Review article

From inflammatory signaling to neuronal damage: Exploring NLR inflammasomes in ageing neurological disorders

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ABSTRACT

The persistence of neuronal degeneration and damage is a major obstacle in ageing medicine. Nucleotide-binding oligomerization domain (NOD)-like receptors detect environmental stressors and trigger the maturation and secretion of pro-inflammatory cytokines that can cause neuronal damage and accelerate cell death. NLR (NOD-like receptors) inflammasomes are protein complexes that contain NOD-like receptors. Studying the role of NLR inflammasomes in ageing-related neurological disorders can provide valuable insights into the mechanisms of neurodegeneration. This includes investigating their activation of inflammasomes, transcription, and capacity to promote or inhibit inflammatory signaling, as well as exploring strategies to regulate NLR inflammasomes levels. This review summarizes the use of NLR inflammasomes in guiding neuronal degeneration and injury during the ageing process, covering several neurological disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, and peripheral neuropathies. To improve the quality of life and slow the progression of neurological damage, NLR-based treatment strategies, including inhibitor-related therapies and physical therapy, are presented. Additionally, important connections between age-related neurological disorders and NLR inflammasomes are highlighted to guide future research and facilitate the development of new treatment options.

1. Introduction

The natural process of aging is an inescapable aspect of human existence. With the current advancements in medical technology, the prevalence of age-related illnesses has risen in tandem with the gradual increase in average life expectancy. Consequently, the mitigation and amelioration of age-related diseases, as well as the enhancement of quality of life, have become prominent areas of research. The ageing process is often accompanied by neuronal degenerative disorders and injuries, including Parkinson's disease,
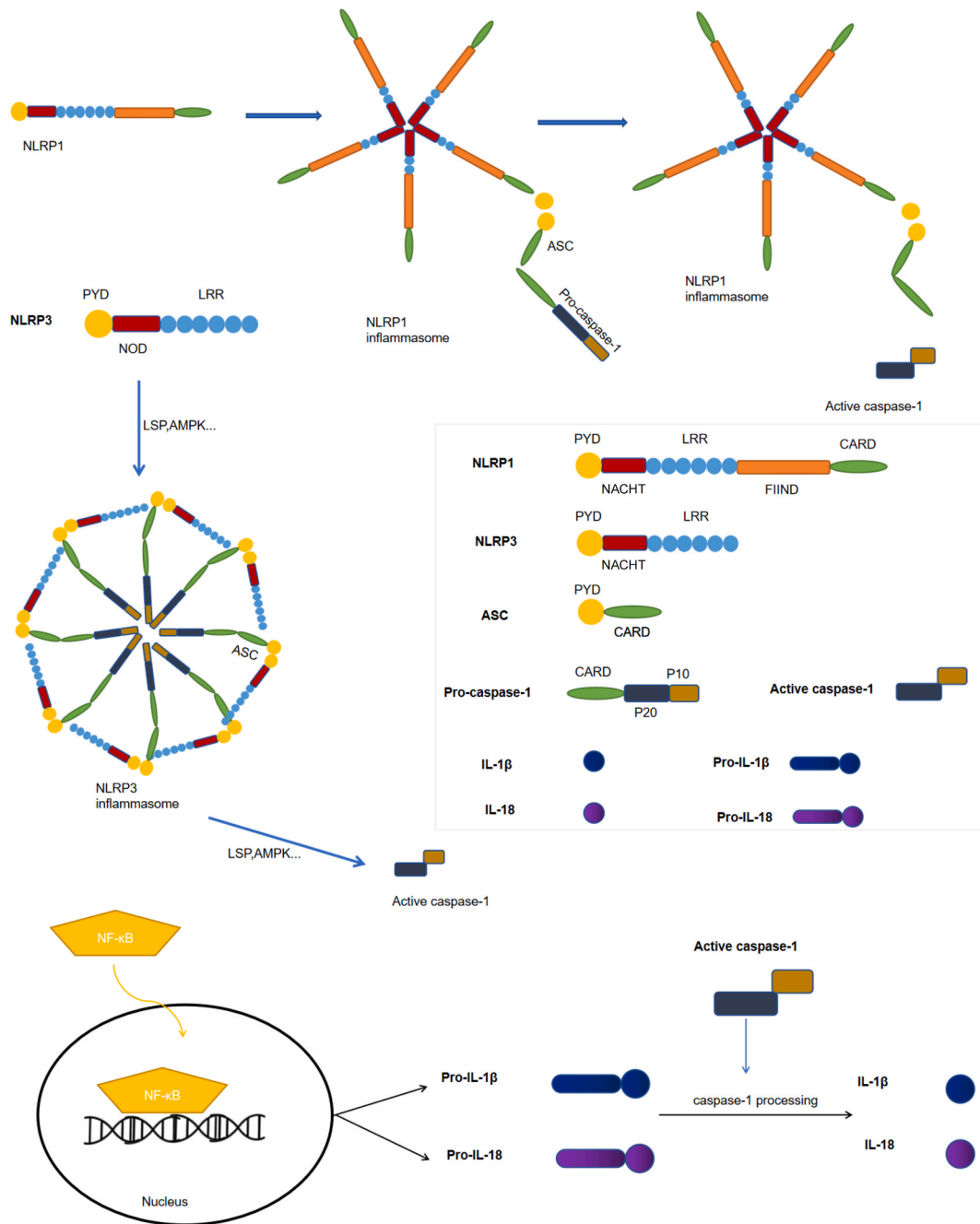
Fig. 1. A model of cell signaling and its activation using NLRP1 and NLRP3 as examples.

The ASC, PYD and CARD, are recruited by NLRP3 upon activation by a risk-associated molecular pattern to form helical fibers. Pro-caspase-1 is then recruited and activated to generate mature caspase-1. Pro-IL-1β and pro-IL-18 are then converted by caspase-1 to mature forms of IL-1β and IL-18; NLRP1 has an N-terminal PYD, a structural domain and LRR. Unlike other NLRPs, NLRP1 has a C-terminal extension containing a FIIND and a CARD. Thus, the steps in NLRP1 inflammasome activation of IL-1β and IL-18 are roughly as follows: the PYD or CARD that activates the PRR is bridged to the CARD of pro-caspase-1. Next, pro-CASP1 undergoes near-sensing autoprotein hydrolysis to produce an active enzyme (CASP1) that cleaves and activates inflammatory cytokines (i.e., IL-1β and IL-18). ASC, apoptosis-associated speckle-like protein; PYD, pyrin domain; NACHT, nucleotide-binding oligomerization domain; NF-κB, nuclear factor kappa B; CARD, caspase activation and recruitment domain; LRR, leucine-rich repeat; FIIND, function-to-investigation domain; CASP1, caspase-1; IL, interleukin; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing; NLRC, nucleotide-binding oligomerization domain, leucine-rich repeat and caspase recruitment domain-containing.

Alzheimer's disease, amyotrophic lateral sclerosis, stroke, and peripheral neuropathy, which tend to progress over time. Neurodegenerative diseases associated with ageing are typified by the gradual and irreversible decline of neuronal cells or their functions, resulting in compromised motor skills, cognitive abilities, and memory. The activation of inflammasomes represents a significant contributor to the onset of neuroinflammation, neurodegeneration, and ultimately, neurodegenerative pathologies.

The inflammasome plays a significant role in the ageing process, where it assembles and becomes activated, contributing to accelerated biological ageing and the development of various age-related neurodegenerative diseases. The inflammasome associated with neurodegenerative diseases consists of the NLR protein complex, which includes an NLR inflammatory monomer, an effector protein (pro-caspase-1), and an adapter protein (apoptosis associated speck like protein, ASC). The adapter protein ASC comprises an N-terminal pyrin domain (PYD) and a caspase recruitment domain (CARD). Notably, NLR inflammatory monomers are structured with an amino-terminal (N-terminal) domain, an intermediate nucleotide-binding oligomerization domain (NACHT), and NOD-like receptors [1].

The innate immune system serves as the first line of defense against pathogens and tissue injuries. Key players in innate immune responses are innate immune cells like macrophages, monocytes, and neutrophils, which express pattern recognition receptors (PRRs). The engagement of PRRs triggers various inflammatory signaling pathways to combat infections and facilitate tissue repair. NOD-like receptors represent a class of intracellular PRRs that recognize pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs). They play a significant role in the assembly and activation of NLR inflammasomes [2]. Recognition of PAMPs or DAMPs by NOD-like receptors initiates the assembly and activation of cytoplasmic protein complexes, known as NLR inflammasomes. This, in turn, activates pro-caspase-1. The activated pro-caspase-1 serves two main roles. First, it leads to the maturation and release of the proinflammatory cytokines interleukin (IL)-1β and IL-18 [3]. For example, activation of the NLRP3, which full name is NOD, leucine-rich repeat and pyrin domain-containing 3,is inflammasome usually requires an initiation signal and an activation signal. The initiation signal activates nuclear factor Kappa B (NF-κB) to induce transcriptional expression of NLRP3 and pro-IL in response to NLR ligands and cytokines. Typical inducers include microbial components such as TLR ligands such as lipopolysaccharide (LPS), and cytokines such as tumor necrosis factor (TNF)-α and IL-1β.
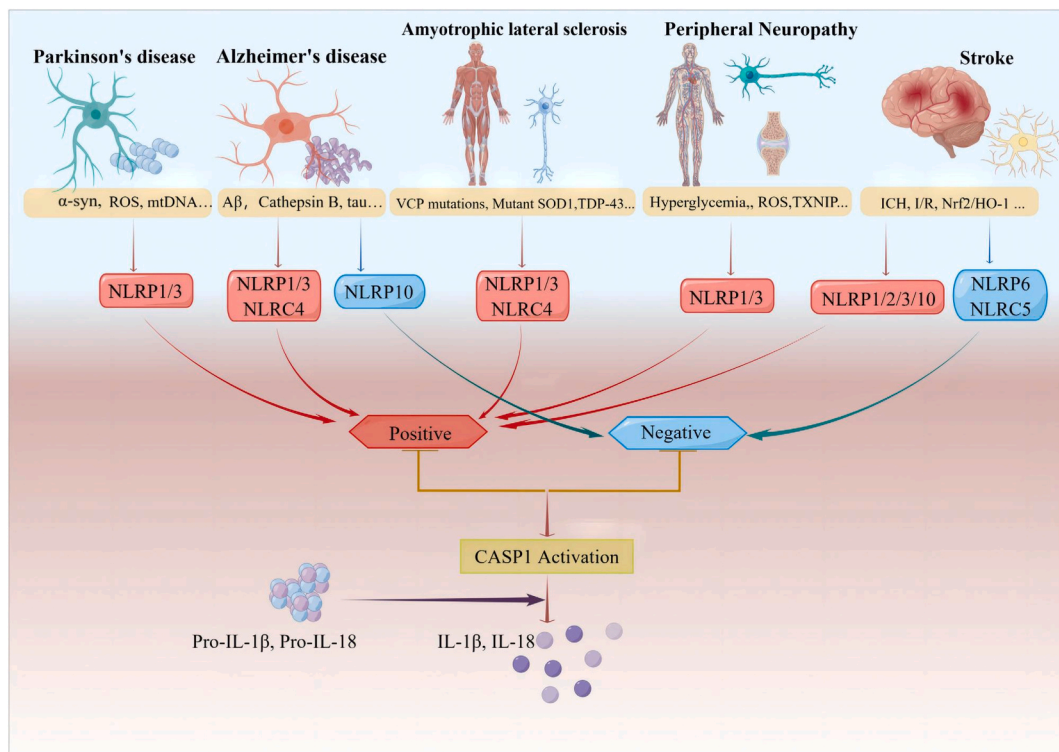
Fig. 2. The pattern of NLR inflammasomes involvement in the activation of pro-inflammatory cytokines.
NLR inflammasomes are linked with several diseases related to neurodegeneration and nerve damage such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, and peripheral neuropathy. Certain NLR inflammasomes including NLRP1/2/3/10 and NLRC4 can trigger the conversion of pro-IL-1β or pro-IL-18 to mature forms of pro-inflammatory cytokine IL-1β or IL-18. In contrast, NLRP10, NLRP6 and NLRC5 exhibit inhibitory effects on the above processes. Aβ, Amyloid β; α-syn, α-synuclein; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; SOD1, superoxide dismutase 1; TDP-43, transactive response DNA-binding protein-43; VCP, valosin-containing protein; TXNIP, thioredoxin-interacting protein; ICH: intracerebral hemorrhage; I/R, ischemia-reperfusion; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; CASP1, caspase-1; IL, interleukin; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing; NLRC, nucleotide-binding oligomerization domain, leucine-rich repeat and caspase recruitment domain-containing.

It should be noted that except for NLRP3, other NLR inflammasomes do not require an initiation signal to induce inflammasome activation and cytokine release; an activation signal is sufficient. The activation signal is triggered by PAMP and DAMP, and upon activation of NLRP3. NLRP3 recruits ASC and forms helical fibers, which subsequently recruit and activate pro-caspase-1, forming an activated inflammatory complex that produces mature caspase-1. Caspase-1 then cleaves Pro-IL-1β or pro-IL-18 to convert into the mature of IL-1β or IL-18 and secreted. In addition, another role of activating pro-caspase-1 is to generate caspase-1 to cleave gasdermin D (GSDMD) and release its N-terminal fragment. This fragment translocates to the cell membrane and induces pore formation eventually leading to cell swelling and death, called cell pyroptosis. Thus, activation of the NLR inflammasome can lead to maturation and release of the pro-inflammatory cytokines IL-18 and IL-1β as well as induction of cellular pyroptosis [4] (Fig. 1).

The inflammasome activation is highly visible in cells of the nervous system in response to the accumulation of large amounts of ageing-related DAMP (e.g., extracellular ATP, urate, misfolded amyloid β (Aβ), mitochondrial damage, oxidative stress, α-synuclein (α-syn) and ceramide) [4]. In the central nervous system (CNS), NLR inflammasome activation is mainly observed in microglia and is also shown in other cells such as astrocytes, neurons and endothelial cells; while in the peripheral nervous system, it is Schwann cells that are closely associated with inflammasome activation [5,6]. Current studies on neurological NLR inflammasomes are mainly focused in the CNS, especially on microglia. During ageing, microglia become overactive, as evidenced by increased numbers of microglia and production of cytokines and cell surface receptors. The active microglia exert pro-inflammatory cytokines produced by inflammasome activation to recruit phagocytes, such as macrophages, to the site of damage to phagocytize the accumulated DAMP. However, as some of the DAMP is difficult to degrade resulting in lysosomal instability, which leads to the release of various enzymes into the cell membrane, as well as the reduced ability of macrophages to phagocytose necrotic cells during ageing, it is difficult to remove DAMP, ultimately leading to the continuous activation of NLR inflammasomes in the nervous system, allowing neuropathy to progress continuously [7]. Therefore, studying the activation mechanisms of inflammasomes in nervous system cells is particularly important to slow down the acceleration of the neuropathy during ageing (Fig. 2).

Inflammasome activation and pro-inflammatory factor release contribute to the chronic low-level inflammation of the biological ageing process, which also leads to the development of many chronic and neurodegenerative diseases. Therefore, ageing is considered a major risk factor for neurodegenerative diseases. Overall, inflammasome signaling is critical for neuroinflammation and neurodegeneration during ageing. Silencing and knockdown of inflammasome signaling components have been shown to attenuate the adverse effects of some neurodegenerative diseases, while activation of inflammasomes directly or indirectly exacerbates the symptoms of some neurodegenerative diseases through positive feedback inflammatory cascades. This article reviews the mechanisms of ageing-related neurodegenerative lesions and the potential mechanisms of NLR inflammasomes in them to provide strategies for future amelioration of such diseases.

2. The role of NLR inflammasomes in ageing-related diseases

2.1. Parkinson's disease

2.1.1. Parkinson's disease and senescence

PD is a slow-progressing neurodegenerative disorder, to which ageing is the greatest risk factor for PD. The prevalence of PD is very high among the elderly, affecting approximately 1 % of the population over the age of 60. The pathological features include deposition of α-synuclein (α-syn) or Lewy vesicles, leading to progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN) of the basal ganglia and striatal axon terminals [8].

PD is associated with the degeneration of dopamine cells in ageing. Dopaminergic neurons (DAn) in the SN of the human brain are susceptible to damage, and their number decreases with ageing. Initial studies indicated SN neurodegeneration and a decrease in SN neurons (SNn) in PD patients because SN areas in the PD brain lost their characteristic dark gray color [9], a characteristic color produced by the accumulation of melanin in a subpopulation of SNn, suggesting that selective degeneration of SNn may be a feature of PD. Further studies showed that melanin accumulation in the SNn is a result of DA oxidation, and the reduction of DA in the SN striatum of PD patients and the presence of DAn loss in the SN of healthy elderly participants suggest that degeneration of DAn in the SN during ageing is the basis of PD [10,11]. The loss of DAn in the SN leads to a significant decrease in striatal synaptic terminal dopamine levels, which ultimately results in the loss of the SN striatal pathway [12]. A number of motor symptoms, such as bradykinesia, rigidity, postural abnormalities, and uncontrollable tremor at rest, are brought on by a decrease in striatal dopamine. These symptoms are all typical motor impairments in PD [13].

Notably, oxidative stress and mitochondrial malfunction may particularly affect the DAn with age. The SN striatum DAn has a very high density of synaptic terminals (up to 1 million per cell in humans) and an unmyelinated axon, which require local mitochondria to support their activity and consume a lot of energy. As a result, the DAn mitochondria must produce a lot of reactive oxygen species (ROS), but it remains difficult to prevent the toxic effects of ROS effects. Additionally, there is proof that DAn degeneration in PD is directly linked to age-related oxidative stress. Enzymatic and non-enzymatic oxidation of dopamine generates ROS, which can induce apoptosis of dopamine neurons. For example, DAn can be disrupted by enzymatic oxidation of endogenous 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-like toxin 1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahy-droisoquinoline or non-enzymatic oxida-tion-generated ROS, initiating cell death program [14]. In contrast, mitochondrial dysfunction in ageing damages DAn due to the proximity of mitochondrial DNA (mtDNA) to the electron transport chain (the main source of ROS), which produces ROS that induce mutations in mtDNA [15], leading to mitochondrial dysfunction and reduced energy production, thereby failing to repair the damaged mitochondria in a vicious cycle. Also, with ageing, mutant mtDNA accumulates in DAn and affects its function [16]. Therefore, both oxidative stress and mitochondrial damage during ageing can lead to the degeneration of DAn and promote the development of PD

disease.

The accumulation of α-syn is one of the factors that impair DAn and is a significant pathological alteration in PD. α-synuclein is a naturally occurring, small intracellular protein primarily found at presynaptic sites in various neurotransmitter systems. In addition to its role in influencing neurotransmitter uptake by regulating membrane transporters, such as the dopamine transporter (DAT), it also impacts presynaptic sites by affecting synaptic vesicle trafficking and recycling [17]. Under certain conditions, α-syn monomers interact to form cytotoxic protofibrils or oligomers whose overexpression is associated with neurotoxicity in PD mouse models, while deposition of misfolded α-syn to form Lewy vesicles has also been shown to be increased in the brains of PD patients [18]. Even while α-syn is present in presynaptic terminals and is expressed throughout the brain, DAn is more vulnerable to the toxic consequences of excessive or malfunctioning α-syn., which may be related to the fact that α-syn can regulate dopamine levels. By interacting with the rate-limiting enzymes TH and ʟ-amino acid decarboxylase (AADC), α-syn can restrict dopamine production in one way. For another, α-syn can disrupt the activity of vesicular monoamine transporter 2 (VMAT2) and DAT and their function in regulating dopamine levels at synaptic terminals, which in turn contributes to the formation of toxic α-syn oligomers [19]. The above α-*syn*-DA interactions may be one of the reasons driving synaptic dysfunction and impaired communication in PD neurons. It is important to discuss the connection between ageing and α-syn. In plasma, α-syn levels declined with ageing, demonstrating a definite relationship between ageing and α-syn [20,21]. In addition, elevated levels of α-syn protein were detected in ageing human SN, with an increase of up to 600 % compared to young adults [22]. Thus, α-syn can be used as a biochemical marker of PD associated with ageing.

Neuroinflammation and degeneration of DAn is common during progressive loss of DAn triggered by α-syn accumulation, which is closely associated with abnormal microglia activity and NLR inflammasome activation. Although neuroglial cell dysfunction in PD is usually considered to be disease-specific, most have also been observed in the elderly brain. Microglia are normally in a quiescent state, and in PD α-syn has been observed to activate microglia [23], which in turn express pro-inflammatory factors from macrophages, activate the NLR inflammasome, and promote the release of cytokines, chemokines, and ROS. It also activates the migration and phagocytosis of macrophages and promotes the degradation of α-syn [24,25]. Although microglia activation may initially be aimed at preventing the accumulation of α-syn in the Lewy bodies of DAn, their chronic activation instead promotes DAn degeneration and neuroinflammation in PD. Similar chronic activation of microglia, as well as elevated levels of pro-inflammatory factors IL-6, TNF-α and IL-1β, can be observed in the ageing brain [26]. Thus, α-*syn*-activated microglia and subsequent activation of the NLR inflammasome have an effect on neuronal cells in PD and ageing brains. And the activation of NLR inflammasome as one of the key steps is involved in the mechanism of neuroinflammation and degeneration that eventually leads to DAn due to α-syn deposition.

2.1.2. Parkinson's disease and NLR inflammasomes

Inflammatory activity plays a crucial role in PD. Both central and peripheral inflammation occur in the prodromal phase of Parkinson's disease and persist throughout disease progression. Fibrillar α-syn is not only important for the progressive loss of DAn, but can also act as an endogenous DAMP triggering the microglia around it and mediating cellular scorching through the secretion of pro-inflammatory cytokines and ROS. The production of those cytokines is mainly regulated by the assembly and activation process of two multi-protein inflammatory complexes, known as NLRP1 and NLRP3.

In the pathological process of PD, α-syn mediates the activation of the NLRP3 inflammasome, which stimulates the release of inflammatory cytokines, thereby exacerbating neuroinflammation leading to DAn neurodegeneration and progressive loss. It was found that compared with the normal healthy population, PD patients had higher IL-1β expression levels and α-syn levels in the peripheral blood. This experiment also found that the expression levels of NLRP3, caspase-1 and IL-1β were suppressed by adding an oligomeric α-synuclein autophagy inhibitor to glial cells, suggesting that oligomeric α-synuclein can activate the NLRP3 inflammatory pathway through autophagy [27].In addition, in BV2 cells, a type of microglia, α-syn was observed to activate the NLRP3 inflammasome followed by the release of caspase-1 and IL-1β [28]. Ac-YVAD-CMK, a caspase-1 inhibitor, was demonstrated to improve the amount of DAn in rat models of 6-hydroxydopamine- and LPS-induced Parkinson's disease in vivo by decreasing the production of the NLRP3 inflammasome signaling protein and decreasing NLRP3 expression [29]. Consistently, NLRP3 knockout mice were resistant to loss of nigrostriatal DAn induced by treatment with the neurotoxin MPTP, which was associated with activated caspase-1 and reduced secretion of IL-1β and IL-18. Thus, increased levels of caspase-1 and IL-1β lead to neuroinflammation and subsequent damage to DAn leading to PD. Regarding the mechanism by which α-syn mediates NLRP3 activation, BV2 cells phagocytose α-syn, increase ROS accumulation by inhibiting AMPK phosphorylation, induce lysosomal swelling and damage, and increase lysosomal histone B expression in the cytoplasm ultimately activating NLRP3 inflammasome [28]. In addition, increased α-syn in PD can induce NLRP3 inflammasome activation and pro-IL transcriptional expression by promoting activation of NF-κB. It was demonstrated that due to α-syn deposition, the expression of toll-like receptor (TLR) −2 and TLR4, which can activate NF-κB, was elevated in the brain and blood samples of PD patients, which in turn can upregulate NLRP3 activation [30–32]. Thus, NLRP3 inflammasome can be activated by α-syn and thus promote DAn neurodegeneration in PD patients.

In addition to α-syn mediated, studies have confirmed the synergistic relationship between mitochondrial dysfunction and NLRP3 activation in the pathogenesis of PD. On the one hand, mitochondrial dysfunction may increase NLRP3 inflammasome activity [33]; on the other hand, NLRP3 causes mitochondrial damage, promotes the release of mtDNA and cytochrome *c* in the cytoplasm, and promotes the production of mitochondrial reactive oxygen species (mtROS) [34]. In contrast, NLRP3 activation in microglia in a PD model was suppressed by mitochondrial autophagy, which decreased inflammation and improved neuronal loss [35]. A further investigation found that cardiolipin, which is found behind the inner mitochondrial membrane, might trigger NLRP3 assembly after moving to the outer membrane, which could establish a connection between mitochondrial damage and NLRP3 in PD [36]. Thus, mitochondrial dysfunction and oxidative stress in the pathological development of PD are involved in the NLRP3 activation step, which exacerbates the damage to DAn.

NLRP3 inflammasomes have other ways to influence PD development besides releasing caspase-1 and IL-1β upon activation to cause neuroinflammation. For example, NLRP3 inflammasome downstream activation of caspase-1 has been shown to produce a neuronotoxic aggregation-prone protein in vitro by cleavage of α-syn, which may impair DAn [37]. Mutations in Parkin (PARK), PARK2, PARK6, and PINK1 (PTEN induced putative kinase 1) have also been found in patients with autosomal recessive early-onset PD. Microglia and macrophages from PARK2 and PINK1 knockout mice and patients with PARK2 mutations have been shown to show heightened NLRP3 inflammasome responses, possibly due to impaired expression of the anti-inflammatory protein A20, which negatively regulates NLRP3 inflammasome activation [38].

In addition to the NLRP3 inflammasome, the NLRP1 inflammasome may also be one of the inflammasomes that are activated by α-syn and thus contribute to neuroinflammation in PD. In animal models, continuous IL-1β expression has been found to have toxic effects on the substantia nigra, which may make PD symptoms more serious. The findings imply that mature IL-1β can be released by α-*syn*-stimulated activated BV-2 cells, which are either generated by neurons in the NLRP1-caspase 1 pathway. The enhanced expression of α-syn enhanced the expression of NLRP1 and IL-1β in SH-SY5Y cells, and this upregulation was further accentuated by the increase in α-syn. Furthermore, some studies claim that α-syn fibers may stimulate inflammasomes or develop ROS to activate NLRP1, ASC, caspase 1, and IL-1β, increasing α-syn aggregates and neurotoxicity. While all these alterations can be alleviated by anti-inflammatory antioxidant compounds such as glycyrrhetinic acid and Chinese herbal medicines (CHM) that protect neurons from
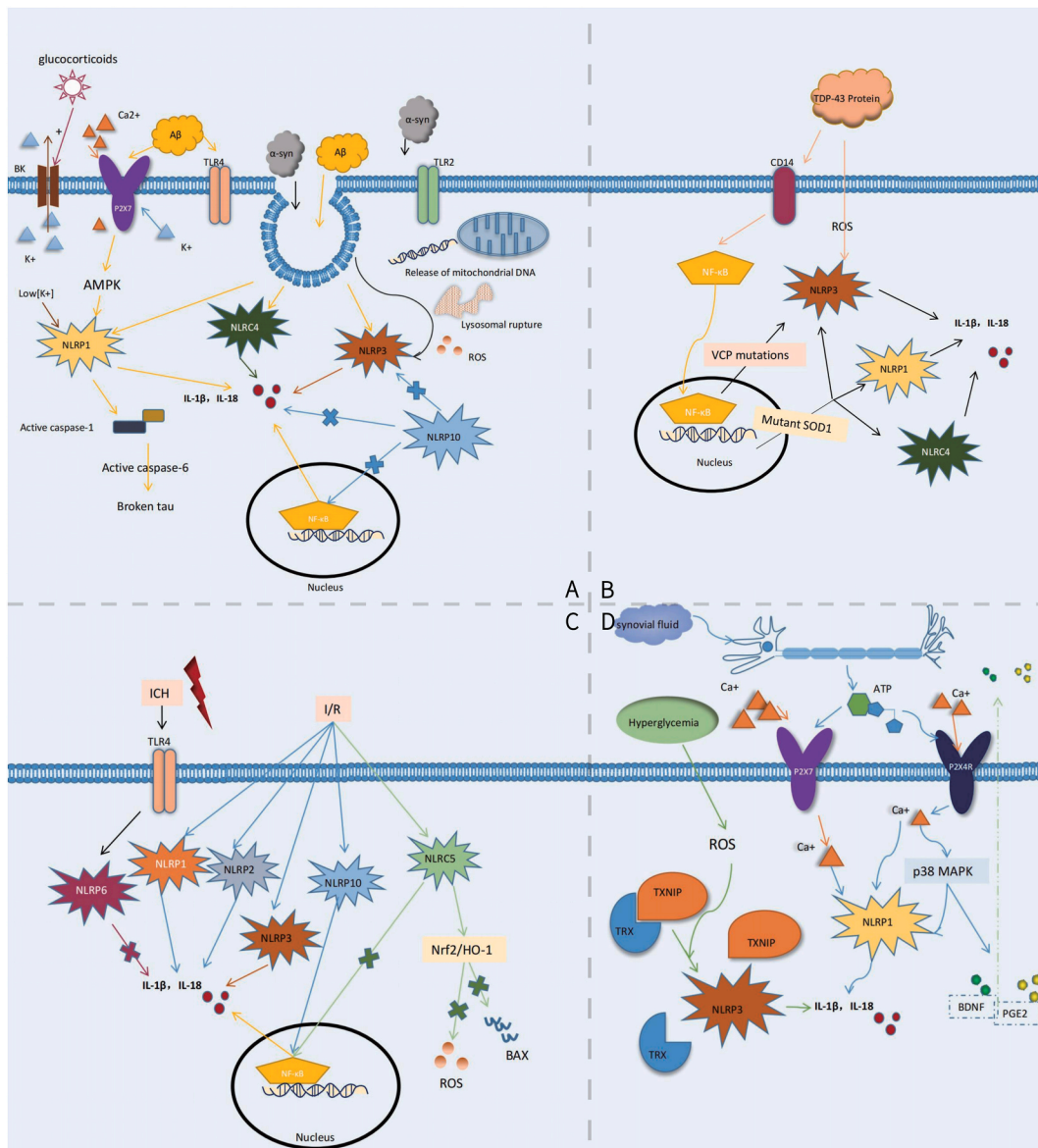
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Fig. 3. A) Cellular patterns of NLR inflammasomes in Alzheimer's disease and Parkinson's disease. α-syn can induce IL-1β synthesis through interaction with Toll-like receptor 2 (TLR2) and inflammasomes; endocytosis of α-syn, which increases ROS accumulation by inhibiting AMPK phosphorylation, induces lysosomal swelling and damage, increases lysosomal protease expression in the cytoplasm, and ultimately activates NLRP3; mitochondrial dysfunction may increase NLRP3 inflammasome activity, and NLRP3 causes mitochondrial damage, promotes the release of mtDNA in the cytoplasm, as well as promotes the production of mitochondrial reactive oxygen species; Aβ triggers the formation of TLR4 heterodimers, which in turn leads to the activation of the transcription factor NF-κB, thus promoting NLRP3 activation and pro-IL-1β transcription; P2X7R is activated by signals released from dying neurons, inducing K+ efflux and Ca2+ influx, promoting NLRP3 activation; NLRC4 is activated in AD and releases IL-1β; NLRP1 can reactivate caspase-6, and tau is further catabolized by caspase-6, thus further inducing negative neurological effects of Aβ; NLRP10 inhibits caspase 1 activation and IL-1β release, negatively regulating the disease. **B)** Cellular patterns of NLR inflammasomes in amyotrophic lateral sclerosis. SOD1 exhibits neurotoxic effects in motor neuron-microglia cultures, where it interacts with CD14 and activates NLRP3, caspase-1, as evidenced by increased production of pro-inflammatory cytokines (including IL-1β and IL-18) and the transcription factor NF-κB; in brain tissue from mutant SOD1 rats, NLRC4 and caspase- 1 activation was shown to be expressed; chronic inflammation caused by NF-κβ signaling stimulation mediates TDP-43 proteinopathy, and TDP-43 activates NLRP3 inflammasomes, leading to increased IL-1β production; VCP mutations are an etiology of ALS and are associated with NLRP3 inflammasome activation. **C)** Cellular patterns of NLR inflammasomes in Stroke. In I/R, NLRP1/3/ 10 exacerbate the symptoms of cerebral ischemia by activating the release of IL-1β and IL-18; in I/R, NLRC5 reduces the expression of Bcl2-associated X protein (Bax) and ROS through the Nrf2/HO-1 pathway, as well as NLRC5 reduces inflammation, oxidative damage, and ameliorates cerebral ischemia by preventing the activation of the NF-κB pathway; in ICH, NLRP6 inflammasome inhibits inflammatory signaling by negatively regulating the NF-κB activation pathway. **D)** Cellular patterns of NLR inflammasomes in Peripheral neuropathy. In diabetes mellitus, the TRX system and TXNIP interact, and when ROS produced by cells during hyperglycemia cause TXNIP to separate from TRX, enabling it to attach to NLRP3, which activates the NLRP3 inflammasome in Schwann cells, causing them to release IL-1β and induce neuroinflammatory injury to Schwann cells; in RA, the inflammatory response in the synovial fluid leads to peripheral nerve injury, and the release of damaged nerve ATP and PG activate P2X4R. Subsequently, high Ca2+ influx into macrophages may activate p38 MAPK, leading to the release of BDNF and PGE2 into synovial fluid and peripheral nerves as well as activating the NLRP1 inflammasome; in RA, Ca2+ influx stimulates P2X7R, inducing the production of pro-inflammatory factors and stimulating the NLRP1 inflammasome.

TLR, toll-like receptor; α-syn, α-synuclein; IL, interleukin; AMPK, adenosine monophosphate-activated protein kinase; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; SOD1, superoxide dismutase 1; TDP-43, transactive response DNA-binding protein-43; VCP, valosin-containing protein; ICH: intracerebral hemorrhage; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; TXNIP, thioredoxin-interacting protein; Bax, Bcl2-associated X protein; TRX, thioredoxin; PG, prostaglandins; p38 MAPK, p38 mitogen-activated protein kinase; BDNF, brain-derived neurotrophic factor; PGE2, prostaglandin E2; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing; NLRC, nucleotide-binding oligomerization domain, leucine-rich repeat and caspase recruitment domain-containing.

tau oligomer/aggregate-induced inflammatory damage [39]. However, generally there is a lack of sufficient direct evidence for α-syn as an NLRP1 inflammasome stimulator. It is still mainly the NLRP3 among NLR inflammasomes that has the clearest association with PD progression (Fig. 3A).

2.2. Alzheimer's disease

2.2.1. Alzheimer's disease and senescence

A neurodegenerative disorder called Alzheimer's disease (AD) causes memory loss and cognitive deterioration. The most significant risk factor for the onset and progression of AD is ageing. The incidence of AD has been shown to increase with age and cellular senescence [40]. According to recent studies, AD is significantly linked to progressive atrophy and widespread neuronal death in the temporal lobe, hippocampus, frontal cortex, and other brain regions [41]. This is caused by phosphorylated neurofibrillary tangles (NFTs) formed by Aβ and tau proteins in aged plaques, which are also more common with ageing [42].

Aβ accumulation in the brain is a pathological feature of AD [43], promoting neuronal degeneration and memory loss in AD, while Aβ is also a potent inducer of cellular senescence [44,45]. The cellular senescence marker p16 is significantly higher expressed in neurons that overexpress the human amyloid precursor protein 695 (APP), according to relevant research in vivo. In turn oligomeric Aβ can also stimulate p16 protein in neurons and increasing levels of Aβ may induce upregulation of p16 in neurons as well as cognitive impairment in AD models [46]. Thus, the AD pathological marker Aβ can accelerate neuronal ageing, and ageing neurons can in turn promote Aβ expression. In addition, brain Aβ load and memory impairment are significantly increased in the brains of mouse AD models with increased numbers of multiple senescent cells, suggesting that increased Aβ can cause neuronal and other cellular senescence in the brain [47]. Studies conducted in vitro have demonstrated that Aβ oligomers cause senescence in endothelial or neuronal cells in culture. For instance, Aβ oligomers promote senescence in brain endothelial cells by upregulating vascular endothelial growth factor (VEGF)-1 [47]. Neuroinflammation plays a key role in AD pathology, and the inflammatory factor IL-1β is increased in AD brain and leads to cellular senescence [44], which may be related to Aβ through activation of the NLR inflammasome. In general, Aβ deposition and senescence in the AD brain can be mutually reinforcing.

Tau is a microtubule (MT) binding protein. tau protein hyperphosphorylation leads to the separation of tau protein from MT and the formation of NFTs leading to neuronal degeneration [48,49]. In the brains of AD patients and animal models, tau pathology has been demonstrated to be connected to senescence in a variety of cell types, including astrocytes, microglia, and neurons [50,51]. Studies have shown that neurons containing NFTs in the brains of AD patients express elevated levels of the senescence marker p16 [52], and that tau-containing NFTs trigger a series of events that are highly correlated with cellular senescence in neuron-containing NFTs in human and mice brains [51]. In addition to neurons, glial cell senescence has also been linked to tau pathology in AD patients' brains. Tau oligomer-containing astrocytes with a senescent phenotype have been seen in the brains of AD patients, and tau-positive,

deteriorating neurons have also been found there [50,53]. These findings imply that tau protein-induced pathological changes in neurons may also cause senescence in peripheral glial cells. Thus, tau proteins in AD and the NFTs formed by their hyper-phosphorylation are closely associated with senescence.

The pathogenesis of AD involves the actions of Aβ and tau proteins on mitochondria, astrocytes, and microglia, in addition to their direct neurotoxic effects, which damage neurons. the induction and reduction of axonal transport in hippocampal neurons affects altering the distribution of mitochondria, along with an increased accumulation of mtDNA mutations leading to increased ROS production [54,55], causing extensive oxidative damage and amyloid lesions. Moreover, this can disrupt nerve terminal activity, leading to dysfunction and synaptic loss, which is associated with memory loss. Phosphorylated tau accumulates in mitochondria during normal ageing and occurs preferentially in synaptic mitochondria. Studies have shown that phosphorylated forms of tau are located in hippocampal synaptic mitochondria in both young and aged mice, with higher accumulation in aged mice [56]. Further during ageing, the imbalance between tau phosphorylation and degradation leads to dissociation of tau from MT and its accumulation in cytoplasmic and cytoplasmic structures including mitochondria. This all may contribute to synaptic failure and cognitive impairment in AD in the elderly. In addition, tau is a substrate for mitochondrial caspase-3, and expression of caspase-cleaved tau fragments in neurons affects mitochondrial function alongside causes mitochondrial calcium levels to be dysregulated [57]. Ca^{2+} dysregulation directly affects tau phosphorylation, APP processing and lysosomal function. In turn, Aβ stimulation of neurons causes a large Ca^{2+} influx that damages mitochondria, impairing neuronal productivity and leading to apoptosis and cognitive impairment [58]. Thus, the deleterious effects of Aβ and tau on mitochondria during ageing ultimately exacerbate AD.

Astrocytes are thought to be activated in the preclinical phase of AD [59], and Aβ deposition and NFTs may promote astrocyte activation. Astrocytes accumulate at sites of Aβ deposition in early AD, and activated astrocytes in late AD surround amyloid plaques and NFTs. Activated astrocytes release pro-inflammatory and cytotoxic factors in neuroinflammation, exacerbating the pathology of AD [60]. Also, The phagocytosis-related genes that are expressed by astrocytes permit the absorption of Aβ and its transportation to lysosomes for destruction. With ageing, impairment of lysosomal function in astrocytes leads to the accumulation of Aβ and phago-cytosed amyloid material in astrocytes, which may be critical in promoting the progression of amyloid plaques [61]. Furthermore, it has been shown that senescent astrocytes can upregulate senescence-related secretory phenotype-related genes via the NF-κB pathway, producing low levels of chronic inflammation and enhancing the senescence state and enhancing age-related neurodegenerative diseases [62]. Thus, astrocytes activated by the senescent phenotype or Aβ and NFTs can exacerbate AD progression.

Aβ and NFTs indirectly activate microglia and lead to the release of various pro-inflammatory factors and neurotoxic mediators. These pro-inflammatory factors and mediators not only attenuate Aβ phagocytosis, but also increase tau phosphorylation and accelerate the formation of NFTs, thus inducing neurotoxicity. In addition, they can promote Aβ production and exacerbate Aβ for-mation of protofibrils and deposition [63]. Toxic Aβ oligomers and protofibrils can be recognized by some receptors expressed by microglia, triggering microglia activation via NF-κB or mitogen-activated protein kinases (MAPKs), initiating the activation of inflammasomes and ultimately leading to neuronal death and the onset of AD [62]. Thus, Aβ and tau-containing NFTs can be involved in the progression of AD by damaging mitochondria, activating microglia and releasing pro-inflammatory factors, damaging astrocytes and reducing clearance, while ageing exacerbates the above pathological processes. It is also possible to find that AD is closely associated with neuroinflammation and pro-inflammatory factors because of the pathological changes and products of progression, including the above-mentioned dysregulation associated with Aβ accumulation and tau-containing NFTs, many of which can act as DAMPs that activate the NLR inflammasomes.

2.2.2. Alzheimer's disease and NLR inflammasomes

There is substantial evidence confirming that Aβ can induce NLRP3 inflammasome activation. In vitro primary microglia stimu-lation of fibrillar Aβ activates NLRP3 inflammasome (caspase-1) production, leading to increased IL-1β secretion in animal models of AD [64]. In Aβ-induced BV-2 cells and APP/PS1 (Aβ precursor protein/presenilin-1) mice, autophagy regulates Aβ through the LRP1/adenosine monophosphate-activated protein kinase (AMPK) pathway, thereby inducing activation of the NLRP3 inflammasome [65]. In turn, intraperitoneal injection of NLRP3 inflammasome inhibitor (JC-124) significantly improved Aβ load in the mouse brain and suppressed neuroinflammation [66]. Mechanistically, Aβ is thought to be a DAMP recognized primarily by PRRs in microglia, astrocytes, and oligodendrocytes, which further initiate and activate the NLRP3 inflammatory complex. As an initiating signal, Aβ binds to CD36 surface receptors, triggering the formation of TLR4 heterodimers, which in turn leads to the activation of the tran-scription factor NF-κB, thereby promoting the transcription of the NLRP3 structural domain and pro-IL-1β and inducing neuro-inflammation [67]. Aβ acts as an activating signal through two different processes. Aβ is known to cause synaptic dysfunction and neuronal damage, and P2X7R is triggered by ATP produced from dying neurons and attracts Pannexin-1 channels, which enable NLRP3 agonists to enter the cell [68,69]. In addition, ATP binds to purinoceptors and induces K^+ efflux and Ca^{2+} influx, and K^+/Ca^{2+} imbalance promotes NLRP3 activation. On the other hand, Aβ plaques can also be incorporated into lysosomes, promoting lysosomal instability and releasing the lysosomal protein hydrolase cathepsin B, which promotes NLRP3 assembly through an unidentified mechanism [70]. In addition, soluble oligomer Aβ induces pore formation in the cell membrane, generates ROS, promotes K^+ efflux through oxidized K^+ channels, promotes NLRP3 activation, and ultimately leads to the production and release of the inflammatory cytokines IL-1β and IL-18 [71].

Less research has been done on the relationship between NLRP3 and tau, but it has also been shown that tau can induce NLRP3 inflammasome activation. Recently, it was shown that synthesis of pre-aggregated tau fragments consisting of the microtubule-binding domain of tau induces IL-1β secretion by primary microglia, the process that can be abolished by NLRP3 inhibitors, demonstrating the dependence of tau on the NLRP3 inflammasome [72]. These findings were confirmed in TauP301S transgenic mice, providing ample evidence for the occurrence of tau-mediated NLRP3 activation. These authors also demonstrated that the activation of NLRP3 by tau

fragment uptake in microglia is mediated through lysosomal instability and subsequent release of cathepsin B. In addition, a recent study showed that NLRP3 is the link between Aβ plaques and NFT formation. This study suggested that injection of APP/PS1 brain homogenate containing Aβ induced tau hyperphosphorylation in Tau22 mice, whereas it did not occur in mice lacking NLRP3 or ASC, demonstrating that NLRP3 is an important mediator of Aβ-induced tau pathology [73]. Overall, both Aβ and tau are involved in the activation of NLRP3, causing a neuroinflammatory response.

NLRP1 is also activated by Aβ in AD. It has been demonstrated that Nlrp1 inflammasome is activated by Aβ produced in the brain of AD transgenic mice, leading to neuronal death, probably due to cellular scorching [74]. Since oligodendrocytes and pyramidal neurons (mainly found in the cerebral cortex, hippocampus and amygdala) express NLRP1, Aβ-induced NLRP1-mediated neurotoxicity may damage these brain regions, which then leads to memory loss and cognitive impairment in AD patients [75]. It was shown that P2X7/pannexin-1 interaction is associated with Aβ-induced neuronal death and that increased extracellular ATP activates P2X7/pannexin-1 signaling. In addition to promoting NLRP1 activation through the same NLRP3 due to K^+/Ca^{2+} imbalance, this signaling can activate NLRP1 through the AMPK signaling pathway, which induces neuroinflammation [76]. Unlike other NLR inflammasomes, after activation of caspase-1, NLRP1 can then activate caspase-6, which further induces the negative neurological effects of Aβ. It has been demonstrated that caspase-1 activation in human primary CNS neurons activates caspase-6 in an NLRP1-dependent manner [77]. the N-terminal end of tau is cleaved by caspase-6 and plays an integral role in the maturation of NFTs in AD [78]. Active caspase-6 itself causes primary human neuronal apoptosis, and activation of caspase-6 has been shown to cause age-dependent neurodegeneration and memory impairment in transgenic mice lacking plaques and NFTs [79]. In summary, Aβ activates NLRP1 leading to neuronal death, and further activation of caspase-6 by activated NLRP1 causes reinjury to nerves and promotes AD progression.

While NLRP1 and NLRP3 positively regulate Alzheimer's disease, the interaction of NLRP10 with ASC in glial cells has the opposite effect. NLRP10 reduces the availability of ASC and prevents it from oligomerizing with the NLRP3 structural domains, thereby inhibiting the NLRP3 inflammatory pathway and acting as a negative regulator of AD.

Aβ accumulates around ASC fibers, forming ASC-Aβ complexes. These complexes stimulate the activation of NLRP3 in nearby microglia while diminishing the microglia's ability to clear Aβ. Consequently, this leads to pyroptosis and the release of significant amounts of ASC, cycling the formation of ASC-Aβ complexes [80]. As Aβ accumulates, the microglia's capacity to clear Aβ gradually declines, potentially contributing to the progression of AD [81]. It was shown that Aβ1-40/1–42 cocktail (protease inhibitor) significantly increased activated caspase 1 and NLRP3 in rat cortex and hippocampus, but significantly decreased NLRP10. In contrast, NLRP10 activation inhibited Aβ-induced development of NLRP3 inflammasome and IL-1β release. Structurally, NLRP10 does not contain a leucine-rich repeat sequence (LRR) structural domain, whereas NLRP3 does. This is thought to prevent ASC from binding to NLRP10 and activating caspase 1. Thus, NLRP10 in AD decreases caspase 1 activity, IL-1β release, and sustained neuroinflammation [82].

In addition, NLRC4 (NOD, leucine-rich repeat and caspase recruitment domain-containing 4) inflammasome levels were found to be elevated in the brains of AD patients [83]. Astrocytes and microglia are thought to produce more cytokines upon exposure to saturated fatty acids [84]. NLRC4 in astrocytes has been shown to be activated and release IL-1β in response to fatty acid stimulation, but the specific inflammasome that allows microglia to release IL-1β upon stimulation has not been identified. In conclusion, NLRC4 may also play a role in AD progression. In summary, NLRP1/3 determined to be influenced by Aβ and tau promotes AD progression, whereas NLRP10 activation negatively regulates neuroinflammation and NLRC4 activation may exacerbate AD through the release of IL-1β (Fig. 3A).

2.3. Amyotrophic lateral sclerosis

2.3.1. Amyotrophic lateral sclerosis and senescence

Amyotrophic lateral sclerosis (ALS) is a rare progressive neurological disease that primarily affects nerve cells in the cerebral cortex, brainstem and spinal cord that are involved in the control of voluntary muscle movements. Age-related musculoskeletal disorders and degenerative changes are prevalent, and neurological changes can develop and contribute to these conditions. Many people believe that younger people are more likely to develop the disease ALS. However, based on studies of relevant population data, the age profile of ALS onset is comparable to that of other age-related neurodegenerative diseases, such as Parkinson's disease. It peaks around 80 years of age, and ALS patients over 80 years of age survive on average 6 months less than younger patients [85]. The neuromuscular junction (NMJ), a synapse critical for motor neuron and skeletal muscle function, is a feature of ageing and amyotrophic amyotrophic lateral sclerosis. The NMJ has negative structural and functional changes with ageing or ALS, including synaptic vesicle loss and dysregulated neurotransmitter release, which result in the degeneration of motor axon nerve ends [86]. Recent studies have shown that ageing is associated with many ALS-related pathogenic mechanisms, including oxidative stress, metabolic problems, protein aggregation, decreased mitochondrial and microglia function, and inflammation [87], and researchers have used RNA-seq to investigate the transcriptional changes that occur in the spinal cord during ageing and the etiology of ALS in mice, ultimately demonstrating a significant overlap between ageing and amyotrophic lateral sclerosis [88]. Therefore, ALS can be seen as an extreme form of ALS in the spinal cord ageing of motor neurons. Thus, we can assume that ALS is a disease associated with ageing [89].

Patients with ALS also exhibit varying degrees of cognitive impairment and have been reported to have neurodegeneration outside of motor areas, although the disease primarily affects the motor system [90]. Whole-brain functional connectivity can be investigated with resting-state functional magnetic resonance imageing (RS-fMRI) [91]: the frontoparietal network (FPN) includes cognitively relevant frontoparietal, suprafrontal, and midfrontal regions [92], while the default mode network (DMN) includes brain regions such as the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC). It was shown that fluctuations in RS-fMRI signals were

selectively reduced in both networks when ALS patients were compared to healthy controls. Furthermore, considerable age-related modulatory effects were seen in RS-fMRI fluctuations, especially in the DMN [93]. Thus, cognitively connected brain regions are affected by ALS neurodegeneration, which is closely associated with ageing.

2.3.2. Amyotrophic lateral sclerosis and NLR inflammasomes

ALS is considered to be a multifactorial disease, and more than 20 genes have been identified in association with the pathogenesis of ALS, including homodimeric enzyme superoxide dismutase 1 (SOD1), transactive response DNA-binding protein (TDP-43),Valosin-Containing Protein (VCP), fused in sarcoma/translocated in liposarcoma protein (FUS/TLS), and C9orf72 [94], any of which mutations in any of these genes may cause ALS.

Mutations in the SOD1 gene are significant in dependent familial ALS, which may lead to alterations in motor neurons and their function through activation of the NLR inflammasome [95]. SOD1 exhibits neurotoxic effects in motor neuron-microglia cultures, where it interacts with CD14 and, together with TLR2 and TLR4, activates pro-inflammatory microglia and releases pro-inflammatory cytokines. In SOD1G93A transgenic rats, the production of NLRP3, caspase-1, pro-inflammatory cytokines (including IL-1β and IL-18) and the transcription factor NF-κB is increased, with NLRP3 predominating [96]. In the brain tissue of mutant SOD1 transgenic rats, NLRP3, NLRC4, absent in melanoma 2 (AIM2, an inflammatory vesicle) and caspase-1 have been shown to be expressed [97]. In another experiment, mutant SOD1 activated caspase-1 and IL-1β in microglia and was proved to be associated with NLRP3 [98]. Thus, it was basically confirmed that producing SOD1 mutations leads to NLRP3 inflammasome activation expression, resulting in neuro-inflammation in ALS. Furthermore, a study explored the gene expression, protein concentration of NLRP1, NLRC4 and AIM2 inflammasome in spinal cord samples from SOD1 mice and ALS patients. The results showed elevated transcript levels of NLRP1 and NLRC4 in symptomatic SOD1 animals, and immunoblotting revealed significantly elevated protein levels of NLRC4, suggesting with the exception of NLRP3, NLRC4 may be very closely related to the pathogenesis of SOD1 ALS [99]. However, in human ALS, only the concentration of NLRC4 protein changed dramatically, and NLRP1 protein only decreased slightly. Therefore, we hypothesized that in human ALS patients, NLRP1 expression is affected by different causes than in mice. In conclusion, NLRP1/3, NLRC4 expression may promote ALS disease progression in SOD1 mutations.

The C-terminal fragment of TDP-43 is another pathological protein associated with ALS, with the vast majority of ALS cases characterized by the deposition of TDP-43 protein in affected neurons. Leaving aside the complex pathology of TDP-43 in relation to the presence of mutant SOD1, when the expression of the gene for this protein is upregulated, it may lead to neurodegeneration through activation of the NLRP3 inflammasome. Chronic brain inflammation caused by NF-κB activation signals, such as LPS, stimulation was found to mediate TDP-43 protein disease [100]. TDP-43 has been shown to activate NLRP3 inflammasomes in primary microglia cultures leading to increased IL-1β production and increased NLRP3 expression has been observed in postmortem tissues from ALS patients [101].TDP-43 protein binds to CD14 receptors in microglia, macrophages and monocytes, leading to NF-κB activation. This stimulates NLRP3 inflammasomes. TDP-43 protein binding also activates inflammasomes by upregulating NADPH oxidase (NOX)-2 and enhancing ROS production. NLRP3 activation has been shown to play a specific role in the upregulation of nuclear TDP-43 as well as in its induced neurotoxicity. In addition, Parkin has been shown to be closely associated with inflammation, mitochondrial stress and neurodegeneration [102]. It promotes the translocation of TDP-43 from the nucleus to the cytoplasm and plays an important role in TDP-43 subcellular localization and toxicity [103]. In sporadic spinal cord samples from ALS patients, TDP-43-containing neurons decrease parkin levels [104]. Since NLRP3 can mediate activation of caspase-1, which has been shown to mediate parkin cleavage [105], it can be assumed that NLRP3 activation may affect TDP-43 toxicity in ALS patients by altering parkin levels. Both FUS/TLS and C9orf72 have been associated with inflammation. For example, activation of the NLRP3 inflammasome can be mediated by C9orf72 through a number of pathophysiological pathways including lysosomal dysfunction, mitochondrial dysfunction, intracellular metabolic imbalance, and intracellular protein aggregation, but it remains to be explored how FUS/TLS, C9orf72, and the NLR inflammasome are linked and thus affect ALS. Overall, it can be determined that ALS with TDP-43 mutation induces NLRP3 inflammasome activation through NF-κB activation leading to neuroinflammation, while activated NLRP3 may in turn affect TDP-43 toxicity through cleavage of parkin.

VCP is one of the genes involved in ALS related to protein metabolism, and one of its main responsibilities is to promote proteasomal degradation of damaged or misfolded proteins, including RNA proteoglycans containing TDP-43 and other ALS-associated proteins [106]. Initially VCP mutations were thought to be the origin of clinical symptoms defined by tendinopathy, bone Peget's disease and frontotemporal dementia (IBMFTD) [107], and eventually VCP was found to be one of the causes of ALS. According to Al-Obeidi et al. VCP mutations are found in approximately 9 % of ALS, 4 % of PD and 2 % of AD patients, although there is no conclusive link between the incidence of ALS and VCP mutations to date [108].A 2017 study using a mouse model of VCP showed a link between VCP protein myopathy and activation of the NLRP3 inflammasome. According to this study, significantly elevated expression of NLRP3, caspase 1, IL-1β and IL-18 was observed in the quadriceps muscle of 2- and 24-month-old VCPR155H/+ heterozygous mice. Furthermore, a significant rise in IL-1(+) F4/80(+) Ly6C (+) macrophages was found in the quadriceps and skeleton of the same mice, which positively correlated with the high expression levels of TDP-43 and p62/SQSTM1 markers in VCP pathology and progressive muscle atrophy [109]. Therefore, we propose that NLRP3 contributes to the link between VCP and ALS (Fig. 3B).

2.4. Stroke

2.4.1. Stroke and senescence

The incidence of stroke is gradually increasing as the elderly population grows. One of the constant risks of stroke is age, which doubles every 10 years after age 55 and accounts for nearly three quarters of all stroke cases [110]. The chances of death and

self-recovery from stroke are also closely related to age. After stroke, the ageing brain experiences a significant inflammatory response that may impair recovery processes such as axonal development. At the most basic level, strokes are classified as ischemic strokes triggered by arterial embolism or cerebral thromboembolism and hemorrhagic strokes caused by cerebrovascular rupture [111]. The focus of this review is on ischemic strokes, which have a much higher incidence.

Approximately 70 %–80 % of stroke cases are ischemic in nature [112]. Ischemic stroke is usually followed by secondary neuroinflammation, both pathological processes that promote further damage and lead to cell death, but in turn can stimulate beneficial effects to promote recovery. In general, ischemia-elicited pro-inflammatory signals rapidly activate microglia, astrocytes, and neutrophils, affect endothelial cells and the blood-brain barrier (BBB), and promote the infiltration of various inflammatory cells into the ischemic zone, exacerbating neuronal death and brain damage. With ageing, the outcome and recovery after ischemic stroke changes with changes in the number, structure and function of the aforementioned cells. It has been shown that aged mouse models of middle cerebral artery occlusion display larger infarct size and higher levels of pro-inflammatory cytokine expression than younger mice [113], confirming the detrimental effects of ageing on ischemic stroke and the exacerbation of inflammation.

Microglia are resident immune cells of the CNS that are activated after ischemic stroke, undergo morphological and phenotypic changes [114], and accumulate at the lesion site and within the surrounding penumbra. Studies in rats using a transient middle cerebral artery occlusion (MCAO) model have shown that microglia change from an M2 phenotype to an M1 phenotype [115]. Normally the M1 phenotype of microglia is usually considered destructive because they activate inflammasomes such as NLR inflammasomes, which in turn release pro-inflammatory cytokines such as TNF-α, IL-1β, IL-12 and IL-6, and the production of ROS and NO, all of which exacerbate brain tissue damage [116]. In contrast, the M2 phenotype of microglia is often thought to prevent inflammation and promote tissue repair. Various experimental studies have shown enhanced expression of M2 microglia after stroke, reduced infarct volume, increased angiogenesis and neurogenesis, and reduced cognitive impairment [117,118]. Ageing may affect the number and translation of M1 and M2 phenotypes. Aged mice have reduced numbers of M2 microglia compared to young mice, and aged brains exhibit long-term M2 response deficits and M1 polarization after ischemic injury, which may contribute to long-term dysfunction and chronic neuroinflammation after stroke in old age.

This phenotypic change in aged microglia can be attributed to multiple complex mechanisms. It is relatively clear so far that the microglia phenotype can be regulated by interactions with neurons and astrocytes. Healthy neurons are regulated by CD200 (ligand for CD200R), CX3CL1 (fractalkine, ligand for CX3CR1 on microglia), neurotransmitters (e.g., GABA) and neurotrophins [119]. Astrocytes are regulated through the secretion of soluble factors such as nuclear factor erythroid 2-related factor 2 (Nrf2) and transforming growth factor (TGF)-β. It is the reduction of these regulatory factors and the increase of various pro-inflammatory factors during ageing that may trigger the shift of microglia to the M1 phenotype [120].

In addition, there is a prolonged hypostimulated inflammatory response after acute stroke, and this prolonged increase in inflammation is also associated with microglial cell senescence. A study examining microglial activation after permanent MCAO in rats showed that despite the cessation of inflammation at the primary infarct site, an increased inflammatory response with a secondary peak of inflammation was observed in the ipsilateral thalamus 7 months after stroke [121]. This secondary peak may be exacerbated by the increased inflammatory environment caused by ageing. Overall, therefore, phenotypic transformation and activation of microglia are closely linked to acute and chronic inflammation in ischemic stroke, and these pathological processes are exacerbated by ageing.

Astrocytes are also key cells in the pathological process of ischemic stroke. It has a similar secretory profile to microglia and also converts to a pro-inflammatory phenotype during ageing or in the event of ischemic stroke, activating NLR inflammasomes and releasing pro-inflammatory factors to induce neuroinflammation, but unlike microglia, astrocyte numbers do not change significantly in the elderly compared to the young [122]. Notably, glutamate transporters in astrocytes, such as glutamate transporter (GLT)-1 and glutamate-aspartate transporter (GLAST), decline with ageing, limiting their regulation of inter-synaptic glutamate concentrations, which can have implications for ischemic stroke and inflammation. Since excessive glutamate input is a key mechanism of neuronal excitotoxicity, loss of glutamate regulation in astrocytes may exacerbate neuronal damage during ageing. Similarly, the regulatory capacity of astrocytes during ischemic stroke is dramatically reduced by glutamate transporter levels shortly after ischemia [123], suggesting that both cerebral ischemia and ageing this further exacerbates glutamate-mediated excitotoxicity via astrocytes in aged cerebral ischemia and induces neuroinflammation.

In addition to glial cells, neutrophils are also involved in ischemic stroke as well as in secondary injury. After stroke, neutrophils undergo structural change and migrate through the endothelial vessel wall and are subsequently attracted to the ischemic zone by chemokines. Neutrophils cause secondary injury in ischemic stroke by releasing pro-inflammatory factors, ROS and matrix metalloproteinases (MMP). These factors damage the endothelial cell membrane and basal lamina, leading to BBB permeability and post-ischemic edema. It has been indicated that the percentage of circulating neutrophils in the blood of aged mice after stroke is significantly higher compared to young mice, and they show more production of reactive oxygen species and MMP in the ischemic brain, which is closely associated with poor neurological prognosis in aged mice after stroke, implying that ageing is a driver of neutrophil-induced neuroinflammation after stroke [124].

In addition to inducing neuroinflammation and brain damage during ischemic stroke, the aforementioned microglia, astrocytes and neutrophils can also produce inflammatory factors that damage the endothelial cell membrane and basal lamina. This can lead to increased BBB permeability and post-ischemic edema, as well as recruitment of peripheral immune cells, including T cells, neutrophils and macrophages, to the site of injury to release more cytokines, which can have further beneficial or detrimental effects on the neurovascular system. Studies have shown that BBB infiltration increases with age and is associated with severe cognitive decline and poor function in elderly stroke patients [125]. Thus, age-related changes in BBB permeability are also a factor in the regression of ischemic stroke. In conclusion, ischemic stroke induces changes in microglia, astrocytes, neutrophils and BBB permeability that activate inflammasomes that drive the development of neuroinflammation and brain damage, and ageing exacerbates the deleterious

effects of these factors and adversely affects ischemic stroke.

Intracerebral hemorrhage (ICH) accounts for approximately 20 % of all strokes. The pathological mechanisms occurring after ICH are broadly based on the immediate compression of adjacent brain tissue by the action and trauma produced during haematoma formation at the moment of ICH onset, i.e., the primary brain injury of ICH. Subsequently, secondary brain damage such as excito-toxicity, oxidative stress and neuroinflammation produced by the stroke exacerbates the white matter damage and leads to neuro-logical deterioration [126]. In the same way as in ischemic stroke, microglia, astrocytes, leucocytes and glutamate are all involved in these pathological changes [127]. In addition, microcirculatory changes are both a cause and a resultant manifestation of cerebral hemorrhage. Such changes can be mediated by endothelial dysfunction, brain self-regulation, and impaired neurovascular coupling, which in turn can promote neuroinflammation and microvascular injury [110]. The microcirculation itself is known to change with age, suggesting that brain state under cerebral hemorrhage stroke is also closely associated with ageing.

2.4.2. Stroke and NLR inflammasomes

The poor prognosis and brain damage in stroke mentioned above is associated with the activation of microglia, astrocytes, neu-trophils and altered BBB permeability leading to the release and spread of pro-inflammatory factors, ultimately causing neuro-inflammation. The production of pro-inflammatory factors is closely linked to the activation of inflammasomes, and some of the NLR inflammasomes have been found to be activated during stroke and involved in the pathological process of the disease.

The NLRP3 has been shown to be a key mediator of inflammation following ischemic stroke. The NLRP3 is first activated in microglia following brain I/R (ischemia-reperfusion) injury and subsequently expressed in microvascular endothelial cells [128], particularly in neurons. Under ischemic conditions in vitro and in vivo, NLRP3 inflammasomes were activated in mouse primary cortical neurons with increased levels of NLRP3, ASC, caspase-1, and IL-1β and IL-18. In addition, the NLRP3 inflammasome component and the pro-inflammatory factors IL-1β and IL-18 which it can release were also found to be elevated in post-mortem brain tissue samples from stroke patients [129]. In turn, some experiments have confirmed that downregulation of NLRP3 expression after ischemia helps to reduce neuroinflammation and brain injury by inhibiting NLRP3 activation. Caspase-1 inhibitor treatment and intravenous immunoglobulin (IVIg) treatment can protect neurons in experimental stroke models by inhibiting NLRP3 inflammasome activity [130]. Moreover, the NLRP3 inhibitor MCC950 has been shown to reduce infarct volume in MCAO mice by downregulating different pro-inflammatory factors and NLRP3-expressing inflammasome components [131]. Another study showed that NLRP3−/− mice reduced infarct volume, edema formation and preserved BBB permeability in an MCAO mouse model [132]. These studies all support that NLRP3 inflammasome activity is increased in ischemic stroke, suggesting that NLRP3 may be a potential target in ischemic stroke and play an essential role in mediating neuronal cell death.

Regarding the mechanisms that induce NLRP3 inflammasome assembly activation in the ischemic brain, the current study con-cludes that potassium efflux, ROS release and lysosomal damage are the main factors. During cerebral ischemia, some Na^+/K^+-ATPase pumps are impaired due to reduced ATP production, leading to increased Na^+ influx and K^+ efflux, which activates NLRP3 [133]. In parallel, the electron transport chain in mitochondria is affected and ROS levels are greatly increased, activating the brain inflam-matory response and the NLRP3 inflammasome, while inducing oxidative stress and stimulating Ca^{2+} ion release. This leads to endoplasmic reticulum (ER) stress damaging organelles and ultimately leading to apoptosis. In addition, cholesterol crystals from atherosclerotic plaques at the site of occlusion fuse with lysosomes, which induces lysosomal membrane rupture and release of cytosolic tryptic proteins into the cytoplasm, which can also activate NLRP3 [134]. Thus, these aforementioned may collectively activate NLRP3 receptors and lead to a cascade of inflammatory responses and brain cell damage.

In addition to NLRP3 activation that positively advances the development of neuroinflammation in ischemic stroke, NLRP1, NLRP2 and NLRP10 inflammasomes have been found to be activated in ischemic stroke and by similar mechanisms. Studies have shown that microglia in the normal brain express the adapter protein ASC, but not NLRP1 or caspase-1, whereas cerebral ischemia due to em-bolism promotes the expression of caspase-1, NLRP1 and ASC, as well as the pro-inflammatory cytokines IL-1β and IL-18, by the relevant cells [135], suggesting that upregulation of the NLRP1 inflammasome in cerebral ischemia promotes the release of pro-inflammatory factors. Other study data found that NLRP2 protein is expressed in the central nervous system, mainly in astrocytes, and that expression is elevated when the brain is ischemic. Oxygen-glucose deprivation (OGD) is one of the conditions that can cause cerebral ischemia and can be used to construct ischemia/reperfusion models, and studies have confirmed that silencing the NLRP2 gene reduces apoptosis in the brain after oxygen-glucose deprivation treatment, suggesting that high expression of NLRP2 in the CNS may also have an important role in the pathophysiology of ischemic stroke [136]. Regarding NLRP10, Li et al. demonstrated a sig-nificant reduction in brain infarct volume in NLRP10 knockout mice in response to acute ischemic stroke inflammation by inducing MCAO injury. Moreover, activation of the TLR-4/NF-κB signaling pathway associated with NLR activation was inhibited, and in-flammatory complex components ASC and caspase-1 were significantly impaired by the loss of NLRP10 [137]. Thus, the NLRP1/2/3/10 inflammasome complexes are all expressed in the ischemic brain and contribute to ischemic brain injury.

All of the above NLR inflammasomes activations promote neuroinflammation and brain injury in ischemic stroke, in contrast to NLRC5, whose expression suppresses the inflammatory response and whose expression is normally suppressed in cerebral ischemia. NLRC5 has a very long C-terminal region with 27 LRRs and is the largest member of the NLR protein family. During cerebral ischemia/perfusion (I/R), mRNA and protein levels of NLRC5 are greatly reduced within oxygen and glucose deprivation (OGD)/reoxygenation (R)-induced neurons. In contrast, when NLRC5 was overexpressed, it inhibited TNF-α, IL-6, IL-1β, ROS, and reduced oxidative damage, apoptosis and inflammatory responses by suppressing the TLR4/MyD88/NF-κB pathway in cerebral ischemia-reperfusion injury [138]. In addition to NLRC5 inhibiting inflammation-related pathways, another study showed that overexpression of NLRC5 increased the expression of B-cell lymphoma-2 (Bcl2), nuclear factor Nrf2, heme oxygenase-1 (HO-1) and genes downstream of the Nrf2/HO-1 pathway [139], resulting in a significant increase in cell viability, suggesting that the promoted Nrf2/HO-1 pathway mediates the

protective effects of NLRC5. Therefore, NLRC5 has also been suggested as a potentially useful therapeutic target in the management of brain I/R injury. Overall, NLRC5 has been shown to be neuroprotective in cerebral ischemic injury and promises to be an effective target for treatment.

ICH is another cause of stroke, and the main mechanism of brain damage caused by it is aseptic neuroinflammation [140]. after ICH, glial cells produce large amounts of pro-inflammatory cytokines, which are activated by innate immune sensors. Extracellular sensors are TLRs, etc., and inhibition of TLR4 has been shown to reduce neuroinflammation and brain damage caused by ICH [141]; intracellular sensors are NLR inflammasomes, etc., and activated NLR inflammasomes can process and release the mature proin-flammatory factors IL-1β and IL-18 [142]. NLR inflammasomes involved in cerebral hemorrhage are NLRP3 and NLRP6. In contrast to cerebral ischemia in which the NLRP3 inflammasome activation promotes neuroinflammation similarly, by inhibiting the NLRP3 inflammasome the ICH-induced brain injury can be similarly attenuated [143]. Conversely, NLRP6 deficiency exacerbates ICH-induced brain injury. The NLRP6 inflammasome is generally thought to contribute to the promotion of peripheral nerve healing and control of immune responses. the NLRP6 inflammasome inhibits inflammatory signaling by negatively regulating the typical NF-κB activation pathway and may also promote recovery from peripheral nerve injury by inhibiting inflammatory responses unre-lated to the inflammasome as well as IL-1β [144]. These findings imply that the NLRP6 inflammasome has a function in preventing brain injury. Furthermore, regarding the enhanced TLR4 signaling after ICH, some experiments have demonstrated that the NLRP6 inflammasome is lost in TLR4 knockout ICH mice, and thus activated TLR signaling may be responsible for the increased expression of the NLRP6 inflammasome. Overall, upregulation of NLRP6 inflammasome expression may protect the brain from ICH-induced brain injury, whereas NLRP3 is upregulated in cerebral haemorrhagic stroke and exhibits pro-inflammatory effects (Fig. 3C).

2.5. Peripheral neuropathy

2.5.1. Peripheral neuropathy and senescence

Peripheral neuropathy is a common neurological disorder with multiple causes. Diabetes, exposure to toxins such as alcohol and chemotherapy, immune-mediated diseases and genetic abnormalities are the most common causes. The prevalence of has been investigated to be between 1 % and 12 % in all age groups, with the prevalence of as high as 30 % in older adults [145]. Many of the peripheral neuropathies currently associated with the elderly are dominated by diabetic complications and immune-related disorders, so we focus on diabetes and immune-mediated-related rheumatoid arthritis (RA) as examples.

Diabetic peripheral neuropathy (DPN) is a classic diabetic complication, and DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy [146]. Diabetic complications are most commonly seen in people aged 65 years and older. Specif-ically, 19.9 % of people aged 65–79 years will develop diabetes. In addition, up to 50 % of people with diabetes will develop neu-ropathy associated with increased age and duration of diabetes [147]. Age is therefore strongly associated with the prevalence of DPN in diabetic patients, and increasing age is the most frequently assessed non-modifiable risk factor in most epidemiological studies of DPN [148]. Inflammation, oxidative stress and mitochondrial dysfunction are the three main changes affecting pathological alterations in DPN, and they are mainly thought to be associated with the ageing process [149]. These pathological changes affect thioredoxin-interacting protein (TXNIP), which plays an important role in peripheral neuropathy causing neuropathic pain. TXNIP, also known as thioredoxin-binding protein-2 or vitamin D3 upregulated protein 1, is a multifunctional protein. TXNIP plays a crucial role in controlling glucose and lipid metabolism as well as proliferation and death. It has a WW structural domain which can binds NLRP3 and an SH-3 structural domain. Increased TXNIP/NLRP3 complexes have been observed in studies to boost IL-1 production and inflammation [150]. Thus, TXNIP action may be a factor contributing to neuropathy in diabetic patients during ageing.

RA is a prime example of an immune-mediated disease and there is a link between its onset and advancing age. Rheumatoid arthritis is a chronic, synovial-focused autoimmune disease that can damage joints and impair mobility. An ageing population, increased life expectancy and the growing prevalence of RA in older people are the main reasons for the increase in the elderly population with RA [151]. Both the innate and adaptive immune systems are affected by ageing. Ageing-related non-specific activation of the innate immune system increases the incidence of chronic inflammation and complications [152], while ageing-induced phenotypic changes and functional deficits in the adaptive immune system lead to disruption of immune tolerance and increased prevalence of autoimmune diseases [153]. According to relevant studies, peripheral neuropathy is a well-known extra-articular symptom caused by rheumatoid arthritis, affecting 75.28 % of patients. The functional impairment caused by peripheral neuropathy in patients with rheumatoid arthritis can worsen and manifest itself in a variety of signs and symptoms, including pain, numbness, pins and needles, and muscle weakness [154]. peripheral neuropathy in RA leading to nerve damage can cause nerve inflammation and worsen the pain experienced by patients. Therefore, studying the pathological mechanisms of peripheral neuropathy can help to alleviate patients' suffering in the future.

2.5.2. Peripheral neuropathy and NLR inflammasomes

There is a role for the NLRP3 inflammasome in the pathology of DPN, which is associated with TXNIP in Schwann cells. The main clinical manifestations of DPN are axonal degeneration and peripheral nerve demyelination, and among peripheral nerve cells Schwann cells are the most numerous glial cells, which maintain peripheral nerve shape and function by wrapping unmyelinated axons, myelinated axons and secreting neurotrophic factors to maintain the shape and function of peripheral nerves [155]. Schwann cells are closely associated with the pathophysiology of DPN and are highly sensitive to glucose and insulin levels. As DPN progresses, they undergo apoptosis, which is closely linked to the neurological TXNIP/NLRP3 axis. TXNIP is contained within the thioredoxin (TRX) system, a key regulator of cell proliferation, apoptosis and glycolipid metabolism, as well as a key factor in intracellular defence against oxidative stress. In high glucose Schwann cells, ROS are released from mitochondria under oxidative conditions, promoting the

separation of TXNIP from the TRX system and its attachment to NLRP3. TXNIP subsequently activates the NLRP3 inflammasome in Schwann cells, causing them to release the pro-inflammatory factor IL-1β, which induces neuroinflammation and damages Schwann cells, while participating in the pathological progression of type 2 diabetes [156]. Therefore, it is expected that the symptoms of DNP can be alleviated by inhibiting the ROS/TXNIP/NLRP3 pathway.

In addition, with respect to Schwann cells only, CXCL12 (C-X-C motif chemokine ligand 12) -CXCR4 (CXC-chemokine receptor 4) signaling regulation may be present in Schwann cells, whose mediated inflammatory injury of peripheral nerves is also associated with NLRP3. In the unilateral sciatic nerve chronic constriction injury (CCI) model-induced neuropathic pain, expression of CXCR4, CXCL12 and NLRP3 was significantly elevated, and it was hypothesized that CXCL12-CXCR4 mediates activation of the NLRP3 inflammasome to increase mechanical pain [157]. Studies have further shown that the CXCL12-CXCR4 axis in nerve sheath cells may be involved in sciatic nerve injury by affecting $[Ca^{2+}]$ i, which can activate NLRP3 inflammasome-related activating stimuli. For example, excessive mitochondrial uptake of Ca^{2+} can lead to mitochondrial damage, and the released ROS and mtDNA can act as NLRP3 inflammasome

Table 1

Role of NLR inflammasomes-related inhibitors in the therapy of neurological disorders.SN, substantia nigra; ASC, apoptosis associated speck like protein; TLR, toll-like receptor; α-syn, α-synuclein; IL-1β, interleukin-1 beta; IL-18, interleukin-18; AMPK, adenosine monophosphate-activated protein kinase; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; TXNIP, thioredoxin-interacting protein; PD, Parkinson's disease; AD, Alzheimer's disease; RA, rheumatoid arthritis; ALS, Amyotrophic Lateral Sclerosis; DPN: diabetic peripheral neuropathy; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing.

Mechanism	Candidate	Target	Disease/Model	Effects/pathways	References
Inhibiting NLR inflammasomes constituents	MCC950	NLRP3, ASC	AD, PD, Stroke, RA	Inhibiting ASC oligomerization and secretion and release of Il-1β and IL-18	[163]
	17 β-estradio	NLRP3, ASC	Stroke, ALS	Inhibiting the formation of NLRP3-ASC complex	[162]
	Glyburide/JCC124	NLRP3, ASC	AD, Stroke	Suppressing K-ATP channels and inhibiting ASC agglomeration	[169]
	Ac-YVAD-CMK	Caspase-1	PD, Stroke	Inhibiting caspase-1 to reduce the ability to process pro-IL-1β into IL-1β	[29]
	MNS	NLRP3, ASC	AD, Stroke	Inhibiting ASC speck formation and oligomerization	[165]
	VX740/VX-765	Caspase-1	AD,Stroke, RA	Covalent modification of the catalytic cysteine residue in the active site of caspase-1 resulting in caspase-1 blocking and resultant cleavage of pro-IL-1β/18	[167]
	Bay 11-7082	NLRP3, Caspase-1	AD, Stroke	Inhibiting ATPase activity of NLRP3	[166]
Inhibiting NLR inflammasomes priming pathway	Calycosin	TLR/NF-κB	PD, Stroke	Inhibiting the TLR/NF-κB and MAPK pathways	[170,171]
	Ginkgo diterpene lactones	TLR4/NF-κB	Stroke	Downregulating of TLR4/NF-κB signaling	[172]
	Cordycepin	TLR2	PD	Decreasing TLR2 mRNA expression	[176,177]
	Procyanidins	TLR4/NF-κB	Stroke, DPN	Inhibiting TLR4-NF-κB-NLRP3 signaling pathways	[170]
	Astragaloside IV	TLR4,ROS	Stroke	Inhibiting TLR4 pathway; reducing ROS production	[171]
	Ibudilast (MN-166) (MediciNova)	TLR4	RA	Inhibiting TLR4 pathway	[180]
	Papaverine	NF-κB	PD	inhibiting NF-κB in SN of PD mice to inhibit the activation of NLRP3 inflammatory bodies	[179]
	Isoliquiritigenin (ILG)	NF-κB	Stroke, DPN	Inhibiting NLRP3 inflammasome activation mediated by NF-κB	[175]
	Parthenolide	Caspase-1/NF-κB	AD, Stroke, RA	Inhibiting NLRP3/NLRC4 inflammasome activation mediated by NF-κB (Inhibiting both the protease activity of caspase-1 and ATPase activity of NLRP3)	[172,173]
	Atorvastatin	Caspase-1/NF-κB	AD, DPN	Inhibiting NLRP3 activation and release of IL-1β. Reducing caspase-1 and NF-κB expression and ROS scavenging	[174]
Inhibiting NLR inflammasomes activation pathway	Fingolimod (FTY720)	ROS	PD, Stroke, ALS	Inhibiting MPTP-induced microglial activation in the SNpc, suppressed the production of IL-6, IL-1β, and tumor necrosis factor-α	[190,191]
	Cyclo (His-Pro)	ROS	ALS	Decreasing protein nitration through downregulating expressions of nitric oxide and ROS	[181]
	Minocycline	ROS	AD, PD, Stroke, ALS	Stoping microglial activation; inhibiting maturation and release of proinflammatory cytokines IL-1β/IL-18	[182]
	Idebenone	ROS	AD, PD, Stroke	Decreasing ROS and cytosolic oxidized mt-DNA, suppressing uncontrolled NLRP3 activation.	[183]
	NSAIDs (Mefenamic acid, Flufenamic acid …)	Cl- channel	AD, PD, RA	Block Cl⁻ channel to inhibit NLRP3 inflammasome activation	[185]
	CA074Me	Cathepsin B	AD	Abrogating the increase in ROS treatment with α-syn aggregates	[186]
	Sinomenine	AMPK	Stroke, RA	Inhibiting the NLRP3 inflammasome mediated by AMPK pathway	[184]

activators and trigger inflammatory responses [158]. Thus, a CXCL12-CXCR4-[Ca^{2+}] i-NLRP3 inflammasome axis may exist in Schwann cells and be associated with inflammatory damage in peripheral nerves.

There may be a link between chronic pain and inflammation caused by nerve injury in RA and NLR inflammasomes. Regarding the NLRP3 inflammasome, which plays a role in many diseases, several studies have shown that NLRP3 mRNA and NLRP3 inflammasome-associated protein are upregulated in monocytes, macrophages in RA patients [159], presumably linking NLRP3 to nerve damage due to inflammation during RA. It is relatively clear from current studies that the NLRP1 inflammasome is an important factor in peripheral neuropathy in RA and is associated with P2X4 and P2X7 receptors. In the pathological process of RA, after the inflammatory response in the synovial fluid leads to peripheral nerve injury, the release of ATP and prostaglandins (PG) from the damaged nerve activates P2X4R and P2X7R expressed on macrophages. Subsequently, the activated P2X4R regulates high Ca^{2+} influx into macrophages possibly activating p38 MAPK, leading to central pain mediators brain-derived neurotrophic factor (BDNF) and prostaglandin E2 (PGE2) release into synovial fluid and peripheral nerves, exacerbating pain perception in RA patients [160]. Significant leukocyte infiltration, synovial hyperplasia and significant cartilage damage have been reported to be attenuated following administration of P2X4R antisense nucleotides (P2X4R gene inhibitors), and NLRP1 inflammasome inhibition has been found, revealing the importance of NRLP1 involvement in inflammasome signaling pathways in the pathogenesis of RA following P2X4R activation [161]. Furthermore, activated expression of P2X7R causes macrophages to produce pro-inflammatory factors that further stimulate the release of IL-1β and IL-18 from NLRP1 inflammasomes on macrophages. In addition, RA-induced P2X4R/P2X7R/NLRP1-mediated neuro-inflammation may be involved in pain propagation in the central nervous system. In turn, chronic inflammation generated in the peripheral nervous system may lead to bone erosion, generating injury signals that can likewise be transmitted to the centre and develop into thermal pain and mechanical hypersensitivity. Therefore, inhibition of P2X4R/P2X7R/NLRP1 expression may be a potential pathway to improve RA symptoms (Fig. 3D).

3. Treatment strategies for delaying age-related diseases based on NLR inflammasomes

3.1. Therapeutic strategies using NLR inflammasomes inhibitors

According to the various studies available, inhibition of the NLR inflammasomes has great potential for the prevention and treatment of neurodegenerative diseases. Depending on the way in which the inhibitors act, they can usually be divided into inhibition of the components of the NLR inflammasomes and inhibition of their activation signals. However, as previously described NLRP3 activation also requires an initiation signal and degenerative neuropathies commonly involve NLRP3 inflammasomes, so inhibitors are broadly classified as (1) inhibiting NLR inflammasomes components, (2) inhibiting NLRP3 initiation signals, (3) inhibiting NLRP3 activation signals, and (4) inhibiting by other means. The table summarizes some of the NLR inflammasomes inhibitors currently being used experimentally or clinically (Table 1).

With regard to inhibition of the NLR inflammasome components, the currently relevant inhibitors aim to inhibit inflammatory complex assembly by targeting the component proteins, mainly NLR inflammasomes monomers such as NLRP3 and NLRC4, ASC adapter proteins, effector proteins such as caspase-1, and IL-1β and IL-18 [29,162]. MCC950, a dimeric sulfonylurea compound, is the most studied and effective inhibitor of the NLRP3 inflammasome. It can inhibit NLRP3 activation by acting on NLRP3 monomers and ASC [163]. It has been shown to reduce the secretion of IL-1β and IL-18 by abrogating ASC oligomerization in human and mouse macrophages [164]. Also, MCC950 can block ATP hydrolysis and inhibit NLRP3 inflammasome formation and activation by directly interacting with the Walker B motif of the NLRP3 NACHT structural domain. The development status of its clinical drug application in RA is currently clinical phase 2. Alternatively, 3,4-methylenedioxy-β-nitroso styrene (MNS) has been shown to specifically block NLRP3-induced ASC spot formation and oligomerization as well as inhibit NLRP3 ATPase activity [165]. In addition to targeting NLR monomeric and adapter proteins ASC, for caspase1, Parthenolide and Bay 11–7082 were shown to directly inhibit activation of the protease caspase-1 to suppress various inflammasomes in macrophages [166].Caspase-1 inhibitor VX-765 in animal models of AD showed neuro protective effects and attenuated neuropathic and cognitive deficits [167], while another inhibitor, VX-740, was undergoing phase II trials in RA but was discontinued due to hepatotoxicity in long-term treatment [168]. In addition, although glyburide is a commonly used drug for the treatment of type 2 diabetes, it has also been found to act on compounds upstream of NLRP3 to inhibit caspase-1 activation and IL-1β secretion, and its intravenous formulation RP-1127 for ischemic stroke and cerebral edema has been entered into clinical phase 2 trials (NCT01454154, NCT01268683) [169]. Finally, although it is possible to inhibit the inflammasome effector proteins IL-1β and IL-18 alone, i.e., by applying IL-1β antibodies or IL-1 receptor antagonists to inhibit the NLR inflammasomes for the treatment of related diseases, their targeting efficacy is controversial and thus it is currently difficult to progress towards clinical application.

The initiation signals for NLRP3 are usually TLR and NF-κB, so by inhibiting this initiation signal an inhibitory effect on the inflammatory response generated by NLRP3 can also be achieved [170–175]. Both of the phytochemicals, calycosin and cordycepin, show neuroprotective effects in the MPTP model of PD via inhibition of the TLR/NF-κB signaling pathway [176,177]. Another natural compound, Ginkgo diterpene lactones (GDLs), inhibits platelet aggregation, astrocyte activation and pro-inflammatory cytokine release, which may be associated with downregulation of the TLR4/NF-κB signaling pathway [178]. Papaverine, a non-addictive opiate alkaloid, is clinically used for the treatment of disorders associated with gastrointestinal spasm and disorders associated with movement disorders. It has also been shown to inhibit NF-κB in the SN of PD mice to suppress NLRP3 inflammasome activation, thereby reducing microglial activation and neuronal cell death. Thus, it is also a potential drug candidate for PD and other neurodegenerative diseases associated with microglial phase initiation and activation. In addition to a number of natural compounds, a small molecule NPT520-34 (Neuropore) (NCT03954600) that has completed phase I clinical trials reduced TLR2 mRNA expression in PD

transgenic mice, resulting in improved neuropathology and motor deficits in these animals [179]. Ibudilast (MN-166) (MediciNova) from the phase II clinical trial in amyotrophic lateral sclerosis (NCT02714036) is also another potential TLR4 antagonist [180].

In degenerative neuropathies, the activation signal of NLR inflammasomes usually involves ion fluxes, release of Cathepsin B in ruptured lysosomes, and ROS. Therefore, by interfering with these mediators the activation of NLR inflammasomes can be blocked and related inhibitors may be potential therapeutic agents for related neuropathies [181–184]. The NSAID flufenamic acid is a well-established ion channel modulator that has been shown to inhibit NLRP3 inflammasomes by a mechanism of action through inhibition of Cl⁻ channels [185]. Cathepsin B released from lysosomes can also be targeted to inhibit NLRP3 activation. Experimentally, it was demonstrated that after treatment of AD models with CA074Me, it could be observed that CA074Me inhibited the conversion of Cathepsin B to the active form, had an ameliorative effect on memory dysfunction and reduced Aβ plaques [186]. Later, this inhibitor was found to inhibit ROS release in neuronal cells intervened with polymerised α-syn [187]. Alternatively, preventing ROS release from damaged mitochondria and ruptured lysosomes may also be a potential treatment for neurodegenerative diseases. In a 6-OHDA/MPTP-induced PD model, the natural compounds Antrodia camphorata polysaccharide and tenuigenin inhibited ROS-NLRP3 activation [188,189]. In addition, Dl-3-*n*-butylphthalide and fingolimod (FTY720), a sphingosine-1-phosphate receptor antagonist, inhibited mtROS, which inhibited NLRP3 inflammasome activation in PD models [190,191]. Of these, the application of FTY720 to ALS and ischemic stroke (IRCT20220423054619N1, NCT04629872) has been entered into clinical phase 2 trials.

In addition to inhibiting structural proteins of the inflammatory complex and inhibiting initiation and activation signals, there are a number of inhibitors that inhibit inflammasome activation by other means. For example, melatonin can reduce neuroinflammation in animal models of PD by reducing NLRP3 inflammasome activation, which is regulated by histone deacetylase silencing information regulator 1 (SIRT1); edaravone (MT-1186) has been shown to switch the M1/M2 phenotype and modulate NLRP3 inflammasome activation, with clinical trials applied to ALS into phase III (NCT04577404) [192,193]. However, how SIRT1 and MT-1186 target NLRP3 is unknown. The novel compound, 5-(3,4-difluorophenyl)-3-(6-methylpyridin-3-yl)-1,2,4-oxadiazole (DDO-7263), can reduce neuroinflammation in vivo by activating the transcription factor Nrf2, the definitive mechanism of which remains to be determined [194].

In addition, in addition to the usual synthetic drugs and natural compounds, stem cell-related biological products can also act as inhibitors of NLR inflammasomes. Mesenchymal stem cells (MSCs) can differentiate into a variety of cell types including neurons and have the ability to self-renew. The neurotrophic factors secreted by stem cells have neuroprotective and neuroregenerative effects. When human mesenchymal stem cells were transplanted into animal models of PD, they reduced the loss of dopaminergic neurons and increased dopamine levels [195]. Additional studies on AD have shown that glia-like cells from human MSCs reduces a β-induced activation of NLRP3 in neural stem cells, increases the viability and proliferation of neural stem cells, and repairs damaged nerves. Furthermore, intra-arterial infusion of MSCs after stroke reduces infarct size and enhances motor function and behavior, and a decrease in TNF-α, NF-κB, NLRP1, NLRP3 and the apoptotic marker caspase-3 can be observed [196]. Moreover, transplantation of human umbilical cord blood-derived pluripotent stem cells (HCB–SCs) co-cultured with lymphocytes in ischemic brain tissue reduced the expression of NLRP3 and related factors, inhibited NF-κB and extracellular signal-regulated kinase (ERK) activity and reduced ischemic brain injury [197]. The above suggests that some stem cell bioproducts can inhibit the associated inflammatory response and may be a therapeutic product for neurological disorders, while there are also many inhibitors of NLR inflammasomes-related compounds with unclear mechanisms that are potential therapeutic agents for neurodegenerative diseases.

Overall, very few inhibitors of NLR inflammasomes are currently being used in the clinical setting for the treatment of neurodegenerative diseases. Although a number of drugs are in clinical trials, as mentioned earlier some inhibitors have been discontinued due to toxic side effects. It is clear that more in-depth research is needed to bring NLR inflammasomes-related inhibitors into clinical use, and the discovery of effective and specific NLRP3 inflammasome inhibitors with fewer side effects should be a major goal of future research. However, there are other research strategies for NLR inflammasomes besides drug development, so we focus on physical therapy, which is more commonly used and generally applicable in the clinic.

3.2. Treatment strategies using physical therapy

In addition to pharmacological interventions, physical therapy is one of the medical treatments that can help improve age-related degenerative neuropathy. It has been shown that lack of adequate exercise training may increase the risk of stroke, AD and PD, while physiotherapy can reduce the risk of developing them [198]. The physiotherapy mentioned here includes patient-initiated physical exercise as well as passive manipulative therapy. It has been suggested from various studies that the improvement of neuropathy by these modalities may involve the modulation of NLR inflammasomes.

As a form of physiotherapy, regular exercise training can improve the symptoms of neurodegenerative diseases. In older adults, for example, aerobic exercise has shown an improvement in cognitive function [199]; moderate aerobic exercise helps maintain peripheral nerve function and is helpful in counteracting the health behaviors associated with DPN in type 2 diabetics [200]. Chronic pain is also a common manifestation of neurological disorders associated with ageing, and the mechanism is broadly based on the immune and nervous systems working in concert to activate pain pathways through interactions between immune cells, glial cells and neurons. Among the numerous interactions are the synthesis and release of neurotransmitters and inflammatory mediators [201], and it is thought that long-term exercise is beneficial in reducing disease-associated inflammatory signaling and may reduce the chronic pain associated with neurological disease [202]. Overall, therefore, exercise has been used as a form of intervention to activate this natural anti-inflammatory mechanism, prompting cells to produce anti-inflammatory cytokines or inhibiting pain from pro-inflammatory cytokines [203]. Cytokines such as IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, TGF-β and TNF-α become active during neuropathic pain in the spinal cord and DRG [204]. Regular exercise in older adults has been shown to reduce inflammation-related

markers [205]. Many of these markers have been shown to be closely associated with NLR activation. Thus, it is reasonable to hypothesize that NLR inflammasomes are involved in the regulation of inflammation-related markers by exercise and that symptoms of neurodegenerative diseases may be improved by exercise.

The regulation of NLR inflammasomes by exercise in certain neurological disorders has now been demonstrated. Existing studies have shown that exercise can attenuate the pathogenesis of AD and PD by downregulating the expression of pro-inflammatory cytokines and inhibiting NLR inflammasomes-mediated microglia activation in patients or animal models [206]. For example, NLRP3 and NLRP1 can be significantly reduced by exercise and supplementation, which can help combat Alzheimer's disease [207]. In PD models, neurotrophins associated with regular physical activity were found to stabilise intracellular calcium concentrations, induce the expression of antioxidant enzymes and inhibit the release of pro-inflammatory cytokines [208]. Notably, moderate-intensity treadmill exercise has typically been shown to significantly inhibit NLRP3 inflammasome activation in the hippocampus, prefrontal cortex and substantia nigra in both mice and rats. These are usually associated with metabolic disorders, hypoxia, ageing, Alzheimer's disease, depression, and cerebral ischemia [209]. In addition, mitochondria are involved in regulating NLRP3 inflammasome activation and it has been hypothesized that mitochondrial adaptations to exercise may influence NLRP3 inflammasome activity. Studies have shown that chronic moderate intensity exercise promotes mitochondrial biosynthesis, enhances antioxidant capacity and inhibits NLRP3 inflammasome hyperactivation [210,211]. Chronic moderate-intensity exercise may reduce mtROS production by modulating mitochondrial mass (mitochondrial proliferation and activation of mitophagy) to improve mitochondrial function and enhance clearance of damaged mitochondria, thereby inhibiting the NLRP3 inflammasome pathway and alleviating excessive inflammatory responses. In addition, physical exercise may also interfere with the NLRP3 initiation signal TLR/NF-κB to delay the onset or progression of neurodegenerative disease. Physical exercise preconditioning has been shown to ameliorate acute ischemic brain injury in rodents, including suppression of TLR4 signaling, which inhibits immune processes. Similarly, significantly lower levels of α-syn were found in PD mice subjected to resistance exercise, along with reduced expression of TLR2 and NF-κB [212]. Taken together, it is reasonable to suggest that physical exercise could mediate the inhibition of neurodegenerative disease by NLRP3 by affecting pro-inflammatory factors, mitochondrial function and the initiation signals associated with it.

Notably, the effects on the status of NLR inflammasomes differed for different exercise intensities. Chronic moderate-intensity running significantly reduced NLRP3 inflammasome activation in peripheral blood mononuclear cells (PBMCs) in healthy men, whereas chronic high-intensity running activated NLRP3 inflammasomes [213]. Meanwhile, chronic moderate intensity exercise significantly reduced the expression of the metabolic disorder-induced inflammatory cytokines TNF-α and IL-6 and increased the expression of mitochondrial proteins, whereas high intensity exercise resulted in mitochondrial dysfunction and increased secretion of pro-inflammatory factors [214,215]. Therefore, the effect of exercise on NLRP3 inflammatory activity depends mainly on the intensity of exercise, and only scientifically appropriate exercise can achieve inhibition of inflammasome activation.

In addition to the common running exercise in experiments, Tai-Chi has been shown to play a role in improving neurodegenerative diseases as an aerobic exercise. Tai-Chi is a cognitive exercise that is usually performed at light to moderate motor intensity. Deep breathing, relaxation, and mental focus are typically synchronized with graceful, slow, and fluid movements as part of the choreographed program. According to research on people with Alzheimer's disease and moderate cognitive impairment (MCI). The discovery that sustained Tai-Chi training has a positive effect on white matter brain networks and cognitive performance seems to support the theory that physical intervention utilizing Tai-Chi training may be a potential strategy for preventing AD [216]. According to a systematic study, Tai-Chi exercise can help people with neurodegenerative diseases reduce their risk of falling and improve their motor function and general cognitive function [217].

Another systematic review reported that many experiments confirmed that Tai-Chi produces anti-inflammatory effects, leading to a reduction in neuroinflammation and neurodegenerative lesions by decreasing pro-inflammatory cytokines (IL-1, 2, 8, 12, interferon-γ, NF-κβ) [218]. In the elderly, tai chi has been shown to have the ability to alter psychological stress levels and attenuate the rate of increase of the stress-related transcription factor NF-κB [219]. Additionally, enhancing the Berg Balance Scale (BBS) and stride length with Tai Chi training for a year was more effective for Parkinson's patients than brisk walking, and this was connected to IL-1β downregulation [220]. There is a definite connection between IL-1, NF-κB, and NLR inflammasomes; for instance, in glial cells, NF-κB can be decreased by lowering circulating levels of IL-1 and IL-6, and the activation of the NLRP3 inflammasome can depend on NF-κB. As a result, it is reasonable to assume that NLR inflammasomes play a role in the Tai-Chi suppression of neuroinflammatory processes such as brain neuropathology (such as ischemia) and neurodegeneration (such as AD).

In addition to active exercise training, massage techniques used in physiotherapy can help address neurological problems associated with ageing [221]. Meridian massage is known to stimulate recovery of brain and motor function after cerebral infarction, reduce neurological damage and repair damaged brain tissue [222]. Studies have demonstrated that Tuina can promote recovery from cerebral ischemia by upregulating the neurotrophic factor BDNF. SIRT-1/BDNF/NF-κB signaling associated with NLRP inflammasome activation is present in ischaemic stroke, and low levels of SIRT-1 and BDNF in the brain are associated with increased expression of TNF-α, NF-κB and interleukins [223]. It is therefore reasonable to suppose that the mechanism of massage to promote recovery from stroke is linked to NLR inflammasomes. In addition, traditional Japanese massage (Anma), Thai massage, reflexology, neuromuscular therapy (NMT) and Tui Na in Chinese medicine have been shown to be effective in treating depression, muscle stiffness and tremor in PD patients [224]. In rats suffering from neuropathic pain, massage inhibits the TLR4 signalling pathway and reduces inflammatory factors [225]. Manipulations such as Gua Sha [226] and Thai foot massage [227] are helpful in diabetic peripheral neuropathy. Although the mechanisms by which these manipulative therapies improve neuropathy are less certain, we hypothesize that NLR inflammasomes contribute to this.

Acupuncture, a commonly used alternative therapy internationally, has also shown significant efficacy in the treatment of neurodegenerative pathologies. In terms of how acupuncture affects the inflammatory body in disease development, more current

research suggests that acupuncture therapy can reduce neuroinflammation in patients with AD and PD by modulating NLRP3 and NLRP1. The NLRP3 inflammasome is a molecular target for neuroprotective and therapeutic interventions in AD, and meta-analyses not only confirm the high safety profile of acupuncture but also suggest that this technique is superior to medication in improving daily living abilities in AD patients and may even enhance the effects of medication therapy [228]. Acupuncture improves hippocampal connectivity, modifies default mode network activity, and activates certain cognitively-related areas in AD patients, according to functional magnetic resonance imaging(fMRI) studies. Manual acupuncture (MA) improved spatial learning and memory in senescence-accelerated prone mouse/8 (SAMP8) after 15 days, and immunohistochemical staining revealed that NLRP3, ASC, caspase-1, and IL-1 positive staining cells became more abundant in the AD group [229]. It is possible that MA can exert its anti-inflammatory effects by inhibiting the NLRP3 inflammasome-induced neuroinflammatory response, negatively regulating the NLRP3/caspase-1 pathway, and reducing IL-1β maturation and secretion in the hippocampus, protecting the nervous system and alleviating the disease in AD patients. In PD, acupuncture has also been shown to increase DA fibre and neuronal levels in the SN, down-regulate glial fibrillary acidic protein, NF-κB and TNF-α, thereby reducing neuroinflammation to protect DAn, which may be associated with the inhibition of NLRP3 initiation signaling [230].

NLRP1 can also be regulated by acupuncture. A study, which similarly used the SAMP8 mouse AD model verified by Western blot, confirmed that NLRP1, ASC, cleaved-caspase-1, IL-1β, and IL-18 may be inhibited in the hippocampus of AD mice by acupuncture at the "Baihui(DU20)", "Shenshu(BL23)", "Xuehai(SP10)," and "Geshu(BL17)" acupoints [231]. As previously indicated, activation of P2X7/pannexin 1 leads to Aβ-induced neuronal death, which in turn activates the NLRP1 inflammasome through the AMPK signaling pathway. Electroacupuncture has been shown to suppress P2X7 receptor-mediated microglial activation and to reduce neuropathic pain [232]. It is inferred that NLRP1 inhibition is a mechanism by which manual acupuncture and electroacupuncture can reduce Aβ-induced neuronal death in AD.

In addition, other neurodegenerative diseases such as ischemic stroke and ALS can be improved by acupuncture-related treatments. For example, acupuncture interventions can significantly reduce the size of infarcted areas in stroke patients, improve cerebral blood circulation to promote regional energy metabolism, inhibit cerebral cortical apoptosis, reduce neurogenic toxicity, alleviate cerebrovascular immune inflammatory responses, and upregulate the expression of anti-apoptotic genes and neurotrophic factors, etc., thereby promoting the proliferation and differentiation of neural stem cells in the focal cerebral cortex and hippocampus [233]; electroacupuncture can reduce the neuroinflammatory response, etc [234]. Modulation of pro-inflammatory factors has been addressed in these studies, but direct evidence for the association of NLR inflammasomes with acupuncture intervention in these neurodegenerative diseases is lacking. Overall, exercise training, manual massage and acupuncture in physical therapy are all viable treatments for neurological related disorders, but more research is needed to explain their association with NLR inflammasomes in the mechanisms by which they exert their efficacy.

4. Conclusions

The development and progression of numerous neurological disorders associated with ageing involve the participation of NLR inflammasomes. The pathogenesis of the ageing process and the inflammatory conditions leads to an increase in various pro-inflammatory cytokines, metabolites, aggregates and chemical reactions. All of these have been shown to activate various NLR inflammasomes in different neurological diseases through different mechanisms, further driving neuroinflammation and disease progression. This review identifies age-related neurological diseases that are specifically related to NLRP1/3/6/10 and NLRC4/5. Among these, with the exception of NLRP6 and NLRC5, which can negatively regulate inflammation onset, the remaining NLR inflammasomes have been found to exhibit pro-inflammatory effects in various neurological diseases, with NLRP3 being the most studied mechanism.

Therapeutic strategies involving the modulation of NLR inflammasomes for neurological related diseases in the elderly have also received attention. Despite the emergence of several experimental inflammasome-targeting inhibitors, only a handful have successfully passed clinical trials, indicating a need for further research and drug development. In recent years, physiotherapy, such as exercise training, Tui Na massage techniques and acupuncture, which have received more attention, have also been shown to improve neurological symptoms by modulating factors related to the inflammasome, although the precise mechanisms of action remain to be explored further. One of the major clinical limitations of inhibitors is their side effects, suggesting that combination therapies may be used to reduce the adverse effects of drugs and increase their efficacy.

In conclusion, this review provides an overview of the links and pathological mechanisms of ageing with neurodegenerative diseases and neurological injury, examines the role of NLR inflammasomes in disease progression, and the therapeutic approaches and applications based on NLR inflammasomes. As neurological disorders are strongly linked to human quality of life and lifespan, further research is required to gain a deeper understanding of the mechanisms underlying the potential therapeutic benefits of NLR inflammasomes in the context of ageing.

List of abbreviations

NOD   Nucleotide-Binding Oligomerization Domain
PYD   Pyrin Domain
CARD   Caspase Recruitment Domain
PRRs   Pattern Recognition Receptors
NLRP   Nucleotide- Binding Oligomerization Domain, Leucine- Rich Repeat and Pyrin Domain- Containing

NLRC	Nucleotide-Binding Oligomerization Domain, Leucine-Rich Repeat and Caspase Recruitment Domain- Containing
NF-κB	Nuclear Factor Kappa B
IL	Interleukin
ASC	Apoptosis-Associated Speckle-Like Protein
TNF	Tumor Necrosis Factor
PAMPs	Pathogen-Associated Molecular Patterns
DAMPs	Damage-Associated Molecular Patterns
Aβ	Amyloid β
PD	Parkinson's Disease
AD	Alzheimer's Disease
α-syn	α-Synuclein
DA	Dopaminergic
DAn	Dopaminergic Neurons
SN	Substantia Nigra
ROS	Reactive Oxygen Species
mtDNA	Mitochondrial DNA
TLR	Toll-like Receptor
CHM	Chinese Herbal Medicines
NFTs	Neurofibrillary Tangles
VEGF-1	Vascular Endothelial Growth Factor 1
AMPK	Adenosine Monophosphate-activated Protein Kinase
ALS	Amyotrophic Lateral Sclerosis
NMJ	Neuromuscular Junction
SOD1	Superoxide Dismutase 1
TDP-43	Transactive Response DNA-binding Protein-43
VCP	Valosin-Containing Protein
BBB	Blood-Brain Barrier
CNS	Central Nervous System
ICH	Intracerebral Hemorrhage
MCAO	Middle Cerebral Artery Occlusion
Nrf2	Nuclear factor erythroid 2-related factor 2
OGD	Oxygen-Glucose Deprivation
RA	Rheumatoid Arthritis
DPN	Diabetic Peripheral Neuropathy
TXNIP	Thioredoxin-Interacting Protein
TRX	Thioredoxin
MSCs	Mesenchymal Stem Cells
TGF	Transforming Growth Factor

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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