Neurochemical Research (2024) 49:834–846
https://doi.org/10.1007/s11064-023-04085-6

REVIEW

The Role of IL-6 in Neurodegenerative Disorders

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Received: 11 October 2023 / Revised: 26 November 2023 / Accepted: 8 December 2023 / Published online: 16 January 2024

Abstract
"Neurodegenerative disorder" is an umbrella term for a group of fatal progressive neurological illnesses characterized by neuronal loss and inflammation. Interleukin-6 (IL-6), a pleiotropic cytokine, significantly affects the activities of nerve cells and plays a pivotal role in neuroinflammation. Furthermore, as high levels of IL-6 have been frequently observed in association with several neurodegenerative disorders, it may potentially be used as a biomarker for the progression and prognosis of these diseases. This review summarizes the production and function of IL-6 as well as its downstream signaling pathways. Moreover, we make a comprehensive review on the roles of IL-6 in neurodegenerative disorders and its potential clinical application.

Keywords Interleukin-6 · Inflammation · Neurodegenerative disorders · Alzheimer's disease · Parkinson's disease

Abbreviations

IL-6	Interleukin-6
AD	Alzheimer's disease
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
HD	Huntington's disease
MS	Multiple sclerosis
CNS	Central nervous system
IL-1β	Interleukin-1 beta
IL-6R	IL-6 receptor
mIL-6R	Membrane-bound IL-6R
sIL-6R	Soluble IL-6R
gp130	Glycoprotein 130
JAK	Janus kinase
STAT	Signal transducer and activator of transcription
NSCs	Neural stem cells
CSF	Cerebrospinal fluid

Introduction

Inclusive of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS), neurodegenerative disorders comprise a heterogeneous group of neurological disorders that induce progressive, irreversible loss of neurons in the central nervous system (CNS) [1]. The brain damage induced by neurodegenerative disorders often leads to a series of dysregulated motor and nonmotor manifestations, culminating in death within years or decades. Furthermore, as aging is a major risk factor for such disorders, older adults constitute the vast majority of patients with neurodegenerative disorders [2]. As the global population ages, the prevalence of neurodegenerative diseases surges. Aside from straining medical resources and public finances, the rising incidence of neurodegenerative disease will severely diminish the quality of life of millions of patients and their caregivers.

Neuroinflammation (i.e., an inflammatory response within the CNS) contributes significantly to the pathogenesis of neurodegenerative disorders [1]. In response to neuronal damage, the sustained activation of innate immune cells in the CNS produces excessive amounts of proinflammation cytokines and induces chronic inflammation, which can compromise synaptic function, energy homeostasis, and protein aggregation, and exacerbate neurodegeneration [3]. Though the close ties between neuroinflammation and neurodegeneration have been established, the specific

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mechanisms underlying the complicated regulatory networks remain elusive and require further investigation.

As a well-characterized proinflammatory component in the CNS, interleukin-6 (IL-6) primarily exerts a negative influence on neurons and plays a pathogenic role in neurodegenerative disorders [4]. This review summarizes the literature on the role IL-6 plays in common neurodegenerative disorders and presents an overview of the drugs that either decrease the expression of IL-6 or block IL-6 signaling to halt or slow disease progression (Table 1).

IL-6 Production and its Mode of Action

IL-6 is encoded by the *IL-6* gene, which is mapped to chromosome 7p21 in human [5]. Mature IL-6 is a single-chain glycoprotein with 184 amino acids that exhibits a typical structure with four long, well-arranged helices and an extra mini-helix [6]. IL-6 is synthesized and secreted by a variety of cell types, such as T cells, B cells, monocytes, fibroblasts, and endothelial cells. Adipocytes and skeletal muscle can also produce IL-6 under healthy conditions [7, 8]. A large-scale meta-analysis involving a population of 12,421 revealed that the average plasma IL-6 concentration in healthy individuals is quite low, ranging from 4.631 to 5.740 pg/ml, and the lowest value was 0 pg/ml [9]. The basal IL-6 level was significantly higher in older adults than in younger people, demonstrating that the expression of IL-6 is age-related. This finding was confirmed in studies of disease-free wild-type mice [9–11]. The age-dependency in IL-6 expression is consistent with the higher susceptibility of older adults to inflammatory diseases.

When confronted with stimuli such as lipopolysaccharides, interleukin-1 beta (IL-1β), angiotensin III, kojic acid etc., the producing cells promptly synthesize redundant IL-6 [12–16]. Moreover, the secretion of IL-6 increases dramatically in progressive stages of inflammatory diseases and cancers. For instance, in pediatric sepsis patients infected with G-bacteria, the level of IL-6 could rise to 1000–1200 pg/ml [17]. Meanwhile, considerably higher IL-6 values have been observed in patients with prostate cancer [18].

The expression of IL-6 can be linked to genetic polymorphisms—especially those in promoter region, such as rs1800795 G/C and rs1800796 G/C. A study reported that the rs1800795 (C) allele produces more IL-6 than the (G) allele [19], while other studies showed the inconsistent results [20, 21]. Concerning rs1800796, available evidence suggests that IL-6 in individuals with rs1800796CC or rs1800796CG are higher than in those with GG genotypes [22]. As the influence of polymorphisms on IL-6 may depend on demographic, ethnic, or racial factors, differences between samples and limitations on their sizes may account for the inconsistency in the literature, large-scale, multi-center, and multi-ethnic research is necessary to resolve the controversies.

IL-6 functions mainly through binding to IL-6 receptor (IL-6R), which appears in the forms of membrane-bound IL-6R (mIL-6R) and soluble IL-6R (sIL-6R). The former is an 80-kDa membrane-bound protein limitedly expressed on the surface of hepatocytes and leukocytes, while the latter is primarily generated by the unbinding of mIL-6R or resulting from the alternative splicing of mRNA [23, 24]. These receptors both show special high affinity for IL-6, however, subsequent signal transduction requires essential assistance of transducer glycoprotein 130 (gp130), which is a 130-kDa transmembrane protein, ubiquitously expressed on the surface of almost every type of cells (except mature granulocytes) and is responsible for transducing intracellular signals through homodimerization [25, 26]. Upon binding IL-6, a transmembrane hexameric complex encompassing 2 IL-6, 2 IL-6R and 2 gp130 assembles and initiate downstream signalings [27]. There are two types of functional hexamers: the IL-6/mIL-6R/gp130 complex is formed only on a few cells that express mIL-6R, while the IL-6/sIL-6R/gp130 complex is formed on cells that lack mIL-6R. IL-6 engages with three distinct signaling pathways to regulate its biological effects: classical signaling, trans-signaling, and cluster signaling. Ultimately inducing anti-inflammatory effects, classical IL-6 signaling occurs when complex IL-6/mIL-6R/gp130 appears on the surface of selected cells. By contrast, trans-signaling results in pro-inflammatory potency. This pathway can be triggered when complex IL-6/sIL-6R/gp130 is present: i.e., on most cells devoid of mIL-6R. Also known as trans-presentation progress, cluster signaling involves the presentation of the pre-formed IL-6–IL-6R complex from dendritic cells to T cells expressing gp130 in a trans manner, leading to subsequent gp130 dimerization in the receiving cells [28]. Regardless of the signaling pathway activated, the dimerization by gp130 constitutes a start switch capable of triggering intracellular signals, including the Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase/Akt, and mitogen-activated protein kinase pathways.

Normal Biological Functions of IL-6 in the Central Nervous System

IL-6 in the CNS is either synthesized and secreted by neurons and glial cells or transported from the outside of the CNS (Fig. 1A) [29–34]. IL-6 levels in the CNS are low under normal physiological conditions but increase sharply under psychological stress, pathological conditions (e.g., AD, PD, and MS), or stimulation with tumor necrosis factor-alpha [35–40].

Table 1 IL-6 inhibitors and their therapeutic effects

Drug	Type	Experiment subjects	Indication	Mechanism	Main results	References
Sulforaphene	IL-6 production inhibitor	LPS-induced BV-2 cells; STZ-treated rats	AD	Inhibits inflammatory cytokines and hyperphosphorylation of tau protein by modulating the PI3K/Akt/GSK-3β signaling pathways	Attenuates neuroinflammation and cognitive deficits	[86]
Verbascoside	IL-6 production inhibitor	LPS-induced BV-2 cells; $A\beta_{1-42}$-stimulated N2a cells; APP/PS1 mice	AD	Suppresses the production of pro-inflammatory mediators by blocking the NF-κB-p65 pathway	Alleviates inflammation	[87]
Sterubin	IL-6 production inhibitor	SCOP-induced rats	AD	Inhibits neuroinflammation and reduced oxidative stress	Improves behavioral activity	[88]
Xanthoxylin hybrids	IL-6 production inhibitor	STZ-treated rats	AD	Inhibits AChE and IL-6	Improves cognitive function	[89]
Tocilizumab	IL-6R inhibitor	STZ-treated rats	AD	Inhibits IL-6R	Attenuates cognitive impairment and histopathological changes	[90]
Echinacoside	IL-6 signaling inhibitor	LPS-induced BV-2 cells; MPTP-induced mice	PD	Inhibits the IL-6/JAK2/STAT3 pathway	Protects against behavioral dysfunction	[120]
Tocilizumab	IL-6R inhibitor	PBMCs of sALS patients	ALS	Inhibits IL-6R	Attenuates inflammation activation	[130]
Tocilizumab	IL-6R inhibitor	sALS patients	ALS	Inhibits IL-6R	Normalizes inflammation and attenuates clinical progression in 3/5 patients	[131]
Tocilizumab	IL-6R inhibitor	ALS patients	ALS	Inhibits IL-6R	Attenuates inflammation	[132]
Tetanus toxin C-terminal fragment	IL-6 production inhibitor	SOD1G93A mice	ALS	Reduces IL-6 levels in tissues drastically affected by the disease	Alleviates inflammation	[133]
Cilostazol	IL-6 signaling inhibitor	3-NP-induced rats	HD	Disrupts the IL-6/JAK2/STAT3 pathway	Improves motor coordination	[144]

IL-6 interleukin-6, *LPS* lipopolysaccharide, *STZ* streptozotocin, *AD* Alzheimer's disease, *PI3K* phosphoinositide 3-kinase, *GSK-3β* glycogen synthase kinase-3β, *Aβ* amyloid-beta, *NF* nuclear factor, *SCOP* scopolamine, *AChE* acetylcholinesterase, *IL-6R* IL-6 receptor, *MPTP* 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, *PD* Parkinson's disease, *JAK* Janus kinases, *STAT* signal transducer and activator of transcription protein, *PBMC* peripheral blood mononuclear cells, *sALS* sporadic amyotrophic lateral sclerosis, *ALS* amyotrophic lateral sclerosis, *CRP* C-reactive protein, *3-NP* 3-nitropropionic acid, *HD* Huntington's disease

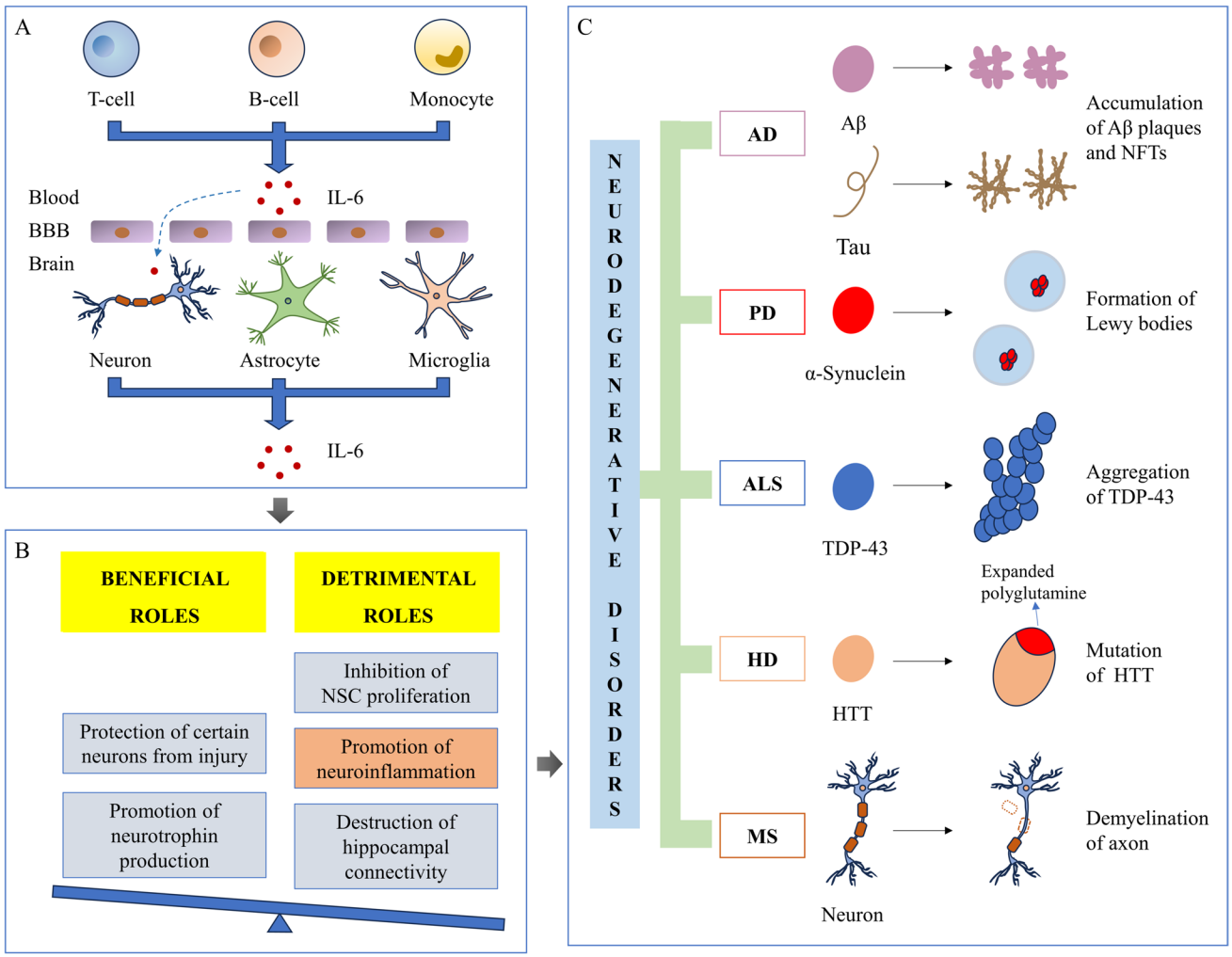

Fig. 1 Pathogenic role of IL-6 in neurodegenerative diseases. In the CNS, IL-6 promotes neuroinflammation and may thus promote the pathogenesis of neurodegenerative disorders. **A** There are two main sources of IL-6 in the CNS: mainly produced by T cells, B cells, and monocytes, circulating IL-6 can cross the blood–brain barrier and reach the CNS; otherwise, IL-6 is secreted by neurons and glial cells. **B** While IL-6 exerts both beneficial and detrimental effects in the CNS, its detrimental effects—especially its promotion of neuroinflammation—commonly dominate during illness. **C** IL-6 participates in the pathogenesis of prevalent neurodegenerative disorders, including AD, PD, ALS, HD, and MS. These diseases have different pathological features: e.g., ALS is characterized by the aggregation of TDP-43, while HD is principally associated with the mutation of HTT. Although the exact mechanism is unclear, the expression of IL-6 generally increases with the severity of these diseases. *BBB* blood–brain barrier, *NSC* neural stem cell, *AD* Alzheimer's disease, *Aβ* amyloid-beta, *NFTs* neurofibrillary tangles, *PD* Parkinson's disease, *ALS* amyotrophic lateral sclerosis, *TDP-43* TAR DNA-binding protein 43, *HD* Huntington's disease, *HTT* huntingtin protein, *MS* multiple sclerosis, *CNS* central nervous system

Effects of IL-6 on Neurogenesis

IL-6 plays a significant role in mammalian neurogenesis, the process whereby neurons and glial cells mature from neural stem cells (NSCs) in specialized niches of the brain [41]. Neurogenesis is a multistage program consisting of proliferation, differentiation, migration, survival, and integration. Proliferation of NSCs is negatively affected by IL-6 [42–44], though the underlying mechanism remains unclear. IL-6 is also a critical regulator of NSC differentiation through inhibiting differentiation of NSCs into neurons while boosting their differentiation into glial cells via the JAK2/STAT3 signaling pathway in dose-dependent manner [43, 45]. In addition, NSCs preconditioned with IL-6 can be reprogrammed and assume new characteristics of tolerance to oxidative stress and angiogenesis induced by STAT3, thus reducing ischemic injury in stroke mice [46].

Effects of IL-6 on Neurons

IL-6 interacts with neurons in a seemingly contradictory manner. On one hand, IL-6 can induce serious injury in cortical pyramidal neurons. Using oxygen consumption rate as an evaluation criterion, cortical neurons exposed to IL-6

had a saliently higher oxygen consumption rate relative to untreated neurons, indirectly implying impaired mitochondrial respiration in the exposed neurons [47]. On the other hand, IL-6 can act as a neuroprotective agent by preserving anterior horn neurons from irreversible virus-induced injury and enhancing the survival of sympathetic neurons [31, 48]. These data demonstrate that effects of IL-6 on neurons may depend on the distribution of brain regions and pathological types.

Effects of IL-6 on Glial Cells

Microglia are the dominant immune cells of the CNS. Exposing microglia to IL-6 potentiates their secretion of inflammatory cytokines, like IL-1β, IL-6 itself, and TNF-α, and promotes their proliferation and repopulation [49–51]. Increased concentrations of IL-1β can induce the production of IL-6 in astrocytes, creating a positive feedback loop between astrocytes and microglia that may result in a hyperinflammatory state—especially in patients with neuroinflammatory diseases.

Besides activating the pro-inflammatory phenotype, IL-6 plays a neuroprotective role in microglia. In acute IL-6 exposure, microglia-like cells will upregulate chemokine secretion and thus recruit additional immune cells to remove necrotic cellular debris at lesion sites [51]. Chronic IL-6 exposure induces microglial proliferation and a desensitized phenotype [52, 53]. Hence, IL-6 not only promotes neuroinflammation and causes neurological impairment, but also repairs brain injury by stimulating the proliferation and regeneration of microglia.

In astrocytes, IL-6 also plays dual functions. It alleviates mitochondrial damage and suppressing astrocyte apoptosis, while it can also recruit T cells to the CNS by enhancing astrocytic CCL20 expression with the aid of sIL-6R and IL-17 [54–57]. More importantly, the conjunction of IL-6 and sIL-6R can promote the expression of neurotrophins in astrocytes in a dose- and region-dependent manner [58]. The dual effect of IL-6 in microglia and astrocytes underscores its clinical potential in the treatment of neurodegenerative disorders.

Effects of IL-6 on Synapse Formation

As key process in the development of the brain, synapse formation is also regulated by IL-6 [59–61]. To determine the correlation between early prenatal inflammation and abnormal neurodevelopment, female mice were injected with IL-6 during pregnancy. The transient elevation of prenatal IL-6 enhanced glutamatergic synaptogenesis and undermined hippocampal connectivity in the offspring [62]. An excessive number of excitatory contacts in the offspring will induce an E/I imbalance: a hallmark of neurodevelopmental defects that cause the development of neurodegenerative disorders in the long term.

Significantly, regardless of the capacity of IL-6 to positively or negatively regulate neural cells, its proinflammatory activities play a dominant role under pathological conditions by bolstering the inflammatory environment and inducing neuroinflammation (Fig. 1B).

The Role of IL-6 in Neurodegenerative Disorders

With the growth of the geriatric population and the attendant rise in the prevalence of neurodegenerative disorders, these diseases are attracting increasing attention from the global research community. The following section reviews the pathological features of several common neurodegenerative disorders (Fig. 1C) and how IL-6 contributes to these diseases.

IL-6 and Alzheimer's Disease

AD is an age-related neurodegenerative disease characterized by progressive cognitive decline and memory impairment. Furthermore, it is listed as one of the leading causes of death in the elderly population, particularly of those aged ≥ 65 years [63–65]. Based on a newly developed prediction model, current number of patients with AD has reached 69 million—a greater figure than the previously estimated 50 million [66], which will continue to increase with the aging population. In consequence, the global economic burden of treating patients with AD will become increasingly heavier and exert an extraordinary influence on society and individuals [64].

Amyloid cascade, tau protein, neuroinflammation, metal ions, and oxidative stress have all been suggested to participate in the pathogenesis of AD and a wealth of evidence has suggested that IL-6 is closely related to these processes. For example, AD is characterized by the appearance and proliferation of beta-amyloid and phosphorylated tau, and the formation of these abnormal proteins can trigger IL-6 production [65, 67]. Elevated IL-6 has proved to promote not only the accumulation of amyloid beta plaques by activating BACE1 and NF-κB [68], but also the generation of neurofibrillary tangles by regulating the CDK5/p35 pathway [69], thus contributing to a vicious circle that leads to exacerbating pathology. Additionally, IL-6 participates in the blood–brain barrier dysfunction, an early pathological hallmark characterized by barrier leakage [70]. By activating the NADPH oxidase pathway, IL-6 downregulate the expression of tight junction proteins in brain endothelial cells, leading to an increase of paracellular permeability. Furthermore, with stimulation of IL-6, $CD4^+$ T cells can

be induced to differentiate into Th17 cells, which contribute to beta-amyloid accumulation and neuronal damage through direct cytotoxic effects of IL-17A [71]. Although heterogeneity in study populations has inevitably yielded controversial findings, most of current literature supports the notion that the levels of IL-6 in the serum, CSF, and stool samples are significantly higher in patients with AD than in controls [67, 72–77]. Elevated IL-6 correlates inversely with hypothalamic/hippocampal volumes and Mini-Mental State Examination scores, and significantly increases the risk of cognitive decline in AD patients [67, 76, 78]. Based on the marked increase in IL-6 of the AD patients, some researchers have suggested that IL-6 may hold the potential to be a useful marker in AD [79–81]. Thereinto, a case–control study has evaluated the diagnostic significance of IL-6 in serum ([AUC] = 0.930), which demonstrated that IL-6 was a promising biomarker to distinguish AD patients from the normal controls [80]. However, further studies are required to find more relevant and stable biomarkers, and to confirm their exact clinical utility in a larger cohort of patients in the future.

Whether IL-6 gene polymorphism contributes to the risk of AD remains unclear. In a study of Chinese Han subjects, participants homozygous for the G allele of rs1800796 were found to have a lower risk of developing late-onset AD [82]. The findings of a Brazilian case–control study contested this conclusion [83]. The ethnic differences between the study populations and their limited sample sizes may account for the contradictory results. While the literature features a similar discrepancy concerning rs1800795, most reports agree that the C allele in CC homozygotes has a negative association with the risk of AD [19, 84, 85]. Hence, whether a genetic polymorphism of IL-6 regulates the risk of AD remains uncertain. Larger, more standardized investigations are needed to settle this question.

Accompanying the discovery regarding the deleterious role of IL-6 in AD, multiple IL-6 production inhibitors have been developed in recent years aim at lowering IL-6 levels to alleviate neuroinflammation in AD [67]. Among them, sulforaphene, verbascoside, sterubin, and xanthoxylin hybrids have shown promising results for the treatment of AD [86–89]. Meanwhile, tocilizumab, a humanized antibody to IL-6 receptor, has thus far been shown to protect against cognitive deficits in AD models [90]. In addition, the neurodegeneration and cognitive impairment of AD mouse models has been almost completely abolished, when IL-6 trans-signaling was blocked specifically (by crossing them with GFAP-sgp130Fc mice) [91]. The results indicate that blocking IL-6 production or signal transduction does indeed alleviate the burden of AD, suggesting that this may be a new potential therapeutic target at early stages of the disease.

While these agents or methods have shown achieved exciting results in cell cultures or animal models, much time and effort remain before they can undergo testing in clinical trials or be used in clinical application.

IL-6 and Parkinson's Disease

PD is the second most common neurodegenerative disease. While it is currently estimated to affect 7 million people worldwide, its prevalence is expected to double in the next 30 years [92], as old age is the most important independent risk factor of this disease [93].

Aside from presenting with motor manifestations such as bradykinesia and resting tremor or rigidity, patients with PD also exhibit depression, anxiety, and cognitive decline. These symptoms may result from a selective loss of dopaminergic neurons and the formation of α-synuclein-containing Lewy bodies [94–99]. Though specific mechanism underlying the development of such symptoms remains unclear, there is a general consensus that neuroinflammation is involved in the pathogenesis of neurodegeneration consequent of PD [97, 100–102].

Among the inflammatory molecules, IL-6, which reflects the neuroinflammatory pathogenesis of the disease, has attracted considerable research interest [103–106]. On one hand, pathological α-synuclein induces the secretion of IL-6 by microglia; on the other hand, overexpressed IL-6 can trigger toxic neuronal iron accumulation by activating the cellular iron sequestration response, leading to dopaminergic cell death and exacerbating neurodegeneration [107–109]. Besides, Th17 cells stimulated by IL-6 can induce dopaminergic neuronal apoptosis via a direct contact or secretion of IL-17A [110, 111].

Similar to AD, the serum and CSF concentrations of IL-6 are markedly higher in patients with PD than healthy controls. This finding reinforces the clinical evidence that the onset of PD is accompanied by an enhanced inflammatory response [38, 112]. Furthermore, a positive correlation was identified between IL-6 level and disease severity whereas those with advanced motor or nonmotor symptoms and fatigue suffer even higher level of IL-6 [113–116]. Finally, elevated levels of IL-6 may be an independent predictor of increased mortality risk in PD patients [117], and statistical evidence from a Mendelian randomization study concluded that increased concentrations of IL-6 were associated with earlier onset of PD [118]. Given these evidence, abnormally high levels of IL-6 may be used as a potential biomarker for early diagnosis, progressive detection, and prognostic evaluation of PD.

IL-6 not only affects the initiation and progression of neurodegenerative processes in PD, but may also contribute to the treatment of the disorder. The treatment of PD mainly includes both pharmacologic and nonpharmacologic therapies. Levodopa remains the most commonly prescribed medication [95, 119]. With an improved understanding of

the pluripotent roles of IL-6 in the pathogenesis of PD, IL-6 inhibitors may become a promising treatment alternative. For instance, the neurotrophic and anti-inflammatory drug, echinacoside, has been demonstrated both in vivo and in vitro to protect dopaminergic neurons by inhibiting the IL-6/JAK2/STAT3 pathway in PD models [120]. Future investigations should thoroughly investigate the role of IL-6 in the pathogenesis of PD to gain greater insight into its clinical potential in preventing and treating PD, as well as improving the affected patients' quality of life.

IL-6 and Amyotrophic Lateral Sclerosis

ALS is the third-most common adult-onset neurodegenerative disease. With a mean onset age of 60 years, ALS is mainly characterized by the cytoplasmic aggregation of TAR DNA-binding protein 43 and the progressive loss of motor neurons in the brain and spinal cord that eventually causes death within 2–5 years of onset [121, 122].

Accumulating evidence implicates involvement of IL-6 associated neuroinflammation in ALS. Relatively high concentrations of IL-6 in serum, CSF, and astrocytes were observed in patients with ALS, indicating an increased inflammatory response [123–126]. Furthermore, an association between higher levels of IL-6 and shorter lifespans was observed in the transgenic SOD1G93A mouse model of ALS [127, 128]. One possible reason for this phenomenon is that IL-6 upregulates the activity of pro-inflammatory endothelial cells through the trans-signaling pathway, thus causing barrier damage and accelerating motor neuron death [129].

A deeper understanding of the IL-6-mediated inflammatory response and its role in ALS may inform the use of IL-6 as a diagnostic and prognostic biomarker, as well as provide clues for an endothelial-IL-6-targeting therapy in the future. Though any such therapy has yet to emerge, the development of other intervention strategies that target IL-6 is already underway. The first IL-6 receptor antagonist tocilizumab has been safely used to normalize inflammation in ALS patients [130–132]. Furthermore, demonstrating its potential as a neuroprotective agent, the tetanus toxin C-terminal fragment helped to reduce the levels of IL-6 levels in SOD1G93A mice [133]. However, studies of anti-IL-6 drugs and their potential in treating ALS are limited in number and scope. Further research is needed to develop novel, more effective therapies.

IL-6 and Huntington's Disease

HD is an autosomal dominant neurodegenerative disorder caused by an aberrant CAG repeat expansion in the HTT gene that compromises cognition, motor ability, and behavior [134, 135]. Though symptoms can manifest at any time during a patient's life, they most commonly begin to present in middle age and remain until death.

Similar to other neurodegenerative diseases, patients with HD and animal models of the disorder exhibit increased plasma levels of IL-6 [136–139]. A combination of plasma IL-6, IL-10, and IL-5 has been shown to discriminate well between premanifest HD and controls (AUC = 0.81) [140]. Mutant huntingtin appears to cause the production of abnormal monocytes, which release excess IL-6 by upregulating the NF-κB signaling pathway and contribute to neurotoxicity [140, 141].Furthermore, IL-6 is detected in elevated concentrations in the saliva and CSF of patients with HD [137, 142]. Higher salivary levels of IL-6 were found to be correlated with higher Total Motor Scores [137], an indicator of disease severity. Hence, salivary IL-6 features potential as a non-invasive biomarker for HD symptom severity. Moreover, in the BACHD murine model of HD, changes in the concentration of IL-6 varied between peripheral organs; higher levels were found in the kidney and heart, and lower concentrations in the spleen [143].

A growing number of supportive and symptomatic management strategies may improve the treatment of HD. Despite the precise molecular mechanisms underlying the elevated expression of IL-6 in patients with HD remaining unknown, the most noteworthy of emerging treatment modalities are those that aim to reduce IL-6 levels. For example, cilostazol's anti-inflammatory and neuroprotective properties may help to alleviate HD symptoms by acting on the IL-6/JAK2/STAT3 signaling pathways [144]. However, recent evidence also suggests that IL-6 deficiency exacerbates dysregulated behavioral phenotypes in HD model mice by affecting genes associated with synaptic function [145]. The inconsistency between these two findings may be explained by the neuroprotective effect of IL-6: i.e., lowering concentrations IL-6 to excess may be harmful, but maintaining IL-6 at a moderate level may improve outcomes for patients with HD. Future research should explore this supposition and determine the optimal level of IL-6 in patients with HD.

IL-6 and Multiple Sclerosis

As chronic and incurable inflammatory demyelinating disease of the CNS, MS is the most common non-traumatic disabling ailment among young adults between the ages of 20 and 40 years [146]. Despite the relatively early onset of MS, aging is the most relevant factor for its clinical consequences and outcomes, as older patients are more likely to suffer permanent disability after developing MS [147, 148]. According to the data from the Multiple Sclerosis International Federation's third edition of the Atlas of MS, the prevalence of MS has risen from 2.2 million to 2.8 million since 2013 [149].

Patients with MS exhibit elevated serum and CSF concentrations of IL-6. The levels of IL-6 are especially high in patients with abdominal obesity because abdominal fat accumulation contributes directly to the overproduction of proinflammatory cytokines [150, 151]. Similarly, increased level of IL-6 receptors on $CD4^+$ T cells were detected in MS patients [152]. Though the precise role of IL-6 signaling in MS pathogenesis has not been fully understood, it is possible that IL-6 promotes the differentiation of $CD4^+$ T cells towards Th17 cells by binding with IL-6R, ultimately causing the demyelination of axons [153]. Alternatively, IL-6 may compromise synaptic plasticity directly, an innate method for the CNS to compensate for MS-induced damage, which in turn exacerbate disease progression [154]. Finally, the rs1818879 polymorphism of IL-6 may influence the subclinical neuroinflammatory activities in MS [155]. These hypotheses could explain the positive correlation between IL-6 values and disease severity [156].

Conclusions and perspectives

This review proposes that IL-6, a core inflammatory cytokine, plays a major role in different neurodegenerative disorders. Currently, it is generally accepted that the expression of IL-6 in peripheral blood, CSF, or other body fluids is abnormally high in patients with neurodegenerative diseases. Furthermore, the degree of elevation tends to correlate positively with the severity of the disease.

Although the specific mechanisms in each of these diseases vary, increased IL-6 induces neuroinflammation, which promotes abnormal protein aggregation, damages functioning neurons, impairs synaptic function, and ultimately exacerbates neurodegeneration. Notably, Th17 cells, which differentiate from $CD4^+$ T cells in response to IL-6 stimulation, have been reported to be associated with the pathogenesis of several neurodegenerative diseases, including AD, PD and MS. Th17 cells and their cytokines can induce the aggregation of misfolded proteins and cause neuronal death, through direct cytotoxic effects or the recruitment of immune cells. Although the exact mechanisms of their function remain to be elucidated, existing data suggest that Th17 cells and Th17-related signaling pathways may be potentially effective therapeutic targets.

Currently, the clinical diagnosis of degenerative diseases is made mostly based on clinical symptoms, which may only appear in advanced stages of the disease, thus precluding therapeutic intervention in early stages. There is a need for seeking markers to reveal early pathogenic events, as well as monitor disease progression and treatment response. Indeed, one of the aims of this review is to analyze the potential of IL-6 as a biomarker for diagnosis, progression and prognosis in neurodegenerative diseases. Based on existing research, the diagnostic ability of IL-6 in AD and HD groups has been preliminarily demonstrated [80, 140]. Regrettably, due to the complexity of the nervous system and the ambiguous pathogenesis of various degenerative diseases, convincing evidence of IL-6 being an effective biomarker in other neurodegenerative diseases is still insufficient. To further confirm the role of IL-6 in neurodegenerative disorders, more in-depth studies are needed.

At present, there are no treatments that can cure neurodegenerative disorders or reverse the physical and mental damage they induce. While some drugs approved by the Food and Drug Administration, such as levodopa, donepezil, riluzole, are used in clinical practice, they only relieve symptoms without improving the outcomes of the diseases [95, 157, 158]. Due to the limited application and efficacy of these medicines, finding new therapeutic targets and developing effective treatment plans remains a priority in the decades to come, and IL-6 shows promise as a candidate for the focus of future investigations. Some novel inhibitors of IL-6 have been shown to be useful in attenuating the development of neurodegenerative disorders in animal models and may proceed to human trials. Development of safe and effective anti-IL-6 therapy will benefit patients suffering from neurodegenerative disorders.

Acknowledgements The authors thank Chenguang Zhang and Wenting Hou for critically reviewing the manuscript.

Author Contributions CS and CZ: designed the study, and drafted the manuscript, CZ: participated in the revision of the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No. 82003809), Beijing Natural Science Foundation (No. 7222157) and Beijing Hospital Nova Project (BJ-2020-087).

Availability of Data and Materials Not applicable.

Declarations

Conflict of Interest The authors declared that no potential conflicts of interest exist.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Written informed consent for publication was obtained from all participants.

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