Published in final edited form as:

Neuroprotection. 2024 September ; 2(3): 182–195. doi:10.1002/nep3.56.

Microglial senescence in neurodegeneration: Insights, implications, and therapeutic opportunities

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Abstract

The existing literature on neurodegenerative diseases (NDDs) reveals a common pathological feature: the accumulation of misfolded proteins. However, the heterogeneity in disease onset mechanisms and the specific brain regions affected complicates the understanding of the diverse clinical manifestations of individual NDDs. Dementia, a hallmark symptom across various NDDs, serves as a multifaceted denominator, contributing to the clinical manifestations of these disorders. There is a compelling hypothesis that therapeutic strategies capable of mitigating misfolded protein accumulation and disrupting ongoing pathogenic processes may slow or even halt disease progression. Recent research has linked disease-associated microglia to their transition into a senescent state—characterized by irreversible cell cycle arrest—in aging populations and NDDs. Although senescent microglia are consistently observed in NDDs, few studies

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Not applicable.

have utilized animal models to explore their role in disease pathology. Emerging evidence from experimental rat models suggests that disease-associated microglia exhibit characteristics of senescence, indicating that deeper exploration of microglial senescence could enhance our understanding of NDD pathogenesis and reveal novel therapeutic targets. This review underscores the importance of investigating microglial senescence and its potential contributions to the pathophysiology of NDDs, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Additionally, it highlights the potential of targeting microglial senescence through iron chelation and senolytic therapies as innovative approaches for treating age-related NDDs.

Keywords

aging; ferritin; microglia; neurodegenerative diseases; senescence-associated secretory phenotype; senescent

1 | INTRODUCTION

Aging is the most significant nonmodifiable risk factor for neurodegenerative diseases (NDDs). This intrinsic and irreversible biological process affects all living organisms, leading to widespread detrimental effects on biological systems, particularly within the central nervous system (CNS). The mechanisms underlying aging are complex and remain poorly understood, with systemic-level investigations posing substantial challenges. Consequently, current research has shifted toward cellular senescence to elucidate fundamental molecular and cellular processes that may provide insights into broader systemic aging mechanisms.[1] Among CNS cell types, microglial cells–resident macrophages of the CNS–are of particular interest due to their roles in neurodevelopment, homeostasis, and responses to injury, infection, and microenvironmental changes. Unlike other CNS cells, microglia originate from the yolk sac rather than the neural tube.[2,3] During embryogenesis, microglia migrate from the yolk sac into the developing nervous system, where they proliferate and establish a self-renewing population within the CNS.[4]

A common pathological hallmark of NDDs is protein misfolding, with each disease being associated with specific misfolded proteins serving as pathognomonic biomarkers.[5] Although many NDDs exhibit overlapping pathologies,[6] the aggregation of misfolded proteins is widely regarded as a primary driver of neurodegeneration. Neuronal viability is heavily reliant on glial support, as neurons depend on glial cells for various essential functions.[7] This has led to extensive research dedicated to understanding the role of glial cells in NDDs, with a particular emphasis on microgliosis, astrogliosis,[8] and the senescence of these glial populations.[9,10] The study of microglial and astrocytic senescence adds complexity by investigating how aging within these glial cells may influence the pathophysiology of NDDs and how proteinopathies might induce cellular senescence (Figure 1).

Emerging evidence indicates that glial cells undergo senescence, potentially contributing to the pathogenesis of NDDs.[11] These cells enter a state of irreversible cell-cycle arrest, characterized by the acquisition of a senescence-associated secretory phenotype

(SASP).[12] This phenotype is defined by the secretion of proinflammatory cytokines, leading to significant alterations in the tissue microenvironment and driving progressive tissue dysfunction over time.[13,14] Senescence has been implicated in microglia pathology, with senescent microglia, similar to disease-associated microglia (DAM), predominantly localized in neurodegenerative regions,[15] such as the substantia nigra (SN) in Parkinson's disease (PD)[16] and the hippocampus in Alzheimer's disease (AD).[17] This selective regional distribution suggests a potential link between microglial senescence and the spatial manifestation of neurodegenerative pathologies.

The spatial distribution of senescent microglia in degenerative brain regions suggests a connection between cellular aging within microglia and the specific anatomical sites of NDD pathology. Furthermore, studies have demonstrated that microglia engaged in the phagocytosis of tau-laden neurons subsequently exhibit a senescent phenotype.[18] For instance, Karabag et al.[19] characterized microglial senescence in the context of tauopathy by exposing primary microglia to 5 and 15 nmol/L of monomeric tau for 18 h, followed by a 48-h recovery period. Their analysis of senescence markers revealed that exposure to 15 nmol/L of tau induced cell cycle arrest, morphological alterations, and SASP release.[19] This research underscores the role of tau in driving microglial senescence, suggesting that senescent microglia are associated with the accumulation of misfolded proteins commonly observed in advanced stages of NDDs among older adults. Thus, microglia are implicated as key contributors to neurodegenerative pathophysiology, particularly in response to pathological conditions such as iron dysregulation—a characteristic feature of senescent microglia. This review aimed to provide a comprehensive update on microglial senescence in NDDs, current methodologies for identifying senescent microglia, and potential therapeutic strategies, including the use of iron chelators and senolytic agents for the treatment of age-related NDDs.

A systematic search of the PubMed and Medline databases was conducted in January 2024 to identify studies investigating microglial senescence and its contributions to various NDDs in both human and animal models. References from the selected literature were systematically reviewed to identify additional relevant studies.

2 | MICROGLIAL MORPHOLOGY AND STATES: PAST AND FUTURE

Microglia were first identified as a distinct cellular entity within the CNS by del Rio-Hortega in 1919.[20] However, their ontogeny remained unclear until 1939 when John Kershman observed their infiltration into the CNS during embryonic development from the mesodermal layer of the yolk sac.[21] Subsequent research on microglia remained limited for several decades until 1986 when Georg Kreutzberg rekindled interest in the field. Kreutzberg's team introduced a pioneering model in the 1960s and 1970s to study microglial activation independent of peripheral monocytes. They observed that following peripheral facial nerve injury, microglial in the facial nucleus became activated and participated in synaptic remodeling, a process termed "synaptic stripping".[22]

In recent years, microglia have been recognized as highly dynamic cells, continuously surveilling their environment and interacting with immune cells, other glial cells,

neural stem cells, and neurons.[23] It is now understood that microglia originate from yolk-sac-derived macrophage precursors and possess distinct genetic profiles, compared with circulating monocytes.[3] Unlike other macrophages that infiltrate the CNS during neuroinflammation,[24] microglia do not undergo continuous renewal from myeloid progenitors but instead maintain their population through local proliferation.[25]

This reliance on self-renewal via cell division is a key factor in the susceptibility of microglial cells to senescence. Repeated rounds of cell division, combined with exposure to environmental factors and stressors such as misfolded proteins, contribute to aging-related changes within microglia, ultimately leading to senescence. Throughout the history of microglia research, their morphology has been a critical indicator of the brain's physiological and pathological states, leading to the development of terminology that describes their functional states. Traditionally, microglia have been categorized as either "resting", characterized by a ramified morphology, or "activated", characterized by an amoeboid morphology. Amoeboid microglia, distinguished by their phagocytic activity and few unramified processes, were considered activated. However, the term "resting" has become outdated as the functions of ramified microglia in synaptic surveillance, pruning, neurogenesis, myelination, and vasculogenesis have been elucidated.[23,26] Ramified microglia secrete neurotrophic factors, such as insulin-like growth factor 1, brain-derived neurotrophic factor, and nerve growth factor, to modulate inflammation and enhance synaptic plasticity.[27,28] Thus, the term "homeostatic" microglia is now preferred to describe ramified microglia under normal physiological conditions.[29]

3 | MICROGLIAL ACTIVATION IN NEURODEGENERATION

Microglial activation is a complex, multifaceted process triggered by various forms of neuronal injury, playing a critical role in disrupting CNS homeostasis. Upon CNS insult, microglia undergo a morphological transition to an amoeboid state, a process known as microgliosis, characterized by reactive proliferation in response to pathological conditions.[30] Following injury, microglia clones reorganize through cell migration and apoptosis, as observed in the facial nucleus post-facial nerve axotomy. In this context, microglia near the lesion may undergo apoptosis or migrate, contributing to the restoration of microglial homeostasis.[31] Recent advancements, such as single-cell RNA sequencing, have revealed that reactive microglia upregulate genes associated with immune responses, neuronal apoptosis, and migration while downregulating homeostatic markers such as transmembrane protein 119, purinergeric receptor P2Y 12/13, C-X3-C motif chemokine receptor 1 (*CX3CR1*), colony-stimulating factor-1 receptor, transforming growth factor-beta, and C-C motif chemokine receptor 3.[32,33] Despite these insights, the precise mechanisms driving excessive microglial migration and cell death due to clonal expansion in damaged regions remain unclear.

Aged microglia exhibit an altered surveillance phenotype, marked by reduced dendritic branching, decreased process motility, and prolonged inflammatory responses to injury,[34] suggesting a diminished neuroprotective capacity. The activation of microglia varies across different proteinopathies,[35] however, it is well-established that in NDDs, microglia rapidly respond to neuronal death induced by protein aggregates by producing an array

of inflammatory mediators, including nitric oxide, interleukin-6 (IL-6), IL-1 β, and tumor necrosis factor-alpha.[36,37] Additionally, activated microglia secrete chemokines that recruit homeostatic microglia to sites of injury.[38,39] Neuronal damage can also trigger the release of fractalkine (*CX3CL1*), which binds to its receptor *CX3CR1*, promoting the release of inflammatory factors and initiating an inflammatory cascade.[40] The *CX3CL1–CX3CR1* axis is crucial for microglia-neuron communication, facilitating the rapid recruitment of microglia to damaged neurons, indicative of a coordinated microglia-neuron response to injury. Studies have shown that *CX3CR1* knockout reduces microglial migration and adhesion, thus offering enhanced neuroprotection.[41] However, *CX3CR1* deficiency can dysregulate microglial responses, leading to increased neurotoxicity in lipopolysaccharide-induced neuroinflammation models, as well as in models of PD and amyotrophic lateral sclerosis (ALS).[42] Moreover, recent research using a cuprizone-induced demyelination model revealed that administering *CX3CL1* significantly promoted oligodendrocyte precursor cell-mediated remyelination in the corpus callosum and cortical gray matter via interactions with microglia.[43] These findings underscore the critical role of the *CX3CL1–CX3CR1* axis in NDDs, highlighting the need for further exploration of therapeutic strategies targeting this pathway.

Microglia can also activate peripheral T cells through antigen presentation, contributing to CNS damage.[44,45] Conversely, neuronal injury may be exacerbated by the cytotoxic factors produced by activated microglia. In the early stages of AD, microglia exert neuroprotective effects by phagocytosing amyloid-beta (Aβ). However, with aging and disease progression, microglia become increasingly activated and proliferative, clustering around neurons. Despite this increased activity, the efficiency of Aβ clearance diminishes, and elevated levels of inflammatory cytokines further contribute to Aβ accumulation,[46,47] demonstrating the complex and evolving role of microglia in AD pathogenesis.

To better understand microglial activation, researchers have employed the M1/M2 paradigm in vitro. In this framework, M1 microglia exhibit pro-inflammatory, neurotoxic characteristics, while M2 microglia promote anti-inflammatory responses.[48,49] This classification conveys the dichotomy of microglia roles, with M1 associated with detrimental effects and M2 with beneficial ones, depending on the microenvironment and pathophysiological conditions.[50] However, recent genome-wide transcriptomic analyses of microglial under various disease conditions have identified a new subpopulation termed DAM.[15,51,52] These studies challenged the classical view of microglia polarization states as strictly pro-inflammatory M1 (classical activation) and immunosuppressive M2 (alternative activation), suggesting that these phenotypes represent extremes within a continuum of microglia states. In vivo, microglia exhibit a spectrum of functional states that cannot be fully replicated in vitro, emphasizing the complexity and diversity of microglial responses in living organisms.[53] Furthermore, the identification of DAM has led to the recognition of a new phenotype, senescent microglia, which represent a subset of DAM[12,54,55] and are implicated in the pathogenesis of various brain pathologies.

4 | SENESCENT MICROGLIA

Over a century ago, the term “senescence” was introduced to describe the final phase of cell differentiation, culminating in cell death.[56] Currently, it remains unclear whether “senescent” and “dystrophic” refer to the same state or represent distinct entities, as these terms are often used interchangeably. Angelova and Brown delineated the differences between these terms, noting that “cellular senescence”, a concept originating in cancer research, denotes a loss of proliferative capacity. In contrast, “dystrophic cells” refer to morphological changes associated with senescence,[11] including deramification, process shortening, gnarling, beading, spheroid formation, and cytoplasmic fragmentation. Streit et al.[57] posited that dystrophy reflects an increased propensity for senescence, particularly observed in microglia during aging and in response to neuropathological conditions. Studies have also used “dystrophy” to describe age-related changes in microglia’s secretory profile, or the SASP.[58,59] A defining feature of senescent microglia is the SASP, which includes a variety of signaling molecules such as growth factors, proteases, reactive oxygen species (ROS), chemokines, and pro-inflammatory cytokines. Senescent microglia secrete elevated levels of pro-inflammatory cytokines like tumor necrosis factor, IL-6, and IL-8, driven by the activation of the p38/mitogen-activated protein kinase and nuclear factor-kappa B pathways. These cells can also induce senescence-like phenotypes in neighboring cells through paracrine signaling,[60,61] contributing to inflammation and potentially increasing the risk for NDDs.

Recent studies have identified senescent microglia as a subset of DAM,[12,54,55] characterized by iron overload.[62] The phenomenon of iron accumulation in aged microglia is intriguing, especially because microglia are not the primary iron-storing cells in the brain. Iron enters the brain through the blood–brain and blood–cerebrospinal fluid barriers via transferrin-mediated endocytosis.[63,64] Research has shown that iron accumulation in brain tissue, induced by treatments, such as ferric citrate, can promote cerebral endothelial senescence.[65] In vitro studies have also linked iron overload to cellular senescence.[66,67] However, whether peripheral iron overload directly induces microglial senescence remains unexplored. Although the broader mechanisms of iron homeostasis are well understood, the specific roles of iron metabolism within the brain, including its uptake, intracellular handling, export, and distribution, remain unclear.[68]

Telomere shortening, a hallmark of aging observed across species, has been documented in aged rat microglia, particularly those associated with dystrophic microglia.[69] Telomere shortening occurs due to the inability to fully replicate chromosome ends during cell division.[70,71] The role of telomere dysfunction in NDDs and brain aging is still debated, with some studies suggesting a link between telomere shortening and age-related NDDs.[72] Another study found that telomere dysfunction correlates with reduced microglia populations without fully inducing an aging phenotype,[73] highlighting the need for further investigation into the relationship between telomere shortening and senescent microglia. Senescent microglia also exhibit decreased phagocytic activity. For instance, Triggering receptor expressed on myeloid cells 2 (*TREM2*), a gene identified as a risk factor for AD through genome-wide association studies, is implicated in this process.[74,75] Research has revealed a correlation between the expression of senescence markers and *TREM2* levels, as

observed in AD mouse models lacking *TREM2*.[75] Rachmian et al.[76] found reduced levels of senescent microglia in *TREM2*-deficient AD mice compared with those with intact *TREM2*. This finding aligns with the work of Keren-Shaul et al.,[77] who concluded that the pro-inflammatory DAM phenotype observed in various CNS diseases appears to be facilitated by *TREM2*. Although recent studies using the 5×FAD mouse model of amyloidosis have shown that senescent microglia expressing high levels of *TREM2* exhibit a distinct signature different from *TREM2*-dependent DAM, research indicates that senescent microglia may indeed be subsets of DAM.[78] Jay et al.[79] discovered that *TREM2* loss in AD mouse models ameliorates early amyloid pathology but worsens later stages, revealing *TREM2*'s distinct functional roles at different phases of AD. They demonstrated that *TREM2* impairment reduces myeloid cell internalization of amyloid throughout the pathology and decreases plaque-associated myeloid cell accumulation by lowering cell proliferation, particularly in the late stage of AD.[79]

The characterization of "aged" microglia encompasses various distinct phenotypes, and the term currently lacks precision and clarity, as noted by Koellhoffer et al.[75] The term "senescent" might not fully capture all forms of "aged" microglia, suggesting a potential distinction between these microglia and other DAM, which may simply become more prevalent with age.[54,80] Additionally, senescent cells exhibit certain morphological and biochemical traits overlapping with quiescent cells, complicating their distinction.[81] This complexity is further compounded by the absence of specific markers exclusive to senescent cells, as no uniform features or biomarkers are common to all senescent cells. The identification of senescent cells depends on factors such as the specific cell or tissue under examination, nature of the stress stimulus, and mechanism through which senescence is induced.[82] Several factors that can lead to cellular senescence have been identified, including telomere shortening,[70] DNA damage,[83] oncogene activation,[84] and metabolic dysfunction.[85] Therefore, the significance of distinguishing senescent microglial cells remains to be fully determined. Currently, the SASP and elevated ferritin levels are the only widely accepted phenotypes for senescent microglia in both the healthy aged population and in aged-related NDDs.[12,86]

5 | MARKERS OF MICROGLIAL SENESCENCE

Several markers have been associated with cellular senescence in brain cells, including nuclear alterations such as the sustained presence of DNA damage response proteins, such as gamma-H2AX,[87] and the reduction of the nuclear lamina protein, lamin B1.[88,89] Additional markers of brain aging include elevated β-galactosidase (SA-β-gal) activity within the lysosomal compartment,[90] increased expression of cyclin-dependent kinase inhibitors, such as cyclin-dependent kinase inhibitor *2A/p16Ink4a* and cyclin-dependent kinase inhibitor 1 A/p21CIP1/wildtype p53-activated fragment 1, which induce stable cell cycle arrest,[91] and heightened lipofuscin accumulation.[92] The identification of specific markers for microglial senescence has recently garnered attention. Among these, ferritin protein accumulation has emerged as a promising indicator of microglial senescence in age-related NDDs.[12]

Dystrophic microglia, commonly observed in aging and NDDs, such as PD and AD, exhibit elevated ferritin levels.[86,93,94] One of the protective roles of microglia is to prevent iron-

mediated oxidative damage to neurons by sequestering free iron within ferritin molecules. Although this activity benefits neurons, it may adversely affect microglia, potentially leading to oxidative damage within these cells.[95,96] The accumulation of neurofibrillary tangles, neuritic plaques, and age-related oxidative damage to neurons is often exacerbated by free iron's capacity to generate highly reactive oxygen radicals via Fenton chemistry.[97] A study by Neumann et al.[12] elucidated that not all dystrophic microglia express ferritin. Using immunofluorescence, their research demonstrated that ferritin-rich dystrophic microglia were found in the hippocampus, adjacent entorhinal cortex, and brainstem regions near the SN or locus coeruleus in aged human brains. They concluded that dystrophic microglia do not display common markers of cellular senescence, such as SA-β-gal and lipofuscin, suggesting that microglial dystrophy may not fully represent a senescent state. This finding emphasizes the necessity of distinguishing between "senescent" and "dystrophic" microglia or considering the possibility that progressive iron accumulation in dystrophic microglia may eventually lead to senescence. Currently, recognized markers for microglia exhibiting a senescence phenotype include the presence of the SASP and ferritin, alongside other senescence markers such as SA-β-gal and lipofuscin (Figure 2).

6 | MICROGLIAL SENESCENCE IN NDDs

NDDs frequently exhibit overlapping pathological features,[6] with patients often presenting with multiple coexisting proteinopathies, and a single proteinopathy may be implicated in various disorders. For instance, AD is characterized by senile plaques composed of Aβ protein and neurofibrillary tangles of hyperphosphorylated tau, whereas PD is distinguished by Lewy bodies containing aggregated α-synuclein. These disorders, collectively classified as proteinopathies, are marked by the abnormal accumulation of misfolded proteins, contributing to neuronal dysfunction and apoptosis.[5] Despite these overlapping pathologies, senescent microglia have been observed across multiple NDDs. Understanding the role of microglial senescence in these diseases could yield critical insights into the pathophysiological mechanisms underlying neurodegeneration and inform the development of targeted therapeutic interventions. Although tau protein is a key misfolded protein implicated in the accumulation of senescent microglia,[19,98] further research is needed to elucidate the specific pathways through which monomeric tau induces microglial senescence.

6.1 | AD

AD, the most prevalent form of dementia, is a progressive neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau.[99] As AD progresses, extensive neurodegeneration occurs throughout the cerebral cortex, significantly impacting the medial temporal lobe structures, including the hippocampal formation and entorhinal cortex.[100,101] Recent studies have underscored the pivotal role of microglial senescence in the pathogenesis of AD.[102,103] Tau protein aggregation, leading to the formation of neurofibrillary tangles, has been implicated in inducing microglial senescence in a concentration-dependent manner. Lau et al.[102] proposed that the accumulation of senescent microglia perpetuates and exacerbates AD pathologies, contributing to glial aging and subsequent senescence.

Pathologically, iron is predominantly sequestered within ferritin in both amyloid plaques and neurofibrillary tangles.[104] However, whether this iron sequestration may induce iron deficiency in adjacent brain regions remains unclear. It has been observed that Aβ 1–42 facilitates the reduction of redox-inactive ferric iron (Fe^{3+}), present as ferrihydrite, into redox-active ferrous iron (Fe^{2+}).[105] This ferrous iron can subsequently catalyze the Fenton reaction, generating harmful free radicals that may exacerbate neuroinflammation.[106] Neuroinflammation plays a critical role in AD, leading to increased intracellular ferritin content in activated microglia, primarily in the form of L-ferritin, which ultimately contributes to a senescent microglia phenotype.[68] Substantial evidence links elevated brain iron levels with increased lipid peroxidation in patients with AD. Apart from other forms of cell death, such as necrosis, pyroptosis, and autophagy, ferroptosis has been proposed as a primary mechanism driving neuronal death in AD and other NDDs.[107–109] Similar to the prion-like propagation of misfolded proteins such as Aβ,[110,111] ferroptosis may also spread rapidly from one cell to neighboring cells.[112] Furthermore, a study by Kenkhuis et al.[113] identified a subset of microglia in patients with AD with elevated expression of the iron storage protein ferritin light chain. These microglia exhibited increased ionized calcium binding adaptor molecule 1 (IBA-1) expression but reduced transmembrane protein 119 and purinergic receptor P2Y 12 expression, indicative of iron accumulation. This subset of activated microglia displayed a morphologically dystrophic appearance, suggestive of a senescent phenotype.[113] Collectively, these findings suggest that microglia iron uptake significantly influences their functional behavior. Moreover, a recent comprehensive review systematically emphasized the link between microglial senescence and AD, proposing that microglial senescence, associated with aging and accelerated by neurodegeneration, constitutes a significant mechanism contributing to the pathogenesis of AD.[86]

6.2 | PD

PD is the second most common NDD after AD.[114] Motor symptoms, including muscle rigidity, resting tremor, bradykinesia, and postural instability, are characteristic features of PD.[115,116] Additionally, nonmotor symptoms, such as sleep disturbances, hallucinations, autonomic dysfunction, olfactory deficits, dementia, and depression, can manifest preclinically, often preceding the onset of motor symptoms.[117] A hallmark feature of PD is the progressive loss of dopaminergic neurons in the SN pars compacta (SNpc) of the ventral midbrain.[118] In PD, the SN exhibits a higher iron concentration, compared with other brain regions, such as the cortex, globus pallidus, and red nucleus, which have lower iron concentrations. Notably, the total iron content in the SN increases with disease progression and correlates with the severity of motor impairment.[119] A key histopathological feature of PD is the presence of Lewy bodies, which are intraneuronal inclusions composed of aggregated α-synuclein. Studies have identified iron within Lewy bodies, with this iron being redox-active.[120,121] Detection of redox-active iron in situ has shown strong labeling of Lewy bodies in SNpc neurons, suggesting that the sequestration of iron within Lewy bodies may serve as a protective mechanism rather than contributing to neurodegeneration. Elevated iron levels in the SNpc of patients with PD are associated with increased ferritin and neuromelanin iron loading.[122,123] Complementary studies over recent decades have observed an accumulation of ferritin-loaded microglia in the SN of patients with PD.[124,125] A study by Jiang et al.[126] provided insights into the molecular mechanisms

underlying excessive iron accumulation in PD, highlighting increased activation of divalent metal transporter-1 (*DMT1*) as a possible factor, although the specific triggers for *DMT1* activation in regions such as the SN remain unclear. Inflammation is thought to play a role in the upregulation of *DMT1* in dopaminergic neurons, with recent findings identifying high mobility group protein B1 as a critical early mediator of inflammation-induced iron accumulation in PD.[127]

Given that aging is the most significant risk factor for PD, Shaerzadeh et al. conducted stereological analyses on microglia and dopaminergic neurons in the SNpc and ventral tegmental area (VTA) of C57BL/J6 mice at different ages (1, 6, 9, 18, and 24 months).[16] Using double-stained sections for tyrosine hydroxylase and IBA-1, they observed an age-related increase in microglia in both regions, whereas the number of tyrosine hydroxylase neurons remained relatively stable after 9 months in SNpc and 6 months in the VTA. Morphometric analyses revealed a decline in microglial complexity and projection area with aging, accompanied by increased cell body size. Furthermore, they found that contact sites between microglia and dopaminergic neurons increased with age, suggesting enhanced support and monitoring of dopaminergic neurons by microglia. This observation implies that intrinsic biological mechanisms within microglia compensate for the age-related decline in morphological complexity, or senescence, thereby maintaining support for neurons in the SNpc and VTA.[16]

7 | HUNTINGTON'S DISEASE

Huntington's disease (HD) is a fatal, autosomal dominant neurodegenerative disorder characterized by involuntary choreiform movements, cognitive decline, and behavioral disturbances. These symptoms result from the expansion of a cytosine-adenine-guanine trinucleotide repeat in the gene encoding the huntingtin protein on chromosome 4, as confirmed by genetic testing.[128] The huntingtin protein is considered "normal" when it contains 15 – 25 cytosine-adenine-guanine repeats; however, when this repetition exceeds 36, it produces a mutant form of huntingtin protein (mHTT), with an expanded polyglutamine tract. This single alteration in the huntingtin protein leads to the full spectrum of clinical manifestations associated with HD.[129] The primary pathogenesis of HD is attributed to the toxic effects of mHTT, though the exact molecular mechanisms underlying this toxicity remain elusive and are believed to involve multiple interconnected pathways,[130] presenting challenges for therapeutic targeting. One promising area of research involves exploring the role of senescent microglia in HD. Dysregulated brain iron metabolism, resulting in elevated iron accumulation in the caudate, putamen, and cortex, has been documented in individuals with HD,[131] suggesting a significant role of iron in the mHTT-induced pathological cascade. However, this view contrasts with the findings of van den Bogaard et al.,[132] who reported no evidence of early iron accumulation as a contributing factor to HD onset, though they did confirm the presence of excess iron in the brains of patients with HD. The first study to report increased brain ferritin and iron levels in an HD model was conducted by Simmons et al.[133] in 2007. This research, which included both R6/2 mice and human patients with HD, demonstrated elevated ferritin immunostaining in the striatum, cortex, and hippocampus, with ferritin-labeled microglia also exhibiting dystrophic features in the R6/2 mice. These findings offer novel insights into

microglial senescence and its involvement in HD pathogenesis.[133] In mammals, cellular iron homeostasis is primarily regulated post-transcriptionally by two cytoplasmic iron regulatory proteins, iron regulatory protein (IRP) 1 and IRP2. These RNA-binding proteins respond to intracellular iron levels by binding to iron-responsive elements within the mRNA encoding ferritin and transferrin receptors.[134] Research on N171-82Q HD transgenic mice has shown increased iron levels in the striatum and cortex, with evidence suggesting that mHTT may upregulate the expression of iron regulatory proteins, such as IRP1, transferrin, and its receptor, potentially contributing to the observed iron accumulation in HD.[135] Reactive gliosis, characterized by reactive astrocytosis and microglia activation, is consistently observed in the striatum of patients with HD.[136] Positron emission tomography studies have confirmed significant microglial activation in affected brain regions, particularly during advanced stages of the disease.[137] To date, the only study linking microglial activation to ferritin overload in HD was conducted by Simmons et al.[133] in 2007. Consequently, further research focusing on the relationship between microglial senescence and HD is needed to deepen our understanding of this aspect in HD pathophysiology.

7.1 | ALS

ALS, also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder characterized by the degeneration of both upper and lower motor neurons.[138] Although traditionally classified as a neuromuscular disorder, recent imaging and neuropathological evidence indicate that ALS also affects nonmotor regions of the neuraxis.[139] The hallmark pathological feature of ALS is the accumulation of inclusion bodies, or Bunina body-like protein aggregates, in the cytoplasm of motor neurons. In approximately 97% of ALS cases, the primary protein component of these inclusions is TAR-DNA-binding protein 43 (TDP-43).[140] However, in patients with mutations in superoxide dismutase type 1 (*SOD1*) or fused in sarcoma, the inclusion bodies predominantly contain *SOD1* or fused in sarcoma proteins, respectively.[141,142]

Elevated ferritin levels in serum and cerebrospinal fluid have been reported in patients with ALS, suggesting a potential role for ferritin as a biomarker for the disease.[143–145] Microglia, the resident immune cells of the CNS, are activated in both the motor cortex and spinal cord in sporadic and familial ALS cases.[146] In a study by Trais et al.,[147] the $SOD1^{G93A}$ transgenic rat model of ALS exhibited reduced lamin B1 expression in the lumbar spinal cord and increased *p16Ink4a* expression in microglia. Additionally, cultured $SOD1^{G93A}$ microglia displayed characteristics of cellular senescence, including a large, flattened morphology, upregulated expression of senescence markers (*p16Ink4a*, p53, matrix metallopeptidase 1, and SA-β-gal), and overexpression of SASP factors.[147] These findings suggest a strong link between microglial senescence and the inflammation and motor neuron loss observed after the onset of paralysis in $SOD1^{G93A}$ rats, indicating that cellular senescence may play a critical role in ALS pathogenesis. TDP-43, an RNA-binding protein with multiple roles in RNA metabolism, is the most common protein found in ALS inclusion bodies. Various mechanisms have been proposed regarding the pathogenic role of aggregated TDP-43 in ALS.[148–150] It has been observed that both wild-type and mutant TDP-43 can induce cytokine production in primary mouse microglia.[151] TDP-43 has also been implicated in microglial phagocytosis, as demonstrated by Paolicelli et al.,[152]

who showed that microglial-specific knockout of *TARDBP* (the gene encoding TDP-43) enhanced amyloid clearance and reduced synaptic loss in an AD mouse model. Recent studies have reported a marked increase in microglial CD68 and high expression of L-ferritin in the motor cortex of patients with ALS, with both markers significantly correlating with phosphorylated TDP-43 pathology in the ALS brain.[153] Although phosphorylated TDP-43 load was notably elevated in both the motor cortex and hippocampus of patients with ALS, only the motor cortex showed increased microglial density and astrogliosis. This evidence suggests that microglia are initially phagocytic during the early stages of ALS but become dysfunctional as the disease progresses, driven by the accumulation of phosphorylated TDP-43.

8 | IRON CHELATION AND SENOLYTICS FOR NDDs

Although the precise etiologies of numerous NDDs remain elusive, accumulating evidence suggests that exposure to metals, such as lead, nickel, mercury, cadmium, and iron, significantly contributes to the pathogenesis of these conditions. This phenomenon has been documented across various animal models,[154–158] underscoring the potential deleterious effects of metal exposure in NDDs. In 1991, McLachlan conducted a pivotal study demonstrating that the iron chelator deferoxamine significantly attenuated the behavioral and cognitive decline observed in patients with AD.[159] Despite the groundbreaking nature of this research, the exploration of iron chelators as therapeutic agents for AD and other NDDs has only recently regained momentum. Researchers are now expanding upon McLachlan's initial findings to evaluate the efficacy of iron chelation therapy in managing symptoms and disease progression across various NDDs as shown in Table 1. Iron chelation therapy has emerged as a potential treatment strategy for NDDs due to the increasing evidence implicating iron in the pathogenesis of these disorders.[165,166] In one study, patients with PD treated with the iron chelator deferiprone over a 6-month period exhibited reduced iron levels in the SN and significant improvements in motor symptoms. However, upon cessation of treatment, iron accumulation recurred, indicating a return to the pathological state.[160] Devos et al.[161] conducted a clinical trial involving newly diagnosed patients with PD who had not yet taken levodopa. Their findings suggested that deferiprone while lowering iron levels, was associated with worse parkinsonism scores as measured by the Unified PD Rating Scale.[161] These contradictory results imply that deferiprone should be considered as an adjunct therapy for NDDs, with careful consideration of patient characteristics, disease stage, and treatment duration.

Research on iron chelation in HD is limited. However, studies utilizing clioquinol and deferoxamine have shown potential in alleviating symptoms in the R6/2 HD mouse model. These effects are thought to arise from the suppression of oxidative activity by mHtt and the reduction of iron-reduced oxidative stress in endosomal and lysosomal compartments.[167,168]

M30, a versatile iron chelator identified as 5-(N-methyl-N-propargylaminomethyl)-8-hydroxyquinoline, has emerged as a potent agent, demonstrating strong inhibition of monoamine oxidases A and B and iron-dependent lipid peroxidation.[162] Studies have confirmed M30's effectiveness in inhibiting lipid peroxidation, showing a higher half maximal inhibitory concentration value than does deferiprone.[169] M30 has shown

therapeutic potential in treating conditions such as AD, age-related cognitive decline, and ALS, enhancing neuroprotective and adaptive mechanisms by activating pro-survival signaling pathways in the brain.[163,164] Additionally, bioactive constituents in green tea and red wine have demonstrated neuroprotective, antioxidant, anti-inflammatory, and ironchelating properties, potentially addressing NDDs at the cellular level by reducing microglia activation, mitigating ROS-induced damage, chelating iron, and promoting cellular growth.[170]

In addition to iron chelation, senolytic drugs have shown promise in treating aged-related NDDs,[171] as senescent cells accumulate in aging brains and neurodegenerative conditions. Senolytics, which selectively induce apoptosis in senescent cells,[172] could mitigate the detrimental effects of cellular senescence in NDDs (Table 2). Dasatinib and quercetin, two senolytic agents, have been successfully used to reduce pathology in mouse models of NDDs.[173] For instance, in a mouse model of tau-dependent NDD marked by the accumulation of senescent microglia and astrocytes in the cortex and hippocampus, the senolytic agent ABT263 (navitoclax), a B cell lyphoma 2 protein inhibitor, significantly reduced *p16Ink4a*-positive senescent astrocytes and microglia, leading to improvements in memory.[175] The success of senolytic treatments in animal models has spurred clinical trials investigating the use of dasatinib and quercetin in patients with early AD.[174] These trials aim to determine whether senolytic therapy can eliminate both senescent cells and the associated SASP, which may have beneficial effects on NDDs.[176] Moreover, metformin, a common antidiabetic drug, has been shown to inhibit cellular senescence in AD and PD by activating microRNA-processing proteins, preventing amyloid plaque deposition in AD, and suppressing α-synuclein phosphorylation in PD.[177,178] Collectively, these findings, along with the therapeutic potential of iron chelators (as detailed in Table 1) and senolytic drugs, present promising and innovative strategies for addressing the underlying pathophysiology of NDDs.

9 | CONCLUSION

The role of microglia in neurodegeneration has been extensively investigated, focusing on identifying diverse microglia phenotypes and their activation across various NDDs. This review underscores previous research on microglial senescence, highlighting its distinct role in NDDs. Despite the challenges in identifying a definitive senescent microglia phenotype, especially given its presence in both healthy aging and age-related NDDs, progress has been hindered by the absence of specific markers. Currently, the increase in the SASP combined with elevated ferritin levels is considered indicative of senescent microglia. However, reliance solely on SASP can be problematic, as several SASP components may stem from the inflammatory milieu of non-senescent microglia. Ferritin, an iron storage protein within microglia, presents as a promising marker. It sequesters iron, preventing its involvement in harmful Fenton chemistry that generates ROS. The accumulation of misfolded proteins in NDDs is associated with increased ferritin levels within microglia, suggesting a potential role of “ferroptosis” in neuronal cell death. The source of this increased ferritin–whether due to iron overload from misfolded proteins or peripheral circulation via the blood-brain barrier through astrocytes–remains unclear. Nonetheless, promising therapeutic strategies for managing age-related NDDs include the use of iron chelators like deferoxamine and

senolytic drugs as adjunct therapies. In conclusion, investigating microglial phenotypes, particularly senescence offers a compelling avenue for understanding the pathophysiology of NDDs. Further research is essential to explore this aspect, potentially unlocking new insights into the etiologies of neurodegeneration and paving the way for innovative therapeutic approaches.

ACKNOWLEDGMENTS

We acknowledge all whose work has contributed to the knowledge reviewed here. Omamuyouwi M. Ijomone receives funding support through the NIH-FIC K43TW011920 for career development and research protected towards the writing and review of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center or the National Institutes of Health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Highlights

Significant findings of the study

- This study highlights the distinct contribution of microglial senescence to the pathophysiology of neurodegenerative diseases.

What this study adds

- This study provides a comprehensive update on microglial senescence in neurodegenerative diseases, current methodologies for identifying senescent microglia, and potential therapeutic strategies, including the use of iron chelators and senolytic agents for the treatment of age-related neurodegenerative diseases.

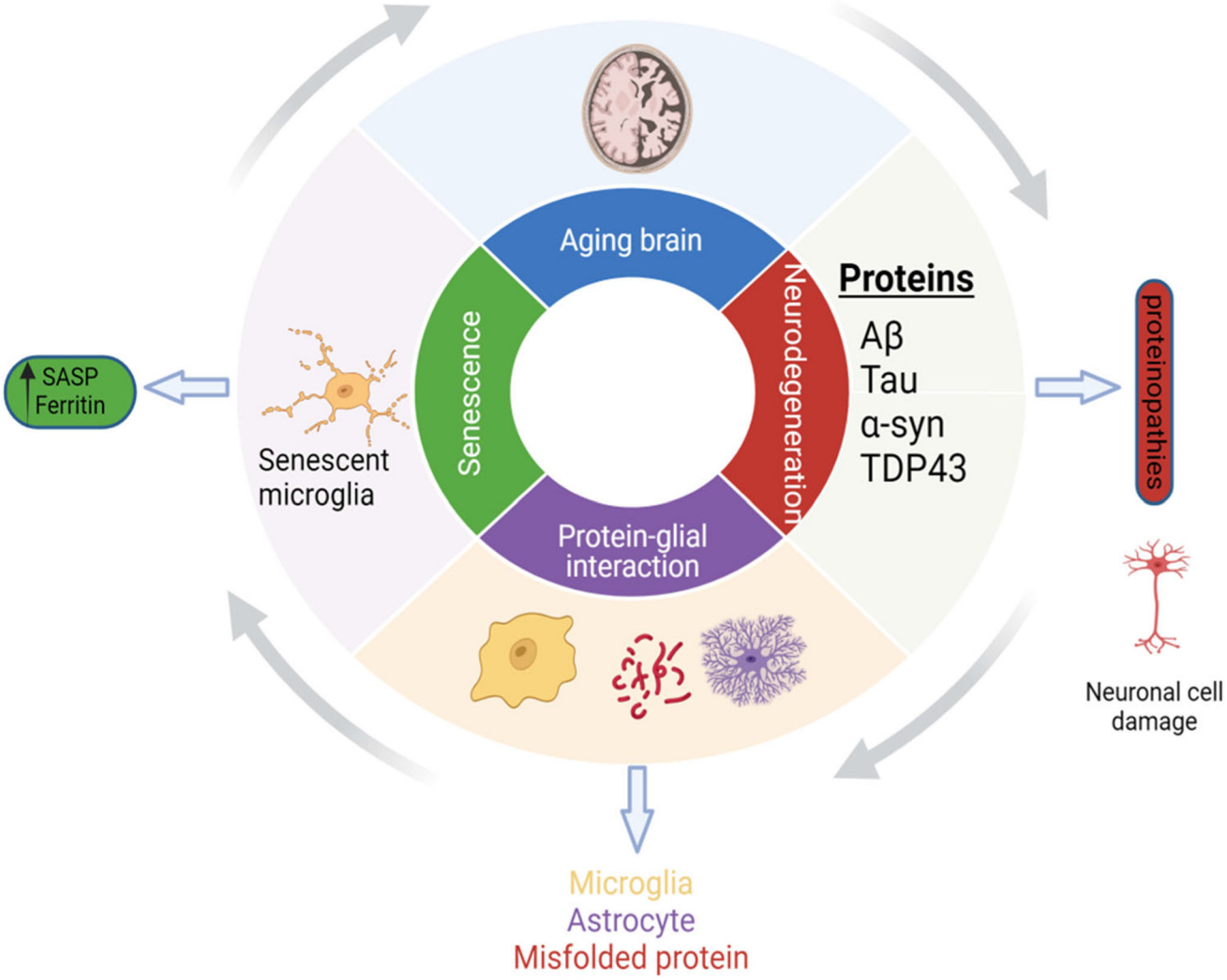

FIGURE 1.

Schematic representation of key pathogenic proteins: amyloid-beta (Aβ), microtubule-associated protein (tau) alpha-synuclein (α-syn), and TAR-DNA-binding protein 43 (TDP-43), implicated in neurodegenerative proteinopathies through their misfolded conformations. These misfolded proteins contribute to the induction of microglial senescence across various age-related neurodegenerative diseases. Specific markers of microglial senescence observed in these conditions include senescence-associated secretory phenotype and intracellular ferritin accumulation. Illustration generated using BioRender.com. SASP, senescence-associated secretory phenotype.

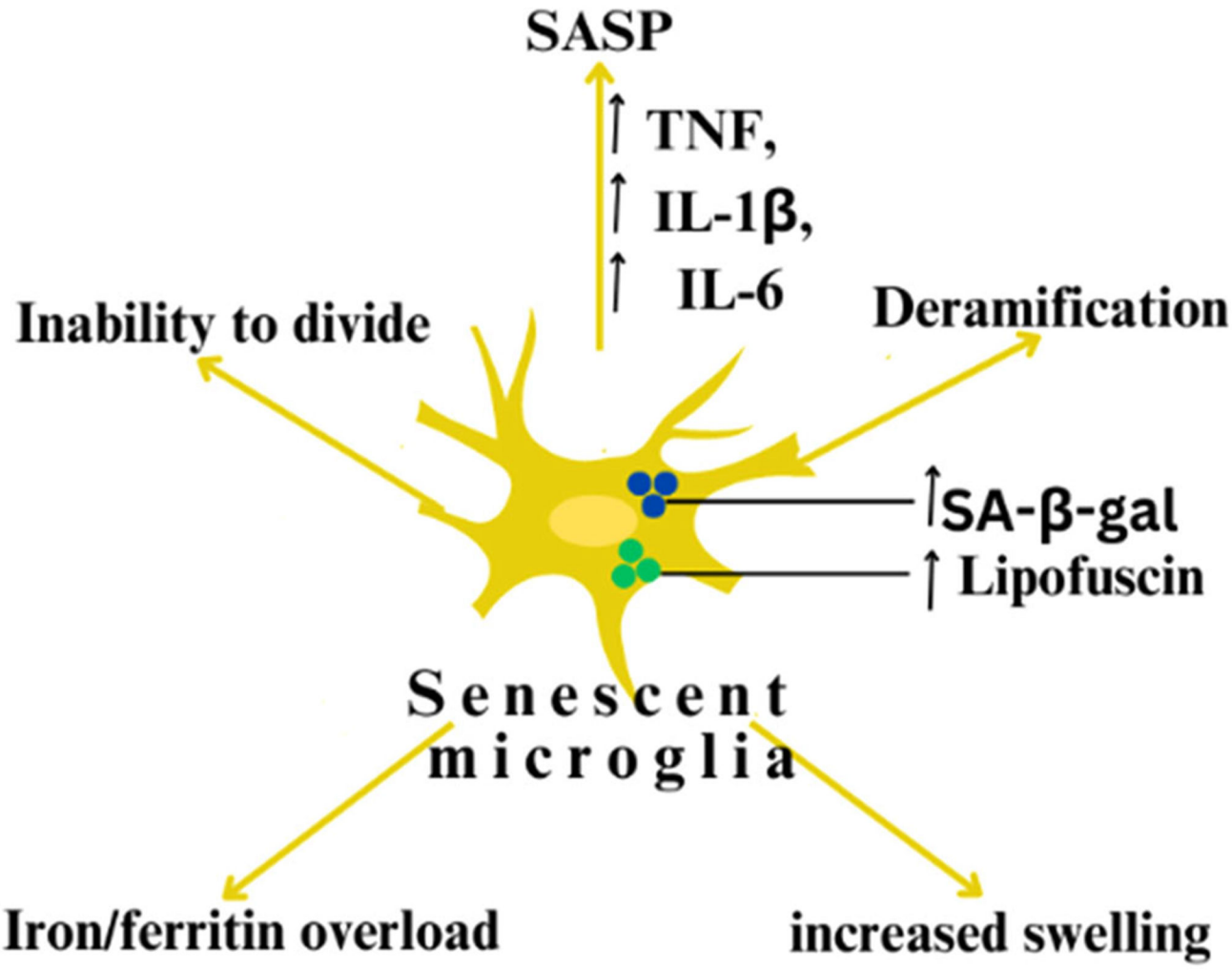

FIGURE 2.

Overview of characteristic features of senescent microglia: expression of senescence-associated secretory phenotype, morphological deramification, mitotic arrest (loss of proliferative capacity), intracellular iron overload, and increased cell body hypertrophy. Cellular senescence markers, such as senescence-associated β-galactosidase (SA-β-gal) activity, and lipofuscin accumulation, are also depicted. IL, interleukin; SASP, senescence-associated secretory phenotype; TNF, tumor necrosis factor.

TABLE 1

Studies evaluating the use of iron chelators on the incidence and progression of neurodegenerative diseases.

Iron chelator for neurodegenerative diseases	Functions	References
Deferoxamine	Mitigates behavioral and cognitive deterioration observed in AD	McLachlan et al.,[159]
Deferiprone	Chelates iron in the substantia nigra, leading to improvements in motor symptoms in patients with PD; not effective in patients newly diagnosed with PD	Devos et al.,[160] Devos et al.,[161]
5-(N-methyl-N-propargylaminomethyl)-8-hydroxyquinoline	Inhibits monoamine oxidase-A and B and iron-dependent lipid peroxidation, showing potential in treating AD, PD, age-related cognitive decline, and amyotrophic lateral sclerosis	Weinreb et al.,[162] Youdim[163] Kupershmidt and Youdim[164]

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease.

TABLE 2

Senolytics approaches for the management of neurodegenerative diseases.

Senolytic drugs for NDDs	Functions	References
Dasatinib and Quercetin	Effectively alleviate pathology in neurodegenerative diseases in both mouse and human studies	Zhang et al.,[173] Chaib et al.,[174]
ABT263 (navitoclax)	Reduces *p16Ink4a*-positive senescent astrocytes and microglia, leading to improved memory function	Bussian et al.,[175] Ng et al.,[176]
Metformin	Impedes cellular senescence in Alzheimer's disease and Parkinson's disease by activating microRNA-processing proteins	Ou et al.,[177] Katila et al.,[178]

Abbreviation: NDDs, neurodegenerative diseases.