Role of aging-related cytokines in neurodegenerative disease (Review)

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Abstract. Neurodegenerative diseases (NDs) are neurological disorders marked by neuronal damage and functional decline, notably affecting human quality of life and imposing substantial burdens on healthcare systems. The increasing prevalence of NDs is associated with intensification of population aging worldwide. Consequently, there is need to investigate effective prevention and treatment strategies. Aging is a risk factor for NDs. Throughout the aging process, alterations in the expression of specific cytokines occur, such as IL-6 and tumor necrosis factor-α, precipitating a cascade of chronic inflammatory responses. The present study provides a comprehensive review of the alterations in cytokines associated with aging in NDs and the chronic inflammatory responses they elicit. Furthermore, it explores the mechanisms by which these cytokines contribute to neuroinflammation, neuronal damage and cell death, thereby proposing a novel research direction for the treatment of NDs through cytokine regulation.

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Abbreviations: α-syn, α-synuclein; Aβ, β-amyloid; ACD, accidental cell death; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP/PS1, amyloid precursor protein/presenilin 1; AAV2/1, adeno-associated virus 2/1 chimeric vector; BACE1, β-site amyloid precursor protein cleaving enzyme 1; BBB, blood-brain barrier; cIAP1/2, cellular inhibitor of apoptosis protein 1/2; CNS, central nervous system; CSF, colony-stimulating factor; CXCL10, C-X-C motif chemokine ligand 10; DAMP, damage-associated molecular pattern; Eμ, immunoglobulin heavy chain enhancer; ErbB, erythroblastic oncogene B; ErbB4, Erb-B2 receptor tyrosine kinase 4; FADD, Fas-associated death domain protein; GM, granulocyte-macrophage; HD, Huntington's disease; HMGB1, high mobility group box 1; HTT, huntingtin; IGF-1, insulin-like growth factor 1; IKK, IκB kinase; IL-1RA, IL-1 receptor antagonist; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ND, neurodegenerative disease; NFT, neurofibrillary tangle; NGF, nerve growth factor; NRG, neuregulin; PCD, programmed cell death; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; RIPK1, receptor-interacting serine/threonine-protein kinase 1; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SN, substantia nigra; SNCA, α-synuclein gene; SOD1, superoxide dismutase 1; TGF, transforming growth factor; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TNFR1, TNF receptor 1; VEGF, vascular endothelial growth factor

Key words: aging, cytokine, neurodegenerative disease, neuroinflammation, treatment

Contents

1. Introduction

Aging is a multifaceted process characterized by the progressive decline of biological function, accompanied by chronic inflammation and disruptions in cellular homeostasis. This process is associated with the pathogenesis of neurodegenerative disease (ND). Throughout aging, immune system dysfunction results in an imbalance between pro- and anti-inflammatory factors, creating a persistent inflammatory microenvironment that exacerbates neuronal damage and synaptic dysfunction (1). Cytokines released by the senescence-associated secretory phenotype (SASP) serve a key role in mediating neuroinflammation and neuronal damage (1). Key aging-associated cytokines include IL-6, tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β) and chemokines such as chemokine (C-C motif) ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10) (2). These factors intensify neuroinflammatory responses by activating microglia and astrocytes, which promote β-amyloid (Aβ)

deposition, τ hyperphosphorylation and α-synuclein (α-syn) aggregation, ultimately resulting in neuronal apoptosis and synaptic dysfunction (2).

IL-6 and TNF-α perpetuate chronic neuroinflammation through the NF-κB signaling pathway, as evidenced in lipopolysaccharide (LPS)-stimulated murine microglial cell lines and LPS-hyperresponsive TNFAIP3/A20-deficient murine neuroinflammation models (3,4). By contrast, TGF-β may serve a dual role, being involved in immune regulation and potentially contributing to fibrosis, as observed in both *in vitro* fibroblast cultures and murine models of tissue injury (3,5). Therapeutic strategies targeting aging-associated cytokines, including neutralizing antibodies, receptor antagonists or gene editing techniques, have demonstrated potential in delaying disease progression primarily in mouse models of obesity, type 2 diabetes and aging; however, their safety and efficacy in human subjects require further validation (6,7). The present study aimed to review the pathological mechanisms and therapeutic prospects of age-related cytokines in ND, providing a theoretical foundation for the development of novel intervention strategies (Fig. 1).

2. Cytokine dynamics in aging: Homeostatic imbalance to chronic inflammation

Cytokine classification and function. Cytokines are soluble proteins or glycoproteins with low molecular weight, typically ranging from 6 to 70 kDa, that facilitate intercellular signal transmission and serve crucial roles in regulating physiological processes such as immune responses, cell proliferation, differentiation, metabolism, apoptosis and tissue repair (8). These molecules are secreted by immune cells, including macrophages, lymphocytes and mast cells, as well as by non-immune cells such as endothelial cells, fibroblasts, astrocytes, microglia and other stromal cells (8).

Pro- and anti-inflammatory cytokines. The cytokine family is diverse and can be categorized based on structural characteristics and functional roles. Structurally, cytokines are classified into families, including TNF, IL, IFN, colony-stimulating factor (CSF), TGF, chemokines and GF (9). Furthermore, cytokines are categorized into pro- and anti-inflammatory factors based on their primary biological effects. This classification is not definitive as certain cytokines, including TGF-β1, IL-6 and IL-10, may display both pro- and anti-inflammatory characteristics depending on the specific microenvironment (9).

Pro-inflammatory cytokines, including members of the IL-1 family, TNF-α, IL-6, IL-8, IL-12, IL-17, IL-18, IFN-γ and resistin, are pivotal in initiating inflammatory responses. However, the persistent presence or upregulation of these cytokines can result in chronic inflammation, which is associated with aging and various age-related diseases, such as cardiovascular disease, diabetes and Alzheimer's disease (AD). Conversely, anti-inflammatory cytokines, such as IL-4, IL-10, TGF-β, IL-13 and IL-1 receptor antagonist (IL-1RA), typically decline during the aging process, promoting the development of chronic low-grade inflammation and accelerating the aging process (10).

Other key signaling mediators: GF, chemokines and CSF. Beyond the classical pro- and anti-inflammatory dichotomy, other families of cytokines and signaling molecules play key roles in intercellular communication and tissue homeostasis. GF, such as nerve GF (NGF), vascular endothelial GF (VEGF), insulin-like GF 1 (IGF-1), neuregulin (NRG), and fibroblast GF, are typically not categorized as either anti-inflammatory or pro-inflammatory (11). As the aging process advances, the levels of GF generally diminish, leading to a marked decrease in the capacity for tissue repair and regeneration. Furthermore, chemokines and CSFs do not directly amplify or inhibit the inflammatory response but primarily modulate immune cell functions (12).

Based on their function, chemokines are classified into inflammatory and homeostatic categories. Inflammatory chemokines enhance the inflammatory response by recruiting immune cells to sites of inflammation and include molecules such as monocyte chemoattractant protein-1 (MCP-1), fractalkine and macrophage inflammatory protein-1 (13). homeostatic chemokines serve a key role in regulating the migration of immune cells, attenuating immune responses, maintaining immune homeostasis and facilitating tissue repair. Key chemokines in this category include CXCL12, CCL18 and CXCL13 (14).

Sustained elevation of pro-inflammatory factors. During the aging process, there is a marked elevation in the levels of pro-inflammatory factors, including IL-6, TNF-α, and IL-1β. These factors contribute to the maintenance of chronic low-grade inflammation by facilitating the activation of immune cells and perpetuating the cytokine cascade (15). For example, IL-6 overexpression in collagen-induced arthritis mice and immunoglobulin heavy chain enhancer (Eμ)-IL-6 transgenic mice promotes inflammation via nuclear factor IL-6-driven transcription (16). Moreover, elevated serum IL-6 in humans is associated with cardiovascular disease and type 2 diabetes (17). TNF-α, primarily acting via NF-κB, contributes to aging-associated pathologies such as muscle atrophy and neurodegeneration. This is supported by studies in LPS-stimulated primary murine macrophages and C57BL/6 mice, where TNF/TNF receptor 1 (TNFR1) ablation alleviates lethality caused by NF-κB pathway deficiency (18,19). Inflammatory chemokines are also upregulated with age, promoting monocyte, macrophage and T cell recruitment to inflamed sites (20). Their continuous elevation sustains chronic inflammation and worsens age-associated diseases (13).

Attenuation and functional dysregulation of anti-inflammatory factors. Under physiological conditions, anti-inflammatory factors are crucial for maintaining immune system balance and homeostasis by mitigating excessive immune responses. During aging, the expression of key anti-inflammatory cytokines such as IL-10 and IL-1RA is typically diminished (21). This compromises the immune system capacity to resolve inflammation. Specifically, lower serum IL-10 levels, as observed in a cross-sectional study of 193 adults aged >60 years, impair the suppression of excessive immune responses and are associated with features of metabolic syndrome (22). Similarly, decreased IL-1RA expression leads to heightened activity of the pro-inflammatory cytokines IL-1α and IL-1β (23,24). By contrast, TGF-β undergoes a

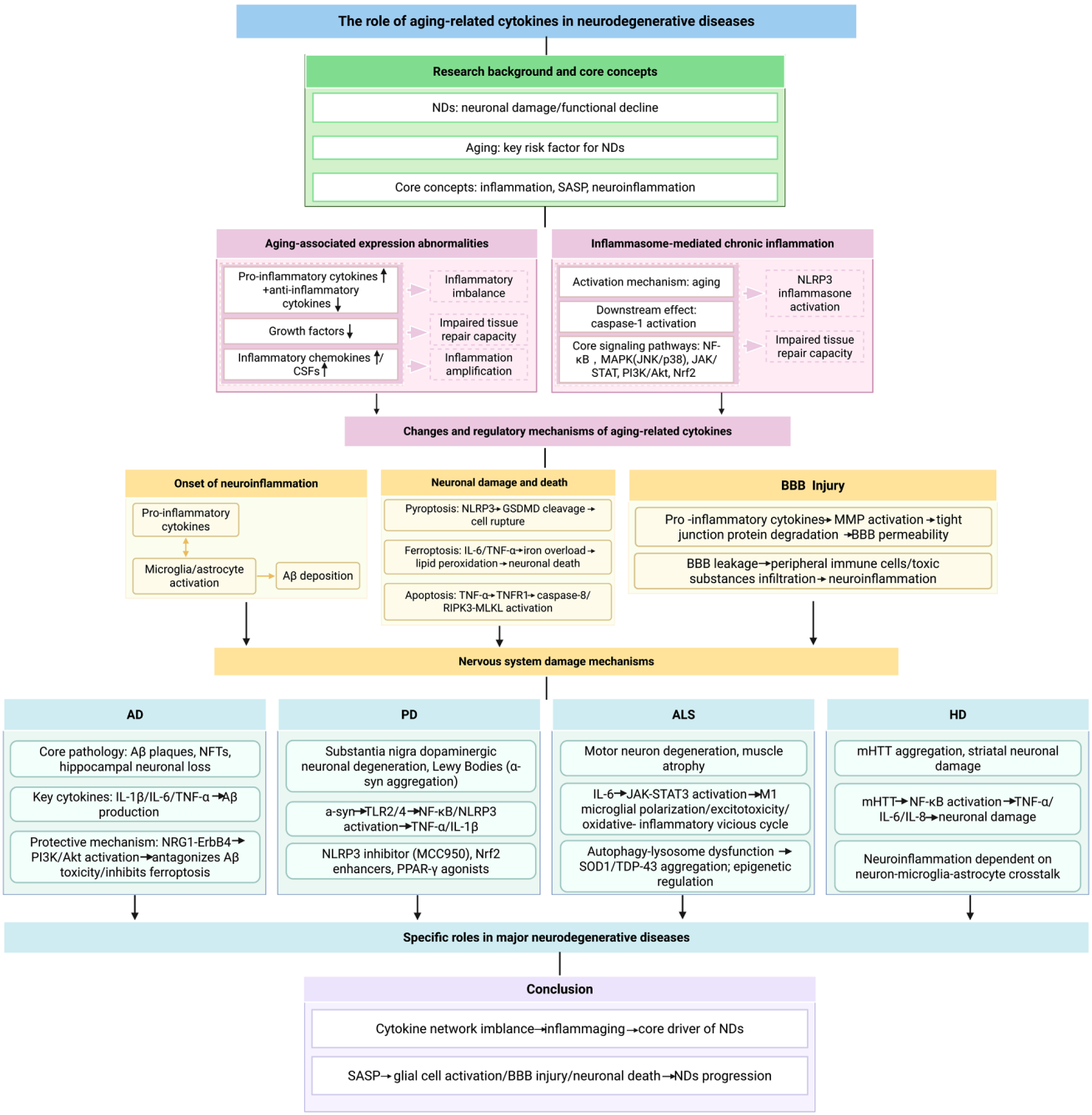

Figure 1. Conceptual framework and logical structure of the present review. ND, neurodegenerative disease; SASP, senescence-associated secretory phenotype; CSF, colony-stimulating factor; GSDMD, gasdermin D; TNFR1, TNF receptor 1; RIPK3, receptor-interacting serine/threonine-protein kinase 3; BBB, blood-brain barrier; Aβ, β-amyloid; NFT, neurofibrillary tangle; NRG1, neuregulin 1; syn, synaptophysin; TDP-43, transactive response DNA binding protein 43; mHTT, mutant Huntingtin.

functional shift rather than a quantitative decline. Although TGF-β serves crucial roles in tissue repair and immune regulation, its signaling becomes dysregulated with age (25). This results in overactivation of the TGF-β pathway, which is associated with pro-fibrotic responses and contributes to tissue senescence and pathological fibrosis, thereby exacerbating chronic inflammation (26).

Generalized decline in GF signaling. Throughout the aging process, GF levels typically decrease, which directly impacts tissue repair, cellular regeneration and immune system functionality (27). To clarify their distinct roles in the aging-associated decline, major GFs can be categorized into two functional groups based on their primary physiological actions: Neurotrophic and angiogenic factors, which support neuronal survival and vascular health, and metabolic and repair-associated factors, which regulate tissue maintenance and regeneration.

Decrease in neurotrophic and angiogenic factors. As individuals age, the concentration of NGF diminishes (28). A deficiency in NGF during aging, as modeled in AD11 anti-NGF transgenic mice, contributes to neurodegeneration resembling AD (29). Similarly, the levels of VEGF typically

decrease with age, which is associated with vascular aging and inadequate tissue oxygenation (30). This can lead to compromised vascular endothelial cell function, thereby impairing tissue repair and regeneration (30). Thus, the decrease in VEGF levels is a notable contributor to age-related declines in vascular function and associated disease, such as cardiovascular disorders (31).

Decrease in metabolic and repair-associated factors. As aging progresses, levels of IGF-1 diminish (32), which can directly impair tissue repair and regeneration, adversely affecting immune function and disease resistance, thereby elevating the risk of infection and illnesses in the elderly population (33). NRG facilitates neuronal survival, migration and synaptic function through interaction with erythroblastic oncogene B (ErbB) receptors (34). With advancing age, NRG expression typically decreases, particularly in ND, and a deficiency in NRG levels markedly impairs neural repair (35). Furthermore, the decrease in NRG levels not only impacts the development of the nervous system but may also exacerbate the progression of ND, thereby accelerating the deterioration of neural function. However, in certain pathological contexts such as AD, regional upregulation of the NRG receptor Erb-B2 receptor tyrosine kinase 4 (ErbB4) has been reported, suggesting a complex, disease stage-dependent regulation (36).

Age-associated increase in M-CSF. The concentration of M-CSF exhibits a positive association with age (37). M-CSF is key in the development and functionality of macrophages, promoting the survival, proliferation and differentiation of mononuclear phagocytes (38). As individuals age, elevated M-CSF levels may enhance macrophage activity, intensifying inflammatory responses (39). Given the critical role of macrophages in pathogen elimination, clearance of damaged cells and facilitation of tissue repair, increased M-CSF levels may contribute to a heightened incidence of inflammatory diseases, thereby worsening age-associated health issues (37).

Role of granulocyte (G-)/G-macrophage (M)-CSF in chronic low-grade inflammation. In chronic low-grade inflammation, as a compensatory mechanism for the declining immune system, levels of G-CSF and GM-CSF rise. This elevation leads to increased production of immune cells, such as neutrophils and macrophages, thereby enhancing immune efficacy. These changes increase the susceptibility of elderly individuals to inflammatory phenomena (40).

Central role of inflammasome activation in inflammaging. Inflammatory senescence is a hallmark of aging, characterized by prolonged immune system activation and a persistent increase in pro-inflammatory factors (41). One of the key mechanisms underlying inflammatory aging is the activation of inflammasomes, which initiate a sustained immune response by promoting the release of pro-inflammatory cytokines such as IL-1β and IL-18 (42). This persistent pro-inflammatory response not only exacerbates tissue damage but also contributes to a decline in immune function (41). Chronic activation of inflammasomes accelerates the aging process and is closely associated with the onset of age-related diseases such as AD, atherosclerosis, and type 2 diabetes (43). Therefore, the continuous activation of inflammasomes is a key driver of age-related immune decline and disease progression.

NLRP3 inflammasome activation by aging-associated stimuli. As aging advances, the intracellular levels of reactive oxygen species (ROS) increase. ROS not only directly damage cell components but also function as signaling molecules to activate the NOD-like receptor protein 3 (NLRP3) inflammasome. In murine bone marrow-derived macrophages, ATP-induced oxidative stress upregulates NLRP3 expression and promotes its cytoplasmic aggregation, thereby activating Caspase-1 and driving IL-1β/IL-18 secretion (44). During aging, mitochondrial function declines, and the damage signals released by mitochondria, such as cytochrome C, activate the NLRP3 inflammasome (45). Concurrently, the increase in mitochondrial peroxides augments ROS production, thereby promoting inflammasome activation (46). Senescent cells typically exhibit damage or leakage of the cell membrane, resulting in the release of intracellular endogenous harmful molecules, such as ATP and uric acid crystals, into the extracellular environment. These molecules serve as danger signals, activating the NLRP3 inflammasome in immune cells and triggering an immune response (47).

Downstream signaling networks amplifying the inflammatory response. During the aging process, the activation of inflammasomes not only influences the immune response through intrinsic mechanisms but also intensifies the inflammatory response by engaging cellular signaling pathways, such as the NF-κB, MAPK, JAK/STAT, phosphoinositide 3-kinase (PI3K)/Akt and Nrf2) signaling pathways.

NF-κB serves as a key transcription factor that governs physiological processes such as immune response, cell proliferation, survival and aging (48). Inflammasomes initiate a cascade of reactions via the activation of NLRP3, thereby facilitating the upregulation of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α. This process is predominantly mediated by the regulatory function of the NF-κB signaling pathway (49,50). The activation of NLRP3 results in degradation of IκB, an inhibitor of NF-κB, thereby alleviating the suppression of NF-κB. This facilitates translocation of NF-κB into the nucleus, where it initiates the transcription of genes associated with inflammation (51). Prolonged activation of NF-κB sustains the pro-inflammatory response in immune cells and may contribute to the progression of aging-associated diseases. Consistent with this, NF-κB activation has been identified as a key mediator of synaptic repair in early-stage AD mouse models (52,53).

MAPK signaling pathway is a key pathway in cell response to external stimuli, involving cell proliferation, differentiation, survival and death (54). NLRP3 inflammasome activates JNK and p38 MAPK through stress signals such as ROS, enhances the secretion of IL-6, TNF-α and other pro-inflammatory factors and maintains and aggravates chronic low-grade inflammation (55). This ROS-MAPK-NLRP3 axis has been validated in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) mouse model, where its inhibition alleviates neuroinflammation and motor deficit (56). Overactivation of MAPK signaling increases

cellular oxidative stress, promotes the aging process and serves a key role in aging-associated diseases, such as PD (57).

The JAK/STAT signaling pathway serves a key role in cytokine signal transduction, primarily regulating cell proliferation, differentiation, immune responses and senescence (58). In aging, the JAK/STAT pathway is activated by pro-inflammatory cytokines, such as IL-6 and TNF-α, thereby amplifying the immune cell response to inflammation, perpetuating chronic inflammation and accelerating the aging process (59). Dysregulation of this pathway is associated with immune system disorders, particularly in aging-associated diseases such as NDs, cardiovascular disease and diabetes. Metabolic stressors can exacerbate inflammation by augmenting JAK/STAT signaling, directly linking this pathway to the pathophysiology of multiple age-related conditions, such as rheumatoid arthritis, atherosclerosis, and PD (60,61).

The PI3K/Akt signaling pathway is key to the regulation of cell survival, proliferation and metabolism and it plays a crucial role in cellular adaptation to stress. While the PI3K/Akt pathway typically exerts an anti-inflammatory effect by inhibiting pro-inflammatory pathways, its prolonged activation may contribute to chronic low-grade inflammation during aging (62). Concurrently, the NLRP3 inflammasome can activate the PI3K/Akt pathway via pro-inflammatory factors, such as IL-6, which are upregulated by the NF-κB signaling pathway, thereby enhancing cytokine secretion and perpetuating chronic low-grade inflammation (63). Excessive activation of the PI3K/Akt pathway may result in the persistence of inflammatory responses, contributing to age-associated metabolic disorders and diminished immune function. In BV-2 murine microglial cells and a transient middle cerebral artery occlusion/reperfusion (tMCAO/R) mouse model of cerebral ischemia-reperfusion, modulation of this pathway directly regulates microglial phenotype and autophagic activity (64).

Nrf2 serves as a key transcription factor in cell antioxidant defense mechanisms, primarily sustaining redox homeostasis via the regulation of antioxidant enzyme expression, including heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (65). Throughout aging, oxidative stress accumulation stimulates Nrf2 activation, thereby augmenting the cell antioxidant capacity (66). In the context of chronic low-grade inflammation, Nrf2 mitigates the accumulation of ROS and lipid peroxidation by modulating the expression of antioxidant genes, which in turn attenuates the activation of NLRP3 inflammasomes (67). Concurrently, Nrf2 suppresses excessive immune responses by upregulating anti-inflammatory factors, such as IL-10 (68). Conversely, during aging, the regulation of Nrf2 becomes impaired. This impairment is driven by upstream factors such as the upregulation of glycogen synthase kinase-3β and leads to a functional decline compromising the cellular responsiveness to oxidative stress, as demonstrated in aged C57BL/6 mouse models of hepatic ischemia-reperfusion injury and senescent L02 hepatocytes (69,70) (Fig. 2).

TGF-β is a pleiotropic cytokine involved in immune regulation, cell proliferation and aging (71). During aging, TGF-β signaling becomes dysregulated, contributing to chronic low-grade inflammation and fibrosis (72). Within the inflammatory network, TGF-β positively modulatse immune responses via Smad-dependent pathways (73). Moreover, it acts with NF-κB and MAPK signaling to promote tissue remodeling. Activation of the NLRP3 inflammasome may exacerbate fibrosis by upregulating TGF-β expression (74).

3. Mechanism of influence of aging-associated cytokines on the nervous system

Occurrence of neuroinflammation. Neuroinflammation has been reported to result in the activation of inflammatory cells within the brain, primarily microglia and astrocytes (75). Concurrently, factors such as immune senescence, mitochondrial dysfunction, autophagy and dysfunction of the ubiquitin-proteasome system contribute to a sustained state of chronic inflammation (76). In this activated state, inflammatory cells release cytokines, which are implicated in the pathogenesis of various types of ND (77), including AD and PD, by inducing neuronal synaptic dysfunction and excitotoxicity.

Under physiological conditions, microglia exhibit phagocytic activity, facilitating the removal of damaged neurons and promoting tissue repair. Concurrently, astrocytes contribute to neuroprotection by clearing debris from the cerebrospinal fluid. During neuroinflammation, IL-1 secreted by activated microglia and astrocytes engages MAPK signaling, leading to upregulation of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and enhanced Aβ formation (78). IL-1 also promotes τ hyperphosphorylation, contributing to neurofibrillary tangle (NFT) pathology, as evidenced by elevated p38 MAPK expression in IL-1β-infused rat brain (79). τ protein is key for the growth and development of neuronal axons, serving as an essential molecule for the assembly and stabilization of the microtubule cytoskeleton (80). In AD, hyperphosphorylated τ proteins are major components of paired helical filaments, establishing a connection to NFTs (81). Furthermore, IL-4 has been shown to impede Aβ clearance, resulting in increased Aβ deposition and amyloid plaque formation (82-84). This is evidenced by experiments in 4-month-old amyloid precursor protein (APP) transgenic TgCRND8 mice with pre-existing plaques (82). Overexpression of murine IL-4 in the hippocampus via adeno-associated virus 2/1 chimeric vector (AAV2/1) notably aggravates cerebral Aβ deposition and plaque burden (82,85).

In addition to their pro-inflammatory role, microglia and astrocytes produce immunosuppressive factors to limit inflammation (86). For example, IL-10 is upregulated in the rat cerebral cortex following LPS injection, with increased mRNA at 8 and protein expression at 24 h post-injection (87). IL-10 has been demonstrated to induce the expression of anti-inflammatory microRNAs, which negatively regulate toll-like receptor (TLR) signaling pathways and modify the stability of inflammatory cytokine mRNA (88).

Cytokines and neuronal damage and death. There are two primary categories of cell death: Accidental cell death (ACD) and programmed cell death (PCD). ACD occurs as a reaction to unforeseen injurious stimuli, such as necrosis (89). By contrast, PCD is an orderly process of self-extinction initiated by gene regulation. PCD occurs in a spatially and temporally constrained manner during normal neuronal development, facilitating the establishment of neural structures and shaping

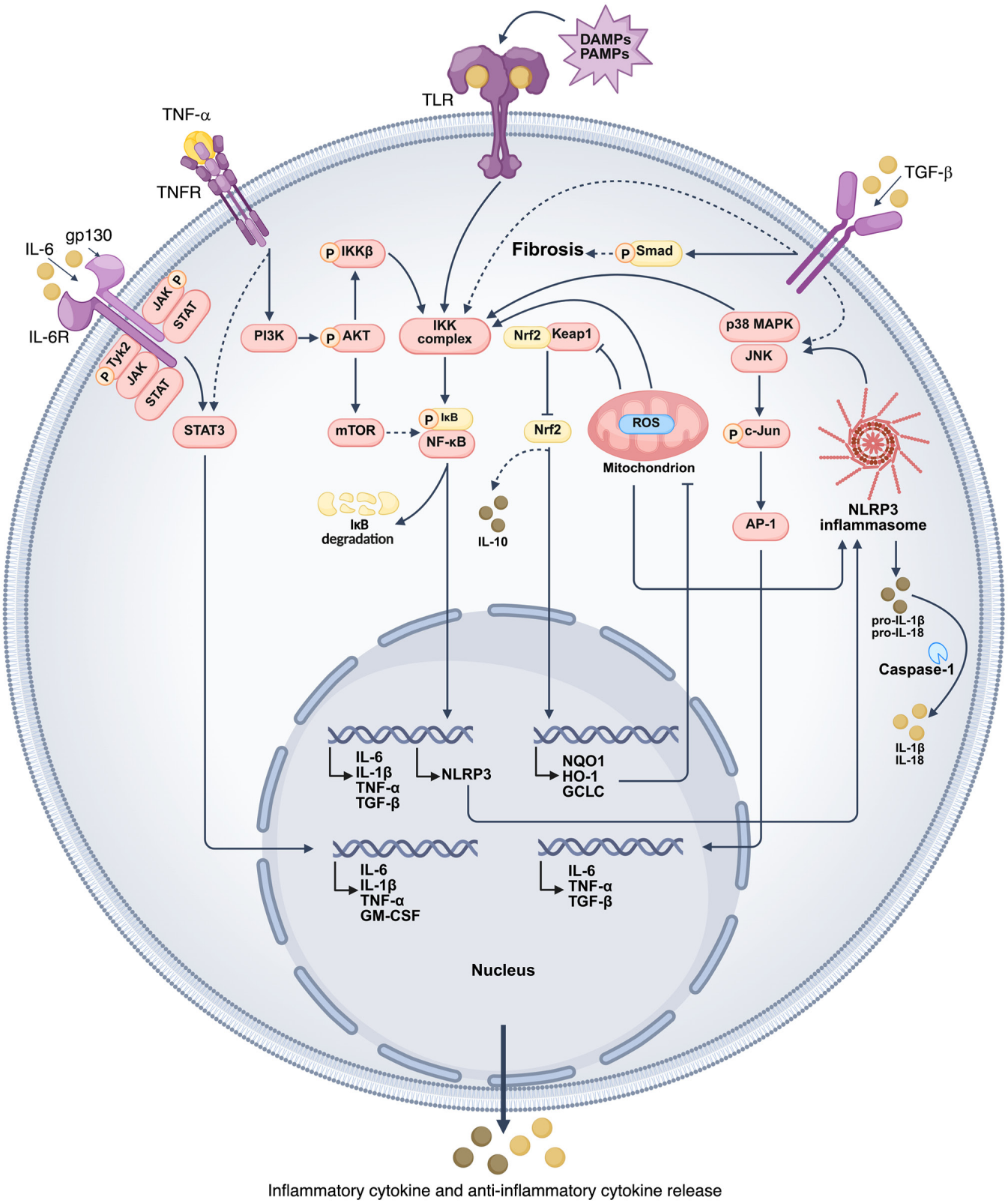

Figure 2. Integrated signaling networks underpin aging and chronic inflammation. TLR-dependent PAMP/DAMP recognition activates NF-κB via IKK-mediated IκB phosphorylation and degradation, enabling nuclear translocation to induce pro-inflammatory cytokine (IL-1β, IL-6, TNF-α) and NLRP3 inflammasome expression. ROS and stress signals trigger MAPK pathways (JNK/p38), which act with NF-κB to amplify secretion of IL-6, TNF-α, and TGF-β, establishing inflammatory-oxidative feedback loops. Further propagating inflammation, cytokine receptor engagement (IL-6R) activates JAK/STAT signaling, sustaining expression of IL-6, IL-1β, TNF-α and GM-CSF, thereby disrupting immune homeostasis. Concurrently, age-associated PI3K/Akt dysregulation promotes NF-κB activation through mTOR, while NLRP3 reciprocally modulates PI3K/Akt, forming maladaptive circuits. Declining Nrf2 function impairs dissociation from Kelch-like ECH-associated protein 1 under oxidative stress, decreasing transcription of cytoprotective genes (HO-1, GCLC, NQO1) and IL-10 production. This exacerbates ROS accumulation, lipid peroxidation and NLRP3 activation. TGF-β signaling drives Smad-dependent fibrosis and acts with NF-κB/MAPK pathways, directly linking chronic inflammation to tissue remodeling and age-associated dysfunction. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; IKK, IκB kinase; GM-CSF, granulocyte-macrophage colony-stimulating factor; HO-1, heme oxygenase-1; GCLC, glutamate-cysteine ligase catalytic subunit; ROS, reactive oxygen species; AP-1, activator protein 1.

the central nervous system (CNS) (90,91). In the pathogenesis of nervous system disease, anomalies in the signaling cascades of PCD, including apoptosis, ferroptosis, autophagy, pyroptosis and necroptosis, are evident (92,93).

Pyroptosis is characterized by cell rupture and the release of cell contents, which leads to abnormal microglial activation, intense inflammation and the promotion of ND (94). Pyroptosis is primarily induced by inflammasome activation (NLRP3) triggered by pathological factors such as mitochondrial dysfunction, ROS accumulation or Aβ during aging. Upon activation, Caspase-1 cleaves gasdermin D, whose N-terminal fragment forms membrane pores, leading to cell swelling, rupture and release of pro-inflammatory cytokines (95,96). Caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms, amplifying inflammation (96). Damage-associated molecular patterns (DAMPs) released by pyrocytes initiate inflammatory responses in adjacent glial cells via interaction with TLR4 or purinergic ligand-gated ion channel 7 receptors, potentially leading to further neuronal damage (97).

Iron-dependent cell death, also known as ferroptosis, represents a distinct form of PCD characterized by iron accumulation in cells (98). This process leads to neuronal damage and cell death through iron-mediated lipid peroxidation. Aging is associated with disruptions in cell iron homeostasis, resulting in iron overload and the generation of excessive ROS via the Fenton reaction (98,99). These ROS oxidize lipids, compromising the integrity of the cell membrane (100). Excessive ROS activate NF-κB, leading to the formation of inflammasomes and the release of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β, which contribute to neuroinflammation (101). Hepcidin, a peptide hormone involved in iron homeostasis, inhibits cell iron efflux by interacting with ferroportin 1 (102). Hepcidin levels are associated with IL-6, which promotes hepcidin expression, thereby increasing intracellular iron levels. Ferritin, an iron storage protein, is upregulated during inflammation via the IL-6/STAT3 pathway (103). Additionally, IL-1β, IL-6 and TNF-α can indirectly induce ferritin synthesis by enhancing hepcidin transcription.

Necrosis was initially identified as an alternative pathway to the death receptor pathway (104). In cell death due to ischemia, physical injury, oxidative stress or pathogen infection, the integrity of the cell membrane is compromised, leading to the release of DAMPs and the activation of immune cells, such as microglia and astrocytes, via pattern recognition receptors. This triggers downstream inflammatory signaling pathways (105). DAMPs trigger the formation of the NLRP3 inflammasome complex through ROS-dependent pathways and promote the maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 via caspase-1-dependent mechanisms (106). High mobility group box 1 (HMGB1), a nuclear protein, is released into the extracellular environment during ACD (107). While HMGB1 has limited direct pro-inflammatory effects, it indirectly enhances the release of pro-inflammatory cytokines by recruiting inflammatory cells such as microglia (108). Under the influence of microglia-derived IL-1α, TNF-α and complement component 1, q subcomponent, astrocytes transform into A1-reactive astrocytes (109). These A1-reactive astrocytes produce CXCL10, which facilitates immune cell infiltration and enables immune cells to cross the blood-brain barrier (BBB) into the CNS, exacerbating neuroinflammation (110).

BBB injury. The BBB serves as a key protective mechanism within the CNS, comprising endothelial cells, pericytes, astrocytic end-feet and a basement membrane. Under physiological conditions, the BBB is notably impermeable; however, in pathological states, the release of vasoactive substances, cytokines and chemical mediators enhances its permeability, thereby compromising its barrier function (111). Damage to the BBB may be associated with the onset of age-associated ND and the deterioration of cognitive function (111-113).

The activation, migration and cytokine release by some immune cells can compromise the integrity of the BBB. Compromised BBB permits the entry of peripheral fibrinogen into the brain, which activates microglia and promotes neuroinflammation (114). During aging, the activation of microglia and astrocytes upregulates MMP activity, resulting in the degradation of tight junction proteins and increased BBB permeability (115). Furthermore, BBB damage facilitates the entry of neurotoxic substances, including plasma protein, inflammatory cells and toxins, into the brain parenchyma, thereby inducing neuroinflammation and neuronal damage (116). In conclusion, aging compromises the integrity of the BBB via endothelial damage and neuroinflammation. This leads to BBB leakage, which exacerbates inflammation and neurodegeneration in the brain, thereby establishing a deleterious feedback loop.

4. Role of aging-associated cytokines in ND

AD. AD is a prevalent neurodegenerative disorder among the elderly, current estimates suggest that 44 million people live with dementia worldwide at present (117). This is predicted to more than triple by 2050 as the population ages. Primarily characterized by cognitive decline, memory impairment, language disturbance and behavioral alteration. The hallmark pathological features of AD include the deposition of Aβ, primarily in the cerebral cortex and hippocampal regions, leading to the formation of amyloid plaques, abnormal phosphorylation of τ protein, resulting in NFTs that compromise neuronal structure and function (118), and neuroinflammation, with extensive research indicating that the inflammatory response is a predominant mechanism in the pathogenesis of AD (119,120).

Aging-associated cytokines and AD. Microglia and astrocytes are capable of initiating an inflammatory response following an injury to the CNS. Aβ rapidly activates microglia, resulting in alteration to their morphological and phenotypical characteristics, which promote phagocytosis and induce localized immune cells (121). However, sustained microglial activation and unresolved inflammation within the brain are detrimental to neurons and synapses, promoting chronic dysregulation of glial cells and contributing to the deterioration of brain structure and function (122). Aβ42 has been shown to induce microglial phagocytosis of viable neurons, resulting in early synaptic loss in AD (123). Following exposure to Aβ, microglia secrete a range of pro-inflammatory cytokines and chemokines, including IL-6, IL-1β, TNF-α, macrophage inflammatory protein-1α and MCP-1 (124). This secretion leads to the recruitment and activation of astrocytes and peripheral immune cells.

Pro-inflammatory cytokines amplifying Aβ and τ pathology. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α play a predominant role in exacerbating AD pathology. They not only maintain the inflammatory environment but also directly interact with and aggravate Aβ plaques and NFTs (84). IL-1β is elevated in the brain of patients with AD, particularly in association with diffuse plaques, and is predominantly produced by activated microglia during early disease stages (125). *In vitro*, IL-1β treatment of human neuroblastoma SH-SY5Y cells enhances APP transcription via NF-κB activation, leading to increased APP synthesis (125). These findings are supported by APP/presenilin 1 (PS1) transgenic mouse models, where IL-1β overexpression is associated with elevated cortical APP levels and accelerated amyloid deposition (125,126). IL-1β also enhances BACE1 and γ-secretase activity via MAPK and JAK/STAT signaling, contributing to Aβ overproduction (127).

Neuroinflammation upregulates BACE1 activity while downregulating the expression of Aβ-degrading enzymes. Inflammatory processes lead to the downregulation of Aβ-degrading enzymes, including insulin-degrading enzyme and neutral endopeptidase, contributing to the accumulation of Aβ in the brain. These effects create a self-reinforcing cycle that accelerates plaque formation (128,129). Moreover, the intermediate form of APP activates microglia, resulting in the excessive secretion of IL-1β, which stimulates astrocytes and promotes the release of pro-inflammatory substances (130).

Another cytokine key to the pathogenesis of neuroinflammation in AD is IL-6 (131). Elevated in the cerebrospinal fluid of patients with AD, IL-6 upregulates pro-inflammatory cytokine production in primary murine microglia and astrocytes, an effect associated with enhanced Aβ plaque deposition and τ pathology in APP/PS1 mice (132). IL-6 promotes acute-phase protein release and vascular permeability in the CNS, amplifying neuroinflammation (133).

TNF-α binding to TNFR1 recruits TNFR1-associated death domain protein, TNFR-associated factor 2/5, receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and cellular inhibitor of apoptosis protein 1/2 (cIAP1/2) to form complex I, leading to canonical NF-κB activation andinflammation (134). When NF-κB activation is blocked (such as by cIAP1/2 inhibition), Caspase-8 is activated, initiating apoptosis (135). If Caspase-8 is suppressed, RIPK1 deubiquitinates and associates with Fas-associated death domain protein (FADD) and receptor-interacting serine/threonine-protein kinase 3 to form complex II, which phosphorylates mixed lineage kinase domain-like pseudokinase and triggers necroptosis, a pro-inflammatory cell death pathway (136,137).

Diminished protective role of anti-inflammatory cytokine IL-10 in AD. IL-10 suppresses NLRP3 inflammasome activity via STAT3 signaling, decreasing IL-1β release and promoting microglial M2 polarization (138). However, in AD, IL-10 expression is typically decreased, which diminishes its inhibitory effect on excessive inflammatory responses. The impaired anti-inflammatory response fuels chronic neuroinflammation and pathological progression.

Neuroprotective potential of NRG1/ErbB4 signaling in AD. As the intercellular signaling proteins that serve as ligands for receptor tyrosine kinases within the ErbB receptor family, NRGs and their corresponding receptors are key to organ development and maintenance, as well as the pathogenesis of NDs (139). Notably, NRG1 may exert a protective effect by modulating the pathological progression of AD. Compared with age-matched normal controls, the immunoreactivity intensities of ErbB4 and phosphorylated ErbB4 are elevated in the neurons of the CA1-2 transition zone in AD brains (36). Furthermore, ErbB4 expression is increased in the medial neurons of the basolateral amygdala cortex and the superior frontal gyrus neurons of patients with AD (36). In the cerebral cortex and hippocampus of APP/PS1 double transgenic mice, ErbB4 immunoreactivity is significantly higher than that in age-matched wild-type controls (36). In APP/PS1 mice, ErbB4 immunoreactivity is elevated in the cerebral cortex and hippocampus compared with wild-type controls (36). These reports suggest that aberrant alterations in ErbB4 may contribute to the pathological progression of AD, while NRG1 exhibits neuroprotective effects against neurotoxicity induced by the Swedish amyloid precursor (36).

NRG1 mitigates the neurotoxic effects associated with the expression of APP C-terminal fragment in SH-SY5Y human neuroblastoma cells, reducing ROS accumulation and mitochondrial membrane potential loss via ErbB4 signaling (140). Another study examined the downstream signaling pathway of NRG1, highlighting its role in counteracting Aβ42-induced neurotoxicity (141). The findings indicate that inhibiting the activation of the PI3K/Akt pathway negates NRG1 ability to prevent Aβ42-induced lactate dehydrogenase release, increases the number of TUNEL-positive cells and elevates ROS accumulation in primary cortical neurons (142). These findings confirm NRG1/PI3K/Akt signaling as a viable therapeutic target for Aβ-induced neurotoxicity in AD (Fig. 3).

Our previous study demonstrated that recombinant Neuregulin-1β treatment alleviates LPS-induced neuroinflammation by reducing the number of microglial cells and astrocytes as well as the expression of IL-1β (143). Moreover, our group recently reported that targeted activation of ErbB4 using the small-molecule agonist 4-bromo-1-hydroxy-2-naphthoic acid (E4A), an NRG1 mimic, exerts neuroprotective effects in multiple disease-related models (144-146). Specifically, E4A alleviates neuronal damage in D-galactose-induced senescence (144), ameliorates cognitive deficit in APP/PS1 mice via dedicator of cytokinesis 3 (DOCK3) signaling (145) and mitigates neuroinflammation in a polystyrene microplastic exposure model (146). These findings not only corroborate the key role of the NRG1-ErbB4 axis in neuronal protection and the regulation of neuroinflammation but also offer direct experimental evidence in support of the cytokine-centered approach for treating AD and other ND.

PD. PD is a neurodegenerative disorder marked by progressive extrapyramidal dysfunction. The primary pathological characteristics of PD include the degeneration of dopaminergic (DAergic) neurons in the substantia nigra (SN), leading to decreased levels of dopamine and the accumulation of α-syn within the cytoplasm and axons of DAergic neurons, forming Lewy bodies (147). Imamura *et al* (148) identified the infiltration of activated microglial cells in the SN of brain of patients with PD postmortem. These activated microglial cells secrete pro-inflammatory cytokines, such as TNF-α, IL-1β and

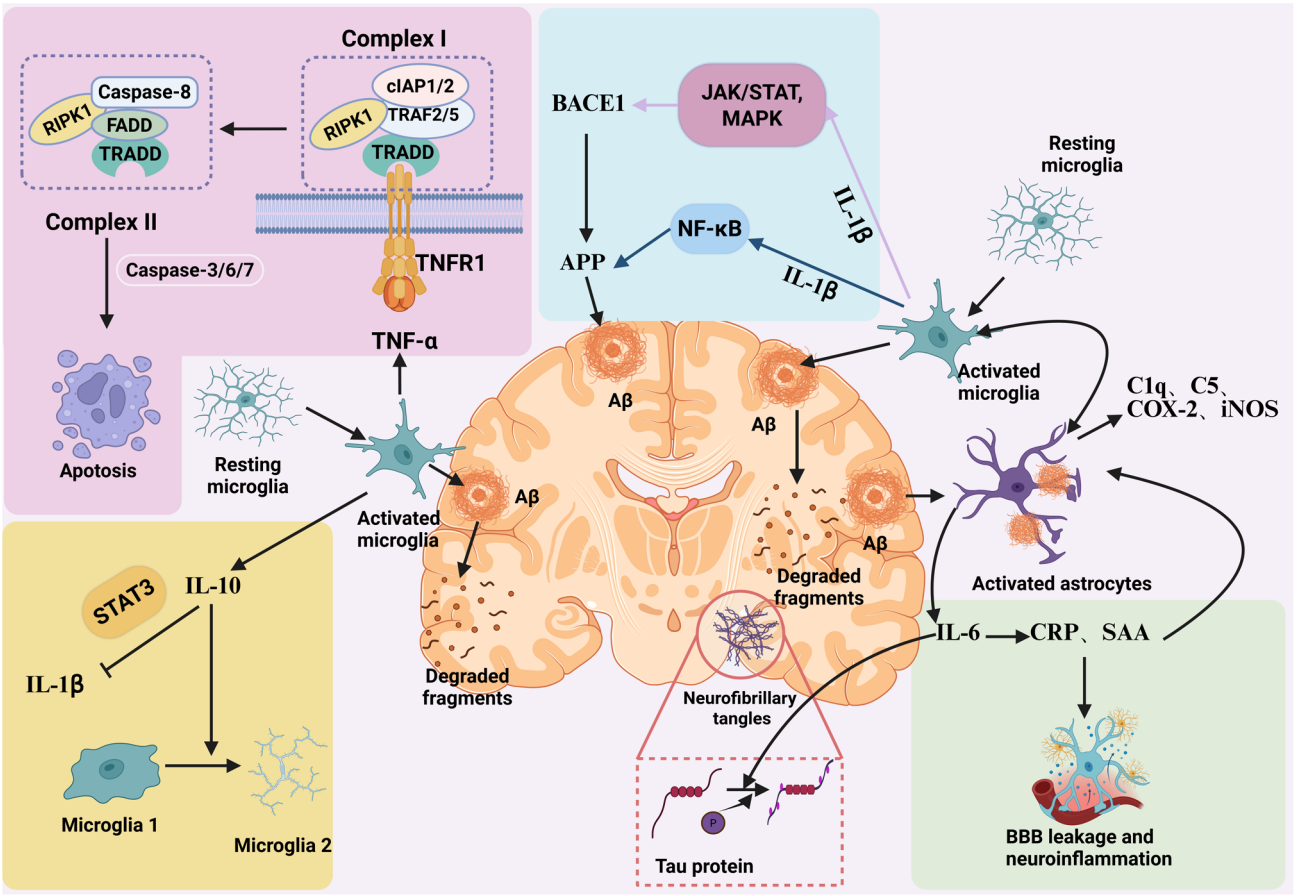

Figure 3. Neuroinflammatory mechanisms in AD pathogenesis. In the early stage, activated microglia secrete IL-1β, which enhances the expression of APP and BACE1 through the NF-κB and MAPK signaling pathways. This process leads to aberrant APP processing and Aβ production, creating a feedforward loop where Aβ aggregates activate microglia to secrete IL-1β and astrocytes to release pro-inflammatory cytokines including C1q, C5, COX-2, iNOS, amplifying the inflammatory cascade. C1q initiates the classical complement pathway by binding Aβ plaques, driving complement activation and subsequent synaptic and neuronal damage; cleavage of C5 generates C5a, a potent chemoattractant that recruits additional inflammatory cells, and C5b, which forms membrane attack complexes to disrupt neuronal integrity. Meanwhile, COX-2 catalyzes the production of pro-inflammatory prostaglandins that increase vascular permeability and activate immune cells in the brain, while iNOS generates nitric oxide (NO) to induce oxidative stress and neuronal dysfunction via free radical-mediated injury. Within the central nervous system, elevated IL-6 and TNF-α levels exacerbate neurodegeneration. IL-6 facilitates Aβ plaque deposition and pathological τ hyperphosphorylation by activating microglia and astrocytes, inducing acute-phase protein CRP and SAA release and BBB permeability, thus sustaining a pro-inflammatory environment. CRP binds to Aβ deposits to activate the complement system, amplifying inflammation and tissue injury, while SAA promotes immune cell recruitment and accelerates Aβ plaque formation. BBB leakage allows peripheral inflammatory cells and molecules to infiltrate the brain parenchyma, impairing waste clearance and worsening neuronal damage. TNF-α interacts with TNFR1 to initiate two cell death pathways. The canonical pathway recruits TRADD, TRAF2/5 and RIPK1 to form Complex I, thereby activating NF-κB-mediated inflammation. When cIAP1/2 are inhibited or Caspase-8 is inactive, RIPK1 deubiquitinates and associates with FADD and receptor-interacting serine/threonine-protein kinase 3 to form Complex II, which phosphorylates mixed lineage kinase domain-like pseudokinase, resulting in necroptosis. IL-10 suppresses the NLRP3 inflammasome activity via the STAT3 pathway, decreasing the release of IL-1β and promoting microglial polarization towards an anti-inflammatory M2 phenotype, thereby enhancing Aβ clearance. Decreased expression of IL-10 in AD disrupts protective mechanisms, causing persistent NLRP3 inflammasome activation, uncontrolled release of IL-1β and IL-18 and chronic neuroinflammation. This dysregulation acts with Aβ toxicity, contributing to synaptic loss and neuronal death, highlighting AD as an interconnected inflammatory-proteostatic disorder. AD, Alzheimer's disease; APP, amyloid precursor protein; BACE1, β-site amyloid precursor protein cleaving enzyme 1; Aβ, β-amyloid; TNFR, TNF receptor 1; TRADD, TNF receptor-associated death domain protein; TRAF, tumor necrosis factor receptor-associated factor 2/5; RIPK, receptor-interacting serine/threonine-protein kinase; cIAP, cellular inhibitor of apoptosis protein; FADD, fas-associated death domain protein; C1q, complement component 1q subcomponent; C5, complement component 5; COX-2, Cyclooxygenase-2; iNOS, inducible nitric oxide synthase; CRP, C-reactive protein; SAA, serum amyloid A; BBB, blood-brain barrier.

IL-6, and express class II major histocompatibility complex (MHC) molecules. These activated microglial cells contribute to neuronal damage in patients with PD (148). Furthermore, neuroimaging studies employing radioactive tracers specific to microglial cell activation have revealed the presence of persistent neuroinflammation in PD (149,150).

Microglial activation by α-syn: TLRs and the inflammasome. The aggregation of abnormal and insoluble α-syn is key in the pathogenesis of PD (151). Misfolded α-syn serves as a DAMP to dysregulate TLR2/TLR4-myeloid differentiation primary response protein 88-NF-κB signaling in microglia, inducing TNF-α and IL-1β production. Treatment of BV2 mouse or primary microglia with aggregated α-syn upregulates the production of TNF-α, IL-1β, MCP-1 and IFN-γ (152). Additionally, α-syn binding to TLR2 triggers NLRP3 inflammasome activation, promoting IL-1β maturation and release (153). These IL-1β-driven neuroinflammatory responses contribute to DAergic neuron degeneration in PD. Furthermore, the knockout of TLR2

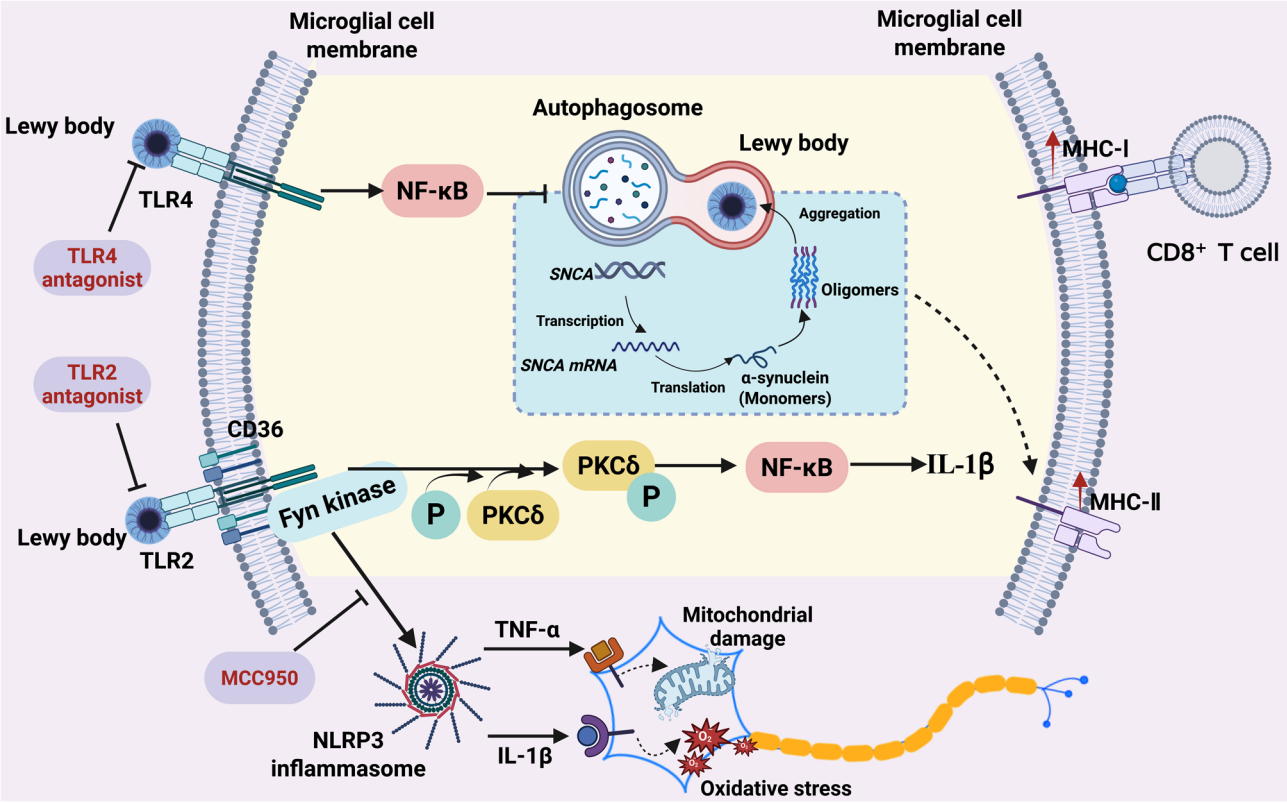

Figure 4. α-synuclein derives microglial inflammation in Parkinson's disease. Misfolded α-synuclein serves as a damage-associated molecular pattern that interacts with TLR2 and CD36 receptors, leading to the recruitment of Fyn kinase and the PKCδ, thereby activating the NF-κB signaling pathway. This results in the release of pro-inflammatory cytokines, including TNF-α and IL-1β. Simultaneously, Lewy bodies facilitate the sequestration of aberrant proteins by autophagosomes via TLR4 signaling; impaired autophagic flux exacerbates the intracellular accumulation of Lewy bodies. TLR2 and TLR4 antagonists can interrupt this process by inhibiting the interaction between Lewy bodies and TLR2/4. The pathological impact of Lewy bodies is intensified by the immune system. Lewy bodies enhance the expression of IFN-γ in microglia, leading to the induction of MHC-I molecule presentation on neuronal surfaces, thereby facilitating the recruitment of $CD8^+$ T cells to target dopaminergic neurons. Chronic neuroinflammation is associated with the persistent activation of the NLRP3 inflammasome. Lewy bodies activate the NLRP3 inflammasome via TLR2, promoting the maturation and release of IL-1β. Small-molecule NLRP3 inhibitor MCC950 effectively decreases inflammasome activation. Furthermore, TNF-α and IL-1β are implicated in mitochondrial damage and oxidative stress within neurons, respectively. TLR, toll-like receptor; PKC, protein kinase C; MHC, major histocompatibility complex; SNCA, α-synuclein gene.

decreases the uptake of α-syn by mouse microglia (154) (Fig. 4).

TLR4-NF-κB activation promotes α-syn sequestration into autophagosomes (155). Inhibition of TLR4 function in BV2 and TLR4 knockout primary mouse microglial cells impedes the uptake of α-syn and suppresses the production of pro-inflammatory cytokines TNF-α and IL-6 (156). Additionally, α-syn upregulates the expression of IFN-γ in microglia, which induces the expression of MHC-I on neurons, thereby enabling selective targeting by $CD8^+$ T cells (157). The α-syn (SNCA) gene encodes α-syn and its overexpression in rat models results in reduced fiber density in DAergic neurons and an increased number of $MHC\text{-}II^+$ microglial cells (158,159). T cells from mice immunized with nitrated α-syn exacerbate neurodegeneration in response to MPTP exposure (160). Furthermore, both type 1 and 17 helper T cells contribute to the enhancement of MPTP-induced neurodegeneration, whereas regulatory T cells exert a neuroprotective effect (161). These results support the role of T cell subsets activated by the immune response induced by α-syn in the pathogenesis of DAergic neurodegeneration. Collectively, these mechanisms establish a chronic neuroinflammatory environment in the PD brain.

Downstream inflammatory mediators and therapeutic targets. TNF-α is upregulated in the mouse striatum prior to DAergic neuron degeneration, implicating it in early PD pathogenesis. Genetic ablation of TNF receptors or pharmacological inhibition of TNF-α (using thalidomide) attenuates MPTP-induced neuronal loss (162,163). A cohort study demonstrated an association between early anti-TNF therapy and decreased PD incidence (164). α-syn binding to TLR2 activates the NLRP3 inflammasome. In patients with PD, NLRP3 colocalizes with microglia in the SN (165). The NLRP3 inhibitor MCC950 attenuates inflammasome activation and mitigates motor deficit, nigrostriatal degeneration and α-syn aggregation in mouse models (165,166). Nrf2 activation by dimethyl fumarate decreases ROS production in neurons of SNCA (p.A53T) transgenic mice and protects against MPTP- and α-syn-induced DAergic neuron damage (167,168). Peroxisome proliferator-activated receptor (PPAR)-γ agonists, such as pioglitazone and rosiglitazone, alleviate MPTP-induced inflammation and protect nigrostriatal function in mice and monkeys; pioglitazone also decreases glial cell activation and prevents DAergic neuron loss in MPTP-treated mice (162,169). Collectively, these findings support targeting TNF-α, NLRP3, Nrf2 and PPAR-γ as therapeutic strategies to impede PD progression.

Amyotrophic lateral sclerosis (ALS). ALS is a neurodegenerative disorder marked by the progressive degeneration of motor neurons, leading to symptoms such as muscle weakness, atrophy and impaired motor function (163). The pathology of ALS involves the degeneration of both upper and lower motor neurons within the spinal cord and cerebral cortex, culminating in the inability to control muscle movements (164). The resultant motor neuron death precipitates muscle atrophy and weakness, leading to mortality, often due to respiratory failure caused by paralysis of the respiratory muscles (170). Neuroinflammation is a prevalent pathological feature in ALS, regardless of the presence of genetic mutations, and is characterized by the infiltration of activated microglia and astrocytes. These activated glial cells produce pro-inflammatory cytokines, which are upregulated in postmortem tissue of patients with ALS (171).

SASP factors: Sustaining neuroinflammation in ALS. Aging cells release pro-inflammatory factors such as IL-6, IL-1β and TNF-α through the SASP, which activate glial cells and initiate chronic CNS inflammation (172). *In vivo* studies demonstrate that systemic administration of recombinant murine IL-6 in C57BL/6 mice promotes microglial polarization toward the M1 phenotype, characterized by elevated CD16/32 expression, and exacerbates neuroinflammation (173-175). IL-6 is a potential therapeutic target for ALS. In superoxide dismutase 1 $(SOD1)^{G93A}$ transgenic mice, IL-6 promotes microglial M1 polarization via JAK2/STAT3 signaling, resulting in TNF-α and ROS release that directly damages spinal motor neurons (176,177). IL-6 also downregulates glutamate transporter 1, causing excitotoxicity, and impairs the Nrf2 antioxidant pathway, resulting in mitochondrial ROS accumulation and NLRP3 inflammasome activation (178,179). These IL-6-driven processes collectively establish an oxidative-inflammatory cycle that accelerates motor neuron death.

Autophagic-lysosomal dysfunction. Paralleling the persistent elevation of inflammatory cytokines, a concurrent failure in cell waste disposal mechanisms contributes to proteotoxicity and disease progression in ALS. With advancing age, autophagic function declines, resulting in the inefficient degradation of aberrant proteins, including transactive response DNA-binding protein 43 (TDP-43) and SOD1 aggregates (180). In the $SOD1^{G93A}$ transgenic mouse model of ALS, these autophagic deficits contribute to motor neuron degeneration. In individuals with ALS, persistent activation of the mechanistic target of rapamycin pathway inhibits autophagy initiation, while mutations in p62/sequestosome-1 compromise substrate recognition (181,182). Additionally, lysosomal acidification disorder, characterized by increased pH, leads to cathepsin inactivation, thereby exacerbating protein toxicity (183).

Epigenetic regulation in the ALS inflammatory landscape. The inflammatory state in ALS is strengthened and regulated by persistent changes at the epigenetic level. Age-associated DNA methylation loss and abnormal histone modifications upregulate pro-inflammatory genes, while suppressing neuroprotective genes (184). For example, microRNA-155 enhances microglial JAK/STAT signaling by inhibiting suppressor of cytokine signaling 1, whereas the downregulation of microRNA-146a disrupts NF-κB pathway regulation, creating a positive feedback loop that drives ALS progression (185). Pro-inflammatory factors, including IL-1α, TNF-α and complement component 1, q subcomponent, A chain, are released by microglia activated by neuroinflammation, inducing neurotoxicity via alterations in astrocyte activity (109). TNF-α activates the Caspase-8/FADD signaling pathway via TNFR1, while IL-6 upregulates the pro-apoptotic protein Bax via the JAK/STAT3 pathway, both of which are implicated in the pathogenesis of ALS (186) (Fig. 5).

Huntington's disease (HD). HD is a deleterious autosomal dominant hereditary neurological disorder, characterized by mood disturbance, weight loss, movement abnormality and dementia (187). The gene responsible for HD was first cloned in 1993, and the highly conserved protein it encodes, whose function remains unclear, is huntingtin (HTT) (187,188). In individuals with HD, the polymorphic trinucleotide repeat sequence CAGn at the 5'end of the gene undergoes expansion beyond the normal repeat threshold, leading to the translation of an extended polyglutamine tract within the protein (187). The proteolytic cleavage of the mutant HTT protein plays a critical role in the pathogenesis of HD (189). Studies utilizing *in vivo* models, such as R6/2 HD mice, demonstrate that these aberrant HTT fragments initiate a complex cascade of compensatory and deleterious molecular processes, including neuroinflammation (190,191). Such processes result in atrophy, fragility and damage to nerve cells, rendering them susceptible to stressors, such as excitotoxic stress, oxidative damage, pro-apoptotic signals, energy depletion, impaired proteolysis and neurophysiological defects. Collectively, these factors may contribute to neuronal death (189).

Key role of microglia in HD neuroinflammation. Compared with other CNS disorders, the involvement of microglia in HD remains insufficiently investigated (192). Singhrao *et al* (193) demonstrated microglial impairment in patients with HD (193). The aforementioned study observed an increased number of microglial cells in the caudate nucleus and putamen, associated with elevated expression levels of complement factors. Sapp *et al* (194) investigated microglial morphological alterations associated with HD and identified structurally activated microglia in the cortex, globus pallidus and neostriatum. Notably, in the cortex and striatum, the aggregation of thymosin β-4-reactive microglia intensifies in parallel with the progression of neuropathological grade (194). Another study reported microglial accumulation in HD tissue and the R6/2 mouse model of the striatum (192).

Cytokine dysregulation in HD. Accumulated HTT expression induces transcriptional alterations in neuronal cells, and it is possible that microglial transcription is similarly impacted (192). Björkqvist *et al* (195) suggested that postmortem tissue from patients with HD exhibit distinct inflammatory characteristics. Specifically, inflammatory molecules such as TNF-α and IL-1β are markedly elevated in the striatum, whereas MMP-9, IL-6 and IL-8 show increased expression in the cortex and cerebellar regions (192). This contrasts with the neuroinflammatory profiles observed in other types of ND, such as PD or AD, which typically involve the upregulation of a broader range of inflammatory

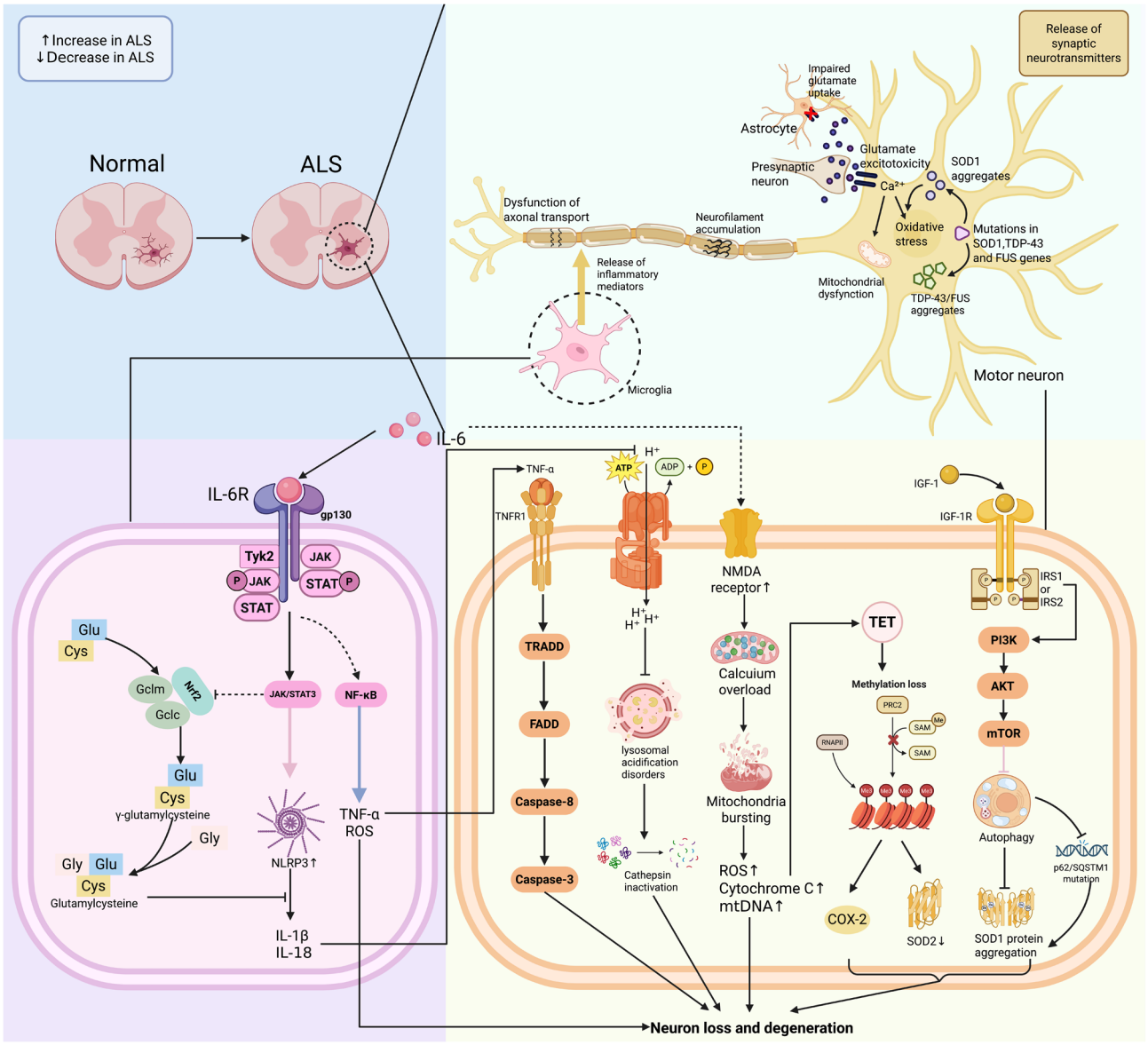

Figure 5. ALS pathology. Senescent cells in the central nervous system secrete IL-6 and TNF-α, which activate microglia and astrocytes, triggering a neuroinflammatory cascade. IL-6 binds membrane receptors (gp130) to activate the Tyk/JAK/STAT3 signaling pathway, prompting microglia to release ROS and TNF-α, which directly damage motor neurons. IL-6 exacerbates excitotoxic injury by hyperactivating NMDA receptors, inducing calcium overload and mitochondrial membrane potential collapse. This process is compounded by IL-6-mediated suppression of the Nrf2 antioxidant pathway, impairing glutathione synthesis and amplifying mtROS accumulation. These oxidative insults activate the NLRP3 inflammasome, promoting maturation and release of IL-1β and IL-18. Autophagic-lysosomal failure further drives ALS progression. IGF-1-mediated hyperactivation of the mTOR pathway suppresses autophagic initiation via IRS, while mutations in p62/SQSTM1 impair clearance of ubiquitinated protein aggregates, such as misfolded SOD1. Lysosomal acidification defects inactivate cathepsin, leading to irreversible proteotoxicity. DNA hypomethylation (methylation) and aberrant histone modification (PRC, RNAPII) upregulate cyclooxygenase-2 and COX-2 while silencing neuroprotective genes such as SOD2. TNF-α activates the Caspase-8/FADD apoptotic pathway via TNFR1 and the adaptor protein TRADD, acting with Caspase-3-mediated autophagy suppression to precipitate irreversible loss of respiratory motor neurons. TDP-43 and FUS pathology aggravates transcriptional dysregulation. This interplay of molecular mechanisms underscores ALS as a disease of multi-systemic dysregulation, highlighting therapeutic opportunities for targeting nodal points within this dynamic network. NMDA, N-methyl-D-aspartate; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3; IGF-1, insulin-like growth factor 1; SQSTM1, sequestosome-1; SOD1, superoxide dismutase 1; COX-2, cyclooxygenase-2; FADD, Fas-associated death domain protein; ALS, amyotrophic Lateral Sclerosis;mtROS, mitochondrial reactive oxygen species; TNFR, tumor necrosis factor receptor-associated death domain protein; gp, glycoprotein; Tyk, Tyrosine Kinase; TRADD,tumor necrosis factor receptor-associated death domain protein; TDP, transactive response DNA binding protein; FUS, fused in sarcoma/translocated in liposarcoma; IRS, insulin receptor substrate; PRC, Polycomb Repressive Complex; RNAPII, RNA polymerase II; Me, methylation.

molecules (196). The presence of inflammatory regulators in the striatum may signify ongoing pathological processes, while the dysregulation of molecules such as MMP-9, IL-6 and IL-8 suggests a more generalized role of mutant HTT protein expression (197). Furthermore, studies have demonstrated that monocytes expressing mutant HTT protein in patients with HD exhibit increased secretion of IL-6 (198-200). By contrast with other neurological disorders, including AD and multiple sclerosis, the involvement of peripheral immune cells, such as neutrophils and lymphocytes, in HD has not been thoroughly explored (201). Furthermore, studies have indicated that significant infiltration of T cells is not observed in postmortem tissue

Table I. Key cytokines, signaling pathways and pathological effects in major neurodegenerative disease.

Disease	Cytokines	Signaling pathways	Primary pathological effects	(Refs.)
AD	IL-1β, IL-6, TNF-α, IL-10	NF-κB, MAPK, JAK/STAT	Aβ plaque formation, τ hyperphosphorylation, synaptic loss, neuronal apoptosis	(118)
PD	TNF-α, IL-1β, IFN-γ	NF-κB, TLR2/TLR4	α-synuclein aggregation, microglial activation, dopaminergic neuron degeneration	(147,148)
ALS	IL-6, TNF-α, IL-1β	JAK/STAT3, NF-κB, Nrf2	Motor neuron death, excitotoxicity, ROS accumulation, autophagy dysfunction	(163,164)
HD	TNF-α, IL-6, IL-8	NF-κB (via mHTT/IKK complex)	mHTT aggregation and neuronal injury in striatum and cortex	(187)

AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; TNF, tumor necrosis factor; TLR, toll-like receptor; mHTT, mutant huntingtin; IKK, IκB kinase; Aβ, amyloid-β; ROS, reactive oxygen species.

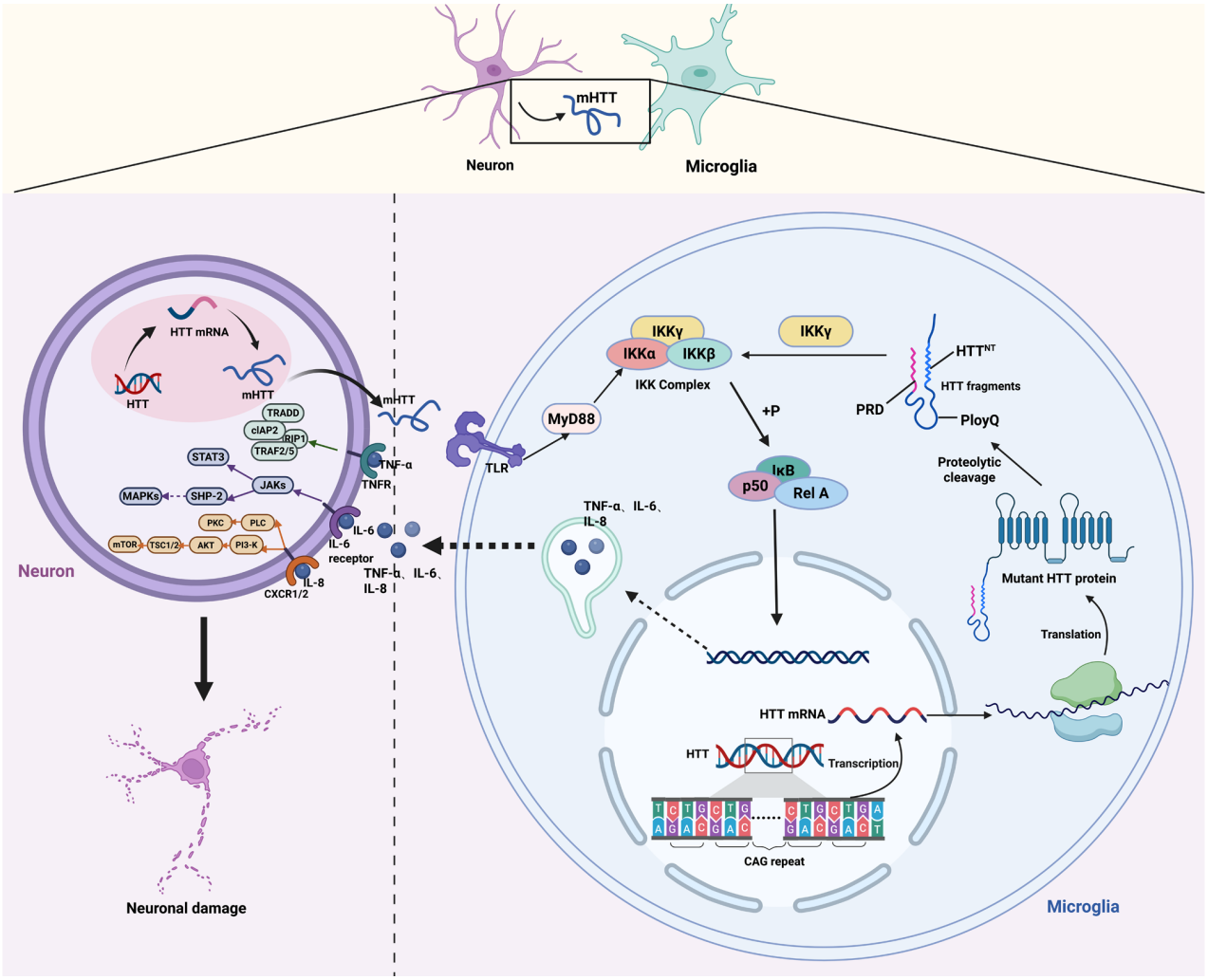

Figure 6. HD is attributed to a CAG repeat expansion within HTT gene. The HTT protein is ubiquitously expressed across human and rodent tissue, with notable enrichment in the central nervous system. mHTT generates soluble fragments and aggregates that disrupt cell homeostasis and exert neurotoxic effects. In microglia, $mHTT^{NT}$ interacts with IKKγ via its PRD and PolyQ tract, leading to the activation of the IKK complex. This results in the degradation of IκB protein, thereby releasing NF-κB dimers that translocate to the nucleus to initiate gene transcription, which upregulates the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-8. In addition to its synthesis in neurons, mHTT is recognized by TLRs on the microglial surface upon its extracellular release, activating the NF-κB signaling pathway and enhancing cytokine secretion, including TNF-α, IL-6 and IL-8. These cytokines are then transported extracellularly through vesicular trafficking and bind neuronal surface receptors such as TNFR, IL-6 receptors and CXCR1/2. Through diverse downstream signaling cascades involving TRADD, cIAP, RIP, TRAF, SHP, PLC, and TSC, these interactions mediate neuronal injury, contributing to the pathogenesis of HD. HD, Huntington's disease; mHTT, mutant Huntingtin; IKK, inhibitor of nuclear factor kappa-B kinase; TRADD, TNF receptor-associated death domain protein; cIAP, cellular inhibitor of apoptosis protein; RIP, receptor-interacting serine/threonine-protein kinase; TRAF, TNF receptor-associated factor; SHP, src homology 2 domain-containing phosphatase; PLC, phospholipase C; TSC, tuberous sclerosis complex; PRD, proline-rich domain; NT, N-terminal; PloyQ, polyglutamine.

of individuals with HD (202,203). Consequently, neuroinflammation in HD is predominantly sustained by the interactions among neurons, microglia and astrocytes (192) (Fig. 6).

5. Conclusion

Cytokines associated with aging are key to the pathogenesis of ND. Throughout the aging process, there is a persistent elevation of pro-inflammatory factors, including IL-6, TNF-α and IL-1β, coupled with a decline in anti-inflammatory factors such as IL-10 and TGF-β. This shift results in inflammaging, which exacerbates chronic neuroinflammation (204,205). This imbalance facilitates the deposition of Aβ, abnormal phosphorylation of τ protein and aggregation of α-syn through the activation of microglia and astrocytes, leading to neuronal apoptosis, synaptic dysfunction and impairment of the BBB (206).

Excessive activation of the NLRP3 inflammasome intensifies the inflammatory cascade, promoting oxidative stress and mitochondrial dysfunction. This creates an inflammation-oxidation feedback loop that accelerates neurodegenerative damage (207). Additionally, cytokines released by the SASP, through the recruitment of immune cells and the dysregulation of signaling pathways such as NF-κB and JAK/STAT, represent a common mechanism underlying diseases such as AD and PD (208,209) (Table I). While interventions targeting cytokines, such as IL-1β neutralizing antibodies and NLRP3 inhibitors in mouse autoinflammatory disease models and inflammatory arthritis models have demonstrated potential in delaying disease progression, their safety and efficacy in humans require further validation (210,211). Future research should investigate the precise regulation of the cytokine network to achieve a balance between neuroinflammation and neuroprotection. Targeting senescence-associated cytokines offers a novel therapeutic avenue for ND.

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Availability of data and materials

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Authors' contributions

XD, XR, YW and WZ conceived the study. XD, XR and YW wrote the manuscript. WZ edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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