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Review

Neuroinflammation and Cellular Senescence in Brain Aging and Neurodegeneration

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ABSTRACT: Against the backdrop of a rapidly aging global population, the incidence of neurodegenerative diseases such as Alzheimer's and Parkinson's continues to rise, imposing a severe socioeconomic burden. Neuroinflammation is recognized as the core mechanism linking physiological brain aging to pathological cognitive decline. This paper aims to systematically elucidate the multi-level activation mechanisms of neuroinflammation during aging and comprehensively evaluate drug intervention strategies targeting this process. Research reveals that the chronicity of neuroinflammation is driven by multiple cellular and molecular events. At the cellular level, aging and dysfunction in microglia and astrocytes lead to their respective transitions toward pro-inflammatory M1 and neurotoxic A1 phenotypes. These changes interact synergistically with blood-brain barrier dysfunction, peripheral immune cell infiltration, and abnormal aggregation of pathological proteins like Aβ and α-synuclein, forming a vicious cycle. At the molecular level, signaling pathways including NLRP3 inflammasome, NF-κB, and JAK/STAT are persistently activated, while epigenetic modifications play crucial regulatory roles. Addressing these mechanisms, this review systematically examines six major intervention strategies: modulating neuroimmune cell function, inhibiting core inflammatory pathways, targeting inflammatory mediators like cytokines, employing senolytics to clear senescent cells, enhancing endogenous anti-inflammatory defenses, and exploring multi-target natural products and drug repurposing. Research indicates that targeting neuroinflammation offers a highly promising new avenue for delaying brain aging and related diseases. However, this field still faces numerous challenges, including target specificity, blood-brain barrier delivery, individual heterogeneity, and difficulties in clinical translation. Future breakthroughs will depend on more precise drug design, innovative delivery technologies, biomarker development, and interdisciplinary collaborative research.

Keywords: neuroinflammation, molecular mechanisms, therapeutic strategies, brain aging, neurodegenerative diseases

1. Introduction

The global demographic structure is undergoing an unprecedented aging transformation. The United Nations projects that by 2050, individuals aged 65 and above will constitute 16% of the world's population, accompanied by a sharp rise in the incidence of neurodegenerative diseases [1]. Diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) have become the primary causes of disability among the elderly, with the associated socioeconomic burden projected to exceed US$2.8 trillion by 2030 [2]. Against this backdrop, maintaining cognitive

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health is not only crucial for individual quality of life but also a central challenge in alleviating pressure on public health systems [3]. In this review, we adopt the term "inflammaging" to describe the chronic, low-grade, and sterile inflammatory state that characterizes systemic aging, and "neuroinflammation" as its manifestation within the central nervous system (CNS), driven by glial cells and infiltrating immune mediators [4]. The related concept of "immunosenescence" refers to the functional deterioration of the immune system with age, which contributes to inflammaging and impaired pathogen clearance. A central focus will be the senescence associated secretory phenotype (SASP), the pro-inflammatory secretome released by senescent cells, which serves as a critical mechanistic link between cellular aging, tissue-level inflammation, and functional decline in the brain [5].

Neuroinflammation, as the innate immune response of the CNS to injury, exhibits distinct characteristics from peripheral inflammation. This process is jointly driven by microglia, astrocytes, and peripherally infiltrating immune cells, forming a complex regulatory network through the release of cytokines (IL-1β, TNF-α), chemokines (CXCL10), and complement proteins [6, 7]. Under physiological conditions, neuroinflammation exerts neuroprotective effects; however, its chronic progression transforms into a neurotoxic process. During aging, neuroinflammation evolves into a persistent feature—termed "brain inflammatory aging"—serving as a pivotal link between physiological aging and pathological cognitive decline. Mitochondrial dysfunction in microglia leads to reactive oxygen species (ROS) accumulation, amplifying inflammatory signals via nuclear factor κB (NF-κB) pathway activation; astrocytes undergo epigenetic reprogramming, promoting the release of the SASP [8, 9].These alterations form a vicious cycle of "inflammation-oxidative stress-DNA damage" alongside Toll-like Receptor 4 (TLR4)/NOD-like receptor pyronin domain-related protein 3 (NLRP3) pathway activation triggered by damage-associated molecular patterns (DAMPs) [10].Notably, systemic factors such as gut-brain axis dysregulation and metabolic disorders exacerbate CNS neuroinflammation through peripheral inflammation, directly promoting Aβ/tau pathology in AD and α-synuclein propagation in PD，establishing it as a core driver of age-related brain dysfunction [11-13].

While the interplay between aging, inflammation, and neurodegeneration has been extensively reviewed, this article provides a focused update on the molecular drivers of CNS-specific senescence and evaluates emerging therapeutic strategies from a pharmacological perspective. We place particular emphasis on recent advances in understanding glial senescence, the gut-brain axis, and the translational pipeline of senolytics/senomorphics, while also critically examining the unique challenges of targeting neuroinflammation compared to peripheral inflammation [14].

2. Mechanisms of Neuroinflammation Activation in Aging

The activation mechanism of aging-related neuro-inflammation is summarized in Table 1.

2.1. Cell-autonomous changes

Neuroinflammation constitutes the CNS immune response to injury, infection, or abnormal stimuli. During physiological aging, the CNS's innate immune cells undergo significant functional dysregulation, transitioning from a protective state to a chronic, low-toxicity yet neurotoxic condition. This transformation becomes a key driver and accelerator of neurodegenerative diseases such as AD and PD. The activation of age-related neuroinflammation constitutes a multifactorial, multi-layered process involving core mechanisms such as functional alterations in CNS innate immune cells, cellular senescence and the accumulation of their secretory phenotype, mitochondrial dysfunction, compromised blood-brain barrier (BBB) integrity, and the infiltration of peripheral inflammatory signals.

2.1.1. Microglial senescence

As the resident macrophages of the CNS, microglia serve as primary effectors and regulators of neuroinflammation. During aging, microglia undergo significant morphological, phenotypic, and functional remodelling, transitioning from a dynamic 'surveillance state' to a pro-inflammatory state characterised by 'hypo-responsiveness' or 'hyperactivation'. This process is termed 'microglial senescence' or 'microglial priming'. Senescent microglia exhibit reduced branching, enlarged cell bodies, increased lysosomal load, and heightened ROS production [15, 16].A pivotal phenotypic shift is the functional polarisation imbalance, shifting from a substitute-activated state (M2-type) with neuroprotective and tissue-repairing functions towards a classical-activated state (M1-type) biased towards releasing pro-inflammatory factors, reactive oxygen and nitrogen species (RONS), and complement components [17, 18].This polarisation imbalance partly stems from age-related epigenetic reprogramming. For instance, recent studies reveal markedly elevated lactate levels in aged microglia and hippocampal tissues from AD model mice, leading to increased histone H3 lysine 18 lactylation (H3K18la). H3K18la directly binds and activates key

genes within the promoter regions of the NF-κB signalling pathway, thereby strongly upregulating the expression of the SASP factors IL-6 and IL-8, forming a persistent pro-inflammatory positive feedback loop [9]. Moreover, age-related mitochondrial dysfunction induces ROS accumulation within microglia, activating the NLRP3 inflammasome. This promotes caspase-1-mediated maturation and release of IL-1β and IL-18, acting as a pivotal molecular switch driving neuroinflammation [17, 19]. Sensitivity of Toll-like receptors (TLRs) to damage-associated molecular patterns is also markedly heightened in aged microglia, further amplifying pro-inflammatory signalling [15]. These chronically activated M1-like microglia not only lose normal synaptic pruning and homeostasis maintenance functions but instead mediate synaptic damage and neuronal toxicity, directly promoting cognitive decline [15, 20].

Table 1. The Activation Mechanism of Aging-Related Neuroinflammation

Activation Mechanism	Characteristics and Molecular Basis	Impact on Neuroinflammation
Peripheral Immune System Infiltration	Breakdown of blood-brain barrier integrity, loss of tight junction proteins, reduction of pericytes. Dysfunction of aging endothelial cells leads to increased permeability.	Allows peripheral immune cells (T cells, monocytes) to enter the brain parenchyma, release pro-inflammatory factors, and exacerbate neuroinflammatory responses.
Damage-Associated Molecular Patterns (DAMPs)	Senescent cells release endogenous danger signal molecules such as HMGB1, S100 proteins, extracellular ATP, and mitochondrial DNA fragments.	Continuously activate microglia and astrocytes through pattern recognition receptors (PRRs) such as TLRs and NLRP3.
Proteostasis Imbalance	Accumulation of misfolded proteins (Aβ, Tau, α-synuclein), dysfunction of protein degradation systems (ubiquitin-proteasome, autophagy).	Pathological proteins act as DAMPs to activate the NLRP3 inflammasome, promote the maturation and release of IL-1β, and form a vicious cycle of neuroinflammation.
Oxidative Stress	Mitochondrial dysfunction leads to excessive ROS production, decreased activity of antioxidant enzymes (SOD, GPx), and dysregulation of iron metabolism.	ROS directly damages neurons and glial cells, activates NF-κB and MAPK signaling pathways, and upregulates the expression of pro-inflammatory genes.
Metabolic Dysregulation	Insulin resistance, abnormal lipid metabolism, lactate accumulation, and impaired brain energy metabolism (decreased glucose utilization).	Promotes neuroinflammation by affecting glial cell energy metabolism and activating inflammatory pathways; lactate induces histone lactylation to regulate inflammatory genes.

2.1.2. Astrocyte Reactivity

In the aging brain, astrocyte 'reactivity' transcends mere morphological alteration, representing a comprehensive reorganisation of genomic transcription-translation-metabolism-lipid signalling. Aging and diverse CNS insults induce reactive astrocyte proliferation, manifesting as cellular hypertrophy and upregulation of glial fibrillary acidic protein (GFAP) [7]. While this response may initially confer protective effects such as isolating damaged areas and providing nutritional support, reactive astrocytes acquire a detrimental phenotype in chronic aging contexts.

Similar to the M1/M2 classification of microglia, prolonged exposure to pro-inflammatory factors can drive reactive astrocytes towards a neurotoxic A1 phenotype. A1 astrocytes lose many normal supportive functions, instead secreting large amounts of complement components, chemokines, and other neurotoxic factors. This directly leads to neuronal and synaptic damage, inhibits synaptic plasticity, and participates in recruiting peripheral immune cells into the CNS. The proportion of A1 astrocytes significantly increases in the aging brain [7, 14].

In vitro primary experiments further demonstrate that combined IL-1β/TNF-α stimulation induces astrocytes to upregulate the glycolytic key enzyme HK2, shifting glycolysis towards the lactate-pyruvate axis and generating substantial lactate. Concurrently, it reduces glutamate transporter GLT-1 expression, leading to excitotoxicity; these alterations are more pronounced in the brain tissue of 18-month-old aged mice. Under ROS or DNA damage stimulation, astrocytes activate the cGAS-STING pathway to upregulate STING protein expression, thereby triggering an intracellular IRF3-SASP-like transcriptional programme that induces C3-dependent phagocytosis of adjacent synaptic structures. Evidently, A1 astrocytes serve as key executors in maintaining the local neuroinflammatory micro-environment, with their metabolic characteristics presenting promising new entry points for precise targeted interventions.

2.1.3. Oligodendrocyte Dysfunction and Aging

Traditionally, research on aging-related neuroinflammation has primarily focused on microglia and astrocytes. However, as the manufacturers and maintainers of myelin in the central nervous system, dysfunction within the oligodendrocyte lineage is equally prominent during aging and serves as a key driver of white matter degeneration and the inflammatory microenvironment [21, 22]. Aging reduces the proliferation and differentiation capacity of oligodendrocyte precursor cells, limiting the replenishment of new cells. Concurrently, mature oligodendrocytes exhibit functional decline and age-like phenotypes [23, 24]. This cell-autonomous aging directly results in failed myelin maintenance, manifesting as myelin thinning, structural disorganization, and loss of white matter integrity. These changes form the structural basis for slowed information processing in the aging brain [22, 25].

Notably, aged or stressed oligodendrocytes are not passive victims but active participants in neuroinflammation. Dysfunctional oligodendrocyte lineage cells, including aged oligodendrocytes and their precursor cells, release proinflammatory cytokines and damage-associated molecular patterns [21]. Furthermore, age-related lipid metabolism abnormalities lead to the accumulation of substances such as neurotoxic cholesterol precursors, further exacerbating local inflammation [22]. Detached myelin debris serve as persistent injury signals recognized by microglia, driving their polarization toward a pro-inflammatory phenotype. This establishes a self-perpetuating vicious cycle: "myelin injury → microglial activation → inflammatory cytokine release → further myelin injury" [22, 25]. Thus, oligodendrocyte senescence serves as the pivotal link connecting white matter structural degeneration with age-related neuroinflammatory homeostasis disruption. Its dysfunction not only impairs neural conduction efficiency but also actively promotes the establishment and maintenance of a pro-inflammatory microenvironment.

2.1.4. Neuronal Senescence and Inflammatory Crossover

Traditional views hold neurons as passive targets of neuroinflammation. Emerging evidence reveals that neurons in the aging brain can actively enter a distinct senescent state termed "neuronal senescence" or "neurescence," becoming a driving source of neuroinflammation [23, 26]. In the context of aging and neurodegenerative diseases like Alzheimer's, some neurons exhibit core hallmarks of senescence — accumulating DNA damage, undergoing metabolic alterations, and displaying a SASP [27, 28].

SASP factors released by these "senescent-like neurons", including diverse inflammatory mediators, chemokines, and proteases, profoundly shape the neuroinflammatory environment [11, 29]. First, neurogenic SASP directly acts on neighboring microglia and astrocytes via paracrine signaling, leading to sustained activation and maintenance of a proinflammatory state in these cells [21]. Second, worsening mitochondrial dysfunction in senescent neurons leads to excessive ROS production and mitochondrial DNA leakage into cytoplasm. These endogenous danger signals, acting as DAMPs, can be recognized by inflammasomes (e.g., NLRP3) within neurons themselves or in glial cells, triggering potent inflammatory cascades [11, 28]. Furthermore, senescent neurons may downregulate "don't eat me" signals on their surfaces, making them susceptible to unnecessary phagocytosis by overactivated microglia. This leads to synaptic loss and impaired neural network connectivity [11].

Thus, a lethal bidirectional vicious cycle forms between neuronal aging and neuroinflammation. On one hand, the chronic inflammatory microenvironment driven by glial cells accelerates neuronal damage and aging. On the other hand, senescent neurons amplify and sustain neuroinflammatory responses by secreting SASP and releasing DAMPs [26, 27]. This self-reinforcing positive feedback loop disrupts the homeostatic equilibrium between neurons and glial cells, constituting the core mechanism underlying the persistence of low-grade chronic inflammation in the aging brain. This directly leads to impaired synaptic plasticity and progressive cognitive decline.

2.2. Extracellular Stimuli and Microenvironmental Alterations

Compromised BBB integrity constitutes a central component of age-related neuroinflammation. Endothelial cell senescence leads to loss of tight junction proteins, facilitating infiltration of peripheral immune cells into the brain parenchyma and exacerbating inflammation. Concurrently, DAMPs released from senescent cells persistently activate glial cells [30, 31].

Protein homeostasis imbalance manifests as abnormal aggregation of β-amyloid (Aβ) and tau proteins, directly activating NLRP3 inflammasomes in microglia to form a vicious cycle of "inflammation-pathological protein deposition" [19, 30]. Oxidative stress increases ROS production via mitochondrial dysfunction, activating NF-κB and MAPK pathways [32]. Furthermore, metabolic dysregulation promotes pro-inflammatory phenotypes by altering glial cell energy metabolism [13].

2.2.1. Peripheral immune system infiltration

The BBB constitutes a critical interface for maintaining homeostasis within the CNS. It is formed by cerebral microvascular endothelial cells (BMECs) and their interstitial tight junctions (TJs), pericytes, astrocytic terminal processes, and the basement membrane. Aging is accompanied by progressive structural and functional impairment of the BBB:(1) Structural integrity disruption: Downregulation or mislocalisation of tight junction proteins , thickening and compositional alterations of the basement membrane, and loss of pericytes [33].(2) Functional impairment: Diminished transcellular transport and weakened regulation of ion/water homeostasis, increasing the risk of vasogenic cerebral oedema [33].(3) Immune barrier failure: Increased expression of endothelial cell adhesion molecules promotes adhesion of peripheral immune cells to the cerebral vascular wall and their infiltration into the brain parenchyma [33, 34]. The mechanisms underlying BBB disruption are closely associated with aging itself and the aforementioned factors: chronic low-grade inflammationsuppresses TJ protein expression; ROS directly damages endothelial and pericellular cells; MMPs become hyperactivated, degrading the basement membrane and TJ proteins; Chronic cerebral hypoperfusion and hypometabolism, arising from impaired cerebral blood flow (CBF) regulation, further compromise the energy supply and function of BBB endothelial cells [32, 34]. BBB disruption exerts a dual pro-inflammatory effect. The primary mechanism involves peripheral pro-inflammatory factor infiltration: elevated circulating pro-inflammatory cytokines under systemic chronic inflammation more readily traverse the compromised BBB into the CNS, directly activating microglia and astrocytes [12, 35]. The second mechanism involves peripheral immune cell infiltration: upregulation of adhesion molecules facilitates the passage of activated immune cells through the BBB into brain parenchyma. These infiltrating immune cells release substantial pro-inflammatory factors and cytotoxic substances, directly attacking neurons while further activating resident CNS glial cells, thereby amplifying local neuroinflammation [36, 37]. Moreover, age-related gut dysbiosis and the resulting intestinal barrier leakage permit increased entry of bacterial products, microbial metabolites to more readily enter the bloodstream. These substances possess pro-inflammatory properties and can also influence the CNS via compromised BBB or vagus nerve pathways, thereby driving or exacerbating neuroinflammation [38, 39]. This gut-brain axis-mediated systemic chronic inflammation (GM-SCI) is recognised as a crucial bridge linking aging, peripheral inflammation, and central nervous system inflammation [39].

2.2.2. Damage-associated molecular patterns

DAMPs are a class of endogenous danger signaling molecules typically released or exposed during cellular injury, stress, or death, thereby activating the innate immune system and driving inflammatory responses. In the aging brain, the accumulation and sustained release of DAMPs represent one of the key drivers of neuroinflammation. DAMPs encompass a diverse array of molecules, including nucleic acids, proteins, ATP, histones, and heat shock proteins. Under homeostatic conditions, these molecules typically do not elicit immune responses. However, following cellular injury, changes in their conformation, localization, or concentration transform them into potent activators of the immune system.

DAMP release mechanisms are diverse, occurring via passive release (e.g., cell necrosis, membrane rupture) or active secretion. For instance, necrotic cells release HMGB1 and ATP, while mitochondrial damage leads to leakage of mtDNA and mitochondrial reactive oxygen species (mtROS), further activating inflammasome pathways [40]. In neurodegenerative diseases, misfolded proteins such as Aβ and α-synuclein are also recognized as DAMPs, activating microglia and astrocytes to promote inflammatory mediator release [41, 42].

Mitochondrial DAMPs (mtDAMPs) are particularly prominent in aging and neurodegenerative diseases. mtDAMPs such as mtDNA, ATP, and mtROS significantly amplify neuroinflammatory responses by activating NLRP3 inflammasomes and cGAS-STING pathways [40]. Research indicates that in Alzheimer's disease and Parkinson's disease, mtDAMP release is closely associated with mitochondrial dysfunction and protein homeostasis imbalance, forming a positive feedback loop that accelerates neuronal damage [40, 42]. DAMPs activate downstream signaling pathways such as NF-κB, MAPK, and inflammasome by binding to their corresponding pattern recognition receptors (PRRs), including TLRs, NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs), thereby promoting the release of pro-inflammatory cytokines [43, 44]. Furthermore, DAMPs can compromise BBB integrity, allowing peripheral immune cell infiltration and exacerbating neuroinflammation [45].

2.2.3. Protein homeostatic imbalance

Aging is accompanied by diminished molecular chaperone function and reduced efficiency of the ubiquitin-proteasome system and autophagy-lysosomal pathways. This leads to impaired clearance of misfolded proteins, resulting in the formation of oligomers and fibrillar aggregates. These abnormally aggregated proteins themselves constitute potent DAMPs capable of

triggering NLRP3 inflammasome activation and pro-inflammatory cytokine storms. Similarly, α-synuclein activates microglia and astrocytes to release inflammatory mediators, playing a pivotal role in PD [14].

2.2.4. Oxidative stress and mitochondrial dysfunction

Aging leads to mitochondrial structural and functional decline, reduced electron transport chain efficiency, and significantly increased ROS production. As previously described in Section 2.1.1, thes Excessive ROS themselves constitute potent damage-associated molecular patterns, thereby triggering NLRP3 inflammasome activation and ultimately leading to a pro-inflammatory cytokine storm.

Mitochondrial dysfunction further impairs ATP production, compromising glial phagocytic clearance capacity and exacerbating protein aggregation. The ApoE4 allele, a major genetic risk factor for AD, has also been shown to directly impair mitochondrial function, increasing mitochondrial Ca^{2+} overload and ROS levels, thereby further promoting neuroinflammation and neurotoxicity [9, 15].

2.2.5. Metabolic disorders

Age-related vascular stiffening and endothelial dysfunction impair cerebral blood flow (CBF) regulation, leading to chronic cerebral hypoperfusion and reduced glucose utilisation efficiency (hypometabolism). Hypoperfusion/hypometabolism causes insufficient energy supply to neurons and glial cells, exacerbating mitochondrial dysfunction and oxidative stress, while simultaneously limiting energy availability required for clearing toxic substances. Accumulation of metabolic waste further stimulates inflammatory responses. Age-related comorbidities like hypertension and diabetes significantly intensify this process [32, 33, 46].

2.3. Epigenetic regulation

The activation of neuroinflammation during aging is closely linked to the regulation of epigenetic mechanisms, particularly alterations in DNA methylation and histone modifications, which significantly influence the expression of inflammation-related genes in glial cells. Epigenetic modifications do not involve changes to DNA sequences but play a crucial role in aging and neurodegenerative diseases by regulating gene transcriptional activity.

DNA methylation, one of the most prevalent epigenetic modifications typically occurring within CpG island regions, exhibits abnormalities associated with heightened inflammatory responses during aging. In the aging brain, hypomethylation within the promoter regions of pro-inflammatory genes leads to their upregulation, thereby exacerbating neuroinflammation [7]. Similarly, in aged microglia, genes associated with inflammatory responses also exhibit demethylation, promoting their sustained activation and release of inflammatory cytokines [10]. Furthermore, the DNA damage response accompanying aging can further alter DNA methylation patterns, affecting the homeostatic function of glial cells.

Histone modifications represent another crucial epigenetic mechanism, encompassing acetylation, methylation, lactylation, and others, which regulate gene expression by altering chromatin structure. Studies reveal decreased levels of histone H3K9 and H3K27 trimethylation (H3K9me3, H3K27me3) in aged microglia and astrocytes, leading to increased transcription of inflammatory genes [31]. Notably, lactylation—a novel histone modification—plays a pivotal role in neuroinflammation: elevated lactate levels within microglia in aging and AD models drive increased H3K18 lactylation (H3K18la), thereby activating the NF-κB pathway and promoting the release of inflammatory cytokines such as IL-6 and IL-8 [47]. This discovery reveals the critical role of metabolic-epigenetic crosstalk in neuroinflammation.

Moreover, dysregulated activity of histone deacetylases (HDACs) and histone acetyltransferases (HATs) also participate in modulating the inflammatory phenotype of glial cells. In AD and aging processes, decreased HDAC activity leads to hyperacetylation of histones at pro-inflammatory gene loci, further amplifying neuroinflammatory responses [7]. These epigenetic alterations are not confined to microglia but are also observed in astrocytes, affecting their phagocytic function, cytokine secretion, and interactions with other neuronal cells [48].

Epigenetic regulation further involves non-coding RNAs and chromatin remodelling complexes, collectively forming a complex network that finely tunes neuroinflammatory responses. For instance, dysregulated expressions of certain miRNAs (e.g., miR-146a, miR-155) in the aging brain impacts key inflammatory signalling pathways like NF-κB [17]. These findings underscore the central role of epigenetic mechanisms in neurodegenerative diseases.

DNA methylation and histone modifications profoundly influence neuroinflammatory states during aging by regulating the expression of inflammation-associated genes in glial cells. Developing intervention strategies targeting these epigenetic pathways—such as employing histone deacetylase (HDAC) inhibitors or modulating lactate metabolism—may offer novel avenues for delaying brain aging and treating neurodegenerative diseases [49].

2.4. Key signalling pathways

During aging, the abnormal activation of multiple signalling pathways constitutes a core mechanism driving neuroinflammation. These pathways not only function independently but frequently form intricate regulatory networks that collectively amplify inflammatory responses, leading to neuronal damage and cognitive impairment. Among these, the NF-κB, NLRP3 inflammasome, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinase (MAPK) pathways play particularly crucial roles.

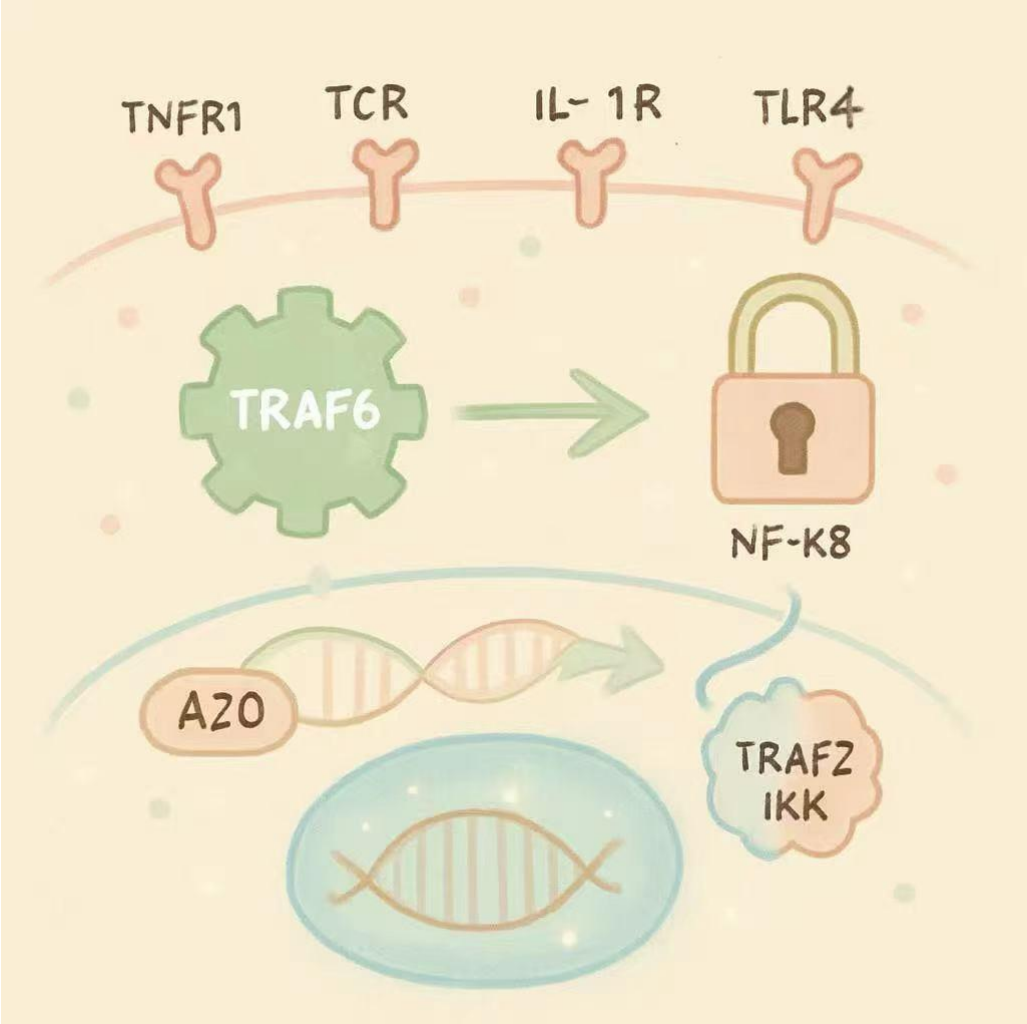

Figure 1. The canonical NF-κB signaling pathway in neuroinflammation. This schematic shows the central pathway controlling proinflammatory gene expression in the aging and diseased brain. The cascade begins when extracellular inflammatory mediators, such as Tumor Necrosis Factor-α (TNF-α) binding to TNFR1 or Interleukin-1β (IL-1β) binding to IL-1R, or Damage-Associated Molecular Patterns (DAMPs) engaging Toll-like Receptor 4 (TLR4), initiate signal transduction. This involves the recruitment of adaptor proteins TNF Receptor-Associated Factor 2/6 (TRAF2/6). These adaptors then activate the IκB kinase (IKK) complex, which phosphorylates the inhibitory protein IκBα. Phosphorylated IκBα is ubiquitinated and targeted for degradation by the proteasome. This degradation releases the primary NF-κB transcription factor complex, typically a p50-RelA (p65) heterodimer, allowing its translocation into the nucleus. Within the nucleus, NF-κB binds to specific κB DNA sequences, driving the transcription of genes encoding pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines, adhesion molecules, and enzymes that further amplify the inflammatory response. A key negative regulator, the deubiquitinating enzyme A20, functions as a feedback brake to restore homeostasis by inhibiting IKK and TRAF activity. In the context of brain aging and neurodegeneration, chronic activation of this pathway in microglia and astrocytes sustains a detrimental neuroinflammatory state, contributing to synaptic dysfunction and neuronal loss. Abbreviations: TCR, T cell receptor. (Figure concept adapted from Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study [52].)

2.4.1. NF-κB Pathway

The NF-κB pathway is the most central transcriptional regulatory pathway in neuroinflammation (Fig. 1). At rest, NF-κB exists in the cytoplasm bound to its inhibitory protein IκB. In the aging brain, multiple stimuli such as oxidative stress, Aβ deposition, and abnormal cytokines activate IκB kinase (IKK), leading to IκB degradation. This releases NF-κB (primarily the p65-p50 dimer) and facilitates its translocation to the nucleus, where it initiates transcription of numerous pro-inflammatory genes [50, 51]. Research indicates that sustained NF-κB activation in microglia and astrocytes is a key driver of age-related neuroinflammation and neurodegeneration [17]. Moreover, NF-κB engages in crosstalk with other pathways; for instance, it potentiates STING signalling by altering its intracellular trafficking, thereby amplifying the type I interferon response and neuroinflammation. In models such as AD, inhibition of the NF-κB pathway effectively attenuates neuroinflammation and improves pathological manifestations [17].

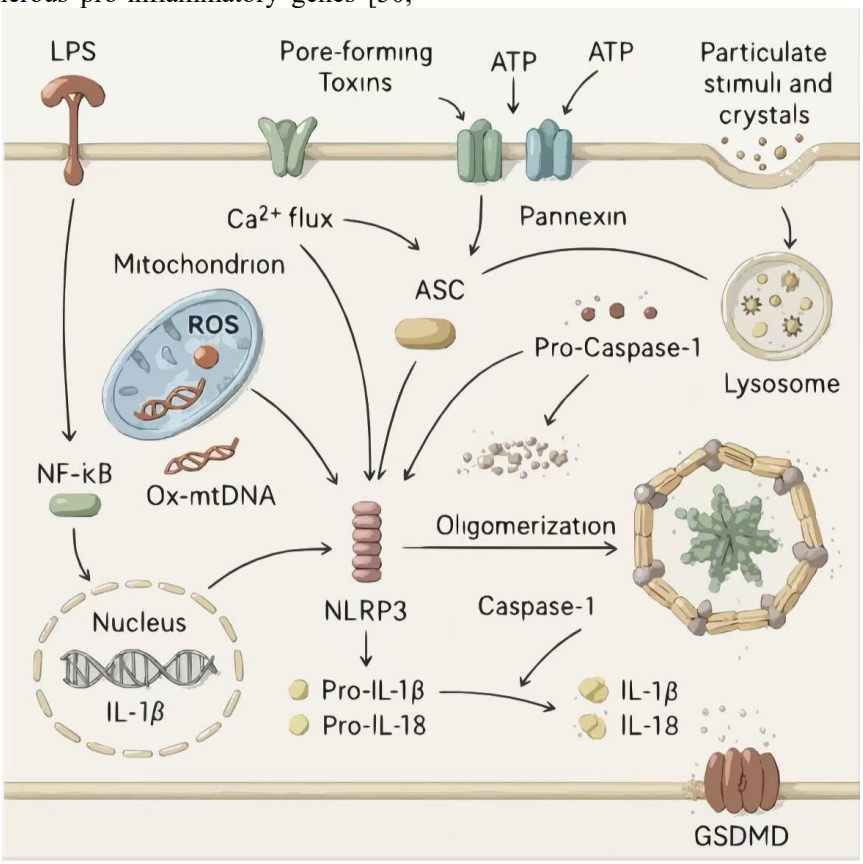

Figure 2. Activation mechanism of the NLRP3 inflammasome in neuroinflammation. The NLRP3 inflammasome is a cytosolic multi-protein complex critical for initiating a potent inflammatory form of programmed cell death called pyroptosis. Its activation is a tightly regulated, two-step process. Signal 1 (Priming): Encounter with Pathogen-Associated Molecular Patterns (PAMPs) via Toll-like Receptors (TLRs) or cytokines like TNF-α leads to activation of transcription factors such as NF-κB. This upregulates the expression of both the NLRP3 sensor protein and the inactive precursor of Interleukin-1β (pro-IL-1β). Signal 2 (Activation): A diverse array of endogenous Damage-Associated Molecular Patterns (DAMPs) provides the triggering stimulus. These include extracellular ATP (signaling through the P2X7 purinergic receptor and inducing K^+ efflux), crystalline structures (e.g., amyloid-β fibrils, cholesterol crystals), microbial toxins, or Ca^{2+} influx. These stimuli converge to induce cellular stress events such as mitochondrial dysfunction (releasing mtROS, mitochondrial reactive oxygen species), lysosomal rupture (releasing cathepsins), and increased cytosolic ROS. These events promote the oligomerization of NLRP3, which then recruits the adaptor protein ASC (Apoptosis-associated Speck-like protein containing a CARD). ASC nucleates the formation of a large speck and recruits pro-caspase-1. The assembled inflammasome facilitates the autocatalytic cleavage and activation of caspase-1. Active caspase-1 then performs two key functions: (1) it cleaves pro-IL-1β and pro-IL-18 into their mature, bioactive forms for secretion; and (2) it cleaves Gasdermin D (GSDMD), whose N-terminal fragments oligomerize to form pores in the plasma membrane. This leads to pyroptosis, a lytic cell death that releases inflammatory contents, thereby amplifying neuroinflammation in conditions like Alzheimer's and Parkinson's disease. (Figure concept adapted from Interplay Between NLRP3 Inflammasome and Autophagy [58]).

2.4.2. NLRP3 inflammatory vesicle pathway

The NLRP3 inflammasome pathway constitutes a multiprotein complex within the innate immune system, whose activation represents a hallmark event in age-related neuroinflammation (Fig. 2). The NLRP3 inflammasome comprises the sensor NLRP3, the adaptor protein ASC, and the effector protein caspase-1. During aging, "danger signals" such as mtROS, Aβ oligomers, and α-synuclein can trigger its assembly [53]. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their active forms and cleaves Gasdermin D (GSDMD), inducing inflammatory pyroptosis and triggering robust inflammatory responses [44]. Research indicates NLRP3 activation undergoes precise regulation by multiple post-translational modifications. For instance, palmitoylation (mediated by ZDHHC7) promotes oligomerisation, whilst SUMOylation (mediated by TRIM28) stabilises NLRP3 protein levels by inhibiting ubiquitination [54, 55]. In diverse models including AD, PD, and cerebral ischaemia, inhibition of the NLRP3 inflammasome significantly alleviates neuroinflammation and neuronal damage, highlighting its substantial potential as a therapeutic target [56, 57].

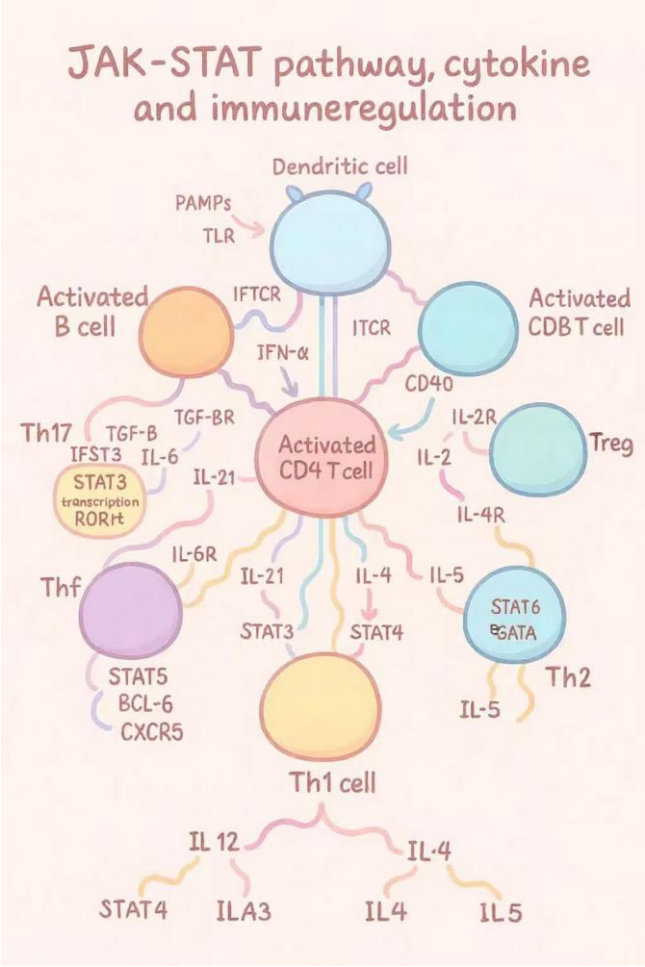

Figure 3. The JAK-STAT signaling pathway in immune and glial cell regulation. This diagram illustrates how the Janus Kinase/Signal Transducer and Activator of Transcription (JAK-STAT) pathway translates extracellular cytokine signals into specific transcriptional programs, determining immune cell fate and modulating neuroinflammatory responses. The pathway is initiated by cytokine binding (e.g., IL-6, IFN-γ, IL-2) to their cognate cell surface receptors, which are associated with intracellular JAK family kinases (JAK1, JAK2, JAK3, TYK2). Cytokine-induced receptor dimerization brings JAKs into proximity, leading to their mutual trans-phosphorylation and activation. The activated JAKs then phosphorylate tyrosine residues on the receptor cytoplasmic tails, creating docking sites for STAT proteins (STAT1-4, STAT5a/b, STAT6). Upon recruitment, STATs are phosphorylated by JAKs on a critical tyrosine residue. Phosphorylated STATs dimerize, translocate to the nucleus, and bind to specific DNA response elements to regulate the transcription of target genes. Key immune cell differentiation pathways shown include IL-6 and IL-21 activating STAT3 to drive RORγt expression and T-helper 17 (Th17) cell fate; IL-12 activating STAT4 for T-helper 1 (Th1) cell differentiation; and IL-2 activating STAT5, which is pivotal for Regulatory T cell (Treg) function and immune suppression. In the context of neuroinflammation, this pathway is activated in microglia and astrocytes by cytokines present in the aged brain. Persistent JAK-STAT signaling, particularly STAT3 and STAT1 activation, promotes a pro-inflammatory (M1) microglial phenotype, enhances astrocyte reactivity, and can directly influence neuronal survival, making it a key therapeutic target. (Figure adapted from Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer [60]).

2.4.3. JAK/STAT pathway

The JAK/STAT pathway serves as the primary signal transduction pathway for numerous cytokines and growth factors, extensively involved in immune regulation, cell proliferation, and survival (Fig. 3). Upon binding to their respective receptors, cytokines activate receptor-associated JAKs, which subsequently phosphorylate STAT proteins. Phosphorylated STAT dimerises and translocates into the nucleus, where it regulates target gene expression [58, 59]. In the aging brain, the JAK/STAT pathway is frequently constitutively activated, promoting the production of pro-inflammatory mediators and contributing to the abnormal activation of microglia/macrophages [25, 58]. Notably, a close relationship exists between the JAK/STAT pathway and NLRP3 inflammasome activation. Research indicates that upregulation of JAK2/STAT3 signalling promotes

histone H3 and H4 acetylation at the NLRP3 promoter, directly enhancing NLRP3 transcription and establishing a positive feedback loop of inflammation [25]. Consequently, JAK inhibitors such as ruxolitinib can downregulate NLRP3 expression by inhibiting STAT3 phosphorylation, thereby exerting neuroprotective effects in ischaemic stroke models [25].

2.4.4. MAPK pathway

The MAPK pathway, particularly the p38 and JNK subpathways, serves as a crucial mediator of stress and inflammatory responses (Fig. 4). p38 MAPK can be activated by diverse stimuli including oxidative stress and inflammatory cytokines, subsequently phosphorylating downstream transcription factors or kinases to promote the synthesis of pro-inflammatory factors such as TNF-α and IL-1β [61]. In the context of aging, sustained p38 MAPK activation not only directly drives inflammatory gene expression but also impedes NLRP3 degradation by inhibiting chaperone-mediated autophagy (CMA), thereby enhancing NLRP3 inflammasome activation [62]. Furthermore, p38 MAPK negatively regulates TFEB, a key autophagy transcription factor, further impairing cellular clearance capacity and exacerbating inflammation [62]. JNK signalling also participates in regulating microglial activation and neuronal apoptosis. Research indicates that deletion of miR-26a-3p within the hippocampus can induce neuroinflammation and behavioural abnormalities by upregulating p38 MAPK-NF-κB signalling [61]. Consequently, inhibiting p38 MAPK effectively ameliorates neuroinflammation and cognitive deficits across multiple models.

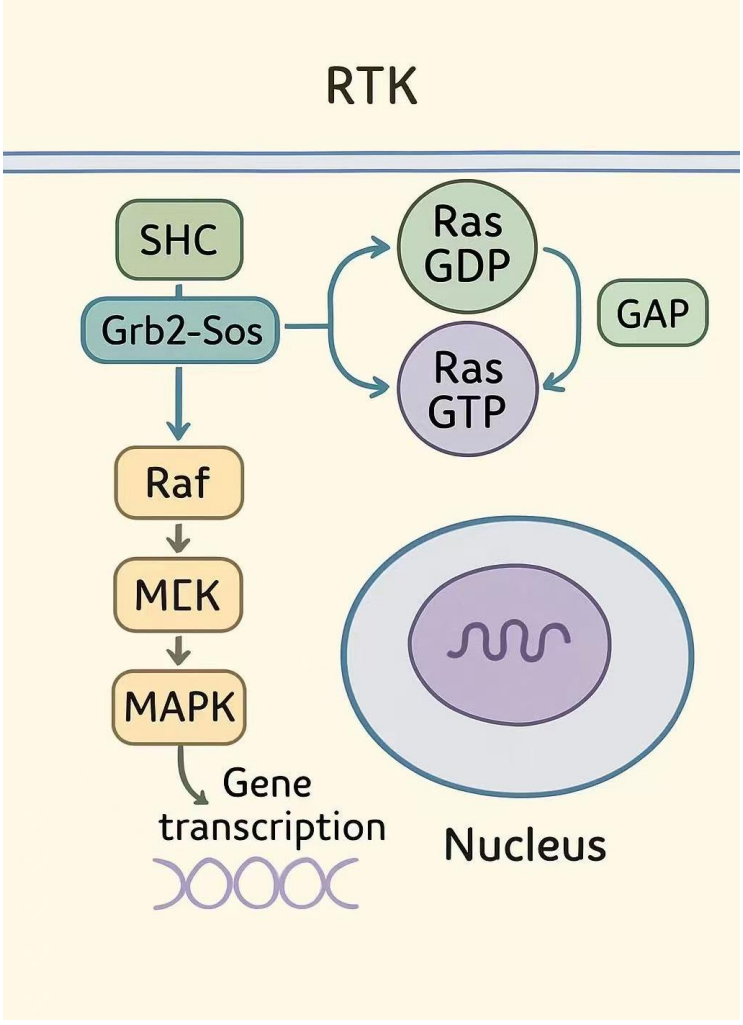

Figure 4. The canonical MAPK/ERK signaling pathway. This figure depicts the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) cascade, a fundamental signaling module that regulates cell growth, differentiation, survival, and—in the context of the brain—synaptic plasticity and inflammatory responses. The pathway is typically initiated by growth factors or other ligands binding to Receptor Tyrosine Kinases (RTKs), leading to receptor autophosphorylation. The adaptor proteins SHC and Growth factor receptor-bound protein 2 (Grb2) are recruited to the activated receptor. Grb2, in complex with the Son of Sevenless (SOS) guanine nucleotide exchange factor, then translocates to the plasma membrane. SOS catalyzes the exchange of GDP for GTP on the membrane-anchored small G-protein Ras, activating it. GTP-bound Ras (Ras-GTP) subsequently recruits and activates the serine/threonine kinase Raf (also known as MAPK Kinase Kinase, MAP3K). Activated Raf phosphorylates and activates MEK (MAPK/ERK Kinase, or MAP2K), which in turn phosphorylates and activates ERK (Extracellular Signal-Regulated Kinase, or MAPK). Activated ERK translocates to the nucleus, where it phosphorylates a wide array of transcription factors (e.g., ELK1, c-Myc), thereby altering gene expression programs. The Ras activation cycle is terminated by GTPase-Activating Proteins (GAPs), which enhances Ras's intrinsic GTPase activity to hydrolyze GTP to GDP. In neuroinflammation, the p38 MAPK and JNK branches of the MAPK family are often more prominently activated by stress and inflammatory cytokines, contributing to glial activation and the production of inflammatory mediators. However, ERK signaling also plays a role in mediating cytokine effects and can influence neuronal survival and plasticity. (Figure adapted from MAPK/ERK Signaling Pathway in Hepatocellular Carcinoma [63]).

2.5. Specific Differences between CNS and Peripheral Senescence Mechanisms

The CNS microenvironment differs significantly from peripheral tissues, resulting in unique characteristics of senescent cell production, clearance, and pathological effects. Firstly, the BBB limits the infiltration of peripheral immune cells (such as T cells and macrophages) into the brain, impairing the clearance of senescent cells in the CNS by systemic immune surveillance and leading to the accumulation of senescent cells in the brain. Secondly, glial cells (microglia and astrocytes), as immune-related cells specific to the CNS, have distinct senescent phenotypes from peripheral immune cells: senescent microglia are mainly polarised to the M1 type, continuously secrete SASP factors, and have impaired phagocytic function, while peripheral senescent macrophages still retain partial tissue repair capabilities [16]; senescent astrocytes are prone to transform into the neurotoxic A1 phenotype, a process specifically regulated by factors such as IL-1α and TNF in the central microenvironment, whereas peripheral fibroblast senescence does not involve such phenotypic switching [7]. In addition, the hypoxic microenvironment, high metabolic demand, and limited regenerative capacity of the CNS make neuronal damage and dysfunction more likely to be caused by inflammation induced by senescent cells, while the regenerative potential of peripheral tissues can partially offset age-related damage [64].

2.6. Sex Differences and Inter-individual Variability in Neuroinflammation

Notable sex differences have been documented in the senescence of astrocytes, microglia, and peripheral cells, encompassing those vital to innate and adaptive immune responses. Interventions that eliminate senescent cells, such as senolytic drugs, can effectively mitigate certain aging-related functional declines. The similarities and differences in senolytic responses between males and females, however, hinge on several critical factors [65]. These include the specific biological system examined, the treatment regimen employed, the existing burden of senescent cells, and the age at which treatment commences. Transcriptomic analysis of human microglia clearly demonstrated higher KDM6A expression in females compared to males with multiple sclerosis (MS), suggesting that KDM6A might contribute significantly to the sex-based differences in susceptibility to MS [66]. Neuroinflammation peaked in the subiculum and was significant exclusively in women, while inflammatory microRNAs (miRNAs) increased specifically in the parietal cortex of women with AD, but not men [67].

Inter-individual variability in neuroinflammation is driven by multiple factors such as genetic background, immune status, comorbidities, and gut microbiota composition. Genetic polymorphisms are key determinants: for example, carriers of the ApoE4 allele have more severe microglial senescence and neuroinflammation, increasing the risk of AD; while the TREM2 R47H mutation impairs microglial phagocytic function, leading to the accumulation of pathological proteins and exacerbating inflammatory responses [8, 68]. Comorbidities such as diabetes and hypertension can amplify neuroinflammation by disrupting the BBB and promoting peripheral immune cell infiltration [68]. Additionally, individual differences in gut microbiota composition affect the production of microbial metabolites (e.g., short-chain fatty acids), which in turn regulate peripheral and central immune responses, leading to differences in neuroinflammatory levels among individuals [39].

3. Neuroinflammation Mediates Aging-Related Brain Dysfunction

The persistent state of low-grade, chronic neuroinflammation during aging, termed 'inflammaging', is not a benign background noise but a core pathophysiological force driving degenerative changes in brain structure and function [39]. This "flame," ignited by aging glial cells, accumulated intracellular and extracellular stressors, and dysregulated immune responses, systematically erodes the brain's foundational health through multiple interconnected pathways [3, 69]. Its destructive consequences span multiple levels, from the most intricate synaptic communication to macroscopic tissue integrity, ultimately manifesting as cognitive decline, neuronal loss, and significantly heightened susceptibility to neurodegenerative diseases such as AD and PD [46, 62]. The detrimental effects of neuroinflammation are multidimensional, not only directly damaging neurons but also altering the neuro-microenvironment, suppressing endogenous repair mechanisms, and disrupting critical physiological barriers, thereby creating a self-amplifying vicious cycle [3, 39]. Gaining a profound understanding of these neuroinflammation-mediated pathological pathways is crucial for identifying and developing effective pharmacological intervention strategies to delay brain aging [46].

3.1. Impairment of Synaptic Plasticity and Cognitive Decline

Synaptic plasticity constitutes the cellular foundation for learning and memory formation, its function being highly

dependent upon intricate molecular regulation and a stable local microenvironment. Within the aging brain, chronic neuroinflammation disrupts this equilibrium through multiple mechanisms, directly impairing synaptic function. Activated microglia and astrocytes persistently release pro-inflammatory cytokines such as tumour necrosis factor-α and interleukin-1β. These cytokines directly interfere with synaptic function. Notably, TNF-α reduces the distribution of α-aminobutyric acid receptor on the postsynaptic membrane by promoting its endocytosis from the synaptic membrane, thereby weakening excitatory synaptic transmission [20]. IL-1β, conversely, activates its receptor, subsequently triggering Src kinase activation. This leads to dysfunction of the N-methyl-D-aspartate receptor) inhibiting hippocampal long-term potentiation (LTP), a persistent enhancement of synaptic efficacy closely associated with memory consolidation, while promoting long-term depression (LTD), ultimately diminishing synaptic strength and impairing memory [15]. Beyond direct synaptic effects, inflammatory mediators also disrupt neurotrophic signalling pathways. Brain derived neurotrophic factor (BDNF) and its receptor TrkB are critical for synaptic plasticity and neuronal survival. A neuroinflammatory environment can downregulate BDNF expression and inhibit its downstream PI3K/Akt and MAPK/ERK signalling pathways, thereby impairing synaptic maintenance and cognitive function [70]. Furthermore, the complement pathway, as part of the innate immune system, plays a key role in synaptic pruning. In aging and neurodegenerative contexts, complement components such as C1q and C3 are abnormally upregulated. These accumulate at synapses, serving as 'eat me' signals recognised by complement receptors on microglia, leading to excessive, non-selective synaptic phagocytosis and unnecessary loss of synaptic connections [20]. This inflammation-driven abnormal synaptic pruning represents a crucial mechanism linking neuro-inflammation to cognitive decline.

3.2. Neuronal damage and death

Chronic neuroinflammation creates an environment highly hostile to neuronal survival by inducing oxidative stress, excitotoxicity, and directly activating cell death programmes, ultimately leading to neuronal injury and death. Activated immune cells, particularly microglia, serve as major sources of ROS and reactive nitrogen species (RNS). Activation of NADPH oxidase (NOX2) constitutes a key pathway for ROS production. Excessive ROS attack lipids, proteins, and DNA, causing mitochondrial dysfunction and further amplifying oxidative stress in a vicious cycle [15]. Neuroinflammation is also closely associated with excitotoxicity. Pro-inflammatory cytokines inhibit astrocytic reuptake of synaptic glutamate and promote its release, resulting in abnormally elevated extracellular glutamate concentrations. Excessive glutamate overactivates NMDA receptors, causing calcium influx overload and subsequently activating a cascade of calcium-dependent enzymes—including calpains, nitric oxide synthase (nNOS), and nucleases—ultimately precipitating neuronal apoptosis or necrosis [68]. Beyond indirect toxicity, inflammatory mediators may directly trigger intrinsic apoptotic pathways in neurons. TNF-α, by binding to TNFR1 on neurons, can recruit adaptor proteins and activate caspase-8, thereby initiating the apoptotic cascade. Concurrently, mature IL-1β produced by NLRP3 inflammasome activation can also directly act upon neurons, exacerbating their pathological changes [11]. Dysfunction of microglia further intensifies neuronal damage. In the aging brain, the phagocytic function of microglia becomes dysregulated. On the one hand, they may fail to efficiently clear debris from dying neurons and misfolded protein aggregates, leading to the accumulation of toxic substances. On the other hand, they sometimes abnormally phagocytose viable neurons and synapses, a process termed 'neuronophagy', which directly results in neuronal loss [37].

3.3. Inhibition of neurogenesis

Neurogenesis in the adult hippocampal dentate gyrus is crucial for learning, memory, and emotional regulation, yet this process significantly declines during aging. Chronic neuroinflammation is one of its primary inhibitory factors. Inflammatory cytokines exert direct suppressive effects on neural stem cells (NSCs) and progenitor cells. Factors such as IL-1β, IL-6, and TNF-α have been demonstrated to inhibit NSC proliferation both in vitro and in vivo, steering their cellular fate towards glial differentiation rather than neuronal differentiation, thereby reducing the generation of new neurons [69] . Neuroinflammation also disrupts neurogenesis supporting microenvironment (niche) within the hippocampus. Pro-inflammatory factors released by activated microglia can impair supporting cell function, for instance by reducing astrocyte secretion of neurotrophic factors and affecting vascular endothelial cell function, thereby diminishing energy and nutrient support for NSCs [71]. Furthermore, neuroinflammation synergises with other pathological changes observed during aging to collectively suppress neurogenesis. For instance, age-related oxidative stress and elevated glucocorticoid levels synergise with inflammatory signals to further inhibit cell proliferation and promote NSC senescence and apoptosis [72]. Notably, suppressed neurogenesis correlates closely with cognitive decline. Hippocampal neurogenesis underpins

pattern separation and cognitive flexibility, with its reduction directly contributing to age-related memory deficits and mood disorders [69].

3.4. White matter damage and demyelination

White matter comprises extensive myelinated axons responsible for high-speed information transmission between distinct brain regions. Neuroinflammation during aging is a key driver of white matter damage and demyelination, primarily achieved through impairment of the oligodendrocyte lineage. The differentiation and maturation of oligodendrocyte precursor cells (OPCs) form the basis for maintaining myelin homeostasis and facilitating myelin regeneration. Pro-inflammatory cytokines, such as TNF-α and IL-1β, exert toxic effects on OPCs and inhibit their differentiation into mature, myelin-forming oligodendrocytes, thereby impairing myelin repair [62]. Activated microglia and infiltrating peripheral immune cells directly contribute to myelin injury. They release reactive oxygen species and matrix metalloproteinases (MMPs), which directly attack and degrade myelin sheaths and oligodendrocytes [16]. Under chronic cerebral hypoperfusion, the inflammatory response is significantly amplified. Hypoperfusion induces hypoxia and energy crises, activating microglia/macrophages and amplifying inflammation via pathways such as NLRP3 inflammasomes, thereby exacerbating white matter lesions—a core feature of vascular cognitive impairment [46]. White matter damage impairs cognitive function by disrupting neural network connectivity efficiency. Diffusion tensor imaging (DTI) studies demonstrate that white matter integrity correlates strongly with slowed processing speed, impaired executive function, and working memory deficits in older adults [68].

3.5. Promotion of neurodegenerative pathologies

Chronic neuroinflammation is not merely a concomitant phenomenon in neurodegenerative diseases, but a key driver propelling their onset and progression. It significantly accelerates pathological processes by forming vicious cycles with the core pathological proteins of these diseases. In AD, neuroinflammation exhibits strong bidirectional interactions with Aβ and tau pathology. Aβ aggregates activate pattern recognition receptorson microglia and astrocytes, triggering inflammatory responses. However, sustained inflammatory activation impairs the phagocytic function of microglia, rendering them incapable of effectively clearing Aβ. Instead, they secrete increased levels of inflammatory cytokines such as IL-1β, which directly upregulates β-secretase (BACE1) expression, thereby promoting Aβ generation and perpetuating a self-sustaining vicious cycle [11]. Regarding tau pathology, inflammatory mediators activate neuronal kinases, promoting abnormal tau phosphorylation and exacerbating neurofibrillary tangle formation. Activated microglia also indirectly facilitate tau pathology propagation between neurons by releasing factors like IL-1β [49]. A similar vicious cycle exists in PD. Misfolded α-synuclein (α-syn) can act as a DAMP, activating microglia via receptors, leading to NLRP3 inflammasome activation and the release of inflammatory cytokines. These inflammatory mediators, in turn, promote α-syn aggregation and intercellular spread, thereby amplifying the pathological process [13]. Genetic studies provide compelling evidence for neuroinflammation's pathogenic role in neurodegenerative diseases. Genome-wide association studies (GWAS) have identified multiple AD risk genes that play critical roles in microglial immune function and inflammatory responses. Dysfunction in these genes alters microglial responses to Aβ and its fragments, thereby influencing disease susceptibility [14].

3.6. Blood-brain barrier dysfunction

The BBB is a critical structure maintaining the stability of the brain's internal environment, composed of endothelial cells, tight junction proteins, astrocytic terminal processes, and pericytes. Chronic neuroinflammation during aging compromises BBB integrity, whereas BBB disruption permits peripheral inflammatory mediators and immune cells to enter the brain, further exacerbating neuroinflammation and creating a vicious cycle. Inflammatory mediators directly damage the BBB's structure. Pro-inflammatory cytokines, such as TNF-α and IL-1β, can downregulate the expression of tight junction proteins in endothelial cells, thereby increasing BBB permeability [73]. Reactive oxygen species and matrix metalloproteinases (MMPs, particularly MMP-9), activated by inflammation, can degrade the basement membrane and tight junction proteins, directly disrupting the physical structure of the BBB [68]. Pericytes are crucial for BBB function and vascular stability. Inflammation and oxidative stress can lead to pericytic degeneration, contraction, or even death, thereby increasing vascular permeability and impairing cerebral blood flow regulation [32]. BBB dysfunction exerts multiple adverse effects on the brain. It permits leakage of substances such as albumin and coagulation factors from the blood into the brain parenchyma, potentially triggering additional neurotoxic reactions. More significantly, BBB disruption facilitates the infiltration of peripheral immune cells—such as macrophages and T lymphocytes—into the central nervous system. These infiltrating immune cells release additional pro-

inflammatory factors, amplifying local inflammatory responses and driving neurodegeneration [39]. Moreover, BBB dysfunction correlates with reduced cerebral capillary density and diminished cerebral blood flow, which further exacerbates energy crises and cognitive impairment [32]. Notably, peripheral inflammatory states such as dysbiosis (intestinal permeability) and periodontitis can indirectly compromise BBB integrity by triggering systemic chronic inflammation, providing a mechanistic explanation for the link between systemic health and brain health [39, 68].

4. Neuroinflammation as a Pharmacological Target in Brain Aging and Associated Disorders

4.1. Targeting Key Inflammatory Cells

Neuroinflammation constitutes a central pathological hallmark of numerous neurodegenerative disorders. Particularly during aging, the sustained activation and phenotypic transformation of microglia and astrocytes emerged as pivotal mechanisms driving disease onset and progression. This section examines the molecular underpinnings of dysfunction in these two key neuroimmune cell types and explores corresponding therapeutic targeting strategies.

As resident immune cells within the central nervous system, the functional disruption of microglia during aging constitutes a pivotal link in the sustained amplification of neuroinflammation and subsequent neuronal injury. Research indicates that age-related microglia exhibit diminished phagocytic function, increased release of inflammatory cytokines, and impaired clearance of toxic proteins such as Aβ, thereby accelerating neurodegenerative processes [74, 75]. In recent years, multiple molecular targets associated with regulating microglial phenotypes have been progressively identified, offering novel avenues for intervening in neuroinflammation.

The identification of novel targets offers hope for disease-modifying therapies. TREM2 is a highly regarded regulatory molecule. Gain-of-function mutations have been established as significant genetic risk factors for AD [74]. TREM2 activation enhances phagocytic function in microglia, promotes their transition towards a neuroprotective phenotype, and suppresses excessive inflammatory responses [74, 76]. Currently, agonistic antibodies targeting TREM2 have entered Phase II clinical trials for AD, aiming to restore its physiological function [76]. Furthermore, identifying other receptors or signalling pathways that drive microglial transition towards anti-inflammatory/reparative phenotypes has become a focal point in current basic research [74, 77].

On the other hand, certain targets already being investigated for drug development have demonstrated potential in regulating microglia. Inhibitors of CSF1R , such as PLX3397/Pexidartinib, achieve the objective of "resetting" microglial function and alleviating neuroinflammation by transiently depleting microglia within the brain, followed by promoting their subsequent reconstitution [78, 79].exidartinib is approved for treating tenosynovial giant cell tumours, with its application in neurodegenerative diseases like AD and amyotrophic lateral sclerosis (ALS) currently under investigation [79]. However, prolonged CSF1R inhibition may impair microglia's normal functions in synaptic pruning and maintaining central homeostasis, necessitating careful optimisation of dosing timing and regimen [80]. Furthermore, antagonists targeting specific pro-inflammatory receptors overexpressed on microglia, such as TLRs and purinergic receptors, are progressing from preclinical to early clinical stages [81, 82].

Astrocytes play a pivotal role in maintaining neuronal metabolic support, electrolyte balance, and blood-brain barrier function. In aging and disease states, they transition from a quiescent to a reactive state, further differentiating into two primary phenotypes: neurotoxicand neuroprotective. The neurotoxic phenotype is abundantly present in pathological brain regions of diseases such as AD and PD [7, 83].

Neuroinflammation during aging is jointly driven by complex interactions and phenotypic transitions between microglia and astrocytes. Precise modulation of key receptors or signalling pathways in these cell types—such as developing TREM2 agonists, CSF1R modulators, TLR antagonists, and drugs regulating astrocyte polarisation and metabolism—represents highly promising disease-modifying therapeutic strategies. Nevertheless, ensuring the spatiotemporal specificity of interventions while avoiding disruption of their physiological functions within the central nervous system remains a primary challenge for future translational research.

In exploring novel targets, current research focuses on identifying key upstream signals driving A1 astrocyte transformation. For instance, IL-1α, TNF, and C1q released by activated microglia synergistically induce A1 conversion, whereupon these cells downregulate their neuroprotective functions and secrete neurotoxic substances such as complement component C3 [7, 84]. Blocking these cytokine signalling pathways or their downstream critical nodesmay suppress harmful astrocytic responses [85]. Conversely, identifying intrinsic pathways promoting their transition to the A2/neuroprotective phenotype remains equally crucial. For instance, research indicates that high-intensity interval training (HIIT) enhances the lymphatic-like clearance of Aβ and p-tau by modulating astrocyte

phenotype and increasing the polarised distribution of their AQP4 aquaporin, thereby improving cognitive function in AD animal models [86]. This suggests the potential for regulating astrocyte metabolism and polarisation through exercise or pharmacological interventions.

Currently, most investigational drugs targeting astrocytic reactivity remain in the preclinical stage and are relatively scarce. Strategies primarily focus on employing neutralising antibodies or small-molecule inhibitors to block key pro-inflammatory factors inducing the A1 phenotype or developing compounds that mimic the effects of neurotrophic factors by activating specific nuclear receptors to promote lipid metabolism and anti-inflammatory functions [84, 87]. For instance, LXR agonists demonstrated the potential to alleviate neuroinflammation and neurodegeneration in tauopathies by promoting glial lipid efflux [87]. Another study indicated that impaired mitochondrial oxidative phosphorylation in astrocytes leads to fatty acid degradation defects, lipid droplet accumulation, and STAT3 acetylation activation, thereby inducing a reactive phenotype and neuroinflammation; restoring their metabolic function may thus represent a novel intervention strategy [85].

4.2. Target core inflammatory signalling pathways

4.2.1. NLRP3 Inflammatory vesicle inhibitors

As described in Section 2.4.2, NLRP3 inflammasome activation is a key driver of cellular senescence and plays a central role in neuroinflammatory processes associated with AD, PD, and cerebral ischemia [88, 89].

MCC950/CRID3/CP-456,773: A potent selective inhibitor significantly attenuating neuroinflammation and neuronal damage in PD, AD, and stroke models. Previously advanced to Phase II clinical trials for rheumatoid arthritis before being paused due to hepatotoxicity; currently undergoing structural optimization to enhance safety [90].

OLT1177 (Dapansutrile): An oral inhibitor demonstrating efficacy in Phase II/III gout trials, currently being explored for AD and traumatic brain injury (TBI). Preclinical studies indicate it suppresses NLRP3 activation in microglia and improves cognitive function. [57].

Tranilast (repurposed drug): A traditional anti-allergy medication identified as an NLRP3 inhibitor, reducing α-synuclein-induced inflammation in PD models. [91].

Challenges: Addressing brain barrier permeability and long-term safety concerns remain paramount [56].

4.2.2. NF-κB pathway inhibitors

NF-κB is a transcription factor regulating inflammatory gene expression. Its excessive activation promotes the release of pro-inflammatory factors such as TNF-α and IL-6, contributing to neurodegenerative processes in AD, PD, and multiple sclerosis. This pathway is activated by upstream receptors including TLR4 and TNFR, forming a positive feedback loop with NLRP3 [92].

Indirect inhibitors: Glucocorticoids and proteasome inhibitors indirectly block NF-κB by inhibiting IκBα degradation. However, systemic toxicity limits their application in neurological disorders [59]. Brain-selective inhibitors: Focusing on IKKβ allosteric inhibitors and peptide molecules targeting NF-κB nuclear translocation. For instance, quercetin alleviates neuroinflammation in diabetic encephalopathy by inhibiting IKKβ phosphorylation. Strategic challenge: Developing centrally selective agents requires balancing anti-inflammatory efficacy with immunosuppression risks [92].

4.2.3. JAK/STAT inhibitors

JAK/STAT mediates signalling for multiple cytokines, whose excessive activation promotes M1 polarisation of microglia and neuronal apoptosis, persisting in AD, PD, and epilepsy [58].

Neurological indication expansion for marketed drugs: Baricitinib- A JAK1/2 inhibitor approved for rheumatoid arthritis and COVID-19. Its mechanism of suppressing peripheral inflammatory cytokines is being explored in an AD Phase II trial, often combined with Aβ monoclonal antibodies to enhance efficacy [93]. Tofacitinib: Reduces Th17 cell infiltration and delays disease progression in an experimental autoimmune encephalomyelitis model.

Drugs in development: Filgotinib: A highly selective JAK1 inhibitor currently being evaluated for its potential in multiple sclerosis [94]. Core challenges: Most JAK inhibitors exhibit blood-brain barrier penetration <10%, necessitating high doses or nanodelivery systems; long-term use may increase infection and thrombosis risks.

4.2.4. p38 MAPK inhibitors

p38 MAPK phosphorylates NF-κB, amplifying inflammatory signals. Activation in AD, depression, and cerebral ischaemia promotes microglial release of IL-1β and TNF-α [58, 95].

Neflamapimod: A p38α inhibitor demonstrating mild cognitive improvement in AD Phase II trials, though with no significant effect on tau pathology. Primary failures included insufficient efficacy and cardiac toxicity [96]. Next-generation inhibitor strategies: Development of brain-penetrant allosteric inhibitors or targeting p38γ/δ

subtypes to reduce side effects. Preclinical studies indicate p38 inhibition restores autophagic flux and reduces NLRP3 activation.

4.3. Targeting Inflammatory Mediators

Neuroinflammation constitutes a common pathological hallmark across multiple CNS disorders, involving intricate interactions between microglia, astrocytes, peripheral immune cells, and the diverse inflammatory mediators they release. Targeting these mediators has emerged as a novel therapeutic strategy for neurodegenerative diseases, autoimmune neuropathologies, and brain injury. This section reviews drug development progress across three key areas: cytokines, chemokines, and the complement system.

4.3.1. Cytokine antagonists/neutralising antibodies

Cytokines serve as pivotal signalling molecules in neuroinflammation, with their dysregulated expression implicated in numerous CNS disorders. Strategies targeting cytokines primarily involve the use of neutralising antibodies or receptor antagonists.

TNF-α inhibitors such as Etanercept, Infliximab, and Adalimumab are widely employed in the treatment of rheumatoid arthritis and inflammatory bowel disease. In recent years, their potential application in neurological disorders has garnered attention. For instance, studies reveal elevated TNF-α expression in depression and AD, suggesting its potential as a therapeutic target. However, systemic administration yields extremely low brain concentration due to BBB limitations, constraining efficacy. Strategies such as focused ultrasound to open the BBB are currently being explored to enhance drug delivery [20].

IL-1β represents another crucial pro-inflammatory cytokine, with its neutralising antibody Canakinumab already employed in autoimmune inflammatory disorders. Post-hoc analysis from the large-scale cardiovascular study CANTOS suggested that Canakinumab may reduce AD risk; however, dedicated AD clinical trials failed to meet primary endpoints, highlighting the importance of intervention timing and patient selection [97, 98].

Furthermore, the IL-6 signaling pathway plays a crucial role in neuroinflammation. Research indicates that IL-6 released by monocytes can regulate the transformation of microglia towards a pro-angiogenic phenotype, thereby promoting repair following brain injury [99]. Consequently, drugs targeting IL-6 and its receptors are also being explored for neurological disorders.

Drugs in development: To enhance BBB penetration, researchers have developed novel drug formats such as bispecific antibodies, nanobodies, and engineered small proteins. These agents specifically bind cytokines and facilitate their crossing of the BBB. Currently, therapeutics targeting IL-17, IL-18, IFN-γ, and others remain in preclinical or early clinical stages [7, 100]. Chemokines play a crucial role in neuroinflammation by regulating the migration and activation of immune cells into the CNS through binding to their receptors. The CCR5 antagonist Maraviroc has demonstrated potential in AD models. Research indicates the CCL5-CCR5 axis promotes activation of microglia and monocytes, exacerbating neuroinflammation and BBB disruption [101]. Maraviroc blocks this pathway and is currently undergoing Phase II clinical trials in AD patients. CCR2, a key receptor for monocyte infiltration, is upregulated in cerebral ischaemia, haemorrhage, and multiple sclerosis. Research indicates that inhibiting CCR2 reduces neuroinflammation and neuronal apoptosis, potentially via the PI3K/Akt pathway [88, 102]. Receptors such as CXCR3 and CXCR4 also participate in T-cell and microglial migration and activation. For instance, the CXCL10-CXCR3 axis promotes CD8+ T-cell infiltration into the brains of AD models, exacerbating neuroinflammation [103]. Consequently, antagonists targeting these receptors are also under development.

The complement system plays a vital role in innate immunity, and recent studies have revealed its critical functions in synaptic pruning, neuroinflammation, and neurodegeneration. C1q, the initiator molecule of the classical complement pathway, participates in pathological synaptic clearance in AD, frontotemporal dementia (FTD), and Huntington's disease (HD). Research indicates that neuronally secreted Nptx2 binds to C1q and inhibits its activity, thereby protecting synapses from phagocytosis by microglia [104]. C3, a core complement component, mediates neuroinflammation and synaptic loss across multiple models including depression, epilepsy, and cerebral haemorrhage [47]. Inhibiting the C3 pathway improves motor dysfunction and visual impairment in animal models [105]. The C5a-C5aR axis also amplifies neuroinflammation. Currently, multiple complement inhibitors, including anti-C1q antibody, C3 inhibitor, and C5aR antagonists, have entered clinical trials for conditions such as Alzheimer's disease, amyotrophic lateral sclerosis, and neuromyelitis optica spectrum disorder [97]. Moreover, TREM2, as a key receptor on microglia, inhibits complement-mediated synaptic clearance by binding C1q; its agonists or mimetic peptides also demonstrate therapeutic potential [106].

4.4. Targeting Senescent Cells

Cellular senescence represents a stable state of cell cycle arrest accompanied by the production of the SASP, characterised by the excessive secretion of pro-inflammatory cytokines, chemokines, and proteases. Senescent cells accumulate in the CNS with advancing age and are widely present in the pathological brain tissue of various neurological disorders including AD, PD, multiple sclerosis (MS), and gliomas [64, 107]. As previously described in Section 2.1.4, SASP induces senescence in neighboring cells through its paracrine effects, collectively creating a chronic inflammatory microenvironment that drives neurodegenerative disease. This environment accelerates disease progression by exacerbating neuroinflammation, impairing synaptic function, disrupting oligodendrocyte maturation, and compromising the blood-brain barrier [108-110]. Consequently, selective clearance of senescent cells (senolytics) or inhibition of their harmful SASP (senomorphics) has emerged as a novel therapeutic strategy for neurodegenerative diseases and brain aging.

4.4.1. Senolytics

Senolytics exert their effects by specifically inducing senescent cell apoptosis, targeting the anti-apoptotic pathways (SCAPs) upon which senescent cells rely for survival.

Dasatinib + Quercetin (D+Q) is the first senolytic combination to undergo extensive research. The combination of Dasatinib and Quercetin effectively eliminates multiple types of senescent cells. Preclinical studies indicate that D+Q alleviates neuroinflammation and tau hyperphosphorylation in tauopathy mouse models while improving cognitive function [110]. In AD mouse models, D+Q treatment reduced senescent microglia and enhanced cognitive behaviour [111]. A Phase I open-label trial showed that after oral administration of D+Q, the concentration of Dasatinib in cerebrospinal fluid (CSF) can reach 0.32±0.11 ng/mL, which is sufficient to exert the effect of clearing senescent microglia, and no serious adverse reactions were observed, only mild gastrointestinal discomfort in a few patients [112]. Compared with single use, D+Q combination therapy has a 2.3-fold higher clearance efficiency of senescent cells in the CNS and can more significantly reduce the levels of SASP factors such as IL-6 and TNF-α in CSF [110]. However, its efficacy appears model-dependent; while robust in tauopathy and chemobrain models, effects in amyloid-driven AD models are more modest, highlighting potential pathophysiological heterogeneity. Crucially, an open-label Phase I feasibility trial confirmed that Dasatinib achieves detectable levels in CSF following oral D+Q administration. The treatment proved safe and well-tolerated, accompanied by alterations in certain CSF inflammatory markers, laying the groundwork for larger-scale clinical trials. Furthermore, D+Q alleviates radiation-induced aging and chemobrain, enhancing cognitive function [112, 113].

Fisetin is another natural flavonoid senolytic agent, potentially exhibiting superior oral bioavailability and safety profiles compared to D+Q. Studies indicate fisetin enhances healthy lifespan in aging animal models, though research on its effects in neurological disorders remains limited. Fisetin demonstrates potential neuroprotective effects in the cuprizone model of MS and emerges as a promising adjuvant therapy worthy of further study [114]. It may enhance remyelination processes and mitigate disability progression in MS patients, potentially through modulation of the ferroptosis pathway. It is currently undergoing clinical exploration as a supplement for improving elderly health.

BCL-2 inhibitors, such as Navitoclax (ABT-263) and ABT-737, are potent senolytic agents. Although Navitoclax (ABT-263) can effectively clear senescent glial cells, its clinical application is limited by haematological toxicity such as thrombocytopenia. The newly developed CNS-specific ABT-263 derivative (e.g., ABT-957) enhances blood-brain barrier penetration (from <5% to 18±3%) by modifying the molecular structure while reducing peripheral tissue distribution. In the EAE model, ABT-957 has better neuroprotective effects than the parent drug and no obvious haematological toxicity [115]. They effectively eliminate senescent like microglia and macrophages expressing BCL-2 family proteins in experimental autoimmune encephalomyelitis (EAE, an animal model of MS), significantly reducing disease severity, neuroinflammation, and neurodegeneration. In glioblastoma (GBM) models, Navitoclax eliminates radiotherapy-induced senescent astrocytes, inhibiting their SASP-mediated promotion of tumour recurrence and thereby prolonging mouse survival [112, 116]. However, their clinical translation is hampered by dose-limiting thrombocytopenia. Novel approaches, such as the development of BCL-xL selective inhibitors or proteolysis-targeting chimeras (PROTACs) that degrade BCL-2, aim to improve the therapeutic window for CNS applications [117]. However, clinical application of such agents is constrained by haematological toxicities including thrombocytopenia; developing CNS-specific or less toxic BCL-2 inhibitors represents a future direction.

Other senolytic strategies are under investigation. Studies indicate that in mTOR-associated focal cortical dysplasia (FCD) epilepsy models, pathologically abnormal neurons exhibit senescent characteristics, and D+Q treatment reduces epileptic seizures [118]. Furthermore, within the COVID-19 context, research indicates SARS-CoV-2 infection induces cellular senescence in human brain organoid cells, while senolytic

treatment mitigates viral load and neuropathological alterations [119]. These findings substantially broaden the application scope of senolytic therapies within central nervous system disorders.

Above all, a critical appraisal reveals key challenges: (1) CNS Penetrance: While D+Q and Fisetin show promise, achieving therapeutic brain concentrations of many senolytics remains a hurdle. (2) Cellular Specificity: Most senolytics target anti-apoptotic pathways (SCAPs) broadly expressed in both senescent and proliferating cells, risking off-target effects. (3) Long-term Safety: Chronic, intermittent senolytic regimens required for age-related diseases raise concerns about immune suppression and impaired tissue regeneration.

4.4.2. Senomorphics

Senomorphics do not eliminate senescent cells but mitigate their harmful effects by inhibiting SASP production or its downstream signalling pathways.

JAK inhibitors represent prototypical senomorphic agents. The JAK/STAT pathway serves as a pivotal signalling hub for numerous SASP factors, including IL-6 and IFN-γ. Inhibitors such as ruxolitinib significantly suppress SASP by blocking this pathway. Although clinical trials directly addressing neurological disorders remain limited, JAK inhibitors constitute a significant senomorphic strategy given SASP's central role.

mTOR inhibitors, such as rapamycin and its analogues (rapalogs), effectively suppress SASP secretion and delay the aging process. Rapamycin has demonstrated neuroprotective effects in multiple models of aging and neurodegenerative diseases. Its complex mechanism of action involves inhibiting protein synthesis and promoting autophagy. Although neuroprotective in models, their systemic metabolic effects (e.g., hyperglycemia, immunosuppression) complicate chronic use for brain aging. Clinical trials are currently investigating the role of rapamycin analogues in the prevention and treatment of Alzheimer's disease.

Other senomorphic strategies include neutralising antibodies targeting specific SASP factors. Research indicates that neutralising Activin A and IL-1α partially restores levels of α-Klotho (an anti-aging protein) in senescent cell co-culture systems [120]. Another promising avenue is the disruption of mitochondrial-SASP crosstalk, given the central role of mitochondrial dysfunction in glial senescence [85]. This provides insights into developing more targeted senomorphic therapies.

4.4.3. Key Barriers to Translation from Preclinical to Clinical Settings

Although senotherapy strategies demonstrate significant potential in preclinical models to reverse age-related functional decline and diseases, and early clinical trials (Phase I/II) have preliminarily validated their safety, translating them into widely applicable therapies for CNS aging and related diseases still faces several critical translational hurdles that require in-depth investigation and resolution.

First, achieving efficient and specific drug delivery to CNS presents a major challenge. While the BBB protects the brain, it also severely restricts the entry of most macromolecules and many small-molecule drugs. Current clinical-stage senolytics (e.g., Dasatinib and Quercetin, D+Q) were not designed for CNS delivery. While Dasatinib presence was detected in CSF during preliminary trials in mild AD patients, its concentration remained significantly lower than in plasma, and Quercetin was not detected, suggesting limited and uncertain CNS permeability [112]. Future development requires novel senolytics capable of actively crossing the BBB (e.g., NKG2D-based CAR-T cell therapies [121] or optimized delivery systems (e.g., engineered exosomes [122] to ensure therapeutic drug concentrations reach effective levels within the brain parenchyma where senescent cells accumulate.

Second, long-term safety and tolerability in elderly populations remain unclear. Elderly patients are often present with multiple comorbidities and polypharmacy, reduced organ reserve function, and potentially increased sensitivity to drug toxicity. For example, dasatinib is known to cause bone marrow suppression, fluid retention, and potential bleeding risks. Although short-term (weeks to months) intermittent D+Q regimens have demonstrated tolerability in IPF and AD patients [112, 123], safety data are entirely absent for long-term, repeated dosing required to address the persistent accumulation of senescent cells. Particularly for interventions targeting the aging brain, the benefits of senescent cell clearance must be carefully weighed against risks that could impact neuronal homeostasis or repair capacity.

Finally, the lack of robust, quantifiable biomarkers correlated with clinical outcomes of CNS aging severely hampers clinical trial design and efficacy assessment. Currently relied-upon SASP factors in blood or CSF (e.g., IL-6) are susceptible to systemic inflammatory interference and exhibit inconsistent variability [124, 125]. Developing non-invasive, highly specific CNS aging imaging technologies (e.g., SA-β-Gal-based PET probes [126] and establishing molecular roadmaps reflecting brain-specific aging processes (e.g., based on epigenetic clocks or transcriptomic signatures [127] are crucial for precisely identifying beneficiary populations, monitoring target engagement, and evaluating therapeutic responses. Overcoming these translational barriers

represents a critical step in advancing senotherapy from concept to addressing the unmet medical need of human brain aging and related diseases.

4.5. Promotion of endogenous anti-inflammatory mechanisms

Aging is accompanied by chronic low-grade inflammation, a core driver of multiple age-related diseases. This inflammatory state arises partly from the persistent accumulation of senescent cells (SnCs) and their secretion of the SASP, rich in pro-inflammatory factors, chemokines, and proteases that disrupt tissue homeostasis. Direct strategies include targeting senescent cell clearance (senolytics) or inhibiting SASP (senomorphics). Alternatively, activating endogenous anti-inflammatory and reparative pathways—such as specific nuclear receptor pathways and adenosine signalling—offers an "inside-out" approach to modulating the inflammatory microenvironment. This aims to restore immune homeostasis and enhance tissue resilience against chronic inflammation associated with aging and neurodegenerative diseases.

4.5.1. Activation of nuclear receptors

Nuclear receptors constitute a class of ligand-activated transcription factors that play central roles in metabolism, inflammation, and cellular homeostasis through gene expression regulation. Activating specific nuclear receptors can initiate extensive anti-inflammatory and antioxidant gene programmes, presenting attractive therapeutic targets for chronic neuroinflammation.

4.5.1.1. Approved Drugs (Off-label use of existing medications):

PPARγ agonists, such as Pioglitazone, are widely used for treating type 2 diabetes. PPARγ activation not only improves insulin sensitivity but also exhibits potent anti-inflammatory and neuroprotective effects. It suppresses activation of microglia and astrocytes, reduces production of pro-inflammatory cytokines, and promotes phagocytic clearance of Aβ [128, 129]. Based on these mechanisms, pioglitazone was once highly anticipated for AD treatment. However, multiple large-scale clinical trials failed to meet primary endpoints of cognitive improvement in patients with mild cognitive impairment (MCI) or AD [129]. Key challenges include dose-limiting adverse effects and potential unsuitability for patients at all disease stages. Researchers are currently exploring its potential for specific patient subgroups or the use of lower doses [130].

Nrf2 activators constitute another significant class of nuclear receptor modulators. Nuclear factor E2-related factor 2 (Nrf2) serves as a pivotal regulator of cellular antioxidant responses. Under resting conditions, Nrf2 binds to its inhibitor Keap1 and undergoes ubiquitination and degradation. Under oxidative stress or upon exposure to specific activators, Nrf2 is released and translocates to the nucleus, initiating the transcription of a series of antioxidant and cell-protective genes, including heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1) [131]. DMF is a marketed drug for treating MS, with one key mechanism of action being activation of the Nrf2 pathway [132]. By enhancing antioxidant capacity, DMF mitigates neuroinflammation and oxidative stress damage, thereby exerting neuroprotective effects. Given that oxidative stress is a common feature across multiple neurodegenerative diseases, DMF and its analogues also hold therapeutic potential for other neurological disorders such as AD, PD, and stroke, with relevant research currently underway [55].

4.5.1.2. Targets with Investigational Agents:

Developing next-generation nuclear receptor modulators represents a current research focus. The objective is to obtain compounds with enhanced efficacy, greater selectivity, and reduced side effects.

Partial agonists of PPARγ or selective PPARγ modulators (SPPARMγ): These compounds aim to retain PPARγ's transcriptional benefits for improving metabolism and suppressing inflammation while avoiding the classic side effects associated with full agonists (such as weight gain and oedema) [130].

LXRs and RXRs agonists: LXRs participate in cholesterol reverse transport and inflammation suppression, while RXRs serve as common heterodimerisation partners for multiple nuclear receptors. Activation of these receptors promotes Aβ clearance and suppresses neuroinflammation, though their side effects on lipid metabolism remain to be overcome [133].

Novel Nrf2 activators: Beyond DMF, numerous natural compounds exhibit Nrf2-activating activity, though their bioavailability and potency are typically low. Developing more potent and selective Nrf2 activators represents a significant research direction [134, 135].

4.5.2. Enhancement of adenosine signalling

Adenosine, an endogenous purine nucleoside, serves as a crucial anti-inflammatory and immunosuppressive signalling molecule in vivo. In the brain, adenosine exerts its effects by activating its G protein-coupled receptors.

Among these, the A2A receptor is highly expressed on immune cells and neurons. Its activation significantly suppresses microglial activation, reduces pro-inflammatory factor release, and promotes neuroprotection [93].

4.5.2.1. Targets with Investigational Agents:

Theoretically, employing A2A receptor agonists could amplify the anti-inflammatory effects of endogenous adenosine, offering a therapeutic strategy for neuroinflammatory disorders. However, systemic administration of A2A receptor agonists carries adverse effects such as cardiovascular suppression and sedation, which constrain their clinical application [136].

Therefore, the current research focus is on developing A2A receptor agonists with high central nervous system selectivity. These compounds are engineered to efficiently traverse the blood-brain barrier whilst exhibiting limited activity and exposure in peripheral systems, thereby minimising systemic side effects [137]. Such agents show promise in preclinical models of Parkinson's disease (where A2A receptor antagonists are already employed for motor symptoms), AD, multiple sclerosis, and traumatic brain injury, suggesting that enhancing central adenosine signalling may mitigate neuroinflammation and improve functional outcomes [138]. Currently, several centrally selective A2A receptor agonists are progressing through preclinical to early clinical studies, though their definitive efficacy and safety remain to be validated in large-scale clinical trials.

Promoting endogenous anti-inflammatory mechanisms represents an "empowering" therapeutic philosophy, complementing strategies that directly inhibit specific inflammatory mediators. Activation of nuclear receptors such as PPARγ and Nrf2 can broadly and coordinately enhance antioxidant, anti-inflammatory, and clearance functions by reprogramming gene expression profiles [132]. Conversely, enhancing endogenous signalling pathways like adenosine aims to harness the body's inherent "braking" systems to suppress excessive immune activation [139]. The development of more targeted therapeutics and precise patient stratification strategies herald renewed promise in this field. Given their fundamental and broad-spectrum mechanisms of action, these approaches hold therapeutic potential for multiple CNS disorders featuring neuroinflammatory components [128].

4.6. Multi-targeted interventions and natural products

The pathogenesis of neurodegenerative diseases (such as AD and PD) is complex, often involving multiple pathological processes including neuroinflammation, oxidative stress, protein misfolding and aggregation, and mitochondrial dysfunction. Single-target drugs often demonstrate limited efficacy in clinical studies, making multi-targeted intervention strategies an emerging research focus. Natural products, with their multi-functional properties, favourable safety profiles, and diverse mechanisms of action, are regarded as ideal candidates for achieving multi-targeted interventions. This section examines the potential of natural compounds with anti-inflammatory and antioxidant activities (such as curcumin, resveratrol, epigallocatechin gallate (EGCG), ginsenosides, and apigenin) in neurodegenerative diseases, addressing challenges in clinical translation and future research directions.

Numerous natural products demonstrate significant neuroprotective effects in preclinical studies. Curcumin alleviates neuroinflammation by inhibiting the NF-κB pathway, enhances antioxidant responses through activation of the Nrf2-ARE pathway, and modulates multiple molecular pathways including apoptosis and cell cycle regulation, thereby improving cognitive function in models of AD and PD [140]. Resveratrol, by activating deacetylases such as SIRT1, improves mitochondrial function, reduces Aβ deposition, and mitigates tau hyperphosphorylation, demonstrating cognitive enhancement in animal studies and some clinical trials [141]. Furthermore, EGCG exerts anti-Aβ aggregation, anti-inflammatory, and antioxidant effects by modulating α-, β-, and γ-secretase activity and inhibiting AChE [142]. Ginsenosides and apigenin, among others, have also demonstrated the capacity to regulate neuroinflammation and enhance synaptic plasticity across multiple models [143]. These natural products typically exhibit multi-targeted, multi-pathway mechanisms of action, enabling simultaneous intervention across multiple stages of disease progression. Consequently, they demonstrate greater potential than single-target drugs in preclinical studies [144].

Despite substantial preclinical evidence, most natural products fail to demonstrate significant efficacy upon entering clinical phases (particularly Phase II/III trials). Curcumin failed to meet primary endpoints in multiple AD clinical trials, primarily attributed to its low bioavailability, rapid metabolism in vivo, and difficulty in achieving therapeutically effective concentrations [145, 146]. Similarly, while resveratrol improved cognitive and cerebrovascular function in postmenopausal women during a 24-month randomised controlled trial, its efficacy varied across populations, and high-dose administration frequently caused gastrointestinal discomfort [145, 147]. Other compounds such as EGCG and apigenin face clinical implementation challenges due to poor stability and limited BBB penetration [142, 148]. Furthermore, trial design flaws—including selection bias,

insensitive endpoints, and inadequate treatment duration—compromise result reliability [134, 149].

To enhance the clinical applicability of natural products, multiple strategies are being extensively explored. Formulation optimisation represents one of the primary avenues, with nanotechnology (such as liposomes, polymeric nanoparticles, and mesoporous silica nanoparticles) employed to improve the water solubility, stability, and BBB penetration of compounds like curcumin and resveratrol [150-152]. For instance, novel delivery systems like curcumin-loaded PLGA nanoparticles and resveratrol-selenium-peptide nanocomposites demonstrate superior bioavailability and therapeutic efficacy in AD animal models [153, 154]. Additionally, research into active metabolites is gaining prominence; curcumin's metabolite tetrahydrocurcumin exhibits stronger anti-inflammatory activity and greater stability, offering potential as a therapeutic alternative to the parent compound [155]. Compound traditional Chinese medicines and natural product combinations demonstrate enhanced effects in suppressing neuroinflammation and improving cognitive function through multi-component, multi-pathway synergistic actions [156, 157].

Future research should prioritise rigorously designed clinical trials, incorporating standardised extracts, optimised delivery routes, stratified analysis using biomarkers, and long-term safety evaluation [158, 159]. Concurrently, leveraging computational biology, structural modification, and novel delivery systems to enhance the pharmacokinetic properties of natural compounds represents a crucial pathway for clinical translation [160, 161]. In summary, natural products offer broad prospects for the prevention and treatment of neurodegenerative diseases through multi-targeted interventions. However, their genuine clinical application remains contingent upon overcoming challenges such as low bioavailability and the lack of robust clinical evidence.

4.7. Improvement of systemic factors

The onset and progression of neurological disorders are frequently closely associated with systemic metabolic, inflammatory, and vascular factors. In recent years, the strategy of drug repurposing has demonstrated significant potential in treating neurodegenerative diseases, particularly for medications already widely used in metabolic disorders (such as diabetes and hyper-lipidaemia). These drugs typically exhibit pleiotropic effects, including anti-inflammatory, antioxidant, vasculoprotective, and insulin-sensitising actions, which may indirectly or directly influence neuroinflammation and cognitive function. This section focuses on evidence and advances regarding metformin, GLP-1 receptor agonists (GLP-1RAs), and statins in improving systemic factors and their potential neuroprotective effects.

As a first-line oral hypoglycaemic agent, metformin possesses not only its classical insulin-sensitising and hepatic glucose output-inhibiting functions, but also demonstrates extensive anti-aging and neuroprotective potential, as evidenced by increasing preclinical and epidemiological studies. Its mechanisms involve activating the AMPK pathway, inhibiting mTOR signalling, mitigating oxidative stress, and suppressing neuroinflammation [162]. In animal models, metformin delays brain aging, improves cognitive function, and reduces Aβ deposition and tau hyperphosphorylation [163, 164]. Multiple observational studies suggest that type 2 diabetic patients on long-term metformin have a lower risk of dementia [165, 166]. Currently, several large-scale clinical trials are underway to validate its anti-aging and neuroprotective effects, such as MILES and TAME. The outcomes of these trials will clarify metformin's clinical value in delaying cognitive decline and the progression of neurodegenerative diseases [167, 168]. However, long-term metformin use requires vigilance regarding potential adverse effects, such as vitamin B12 deficiency, which may conversely exert detrimental effects on the nervous system [169].

GLP-1 receptor agonists have become pivotal therapeutics for managing type 2 diabetes and obesity, with their neuroprotective effects gaining significant attention in recent years. These agents not only confer indirect benefits through glucose and weight regulation but also exert direct effects by acting on GLP-1 receptors within the central nervous system. They inhibit neuroinflammation, reduce oxidative stress, promote neurotrophic factor expression, and suppress pathological aggregation of amyloid-β and α-synuclein [170, 171]. Preclinical studies consistently report significant ameliorative effects of GLP-1RAs in models of AD and PD [172, 173]. Retrospective studies and cohort analyses further indicate that diabetic patients using GLP-1RAs exhibit a reduced risk of neurodegenerative diseases [61, 174]. Particularly promising are two ongoing Phase III clinical trials evaluating semaglutide for early-stage AD treatment. Positive outcomes would provide compelling evidence for repurposing such agents in neurology [175, 176]. Furthermore, next-generation dual or triple receptor agonists are under development, aiming to further enhance their neuroprotective efficacy.

Statins, as widely used lipid-lowering agents, reduce low-density lipoprotein cholesterol (LDL-C) by inhibiting HMG-CoA reductase, while also exhibiting multifaceted effects including anti-inflammatory, antioxidant, and endothelial function-improving properties. Epidemiological studies and meta-analyses indicate that

statin use is associated with reduced risks of all-cause dementia, Alzheimer's disease, and vascular dementia [177, 178]. These effects may relate to statins' reduction of cerebral vascular lesions, inhibition of microglial activation, and modulation of immune responses [179, 180]. However, randomised controlled trials and the neurocognitive effects of statins remain controversial, with some studies failing to demonstrate significant cognitive improvement [181, 182]. Furthermore, statin lipophilicity, dosage, and treatment duration may influence their neuroprotective effects. Long-term use necessitates monitoring for potential adverse reactions, such as the risk of new-onset diabetes and cognitive complaints in individual patients [183, 184]. Current evidence suggests that statin benefits for neurocognition may primarily manifest in populations with established vascular risk factors, rather than in the general elderly population [185,186].

5. Challenges and Future Perspectives in Pharmacotherapy

Neuroinflammation, as a core pathological mechanism in multiple neurological disorders, has emerged as a key therapeutic target. However, pharmacological strategies addressing neuroinflammation face multiple challenges in development and application, including target specificity, drug delivery efficiency, timing of intervention, individual heterogeneity, and clinical translation hurdles. This section systematically reviews the primary challenges confronting current pharmacological interventions and explores potential future directions based on recent research advances.

5.1. Target specificity and off-target effects

Neuroinflammation involves diverse cell types and signalling pathways, which also contribute to maintaining central nervous system homeostasis under physiological conditions. Consequently, developing drugs that precisely target pathological states rather than physiological functions presents a significant challenge. For instance, although TSPO is a commonly used PET imaging target in neuroinflammation, its expression is not confined to activated microglia but is also present in astrocytes and endothelial cells. This lack of cell specificity fails to distinguish between neuroprotective and neurotoxic inflammatory responses [187]. Similarly, interventions targeting the complement system have demonstrated potential in animal models to mitigate age-related blood-brain barrier dysfunction and neuroinflammation, yet their safety and efficacy in humans require further validation. Moreover, numerous inflammatory pathways play pivotal roles in systemic immune responses, and their systemic inhibition may induce side effects such as immunosuppression [49, 188]. Consequently, future research should focus on developing more cell-type- or activation-state-specific regulatory strategies. This includes utilising single-cell sequencing and spatial transcriptomics to identify disease-specific inflammatory subpopulations, thereby enabling the design of more precise interventions [189,190].

5.2. Blood-brain barrier penetration

The BBB is a vital physiological structure protecting the brain, yet it severely restricts the delivery of most therapeutic agents—particularly macromolecular drugs such as antibodies, peptides, and nucleic acid therapeutics—into the brain. Currently, multiple strategies are being explored to overcome this barrier. Nanotechnology platforms can significantly enhance drug BBB penetration through surface modifications, demonstrating synergistic anti-inflammatory, antioxidant, and anti-Aβ aggregation effects in AD animal models [191-193]. Exosomes, as natural nanocarriers, possess excellent biocompatibility and low immunogenicity, enabling them to naturally traverse the BBB and demonstrating immense potential in treating neurodegenerative diseases and brain cancers. Focused ultrasound (FUS) combined with microbubble technology enables reversible, localised opening of the BBB, providing a physical solution for intracerebral delivery of macromolecules such as antibodies and neurotrophic factors. This approach has now entered clinical trials for treating AD and glioblastoma [194, 195]. Additionally, receptor-mediated endocytosis represents another crucial bionic delivery strategy [196]. In the future, integrating these delivery technologies with smart materials responsive to disease microenvironments holds promise for achieving more precise and efficient intracerebral drug release.

5.3. Disease stage and timing of treatment

Neuroinflammation may play distinctly different roles at various disease stages: in early disease, it may represent a protective response attempting to clear abnormal protein aggregates; whereas chronic, uncontrolled inflammation can induce neurotoxicity. This duality renders the selection of treatment timing critically important. Imaging studies indicate that in the AD disease course, microglial activation may precede the widespread dissemination of tau pathology, occurring even in the preclinical stage [197, 198]. However, multiple clinical trials of anti-inflammatory drugs in patients with moderate-to-severe AD have failed to yield positive results, likely because intervention occurred too late, when the inflammatory

process had become complex and difficult to reverse [199, 200]. Consequently, future intervention strategies should prioritise the prodromal or early disease stages. This necessitates developing biomarker systems capable of identifying high-risk individuals before symptom onset and monitoring their neuroinflammatory levels. Furthermore, preventive interventions—such as modulating gut microbiota or implementing lifestyle modifications—may prove crucial in delaying disease onset [150, 201].

5.4. Individual Heterogeneity

Significant individual heterogeneity exists among patients, encompassing genetic background, immune status, comorbidities, and gut microbiota composition. These factors collectively determine neuroinflammatory phenotypes and treatment responses. For instance, TSPO PET studies reveal elevated TSPO levels typically observed in major depressive disorder patients, whereas reduced levels may be seen in schizophrenia patients, underscoring divergent neuroinflammatory characteristics across disease contexts [202]. In AD, individuals harbouring different risk gene variants may respond disparately to identical anti-inflammatory strategies. Consequently, a "one-size-fits-all" therapeutic approach is likely ineffective. Precision medicine strategies necessitate patient stratification based on individual "inflammatory signatures" [200]. This approach utilises blood-based neuroinflammatory biomarkers to classify AD patients, thereby providing a basis for personalised anti-inflammatory therapies. In the future, integrating multi-omics data with artificial intelligence analysis holds promise for constructing more comprehensive patient stratification models, guiding clinical trial enrolment and clinical treatment decisions.

5.5. Biomarker development

Reliable, non-invasive biomarkers capable of dynamically reflecting neuroinflammatory states are crucial for advancing therapies targeting neuroinflammation. Currently, biomarker development primarily focuses on two avenues: imaging and humoral detection. In imaging, TSPO PET remains the most commonly used neuroinflammatory imaging tool in clinical research, though its interpretation is constrained by factors such as genetic polymorphisms and cellular source contamination [187, 203]. Novel PET tracers targeting receptors such as P2X7R, CSF1R, and MAO-B are under development to achieve enhanced specificity and signal-to-noise ratios [202, 204]. Regarding humoral markers, blood-based assays hold greater appeal due to their non-invasive nature. Research indicates that blood GFAP effectively reflects astrocyte activation, correlating with intracerebral Aβ deposition and cognitive decline [200]. sPDGFRβ has been proposed as a plasma biomarker for perivascular cell injury and BBB dysfunction [205]. Furthermore, contents within brain derived exosomes offer a unique window into inflammatory states within the brain [206]. In the future, integrating multimodal imaging data with multiple inflammatory factor combinations in blood and cerebrospinal fluid, and employing machine learning algorithms for combined analysis, hold promises for constructing more sensitive and specific neuroinflammation indices for early diagnosis, prognosis prediction, and treatment monitoring.

5.6. Barriers to Clinical Translation

A significant gap exists between translating preclinical research findings into effective human therapies. One major challenge lies in the limitations of animal models. Many neurodegenerative disease models primarily mimic Aβ or tau pathology but cannot fully replicate the complex neuroinflammation networks and age-related factors observed in human disease [189]. Furthermore, species differences in drug metabolism, target binding affinity, and immune system responses mean that therapeutic effects observed in animal models may not translate to humans. Clinical trial design itself presents complexities: how to select endpoints that best reflect the drug's mechanism and clinical benefit? How should highly heterogeneous patient cohorts be correctly stratified based on biomarkers? How can the risks of long-term immune suppression be assessed? Recent adverse events in anti-Aβ antibody trials, such as amyloid-related imaging abnormalities (ARIA), underscore the imperative for rigorous safety evaluation of brain-targeting immunomodulatory therapies [200]. Overcoming these translational barriers requires enhanced interdisciplinary collaboration, utilising humanised mouse models, human induced pluripotent stem cell (iPSC)-derived organoids, and chimeric models to better mimic the human disease environment [189, 207]. Innovative approaches such as adaptive trial design and basket trials should also be employed.

5.7. Combination Therapeutic Strategies

Given the complexity of neurodegenerative disease pathology, monotherapy targeting a single pathway may prove insufficient to halt disease progression. Combination of therapeutic strategies, simultaneously targeting multiple aspects of neuroinflammation or addressing multiple pathological processes, represent an inevitable future direction. For instance, in AD,

combining anti-Aβ therapies with anti-inflammatory agents may more effectively clear plaques and suppress secondary inflammatory responses triggered by them [200]. Similarly, integrating neuroinflammatory drugs with neuroprotective agents or lifestyle interventions may yield synergistic effects [208]. Nanoplatforms offer an ideal vehicle for synergistic therapies. For instance, the hybrid-membrane-coated nanoparticles developed by Lin can simultaneously load drugs with distinct mechanisms, achieving synergistic effects in an AD mouse model [191]. Future combination strategies require a deep understanding of disease pathway networks to rationally select synergistic drug combinations, alongside careful assessment of their pharmacokinetic interactions and cumulative toxic side effects.

5.8. Emerging Technologies

With deepening understanding of the relationship between neuroinflammation and aging, a series of emerging technologies are gradually transitioning from laboratory research to clinical translation, offering new strategies for intervening in age-related neuro-inflammation. These technologies span multiple cutting-edge fields including gene therapy, cell therapy, and microbiota-gut-brain axis modulation, demonstrating significant potential and diversity.

In gene therapy, strategies based on RNA interference (RNAi) and antisense oligonucleotides (ASOs) are being employed to specifically suppress the expression of pro-inflammatory genes. For instance, lipid nanoparticle (LNP)-mediated siRNA delivery systems effectively target brain microglia to inhibit key transcription factors like PU.1, thereby reducing neuroinflammation [207]. Furthermore, the use of adeno-associated virus (AAV) vectors to deliver gene editing tools or repair genes has demonstrated potential in preclinical models to modulate neuroinflammation and delay neurodegenerative processes [101]. While most of these technologies remain in preclinical stages, certain ASO therapies targeting other neurological disorders have advanced into clinical trials.

Cell therapy represents another promising avenue. Transplantation or in vivo expansion of regulatory T cells (Tregs) can suppress excessive microglial activation and neuroinflammation, with improvements in cognitive and motor function observed in animal models of AD and PD [101]. Furthermore, microglia derived from induced pluripotent stem cells (iPSCs) or brain organoid models provide robust platforms for high-throughput screening of anti-inflammatory drugs and personalized therapeutic strategies in vitro [189]. While most cell therapies remain in preclinical development, their application in regenerative medicine is advancing rapidly.

Interventions targeting the microbiota-gut-brain axis (MGBA) have garnered significant attention in recent years as a non-invasive approach. Studies indicate that modulating gut microbiota composition through probiotics, prebiotics, or dietary interventions can influence peripheral and central immune states, reduce neuroinflammation, and improve cognitive function [201, 209]. For instance, oral administration of resveratrol-containing nanocomposites not only inhibits Aβ aggregation but also modulates gut microbiota, thereby exerting multifaceted therapeutic effects in AD models [191]. Fecal microbiota transplantation (FMT) has demonstrated potential in animal models, though its clinical application for neurological disorders remains in early exploratory stages.

Furthermore, novel drug delivery technologies and nanomedicine platforms have significantly advanced the development of these emerging therapies. For instance, biocompatible carriers such as exosome-based and hybrid cell membrane-coated nanoparticles enhance brain targeting of drugs while reducing systemic side effects [192, 206]. FUS combined with microbubbles for non-invasive, reversible blood-brain barrier opening has entered clinical trials to enhance delivery of therapeutic antibodies or nucleic acid drugs to the central nervous system [195].

Although these emerging technologies demonstrate significant application potential, their maturity varies considerably. Most gene and cell therapies remain in preclinical or early clinical stages, while certain microbial interventions and delivery technologies have seen individual products enter the market or advance to late-stage clinical trials. Future research must further optimize the safety, targeting, and scalability of these technologies. Biomarker-guided personalized treatment strategies will be crucial for driving their clinical translation.

5.9. Towards Precision Intervention in Age-Related Neuroinflammation

The evolving landscape of research on neuroinflammation and senescence highlights a paradigm shift from broad anti-inflammatory approaches towards precision interventions. Future success will depend on several convergent strategies. First, target refinement is paramount. The development of allosteric modulators, biased agonists, and cell-type-specific delivery systems (e.g., using nano-carriers functionalized with glial-specific ligands) will enhance efficacy while minimizing off-target effects on essential homeostatic functions [46,193]. Second, biomarker-driven stratification must become the cornerstone of clinical trials. Integrating data from advanced neuroimaging (e.g., next-generation TSPO or P2X7R PET ligands), CSF proteomics, and blood-

based assays for GFAP or NfL will enable the identification of patient subgroups with active "neuroinflammatory endophenotypes" most likely to respond to specific therapies [187, 200, 205]. Third, timing is critical. Preventive or early interventions, guided by pre-symptomatic biomarkers, may be fundamentally more effective than treating established neurodegeneration, necessitating long-term studies in at-risk populations [198,199]. Fourth, combination therapies that simultaneously target multiple nodes of the neuroinflammation-senescence network (e.g., a senolytic alongside a cytokine inhibitor or a metabolic modulator) or that pair neuroimmune modulation with disease-specific pathology clearance (e.g., anti-Aβ antibodies) hold great promise for synergistic effects [46, 191]. Finally, embracing individual complexity—including sex differences, genetic background (APOE, TREM2 status), gut microbiome profile, and systemic health—will be essential for personalizing treatment [201, 202, 209]. The integration of artificial intelligence with multi-omic data holds the key to unlocking this complexity. By advancing on these fronts, the field can transform the persistent challenge of neuroinflammation from an intractable problem into a therapeutically addressable driver of brain aging, paving the way for meaningful preservation of cognitive health in our aging population.

6. Conclusion

The global trend towards population aging presents unprecedented challenges, making the maintenance of brain health and prevention of age-related neurodegenerative diseases critical public health priorities. This review systematically elucidates the pivotal role of neuroinflammation as a core driver of brain aging, bridging the gap between fundamental aging processes and the pathogenesis of cognitive decline and neurodegenerative diseases such as AD and PD. Neuroinflammation manifests as chronic activation of microglia and astrocytes, infiltration of peripheral immune cells, and a persistent low-grade inflammatory state mediated by cytokines, chemokines, and complement proteins. It is not merely a bystander but a key instigator within the aging brain—the manifestation of 'inflammatory aging' within the CNS.

The mechanisms activating neuroinflammation during aging are multifaceted. Cellular autonomous changes—such as microglial senescence and its associated SASP, alongside astrocytic transition to a pro-inflammatory A1 state—collectively foster an inflammogenic environment. This situation is exacerbated by extracellular stimuli and microenvironmental alterations, including age-related BBB disruption, accumulation of DAMPs, proteomic dysregulation involving Aβ and tau, heightened oxidative stress, systemic metabolic dysregulation, and epigenetic modifications. These diverse triggers converge upon a set of core inflammatory signalling pathways, most notably the NLRP3 inflammasome, NF-κB, JAK/STAT, and p38 MAPK pathways, which act as master regulators amplifying and sustaining neuroinflammatory responses.

This persistent neuroinflammatory state imposes severe detrimental consequences upon brain function. It directly impairs synaptic plasticity and long-term potentiation, thereby inducing cognitive deficits; it promotes neuronal injury and death via neurotoxic mediators and impaired phagocytic clearance, suppresses hippocampal neurogenesis, and disrupts white matter integrity by damaging oligodendrocytes. Crucially, it accelerates the vicious cycle of pathological protein accumulation and propagation in AD, PD, and other tauopathies. Moreover, neuroinflammation further induces blood-brain barrier dysfunction, forming a self-perpetuating cycle of injury.

From a pharmacological perspective, targeting neuroinflammation represents one of the most promising strategies for delaying brain aging and mitigating associated diseases. This review broadly assesses intervention strategies, categorisable as follows: Firstly, targeting inflammatory cells: modulating microglial function and astrocytic reactivity; Second, targeting core signalling pathways: inhibiting key nodes such as the NLRP3 inflammasome, NF-κB, JAK/STAT, and p38 MAPK; Third, Targeting inflammatory mediators: employing cytokine/chemokine/receptor antagonists and complement system inhibitors; Fourth, targeting senescent cells: employing senolyticsand senomorphics to eliminate or quiesce cells producing SASP; Fifth, enhancing endogenous anti-inflammatory mechanisms: activating nuclear receptors and strengthening adenosine signalling pathways; Sixth, exploring multi-target and natural approaches: investigating plant-derived compounds and repurposing drugs targeting systemic factors.

Despite a rich pipeline of therapeutic candidates, translating anti-neuroinflammatory strategies into effective clinical treatments faces significant hurdles. For instance, achieving target specificity proves challenging due to the pleiotropic nature of inflammatory pathways in physiological homeostasis, raising concerns about target organ toxicity; the blood-brain barrier remains a formidable barrier, particularly for biologics such as antibodies, necessitating innovative delivery systems like nanocarriers, focused ultrasound, or engineered vectors to achieve CNS penetration; The optimal intervention window remains unclear, given neuroinflammation's potentially dual roles across disease stages; preventive strategies for pre-symptomatic individuals may

fundamentally differ from treatments for established disease. Significant individual heterogeneity in neuroinflammatory responses underscores the need for precision medicine approaches guided by validated neuroinflammatory biomarkers (e.g., TSPO-PET imaging, cerebrospinal fluid/blood inflammatory panels) to identify responsive patient subpopulations. The translational gap between rodent models and human disease, coupled with the complexity of chronic disease clinical trial design, has led to promising preclinical data being followed by multiple failures.

Future directions must therefore focus on overcoming these challenges. This necessitates developing more specific and safer therapeutics, including allosteric inhibitors, biased agonists, and targeted degradation strategies; advanced novel CNS delivery technologies to enhance brain bioavailability; discovering and validating reliable non-invasive biomarkers for patient stratification and monitoring treatment response; designing smarter clinical trials featuring optimised endpoints, patient selection, and long-term safety monitoring; exploring rational combination therapies targeting multiple facets of neuroinflammation or integrating anti-inflammatory agents with disease-modifying treatments (e.g., anti-Aβ antibodies); and investigating emerging approaches such as gene therapy, cell therapies (e.g., regulatory T cells), and interventions targeting the gut-brain axis.

In summary, neuroinflammation undoubtedly represents a pivotal hub within the complex network of brain aging and neurodegeneration. Successfully modulating this process through pharmacology holds immense potential to safeguard cognitive function, delay disease onset, and enhance quality of life in aging populations. While the path forward presents challenges, the ongoing convergence of fundamental neuroimmunology, advanced drug design, and clinical neuroscience is paving the way for a new era of therapeutic innovation. The ultimate goal—regulating the fires of neuroinflammation and ushering in a revolution in brain health for the elderly—is achievable, requiring sustained and collaborative efforts from the scientific and medical communities.

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