Neurology

Role of NLRP3 Inflammasomes in Neurodegenerative Diseases

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ABSTRACT

Large-scale neuronal degeneration in the human brain is a hallmark of neurodegenerative diseases. These diseases range in location and cause, but they all have neurodegenerative characteristics in common. Neurodegenerative diseases, which have almost no effective treatment options, tend to progress irreversibly and cause large socioeconomic and healthcare costs. In recent years, due to the increase in the elderly population, neurodegenerative diseases that have a risk factor with aging are becoming increasingly common. Evidence that neurodegenerative diseases, which have an important place in public health, may be caused by neuroinflammation, has led to comprehensive investigation of neurodegenerative diseases in this regard. Inflammasomes are innate immune system-associated multiproteins that regulate caspase-1 activation and induce inflammation. The NLRP3 inflammasome is the most researched inflammasome and also located in microglia, its activation mediates the maturation and secretion of the inflammatory cytokines interleukin-1beta (IL-1β) and IL-18, thus exerting its effects in the central nervous system. Within the scope of this review, experimental and human studies evaluating the role of NLRP3 inflammasome activation and the effects of its inhibition in neurodegenerative diseases frequently encountered in society have been compiled with studies from past to present.

Keywords: Neurodegenerative disease, neuroinflammation, NLRP3

Introduction

The human body possesses both innate and adaptive immunity, which allow it to fend against pathogenic attacks. One of the important events that show that these immune systems are activated is inflammation.[1,2] An intricate cellular and molecular defensive process known as inflammation is triggered by a number of different events, including stress, damage, and infection.[3] The response of the central nervous system (CNS) to damage caused by pathogens such as infection, trauma, ischemia, and the inflammatory response that helps support the repair of nervous tissue by eliminating damaged tissues and pathogens is defined as neuroinflammation.[1,4] During neuroinflammation, astrocytes and microglia are activated, and pro-inflammatory cytokines are released. Insufficient or excessive inflammation brought on by dysregulation in inflammatory pathways might result in chronic infections or systemic inflammatory disorders.[1] As with many other diseases, these alterations in inflammatory processes contribute to the pathophysiology of neurodegenerative diseases. It is thought that these modifications in inflammatory mechanisms open up new research avenues for potential novel therapeutic approaches.[3]

Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are endogenous signals secreted due to host or environmental hazards like cellular stress and metabolic imbalance. Pattern recognition receptors (PRR) are used to mediate the recognition of these pathogenic agents.[5,6] Activation of PRRs results in 2 ways: increase in pro-inflammatory gene expression or activation of inflammatory caspase 1.[5] Microglia and astrocytes are the primary innate immune cells found in the CNS. Pattern recognition receptors are mostly expressed by microglia and astrocytes in the CNS, where they support innate immunity.[6-8]

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As of now, retinoic acid-inducible gene-I (RIG-I)-like receptors (RLR), nucleotide-binding and oligomerization domain-like receptors (NLR), absent in melanoma 2 (AIM-2)-like receptors (ALR), and transmembrane proteins like Toll-like receptors (TLR) and C-type lectin receptors (CLR) are among the known PRR families.[9] Pattern recognition receptors can be membrane-bound and detect signals in the extracellular environment or the endosome, as in the case of TLRs, or they can be intracellular, as in the case of NLRs and ALRs.[6,10]

Nucleotide-binding and oligomerization domain-like receptors recognize PAMPs and DAMPs and activate downstream molecules, which in turn trigger inflammation by inducing inflammasome formation.[9] There are at least 23 identified members of the human NLR family, of which NOD-like receptor 3 (NLRP3) also recognizes metabolic stress associated with microbial particles, infection, and sterile inflammation.[5,6] The NLRP3 inflammasome, which was first discovered in 2002, is a cytosolic multiprotein complex that triggers pro-inflammatory caspase 1, which in turn causes pyroptosis and the development and production of the inflammatory cytokines IL-18 and interleukin 1 beta (IL-1β).[2,4,6,9,11-13] NLRP3 activation initiates the innate immune response upon PAMP and DAMP recognition.[9,14] The cytosolic NLR, ALR, and pyrin receptors, procaspase 1, and apoptosis-associated speck-like protein (ASC), which has a caspase recruitment domain, make up the core component of an inflammasome.[6,9,13] Composed of a caspase recruitment domain (CARD) and pyrin domain (PYD), the ASC serves as an adaptor between procaspase 1's CARD and pyrin's NLR. The ASC consists of a PYD and a CARD and functions as an adapter connecting NLR or the PYD of pyrin and the CARD of procaspase 1.[6,9] The leucine-rich repeat (LRR) domain at the C-terminus, the conserved central nucleotide-binding and oligomerization domain (NACHT), and the N-terminal PYD domain make up the NLRP3 protein.[9,11]

For the NLRP3 inflammasome to function, the first signal (the priming phase) is triggered by cytokines like IL-1β and tumor necrosis factor alpha (TNF-α) or PAMPs. Among these, TLR binding to receptors activates transcription nuclear factor kappa B (NF-κB). NLRP3 activators produce PAMPs or DAMPs deliver the second signal, also referred to as the activation stage.[2,9,15] Next, through homotypic interactions between NACHT domains, the NLRP3 protein oligomerizes. Using PYD–PYD interactions, oligomerized NLRP3 functions as a scaffold to connect with ASC and initiate the production of helical ASC filaments. Procaspase 1 engages in CARD–CARD interactions with assembled ASC.[16] When the induced inflammasome is stimulated, PRR proteins oligomerize and pre-existing procaspase-1 zymogens are drawn to the complex, which causes autoactivation and the production of active caspase 1. Following this autoactivation, pro-IL-1β and pro-IL-18 propeptides that are physiologically inert are transformed into mature cytokines that are released by the cell via caspase 1. Moreover, pyroptosis, a pro-inflammatory cell death that results in an early rupture of the plasma membrane, can be induced by caspase-1. Consequently, it is able to discharge its soluble intracellular portion, which sets off the inflammatory reaction.[17]

All neural cell types express the NLRP3 inflammasome under normal and pathological conditions, and NLRP3 is the most studied inflammasome in microglia in neurodegenerative diseases.[18-24] The functions of inflammasomes in stimulating inflammation in neurodegenerative diseases are still being investigated.

NLRP3 Inflammasome Activation and Its Relationship with Neurodegenerative Diseases

Increased loss of neurons in the CNS is a hallmark of a class of neurological conditions known as neurodegenerative diseases. Memory loss, forgetfulness, agitation, and impairment of motor functions are the main symptoms.[25] Although the distinguishing features of these diseases include neuronal loss, reactive gliosis, and abnormal protein accumulation in disease-specific regions in the CNS, the importance of the innate and adaptive immune systems in the pathophysiology of the diseases has been emphasized in recent years.[25-27] The CNS contains many different cell types, including neurons, endothelial cells, macrophages, and glial cells such as oligodendrocytes, astrocytes, and microglia.[27] Microglia activation has been shown to play a role in various neurodegenerative diseases resulting in inflammatory responses.[28] Of all the cells in the brain, microglia, which resemble resident macrophages and are found throughout the brain and spinal cord, comprise 10%-15%. In a healthy CNS, microglial cells serve as the first line of defense against pathogens.[25] In the beginning, microglia activation protects neurons and aids in the elimination of necrotic neurons. Nevertheless, persistent overactivation by PAMPs/DAMPs, results in long-term neuroinflammatory reactions and may hasten the onset of some neurodegenerative illnesses.[25,28] Cytokines, which lead to the formation of more inflammatory molecules by activating astrocytes and microglia, can create a feedback loop. Furthermore, the released inflammatory chemicals have the ability to stimulate other cells, such as lymphocytes and monocytes, to penetrate the blood–brain barrier and enhance CNS neuroinflammation.[3] These alterations consequently result in neurotoxicity and accelerate the development of neurodegenerative illnesses.[25]

Microglia, the brain's primary innate immune cells, are primarily responsible for inflammasome stimulation, but other CNS cell types have also been shown to express inflammasomes.[6,17] The majority of NLRP3, the first inflammasome found in brain research, is found in microglia. Inflammasomes can be triggered in the CNS in response to autoimmune-mediated damage (like MS) or acute trauma (like stroke and traumatic brain injury), as well as the buildup of misfolded or aggregated proteins in the brain (like AD, ALS, and PD).[6] While NLRP3 is the most often-researched inflammasome in the CNS, several other inflammasomes, such as NLRP1, NLRP2, NLRC4, and AIM2, are also linked to the development of neurodegenerative disorders.[29] In general, it is believed that the creation of the chronic inflammation process, which leads to neuron loss and neurodegeneration, is greatly influenced by the increase in IL-1β and IL-18 cytokines. Thus, it is common to find elevated levels of IL-1β and IL-18 in CNS infections, brain injuries, and neurodegenerative illnesses.[30-36] Also, these cytokines contribute to cognition, learning, and memory processes in addition to being crucial for physiological activities in the CNS.[6] By releasing more inflammatory mediators and DAMPs, pyroptosis contributes to the pathophysiology caused by inflammasomes. It has been demonstrated that the cell death processes of apoptosis and necroptosis encourage neuroinflammation and neuronal degeneration in neurodegenerative diseases.[37]

Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis and NLRP3 Inflammasome Activation

Multiple sclerosis (MS) is a common autoimmune, demyelinating, neurodegenerative disease of the CNS. More than 2 million people worldwide have this disease, placing a serious social and economic burden on patients.[38-41] Jean-Martin Charcot reported it for the first time in 1868.[40] Chronic inflammatory processes in the CNS also contribute to this pathology, which occurs in 2 general phenotypes: MS (relapsing–remitting MS, RRMS), which progresses with attacks and remissions, and progressive MS.[39,42] In MS disease, immune cell infiltration from the periphery to the blood–brain barrier causes local microglia and astrocyte activation, and the activation of these cells in the acute phase

is accompanied by demyelination and plaque formation.[41,43,44] Even though the precise origin of MS is still unknown, the disease's main neuropathological features include inflammatory demyelination, neurodegeneration, and axonal loss. In MS patients, nerve transmission is compromised by inflammation-mediated myelinated axon loss. Cognitive and autonomic functions are also compromised, in addition to sensory and motor functions.[16,40,41]

Further in vivo or experimental research has demonstrated the involvement of NLRP3 inflammasome-related molecules in the pathophysiology of multiple sclerosis. IL-1β and IL-18 have been demonstrated to be important factors in experimental autoimmune encephalomyelitis (EAE), a commonly used mouse model of MS, and they are linked to the NLRP3 inflammasome activation pathway.[45,46] Another factor controlling the activation of NLRP3 is the increase in extracellular ATP level. Large molecules like ATP, which are present in neurons and glia in the CNS as well as macrophages and T cells in the immune system, can pass through the nonselective plasma membrane channel known as pannexin 1. When pannexin 1 is turned on, it allows the release of ATP into the extracellular space. Thus, blocking ATP inflow via pannexin 1 prevents the activation of the NLRP3 inflammasome. Pannexin-1 channel blocking causes the start of EAE to be delayed. Furthermore, in EAE, dendritic cells' hydrolysis of extracellular ATP prevents the activation of the NLRP3 inflammasome. In conclusion, neuroinflammatory damage in the diseased spinal cord is facilitated by a pannexin-1-mediated route (ATP release and/or NLRP3-activated inflammatory activation). Additionally, it suggests that NLRP3 activation suppression through pannexin-1 modulation can be a potential target for MS therapy.[47] In a different study, it was shown that gasdermin d (GSDMD)-mediated inflammasome activation and pyroptosis occurred in both macrophages and microglias and myelin-forming oligodendrocytes in the CNS of MS patients and EAE. This study clearly shows that NLRP3 inflammasome activation and related pathways play a role in the pathogenesis of MS and EAE.[48] In another study, it was shown that the MS was delayed and its severity decreased in NLRP3 (–/–) mice. It has been shown that NLRP3 plays a critical role in the induction of EAE through caspase 1-dependent cytokines.[46] In the same study, it was shown that IL-18 was necessary for the development of EAE. It has been interpreted that the decreased IL-18 observed in NLRP3 (–/–) mice with EAE may lead to reduced EAE severity and decreased cytokines.[46] In human studies with MS patients, it was observed that increased IL-18 levels in serum and CSF were associated with MS.[30,49] Even, IL-1β levels in CSF correlate with cortical pathology in the very early stages of MS.[49] In another study, miR-223-3p and NLRP3 activation, which are negative regulators of immune signaling pathways, were investigated. An increase in NLRP3 and miR-223-3p levels was detected following experimentally induced demyelination in the animal model. Then, mice were given the NLRP3 inhibitor MCC950 and endogenous miR-223-3p, and axonal damage was observed to decrease.[18] Additionally, treatment with MCC950 not only alleviated demyelination in the brain, but also reduced oligodendrocyte loss and microglia and astrocyte activation.[50] At the same time, studies are being carried out to develop therapeutic strategies through these pathways. The effectiveness of clemastine in the treatment of MS was evaluated on the NLRP3 pathway, and it was shown that this pathway was inhibited by clemastine treatment in the EAE model.[21] In a study investigating the connection between NF-κB and NLRP3 in EAE, NLRP3 increased after EAE in mice. It was shown that after BAY11-7082 treatment, which is an NF-κB inhibitor, both NF-κB and NLRP3 levels decreased, thus NLRP3 playing a role in the development of EAE.[19] In recent years, many more such compounds have been tried to reduce NLRP3 inflammasome expressions and develop new treatment approaches for MS.[22,51] When these studies are evaluated together, it is shown that further studies are required to determine the correlation between NLRP3 and related cytokines and MS, but the importance of NLRP3 in MS physiopathology is also emphasized and it is shown that it may be an important therapeutic target in treatment.

Alzheimer's Disease and NLRP3 Inflammasome Activation

Alzheimer's disease is characterized by widespread neuronal cell death, progressive memory impairment and cognitive impairments, and a common cause of dementia.[52-56] Approximately 70% of cases of neurodegenerative illnesses are caused by AD.[56] There is currently no recognized cause for the illness, and there is no known treatment.[57] Its effects are irreversible. The pathophysiology of AD is commonly acknowledged to involve the buildup of aggregated Aβ to form amyloid plaques. However, the cellular events that result in the loss of neuronal function caused by plaques are not well understood, thus, it is crucial to investigate their impact on their cellular environment.[53,54,56-59] Although its pathophysiological mechanism is not fully understood, it is increasingly accepted that neuroinflammation is one of the main mechanisms in AD.[60,61] At the same time, several in vitro studies with microglial cells have shown that these cells secrete high amounts of cytokines upon stimulation with Aβ.[62-64] In fact, in clinical trials conducted with nonsteroidal antiinflammatory drugs before the onset of AD, it has been suggested that inhibition of the immune response reduces the occurrence of the disease.[65] Although microglia show repair activity by removing Aβ plaques by phagocytosis, Aβ accumulation may also trigger the activation and production of inflammatory mediators in microglial cells. In addition, the inflammatory state that begins in microglia cells may also affect other CNS cells, leading to loss of synaptic function or neuronal damage.[6] This approach suggests that pharmaceutical intervention through immunological pathways may have considerable therapeutic promise by delaying the onset of disease through systemic suppression of inflammation or vaccination against Aβ plaques.[53]

Microglia and astrocytes can promote neuron death, pyroptosis, and the neuroinflammatory response by stimulating Aβ plaques and activating the intracellular NLRP3 inflammasome.[66] Many recent studies have linked the development of AD to the inflammasome and inflammasome pathway-related cytokines.[53,67-70] In a study using different experimental transgenic Alzheimer's animal models (wild-type CD1 and APPSwe/PS1 mice), increased expression of IL-1β in microglia surrounding Aβ plaques was reported after Aβ-42 was injected into the hippocampus of the animals.[58] In another study, peripheral blood mononuclear cells (PBMCs) isolated from blood taken from mild, moderate, and severe AD were stimulated with lipopolysaccharide (LPS) and/or Aβ, and it was shown that parameters related to the inflammatory pathway increased by PCR, confocal microscopy, and ELISA methods. It has been shown that these may be useful in the diagnosis and prognosis assessment of AD and also an indication that PBMCs may contribute to neuroinflammation in AD by crossing the blood–brain barrier.[71] Direct inflammasome activation has not been evaluated, but it has been shown that IL-1β, one of the related cytokines, causes memory loss (amnesia) by injecting it into the dorsal hippocampus in rats, and blocking or neutralizing it with melanocortin receptors reduces cognitive impairment. Suppressing the release of these cytokines in AD, where cognitive dysfunction is observed, suggests that it will be an important target in the treatment of AD.[32] In an in vitro study conducted with bone marrow-derived macrophages and microglia isolated from mice in which inflammasome pathway-related components were knocked out, it was shown that fibrillar Aβ, when phagocytosed by

microglia, activates the NLRP3 inflammasome pathway.[53] Also, treatment strategies were studied in AD models. A study by Ruan et al demonstrated that a curcumin-based nanoparticle effectively decreased the formation of β-amyloid plaques in APP/PS1 transgenic mice. One possible mechanism for this effect could be the inhibition of NLRP3, which in microglia tends to congregate around Aβ plaques.[72] Cai et al conducted in vivo and in vitro studies to examine the effects of salidroside on AD. According to data obtained in in vivo studies, Aβ accumulated in the hippocampus increases IL-1β and IL-18 expression due to NLRP3 activation. It reduced pyroptosis by downregulating the expression of IL-1β and IL-18 in salidroside-treated groups. In vitro study results revealed also increased expression levels of NLRP3 and related proteins.[73] Many similar studies have shown activation of NLRP3 and inflammatory cytokines due to Aβ formation.[74-77] According to these research, NLRP3 activation is crucial for the pathogenesis and progression of AD by causing NLRP3 in microglia to trigger a chronic neuroinflammatory response. Preventive measures against NLRP3 or inflammatory cytokines resulting from its activation may reduce Aβ deposition and Tau phosphorylation due to reduced inflammatory activity in AD patients, thus ameliorating AD-associated behavioral abnormalities.

Amyotrophic Lateral Sclerosis and NLRP3 Inflammasome Activation

The deadly neurodegenerative illness known as amyotrophic lateral sclerosis (ALS) strikes adults and is defined by a progressive loss of motor neurons in the brainstem, spinal cord, and motor cortex. This results in muscular atrophy, paralysis, and death in a matter of 1-5 years.[54,78-80] Breathlessness, dysphagia, dysarthria, and general motor dysfunction are experienced by the patients. The chance of acquiring ALS may be influenced by environmental exposure of xenobiotics and genetic variables.[79] Current treatments for ALS are inadequate. Therefore, there is a need to understand the mechanisms that lead to ALS pathology in order to identify new therapeutic targets that can be used to treat or prevent disease progression.[78] Superoxide dismutase 1 (SOD1) gene is mutated in 20% of cases of familial ALS. Expression of mutant SOD1 is required in many experimental models of ALS.[81] A mutation in SOD1 disrupts cellular homeostasis in neurons and glial cells by causing hazardous misfolding and aggregation of SOD1. Neuroinflammation mediated by glia occurs with neurodegeneration in ALS, hastening the course of the disease.[80] While the exact cause of ALS is still unknown, new research indicates that activation of macrophages and microglia may be facilitated by the innate immune system.[78]

Neuroinflammation coexists with the loss of motor neurons in ALS patients. Meisner et al investigation revealed misfolded mutant SOD1 as an endogenous danger signal linked to disease, which microglia recognize and use to trigger inflammation through caspase-1-dependent IL-1β maturation. They showed that IL-1β maturation is correlated with the extent of mutant SOD1's amyloid-like misfolding.[80] Aggregates of ALS proteins are strong inducers of the immunological response in microglia.[78] Components of the NLRP3 inflammasome have been shown to express more when humans and experimental animal models are involved.[79,82,83] Nonetheless, conflicting findings can be found in the literature. According to a study, NLRP3 is not expressed by microglia from SOD1^{G93A} mice or human ALS patients.[83] An additional investigation demonstrated that NLRP3 was not necessary for SOD1^{G93A}-mediated caspase-1 activation and IL-1β generation in microglia.[80] TLR4 and NF-κB were found to be elevated in the brains of SOD1^{G93A} rats that had inflammasome activation, according to Gugliandolo et al study. These are the cues that initiate the process of inflammation. It has been demonstrated that elevated levels of caspase 1, NLRP3, IL-18, and IL-1β assess brain inflammation. Finally, they showed that NLRP3 inflammasomes were activated in the brains of SOD1^{G93A} rats. This implies that inflammation is a major factor in ALS.[79] In vivo experiments in the spinal marrow of SOD1^{G93A} mice and postmortem tissues from human sporadic ALS patients have both shown NLRP3 activation. This demonstrates that elevated amounts of mature IL-1β protein correspond with increased levels of NLRP3 inflammatory proteins in the spinal cord astrocytes of pre- and early symptomatic SOD1^{G93A} mice. According to this study, human ALS postmortem tissues have also higher levels of NLRP3, ASC, IL-18, and active caspase 1 than those of control individuals. Primary glial culture studies and double-fluorescence staining of human ALS tissue and spinal cord slices from SOD1 mice demonstrated that astrocytes are primarily responsible for NLRP3 and ASC expression.[83] Bellezza et al'mechanism of inflammasome activation was investigated in mouse microglial cells that overexpressed hSOD1^{G93A}, and it was verified in the mice's spinal cord. For the first time, it has been demonstrated that in SOD1^{G93A} microglial cells, peroxynitrite activates caspase1 and the downstream inflammatory cascade, perhaps contributing to one of the multiple pathogenic processes associated with ALS. This study looked into the relationship between NLRP3 inflammasome activation and protein nitration brought on by an acute inflammatory stimulus (LPS) as a potential cause of chronicity in the setting of ALS. In research using SOD1^{G93A} microglial cells, LPS boosted caspase-1 activation and activated the NLRP3 inflammasome. Upon caspase-1 activation, there was a notable rise in IL-1β release. Furthermore, it has been demonstrated that LPS activates caspase 1 in SOD1^{G93A} microglial cells by causing peroxynitrite to develop. According to this study, oxidative and nitrosative stress-induced peroxynitrite production may be a key factor in the activation of inflammasomes and may be a viable target for ALS therapy.[82] However, in another ALS model conducted with the TDP-43 mouse, enhanced regulation of microglial NLRP3 has been shown.[84] Moreover, there was increased expression of caspase 1 and active IL-18 in the motor cortex and spinal cord of ALS patients. In TDP-43 transgenic mice, ASC and IL-18 expression increased only in microglia, while GSDMD and NLRP3 levels increased in microglia and astrocytes to a lower amount.[85]

When all of these data are taken into consideration, it appears that astrocyte NLRP3 inflammasomes are important for ALS neuroinflammation and that astrocytes and microglia secrete potentially neurotoxic cytokines to go from a neuroprotective to a pro-inflammatory phenotype.

Parkinson's Disease and NLRP3 Inflammasome Activation

Parkinson's disease (PD) affects 2%-3% of those 65 and older. Globally, PD has resulted in the death of 117000 people and has impacted the lives of 6.2 million people. Although the disease's first symptoms include stiffness, rigidity, tremors, bradykinesia at rest, and trouble in walking, behavioral issues, depression, anxiety, and dementia are also commonly seen in the disease's severe stages.[16,54,86-88] According to epidemiological studies, the prevalence of Parkinson's disease in adults over 60 in Europe and the United States is currently 1%. However, as the population ages and life expectancy rises, the number of Parkinson's patients is predicted to rise by more than 50% by 2030. There is currently no theory to explain the cause of dopaminergic neuron loss and no apparent mechanism linking to the pathophysiology of PD. Still, a growing body of research indicates that multiple pathogenic factors contribute to PD.[86] Among these, one of the key pathogenic causes is increased alpha-synuclein (α-Syn) aggregation.[59,86] This disease results in the formation of Lewy bodies, which are fibrillary misfolded α-Syn aggregates that frequently cause the death

of dopaminergic neurons.[89] Damaged neurons produce aggregated α-Syn into the extracellular area, which then activates microglial cells.[90] It is believed that the development of PD is significantly influenced by inflammatory responses mediated by inflammatory cytokines, such as IL-1β generated from microglial cells.[87]

alpha-Syn aggregates can induce NLRP3 inflammasome activation by activating microglial cells, which exacerbates neuroinflammation in PD.[87,91] Yan et al found in 2015 that NLRP3$^{-/-}$ animals were more resistant to developed PD in a mouse model produced by loss of nigral dopaminergic neurons triggered by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. This provides in vivo proof of the connection between PD and the NLRP3 inflammasome.[92] Similar results were obtained from another study, which demonstrated that NLRP3$^{-/-}$ mice were more resistant to the development of PD in mice that had rotenone-induced parkinsonism.[93] For the first time, it was demonstrated in the 2016 study by Zhou et al. that NLRP3 inflammasome activation plays a crucial role in the pathophysiology of PD and induces microglia-mediated neuroinflammation and dopaminergic neuronal degeneration. Nevertheless, it has also been demonstrated that alpha-Syn activates the NLRP3 inflammasome by lysosome damage and microglial endocytosis. Moreover, data from both in vitro and in vivo experiments have demonstrated that miR-7, a microRNA known to play a role in PD via controlling α-Syn, targets NLRP3 expression and prevents the activation of the NLRP3 inflammasome in PD model mice.[94]

The 2 most common animal models of PD are those produced by 6-hydroxydopamine (6-OHDA) and LPS. Many clinical and physiological characteristics, including a decrease in dopamine activity and its content in the brain, are similar to human PD. These models include degeneration and death of dopamine neurons as well as proliferation and activation of glial cells. It has been demonstrated that dopaminergic neurons can be preserved in PD models produced by 6-OHDA and LPS by blocking the NLRP3 cascade axis activity through the administration of a Ac-YVAD-CMK, caspase-1 inhibitor.[95] In patients with autosomal recessive early-onset PD, mutations were detected in genes associated with the disease. In the studies of Mouton-Liger et al in 2018, it was shown that patients with PARK2 mutations exhibited an aggravated NLRP3 inflammasome response. It has been demonstrated that the sulfonylurea-containing substance MCC950 corrects dopaminergic degeneration by preventing NLRP3's canonical and noncanonical activation as well as IL-1β activation.[96] Apart from these studies conducted in experimental animal models, histological studies in human studies conducted on PD have also found that NLRP3 expression is increased in the mesencephalic neurons of PD patients.[97] According to a different study, serum IL-1β and caspase-1 activity and IL-1β and IL-18 levels in the cerebrospinal fluid increased in Parkinson's patients.[94,98] In another in vivo human study, the NLRP3 inflammasome and ASC and caspase 1 are increased in microglia in areas of dopaminergic cell loss in PD patients.[99]

TLR4, one of the main innate immune receptors activated in PD, and its downstream molecule, TAK1, can stimulate neuroinflammatory responses. In Quan et al's study, it was shown that the protein expression of NLRP3, active caspase 1, GSDMD-N, and mature IL-1β was significantly increased in the PD rat model. It has also been shown for the first time that interferon regulatory factor 7 (IRF7) increases in PD and the regulatory relationship between NLRP3.[23] In in vivo, in vitro, and human studies, Li et al tried to elucidate the molecular mechanism between nuclear receptor-related 1 (NURR1) and miR-30e-5p and NLRP3 in microglia. Microglia express the ligand-activated transcription factor NURR1, which may be a PD susceptibility gene. Nuclear receptor-related-1 expression has anti-inflammatory properties, since it has a negative correlation with the expression levels of inflammatory cytokines. NLRP3 and IL-1β levels were found to be high in blood samples collected from patients with PD. The absence of NURR1 led to increased alpha-syn aggregation and NLRP3 activation in the mouse model.[100] Studies were also conducted for the treatment of PD through this pathway. It was shown that the neurotoxic effect of levodopa, which is used for treatment of PD due to excessive accumulation, was reduced when given together with *Nardostachys jatamansi* (NJ, Chinese medicine). It has been shown that inhibition of NLRP3 activation by IL-1β and IL-18 and caspase-1 inhibition underlies this effect.[20]

Therefore, it may be concluded that the NLRP3 inflammasome is essential to both the pathophysiology and inflammation-induced degeneration of dopaminergic neurons in PD. In order to alleviate neuroinflammation in PD, the role of these pathways in the pathogenesis of the disease should be fully understood and revealed. Upon confirmation, inhibitors of the NLRP3 inflammasome pathway could potentially serve as a significant therapeutic target for the creation of novel treatment models aimed at treating the disease during its initial phases. And these molecules may help lessen the symptoms of Parkinson's disease and demonstrate some neuroprotection.

Conclusion

Inflammasomes are currently thought to be key regulators of innate immunity and play a crucial role in the host's defense against infections and stressful environments. On the other hand, the activation of these multiprotein complexes also adds to the detrimental environment that fosters the emergence of neurodegenerative illnesses. Neurodegenerative diseases are one of the main causes of death worldwide, affected by many factors such as age, genetics, and trauma. Although it negatively affects the quality of human life, treatment options are unfortunately few and generally aimed at improving the quality of life or slowing down the progression of the disease. Although it has been thought for years that these diseases are caused by the accumulation of various proteins in the brain, studies have shown that the innate and adaptive immune system may also be related to this with microglial cells. Within the scope of this review, we examined and compiled the role of microglial NLRP3 inflammasome activation and related inflammation parameters in neurodegenerative diseases with a high incidence in society. Many studies focusing on understanding the role of inflammasomes in neurodegenerative diseases have taken their place in the literature. And looking at the evidence provided by these studies, there is a link between NLRP3 and neurodegenerative diseases, but its exact role and mechanisms need to be proven in further studies. Considering these studies, it becomes clear that inhibiting neuroinflammation, which is thought to cause these neurodegenerative diseases, may be a therapeutic target. Although the role of inflammasomes, especially NLRP3, has been extensively investigated, there is a gap in the literature regarding their effectiveness and how to use them in the treatment of these diseases. These studies are important to provide more evidence and targets for understanding the mechanisms of diseases and researching new treatment methods. Activation of the NLRP3 inflammasome and related parameters in the development of neurodegenerative diseases should be investigated in detail, and after the roles of all these parameters in the development of these diseases are precisely defined, they should be transformed into a therapeutic strategy in studies on prevention and treatment.

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