibrillar α-synuclein induces IL-1β production in a caspase-1 and NLRP3-dependent manner (Codolo et al., 2013). Within the brain, mitochondrial dysfunction is associated with oxidative stress and is a well-established cause of neurodegeneration in PD (Abou-Sleiman et al., 2006; Di Maio et al., 2016; Martinez and Greenamyre, 2012; Moon and Paek, 2015). In fact, many genes related to developing PD in later life contribute to mitochondrial dysfunction (Billingsley et al., 2019; Gao et al., 2022). Furthermore, progressive mitochondrial dysfunction is associated with ageing (Chistiakov et al., 2014). Remarkably, mitochondrial dysfunction is associated with increased NLRP3 activation, ASC speck formation and IL-1β secretion in a dose-dependent manner (Sarkar et al., 2017). Moreover, investigations by Zhou et al. have highlighted that α-synuclein upregulates NLRP3, caspase-1 and IL-1β in an immortalized murine microglial cell line, and this is reversed by caspase-1 blockade by zYVAD (Zhou et al., 2016). Midbrain dopaminergic neurons exposed to conditioned media from these microglia demonstrate a significant reduction in neuronal numbers, indicating that inflammasome activation may perpetuate dopaminergic neuronal loss, contributing to PD pathology (Zhou et al., 2016). Furthermore, transgenic A53T$^{tg/tg}$ mice that overexpressed α-synuclein had greater levels of microglial activation within the SNc than wild-type mice, but this was ameliorated by caspase-1 knockout (Zhou et al., 2016). Alongside other evidence, it can be said that the NLRP3 inflammasome plays a significant role in PD pathophysiology by mediating neuroinflammation (Hu et al., 2019; Lee et al., 2019; Li et al., 2021; Wang et al., 2019b; Yan et al., 2020).

4. Inflammasomes in age-related eye diseases

Pathological inflammasome activation has also been implicated in various age-related eye diseases (Mugisho et al., 2019c). During ageing, several degenerative processes occur within the retina, such as free-radical-induced oxidative damage, endothelial cell activation, and increased local concentrations of inflammatory cytokines (Xu et al., 2009). Alongside these changes, neuronal density within the retina declines with age, and lipofuscin accumulates within RPE cells (Xu et al., 2009). Although the retina was classically thought to be an immune-privileged organ, along with progressive age-related BRB breakdown, inflammatory activation and microglial infiltration may occur in ocular tissues with the progressive activation of the NLRP3 inflammasome (Mugisho and Green, 2022; Xu et al., 2009). Furthermore, age-related lipofuscin accumulation and lysosomal destabilisation within retinal cells may also activate the inflammasome during ocular disease (Tseng et al., 2013). In particular, pyroptosis and IL-1β production contribute to ocular diseases, including keratitis, dry eye, cataracts, glaucoma, uveitis, AMD and diabetic retinopathy (Zhang et al., 2021b). Regarding age-related eye diseases, several studies have suggested that this chronic self-perpetuating inflammatory process mediated by the inflammasome is particularly prominent in AMD, cataracts, and glaucoma (Fig. 2).

4.1. Inflammasomes in age-related macular degeneration (AMD)

AMD is the leading cause of blindness in the population over 60 (Wong et al., 2014). Clinically, AMD is characterized by the accumulation of metabolic by-products between the basal lamina of the RPE and the Bruch's membrane, known as drusen (Abdelsalam et al., 1999). Various studies have demonstrated that the pathobiology of AMD is linked to lipofuscin accumulation within RPE cells and oxidative stress

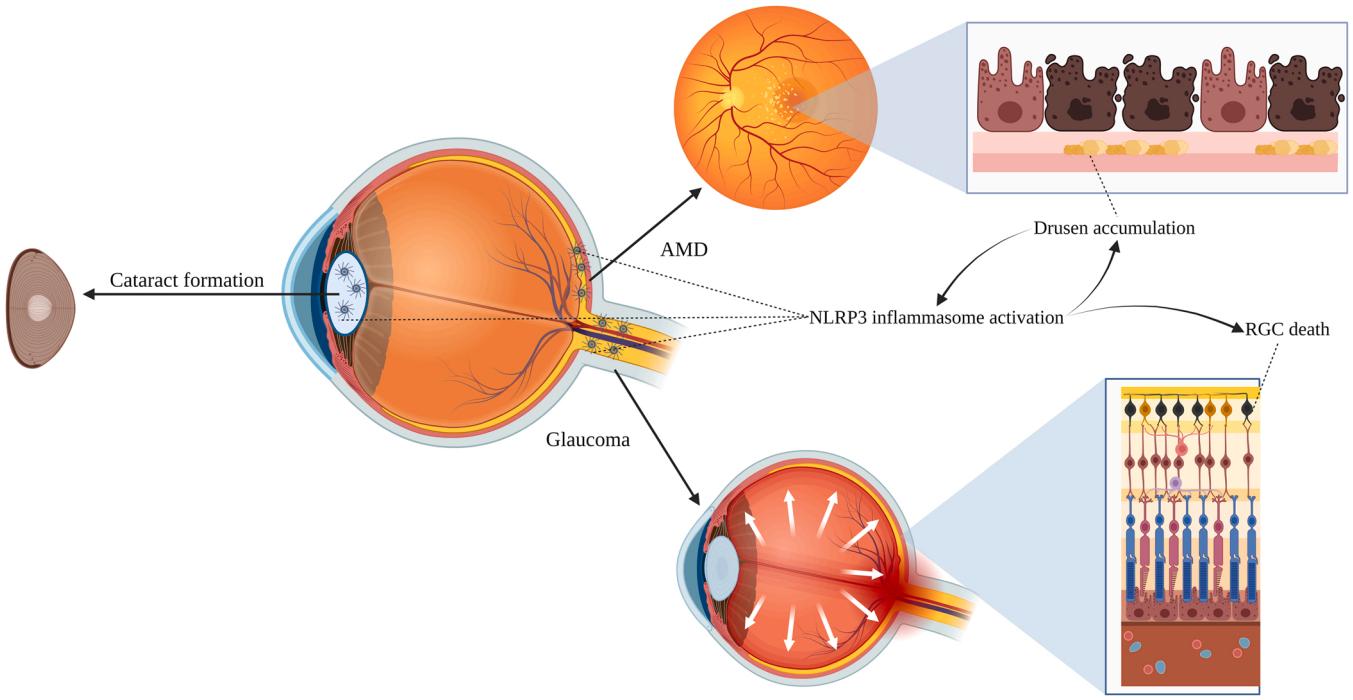

Fig. 2. Illustrative diagram showing progressive inflammasome activation with age, resulting in increased inflammation and cytokine production within the eye. These changes promote the development of various age-related eye diseases, including cataracts, AMD, and glaucoma. In AMD, NLRP3 activation may increase drusen deposition between Bruch's and the RPE basement membranes. Drusen itself may also further activate the inflammasome. In glaucoma, inflammasome activation results in retinal ganglion cell death, contributing to visual field loss. Figure created with BioRender.com.

(Katz, 2002; Petrukhin, 2013; Suter et al., 2000). However, while the risk factors for AMD are relatively well-defined, the exact pathophysiology of AMD is yet to be fully elucidated. Various reports have suggested that inflammaging is vital for AMD disease manifestation, where the NLRP3 inflammasome, proinflammatory cytokines, and immune cell infiltration play a key role (Celkova et al., 2015; Ildefonso et al., 2016; Nita et al., 2014; Whitcup et al., 2013).

With increasing age, RPE cells degenerate, resulting in drusen formation and accumulation (Bonilha, 2008). The constituents of drusen are complex but include complement proteins such as complement factor C1Q and even amyloid-β (Doyle et al., 2012; Hageman and Mullins, 1999). Regarding the role of drusen in inflammation, previous investigations by Doyle et al. have suggested that drusen isolated from AMD donor human eyes can activate the NLRP3 inflammasome, observed as increased IL-1β and IL-18 production and more prominent ASC speck formation (Doyle et al., 2012). Similar findings were identified with carboxyethylpyrrole, a biomarker of AMD, and complement factor C1Q, which are both able to activate the inflammasome and induce AMD-like pathology in mice (Doyle et al., 2012). Interestingly, Doyle et al. primarily described these findings in peripheral blood cells, which may suggest that peripheral or systemic inflammation may contribute to AMD development alongside local ocular inflammation (Doyle et al., 2012).

Within human eyes, immunohistochemical analyses have indicated that NLRP3 is upregulated with geographic atrophy, whilst in neovascular AMD, NLRP3 is upregulated in the RPE and basement membranes compared to age-matched controls (Tseng et al., 2013). During the pathobiology of AMD, lipofuscin accumulates within RPE cells and destabilizes RPE lysosomes (Schütt et al., 2002). Lysosomal destabilization, in turn, activates NLRP3 in ARPE-19 cells cultured with a lysosomotropic agent, L-leucyl-L-leucine methyl ester (Leu-Leu-OMe) (Tseng et al., 2013). Likewise, studies have demonstrated that exposure of RPE cells to oxidative stress and lipid peroxidation, which are known to be implicated in the ageing process of cells and AMD, can also activate the inflammasome in human ARPE-19 cells (Kauppinen et al., 2012).

Accumulation of amyloid-β with age is not exclusive to the brain, and it may also accumulate within the retina with age or during AMD, particularly within drusen or between the layers of the retina (Liu et al., 2013; Wang and Mao, 2021). Akin to the process in the brain, amyloid-β has been shown to activate the inflammasome in the eye. Intravitreal injection of amyloid-β has been shown to increase IL-18, IL-1β, caspase-1 and NLRP3 gene expression within the RPE, choroid and retina in vivo, alongside increased vitreous concentrations of IL-1β and IL-18 (Liu et al., 2013). These findings confirm previous research highlighting the activation of the NLRP3 inflammasome by amyloid-β in LPS-primed ARPE-19 cells (Wang et al., 2017a). Particularly, elevated levels of IL-1β results in angiogenesis by inducing the production of VEGF and RPE inflammation in AMD, resulting in disease progression (Celkova et al., 2015). Indeed, these results indicate that the inflammasome contributes to AMD pathophysiology during ageing.

4.2. *Inflammasomes in cataracts*

Cataracts refer to the age-related opacification, hardening and thickening of the human crystalline lens with age, which causes visual impairment (Liu et al., 2017). The main risk factor for cataractogenesis is age, but other factors, including corticosteroid administration, genetics, trauma, diabetes mellitus, alcohol, smoking, and radiation, have also been implicated (West and Valmadrid, 1995). The aetiology of cataract formation is multifaceted; however, ROS-mediated damage to lens epithelial cells (LECs) is known to cause lens opacification, disruption of homeostasis, and maturation of cataracts (Liu et al., 2017). ROS is known to activate the inflammasome in LECs, and inhibition of the inflammasome has been shown to reduce apoptosis of H_2O_2-induced LECs (Zou et al., 2020). Furthermore, NLRP3 knockout and inhibition of the IL-1 receptor in mice prevented cataract development (Marneros, 2016). These findings were similarly replicated in human LECs exposed to white photooxidative LED light in which NLRP3 and IL-1β production was observed (Lledó et al., 2022). Taken together, these findings suggest that the inflammasome may be implicated in cataractogenesis (Lledó

et al., 2022).

4.3. Inflammasomes in glaucoma

Glaucoma is a common neurodegenerative disease of the retina, characterized by chronic and progressive degeneration of retinal ganglion cell axons and the optic nerve head (Weinreb et al., 2014). With respect to age, primary open-angle glaucoma (POAG) is the main type of glaucoma that occurs increasingly with age (Coyle et al., 2021). Often patients with glaucoma may have elevated intraocular pressure. However, this is not always the case, as up to 40% of patients may be normotensive (Coyle et al., 2021). Unfortunately, the pathophysiology of glaucoma is poorly understood and is not curable, and currently, the only modifiable risk factor is intraocular pressure.

Recent investigations have suggested that inflammation may play a role in the pathophysiology of glaucoma (Kamat et al., 2016; Rieck, 2013). Akin to findings in neurodegenerative diseases in the brain, activated microglia at the optic nerve head and increased proinflammatory cytokine production are observed within models of glaucoma (Coyle et al., 2021; Yuan and Neufeld, 2001). Notably, increased IL-1β and IL-18 are also observed and are associated with the NLRP3 inflammasome. Indeed, chronic low-grade inflammation is a feature of glaucomatous eyes (Markiewicz et al., 2015; Zhou et al., 2005). Furthermore, oxidative stress through increased ROS production with ageing is thought to occur during glaucoma disease progression (Adornetto et al., 2019; Xu et al., 2009).

Regarding the NLRP3 inflammasome in glaucoma, mouse models of acute glaucoma with optic nerve crush show increased retinal microglia expression of NLRP3, which appears to promote ganglion cell death. The death of RGCs is ameliorated with NLRP3 knockout (Puyang et al., 2016). In studies of murine hypertensive glaucoma, NLRP3 and ASC speck formation have a temporal association with the elevation of proinflammatory markers GFAP (glial fibrillary acidic protein), IL-1β, IL-18, and TNF-α and the infiltration of $Iba1^{+}$ immune cells into the ONH (Gregory-Ksander et al., 2017). These studies similarly showed that axonal and RGC damage by elevated IOP was dependent upon the activation of inflammasome components, which suggests that the NLRP3 inflammasome is indeed implicated in the pathogenesis of glaucoma (Gregory-Ksander et al., 2017; Pronin et al., 2019). IL-1β is thought to induce fibrosis at the lamina cribrosa in glaucoma, adding to microglial cell activation and infiltration, along with RGC death which contributes to the pathological signs and symptoms of glaucoma (Coyle et al., 2021; Liu et al., 2019; Yoneda et al., 2001). At the same time, the activation of inflammasomes in glaucoma does not appear to be isolated to the NLRP3 inflammasome. Recent investigations have shown that the NLRP12, NLRP3, NLRC4 and NLRP1 may all play roles and interact with one another to induce pyroptosis, RGC death and inflammation in models of acute glaucoma (Chen et al., 2020; Chi et al., 2014).

Additionally, in glaucoma, ROS is suggested to play a role in disease pathogenesis, contributing to inflammaging and RGC apoptosis by activating the NLRP3 inflammasome (Alqawlaq et al., 2019). Glial cells at the optic nerve may also be activated during glaucoma, perpetuating inflammation through the inflammasome pathway in humans and mice (Gregory-Ksander et al., 2017). Similar to AD and PD, amyloid-β has also been found to accumulate in glaucomatous eyes during disease manifestation. Amyloid-β immunolabelling is increased in the RGC retinal layer in an ocular hypertensive murine model of glaucoma alongside a concomitant decrease in amyloid precursor protein (APP), indicating abnormal amyloid-β deposition (Guo et al., 2007; McKinnon et al., 2002). Amyloid-β has also been identified to induce apoptosis of RGCs, with intravitreal administration of amyloid-β resulting in RGC loss (Guo et al., 2007; Simons et al., 2021). In general, increased retinal deposition of amyloid-β has been thought to be linked with multiple retinal pathologies (Yoneda et al., 2005). Since amyloid-β is associated with NLRP3 inflammasome activation and contributes to chronic inflammasome through the upregulation of inflammatory cytokines, the pathophysiology of glaucoma may also be linked to the NLRP3 inflammasome (Chen et al., 2021a; Lei et al., 2017; Liu et al., 2013; Liu et al., 2014; Liu et al., 2020; Narendran et al., 2021; Wang et al., 2017a; Wang et al., 2017b).

5. Inflammasomes as the common link between age-related diseases in the eye and brain

The retina is an anatomical extension of the central nervous system, where pathology in the brain is often reflected in the retina (London et al., 2013; Marchesi et al., 2021). This link is much more profound with age-related neurogenerative diseases in the eye and brain, such as AD, PD, AMD, glaucoma, and cataracts. Functionally, various studies have shown visual dysfunction in AD where both human AD patients and mice models of AD demonstrate poorer contrast sensitivity, visual acuity, and visuospatial and visuomotor deficits (Ashok et al., 2020; Cronin-Golomb, 1995; Gilmore and Levy, 1991; Gupta et al., 2016b; Perez et al., 2009; Polo et al., 2017; Rizzo et al., 2000; Salobrar-García et al., 2019). Surprisingly, this is the same with PD. PD patients may exhibit poorer colour perception, contrast sensitivity, visual acuity and visual processing speed (Archibald et al., 2009, 2011; Büttner et al., 1993; Lin et al., 2015; Nowacka et al., 2014; Rodnitzky, 1998; Uc et al., 2005). On a biochemical level, the pathways underlying the pathogenesis of these diseases share many similarities. Common characteristics include oxidative stress, chronic neuroinflammation, and amyloid-β or α-synuclein accumulation. Moreover, as discussed for each disease above, inflammasome activation appears to play a role in the pathogenesis of these age-related cognitive diseases of the brain and the eye.

Amyloid-β accumulates in the retina and lens during AMD, glaucoma, and cataracts (Goldstein et al., 2003; Guo et al., 2007; Liu et al., 2013; McKinnon et al., 2002; Wang and Mao, 2021). The same is true with AD. Amyloid-β accumulates within the brain in parallel with ocular tissues, including the retina, lens, cornea, aqueous humour, vitreous humour and around choroidal blood vessels (Choi et al., 2019; Dong et al., 2018; Hart et al., 2016; Koronyo et al., 2017; Koronyo et al., 2012; Kwak et al., 2020; Liu and Zhu, 2017; Melov et al., 2005a; Prakasam et al., 2010; Shi et al., 2020; Wright et al., 2019). Similarly, α-synuclein has been reported to accumulate within the lens, retina and optic nerve in PD and may also occur with increasing age in individuals without neurocognitive disorders (Klettner et al., 2016; Leger et al., 2011; Muchowski et al., 2008; Ortuño-Lizarán et al., 2018; Rahimi et al., 2015; Veys et al., 2019). Furthermore, reports have suggested that α-synuclein predominantly accumulates within the ganglion cell layer (GCL), inner plexiform layer (IPL) and inner nuclear layer (INL), paralleling the death of dopaminergic amacrine cells within the inner retina (Bodis-Wollner et al., 2014; Burns et al., 2005; Indrieri et al., 2020; Leger et al., 2011; Martínez-Navarrete et al., 2007). Indeed, the pathological findings that occur in age-related diseases of the brain are often reflected in the retina, which further suggests a strong interconnection between cortical and retinal tissues.

Amyloid-β and α-synuclein activate the NLRP3 and other inflammasomes in multiple tissues and contribute to the pathophysiology of age-related disease pathogenesis in both ocular and cerebral tissues (Ising et al., 2019; Tan et al., 2014). This may suggest a common pathway in neurodegenerative diseases of the eye and brain (Chen et al., 2021a; Gordon et al., 2018; Lei et al., 2017; Li et al., 2021; Liu et al., 2013; Liu et al., 2014; Liu et al., 2020; Narendran et al., 2021; Pike et al., 2021; Scheiblich et al., 2021; Wang et al., 2017a; Wang et al., 2017b). In particular, amyloid-β accumulation appears to accumulate in AD, glaucoma, AMD and cataracts, further emphasising a robust link between the molecular pathways underpinning age-related diseases of the brain and the eye (Gupta et al., 2016a).

Although the NLRP1, AIM2, and NLRC4 inflammasome may also be linked to the pathogenesis of neurodegenerative diseases of the eye and brain, the most common denominator appears to be the NLRP3 inflammasome (Freeman and Ting, 2016; Yerramothu et al., 2018).

Taken together, this may suggest that disease pathways between age-related diseases in the eye and brain may indeed stem from similar underlying pathways, where the inflammasome plays a vital role in pathogenesis.

Alongside these findings, cerebral neurodegenerative diseases and age-related eye diseases share several similar characteristics, and their epidemiology is intimately linked. Clinical studies have shown that individuals with AD and PD are at an increased risk of developing ocular diseases such as AMD, glaucoma, cataracts, and vice-versa (Bayer et al., 2002a; Bayer et al., 2002b; Chen et al., 2021b; Choi et al., 2020; Chung et al., 2014; Goldstein et al., 2003; Lai et al., 2015; Rong et al., 2019). Furthermore, several pathological signs of age-related eye diseases, such as retinal thinning, neuronal loss, astrogliosis, and protein deposition in the retina appear to be much more prevalent in patients with AD and PD (Gupta et al., 2016b; Liu et al., 2009; Ning et al., 2008; Ohno-Matsui, 2011; Perez et al., 2009). In fact, a recent meta-analysis by Rong et al. which included 21 studies and over 7 million patients, found that individuals with dementia were 1.24 times more likely to develop AMD compared to controls, while those with AD were 2.22 times more likely to develop AMD (Rong et al., 2019). Choi et al. showed that in a population of 308,340 participants from South Korea above 50 years of age, participants with AMD were significantly more likely to develop PD despite adjusting for various confounding factors, including lifestyle behaviours such as smoking, exercise and alcohol (Choi et al., 2020). Similar findings have been found with glaucoma and cataracts, all of which are summarised in Table 1. Overall, this suggests a strong interconnection between age-related eye diseases of the brain and the eye, which is likely mediated through the NLRP3 inflammasome.

6. Evidence for pharmacological inflammasome blockers in ameliorating age-related brain and eye diseases

Given that inflammasomes are implicated in the pathogenesis of age-related diseases of the eye and brain, inflammasome blockers have been developed to mitigate the progression of these diseases. Several pharmacological inflammasome blockers targeting both upstream and downstream pathways have been studied, which are summarised in Table 2 and Table 3.

However, one upstream molecular pathway of current interest involves connexin43 hemichannels. Connexin43 hemichannels contribute to NLRP3 inflammasome activation by releasing ATP into the extracellular space, which can serve as the second activation signal for the inflammasome (Mugisho et al., 2018). Within the brain, various reports have shown that connexin43 hemichannels are upregulated and activated within hippocampal astrocytes of AD (APP/PS1) mice that were in contact with amyloid-β plaques (Mei et al., 2010; Yi et al., 2016). Congruently, post-mortem analyses of humans clinically diagnosed with AD have been found to have increased expression of connexin43 in astrocytes within the brain parenchyma as well (Nagy et al., 1996). Furthermore, amyloid-β may cause the upregulation of connexin43 hemichannels and the excessive release of neurotoxic ATP, glutamate and activation of the P2X7 receptor, causing inflammation and neuronal death (Koulakoff et al., 2012). As noted above, the release of ATP contributes to NLRP3 activation, contributing to chronic inflammation and disease pathogenesis (Mugisho et al., 2018). With connexin43 knockout in AD mice, ATP and glutamate release are reduced, alleviating neuronal damage, oxidative stress and plaque formation in the hippocampus (Yi et al., 2016). Likewise, in PD, connexin43 is enhanced in the basal ganglia regions of a rat PD model, correlating with the location of dopaminergic neurons involved in PD pathology (Kawasaki et al., 2009). In another mouse model of PD, increased connexin43 expression is associated with an elevated inflammatory response and dopaminergic cell death and is reversed by connexin43 blockade with the connexin mimetic peptide Gap 27 (Zhao et al., 2022).

In AMD, Guo et al. showed that connexin43 channels were upregulated in a light-damaged mouse model of AMD, and this correlated with increased oxidative stress, inflammation, and vascular breakdown (Guo et al., 2014). These findings were similarly identified in human AMD patients compared to controls (Danesh-Meyer et al., 2016). Glaucomatous eyes have also been shown to have elevated levels of connexin43 expression. Kerr et al. showed that in human eyes with primary open-angle glaucoma, connexin43 is upregulated at the level of the lamina cribrosa and the peripapillary retina alongside glial activation (Kerr et al., 2011). In models of glaucoma and optic nerve injury, connexin43 is also upregulated in the retina and the optic nerve head (Batsuuri et al., 2021; Kerr et al., 2011). In fact, one particular murine model of experimental glaucoma showed that knockout of connexin43 resulted in increased RGC viability and reduced astrocytic reactivity in

Table 1
Clinical links between age-related diseases of the brain and eye.

Linked diseases	Findings	References
AD → AMD	AD is associated with concurrent amyloid-β deposition within multiple retinal layers, retinal thinning, RGC death, microglial infiltration and astrogliosis.	(Gupta et al., 2016b; Liu et al., 2009; Ning et al., 2008; Ohno-Matsui, 2011; Perez et al., 2009)
AMD → cognitive impairment	Severity of AMD correlates with cognitive function.	(Wong et al., 2002)
Dementia and AD ↔ AMD	Patients with dementia were 1.24 times while AD patients were 2.22 times more likely to develop AMD. AMD patients were 2.42 times more likely to develop AD or cognitive impairment.	(Rong et al., 2019)
AMD → AD	Individuals who develop AMD at a younger age are 1.97 times more likely to develop AD than matched controls.	(Wen et al., 2021)
AMD → PD	Patients with AMD are more likely to develop PD, even after adjusting for confounders.	(Chen et al., 2021b; Choi et al., 2020; Chung et al., 2014)
AD → glaucoma	Decreased cognitive function in AD is associated with RNFL thinning, GCL loss and decreased macular thickness.	(Asanad et al., 2019; Iseri et al., 2006; Parisi et al., 2001)
AD → glaucoma	Decreased macular volume in AD patients.	(Blanks et al., 1996b; Iseri et al., 2006)
AD → glaucoma	Increased pan-retinal neuronal loss, astrocytosis, Müller cell gliosis and signs of retinal inflammation in AD subjects.	(Blanks et al., 1996a)
AD and PD → glaucoma	Glaucoma rates are four times higher in patients with AD and PD compared to matched controls.	(Bayer et al., 2002a; Bayer et al., 2002b)
Glaucoma → PD	Glaucoma patients have a higher risk of developing PD.	(Lai et al., 2017)
PD → glaucoma	GCL and inner retinal thinning in patients with PD.	(Sari et al., 2015; Satue et al., 2017; Živković et al., 2017)
AD → cataracts	Amyloid-β may be deposited within the lens at concentrations comparable to the brain in patients with AD and is associated with supranuclear cataract formation.	(Goldstein et al., 2003)
AD → cataracts	AD transgenic mice are more likely to develop cataracts than controls.	(Melov et al., 2005b)
PD → cataracts	Humans and mice with PD have higher concentrations of α-synuclein expression within the lens.	(Klettner et al., 2016; Muchowski et al., 2008)
PD → cataracts	Patients with PD are more likely to develop cataracts, even after adjusting for confounders.	(Lai et al., 2015)

Table 2
NLRP3 inflammasome inhibitors in cerebral neurodegenerative diseases.

Inhibitor	Mechanism of action	Cerebral disease	Findings in the disease model	Reference
OLT1177	Selective NLRP3 inhibition	AD	Improved cognitive function and synaptic plasticity. Reduced plaque formation, cytokine production, microglial activation and inflammation.	(Lonnemann et al., 2020)
β-hydroxybutyrate	Prevention of potassium efflux	AD	Reduced plaque formation, microgliosis, ASC speck formation and caspase-1 activation.	(Shippy et al., 2020)
Anakinra	IL-1 receptor antagonist	AD	Improved cognitive function, reduced plaque deposition, reduced IL-1β secretion and NFkB activation.	(Kitazawa et al., 2011; Qi et al., 2018)
Ac-YVAD-CMK	Caspase-1 inhibition	AD	Improved spatial learning, memory ability and reduced senile plaque deposition.	(Gu et al., 2021)
MCC950	Selective NLRP3 inhibition	AD	Improved long-term potentiation and synaptic plasticity.	(Qi et al., 2018)
		PD	Improved motor performance, reduced inflammation, neuronal death, α-synuclein accumulation, inflammasome activation and IL-1β levels.	(Gordon et al., 2018; Huang et al., 2021)
Celastrol	Regulation of Nrf2-NLRP3-caspase-1 axis	PD	Better motor performance and neuroprotection while reducing dopaminergic neuronal loss and neuroinflammation.	(Zhang et al., 2021a)
Dopamine	Drd2 agonism, inhibiting NLRP3 inflammasome oligomerisation through β-arrestin2.	PD	Reduced NLRP3 inflammasome activation and IL-1β release in the astrocytes and midbrain of mice.	(Pike et al., 2022; Zhu et al., 2018)
UNC9995	Drd2 agonism, inhibiting NLRP3 inflammasome oligomerisation through β-arrestin2.	PD	Prevented dopaminergic cell loss and glial cell activation. Reduced NLRP3 inflammasome activation, IL-1β production and inflammation.	(Zhu et al., 2020)
Gap26	Direct inhibition of connexin hemichannels, preventing ATP release and inflammasome activation.	AD	Reduced gliotransmitter release.	(Yi et al., 2017)
		PD	Attenuated dopaminergic neuronal death and prevented microglial activation.	(Maatouk et al., 2019)
Gap27	Direct inhibition of connexin hemichannels, preventing ATP release and inflammasome activation.	PD	Attenuated dopaminergic neuronal death, reduced microgliosis and astrogliosis, along with reduced production of inflammatory cytokines, including IL-1β.	(Zhao et al., 2022)
Gap19	Direct inhibition of connexin hemichannels, preventing ATP release and inflammasome activation.	PD	Attenuated dopaminergic neuronal death and prevented microglial activation	(Maatouk et al., 2019)
Gastrodin	Downregulation of connexin43 expression	PD	Reduced connexin43 expression in models of Parkinson's disease.	(Wang et al., 2013)

the optic nerve head (Batsuuri et al., 2021).

Connexin43 hemichannel modulators are, therefore, of great therapeutic potential, particularly in chronic inflammatory diseases. One of these drugs, Tonabersat, was thought to inhibit connexin26 gap junctions and was well-tolerated when used to treat migraines with aura caused by cortical spreading depression (Hauge et al., 2009). Tonabersat, however, has now been shown to inhibit connexin43 hemichannel opening, preventing the release of ATP (Kim et al., 2017). Specifically, Tonabersat inhibits inflammasome formation and the release of inflammatory cytokines in an in vitro ARPE-19 cell model of diabetic retinopathy (Lyon et al., 2020). Tonabersat also ameliorated inflammatory damage in a light-damage animal model of AMD and a spontaneous rat model of diabetic retinopathy (Kim et al., 2017; Mat Nor et al., 2020).

Another connexin43 hemichannel inhibitor is Peptide5, a connexin43 mimetic peptide. Peptide5 has been shown to limit damage in multiple in vivo models of disease, including retinal ischaemia/reperfusion, the light-damaged AMD model, chronic pain and spinal cord injury (Danesh-Meyer et al., 2012; Guo et al., 2016; O'Carroll et al., 2008; O'Carroll et al., 2013; Tonkin et al., 2018). Furthermore, Mugisho et al. showed that Peptide5 effectively reduced inflammation, and IL-1β secretion, reduced microglial infiltration, inhibited the inflammasome, and reduced disease severity in an in vivo model of diabetic retinopathy (Mugisho et al., 2019a). Furthermore, Peptide5 was effective in reducing vascular breakdown and retinal ganglion cell death following retinal ischaemia, which are processes that are thought to occur in late glaucoma (Danesh-Meyer et al., 2012). Other connexin43 hemichannel inhibitors include Gap19, Gap26 and Gap27. Gap19 was able to prevent apoptosis and necrosis in human lens epithelial cells, which are processes that are known to occur during cataractogenesis (Figueroa et al., 2020). Gap27, on the other hand, was effective in improving wound healing, reducing inflammation and preventing neovascularisation of the cornea during epithelial injury (Elbadawy et al., 2016). Within the CNS, Gap19, Gap26 and Gap27 could prevent inflammation and cell death in models of AD and PD, suggesting that these connexin43 hemichannel inhibitors have therapeutic potential in neurological diseases as well (Abudara et al., 2014; Maatouk et al., 2019; Zhao et al., 2022). Furthermore, both Gap19 and Tonabersat have been very effective in slowing disease progression, conferring neuroprotection, and reducing both astrocytosis and microgliosis in models of amyotrophic lateral sclerosis (Almad et al., 2022).

Taken together, pharmacotherapeutics targeting connexin43 are of great interest in treating age-related neuroinflammatory diseases of both the eye and brain. These findings indicate that the connexin43 hemichannel may be a key drug target to regulate the NLRP3 inflammasome and modulate inflammaging.

7. Conclusion

Age-related diseases of the eye and brain share various similarities in pathophysiology, including ROS production, chronic inflammation, and neurotoxic protein aggregation. The NLRP3 inflammasome is a common denominator in these age-related diseases. In particular, the inflammasome plays a vital role in mild cognitive impairment, AD, PD, AMD, glaucoma, and cataracts. The current literature presents promising evidence that targeting the inflammasome in these diseases may be able to limit tissue damage, neuronal degeneration and slow disease progression. Of particular interest, connexin43 channel inhibitors may be a critical upstream therapeutic drug target for age-related diseases in the eye and brain.

Funding

OOM was supported by a Neurological Foundation First Fellowship (grant number: 2001 FFE) and an Auckland Medical Research Foundation Project Grant (Grant number: 1121013). AK was supported by the Freemasons of New Zealand (501029) and Frederich Kurtstein Anthonsen Glaucoma Research Trust New Zealand (3725325) project

Table 3
NLRP3 inflammasome inhibitors in age-related eye diseases.

Inhibitor	Mechanism of action	Cerebral disease	Findings in the disease model	Reference
MCC950	Direct NLRP3 inhibition	AMD	Reduced NLRP3 inflammasome activation, inflammatory cytokine release and cellular death.	(Sui et al., 2020; Wang et al., 2019a)
		Glaucoma	Prevention of RGC death and axon degeneration.	(Krishnan et al., 2019)
IFM-632	Direct NLRP3 inhibition	AMD	Reduced NLRP3 inflammasome activation, inflammatory cytokine release and cellular death.	(Wang et al., 2019a)
IFM-514	Direct NLRP3 inhibition	AMD	Reduced NLRP3 inflammasome activation, inflammatory cytokine release and cellular death.	(Wang et al., 2019a)
Pegcetacoplan (complement C3 inhibitor)	Prevention of membrane attack complex (MAC) formation, preventing calcium influx (Triantafilou et al., 2013)	Geographic atrophy secondary to AMD	Reduction in the rate and progression of geographic atrophy.	(Goldberg et al., 2022; Liao et al., 2020)
Avacincaptad pegol (complement C5 inhibitor)	Prevention of MAC formation, preventing calcium influx (Triantafilou et al., 2013)	Geographic atrophy secondary to AMD	Reduction in the rate and progression of geographic atrophy.	(Halawa et al., 2021; Jaffe et al., 2021)
A438079	Direct P2X7R inhibitor	Glaucoma	Reduced RGC death and inflammatory cytokine release.	(Zhang et al., 2019)
Sulforaphane	Reduces ROS, regulates the NFkB and the Nrf2 pathway	Glaucoma	Prevented RGC death and retinal thinning.	(Gong et al., 2019)
Kaempferol	Regulates NFkB pathway	Glaucoma	Prevented RGC death and retinal thinning.	(Lin et al., 2019)
Vinpocetine	Inhibits NFkB pathway	AMD	Reduced NLRP3 activation and inflammatory cytokine production in RPE cells.	(Liu et al., 2014)
Puerarin	Reduces ROS and regulates the Nrf2 pathway	AMD	Reduced NLRP3 activation and inflammatory cytokine production in RPE cells.	(Wang et al., 2017b)
Melatonin	Reduction of ROS production	Cataracts	Prevented lens epithelial cell death, ROS production and inflammasome activation.	(Lledó et al., 2022)
Peptide5	Connexin43 mimetic peptide, inhibiting hemichannel function.	AMD	Prevented photoreceptor death, retinal thinning and inflammation.	(Guo et al., 2016; Mat Nor et al., 2018)
Tonabersat	Selectively blocks connexin hemichannels	AMD	Reduced retinal inflammation, preserved retinal photoreceptor function and attenuated retinal microgliosis.	(Mat Nor et al., 2020)
		DR	Reduced inflammation, microvascular aneurysms and retinal function.	(Mat Nor et al., 2020)
Gap19	Direct inhibition of connexin hemichannels, preventing ATP release and inflammasome activation.	Cataract	Reduced calcium influx, prevented apoptosis and necrosis in human lens epithelial cells.	(Figueroa et al., 2020)

grants. CRG holds the W&B Hadden Chair in Ophthalmology

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Odunayo O Mugisho reports financial support was provided by Neurological Foundation of New Zealand. Odunayo O Mugisho reports financial support was provided by Auckland Medical Research Foundation. Odunayo O Mugisho has patent licensed to InflammX Therapeutics. Colin R Green has patent licensed to InflammX Therapeutics. CRG is a founding scientist of InflammX Therapeutics Inc. USA.

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