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The Contribution of Neuroinflammation to Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a heterogeneous neurodegenerative disease involving multiple etiologies and pathogenesis, in which chronic neuroinflammation is one of the hallmarks of PD pathophysiology. Neuroinflammation is probably a fundamental immune response to protect neurons from harm and compensate for neuronal damage, but at the same time, its neurotoxic effects exacerbate neuron damage. Chronic release of pro-inflammatory cytokines by activated astrocytes and microglia leads to the exacerbation of DA neuron degeneration in the SNpc. In this review, we will summarize the relationship between the common pathological mechanisms of neuroinflammation in PD and highlight the potential therapeutic interventions targeting neuroinflammation.

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INTRODUCTION:

Inflammation is a primary biological process against any injury, or infection suffered by cells or tissues. Neuroinflammation is a protection mechanism of the central nervous system (CNS) in response to any insults and injury. [3]In most circumstances, it constitutes a favorable process that perishes once the danger has been suppressed and stability has been restored. Although, prolonged neuroinflammatory processes may aid in the cascade of events ceasing within the successive neuronal damage observed in many neurodegenerative diseases, most prominently in Parkinson's disease (PD) and Alzheimer's disease (AD).[2,6] Parkinson's disease is the second most typical neurodegenerative disorder of the brain.[7]It's marked by a slow and continuous degeneration of dopaminergic neurons in the substantia nigra. However, the neurodegeneration mechanisms in PD are not completely understood, evidence claims that neuroinflammatory mechanisms have the potential to contribute to the degeneration of neurons that happens in PD. [1]This inflammation is regulated by the production of various cytokines, reactive oxygen species, chemokines, and secondary messengers. These mediators are arises from resident CNS glia (astrocytes and microglia), peripherally derived immune cells, and endothelial cells.[26]In neuroinflammatory conditions, activated glial cells release neurotoxic and pro-inflammatory factors that trigger neuronal damage and neurodegeneration. During this Review, we explain the evidence in terms of neuroinflammatory processes in Parkinson's disease, and also the cellular and molecular pathways coupled with neuroinflammation involved in the degenerationof dopaminergic neurons.[2] At last, we concluded feasible therapeutic targets associated with inflammation that might contribute to bogging down the progression of this neurodegenerative disease.[2]

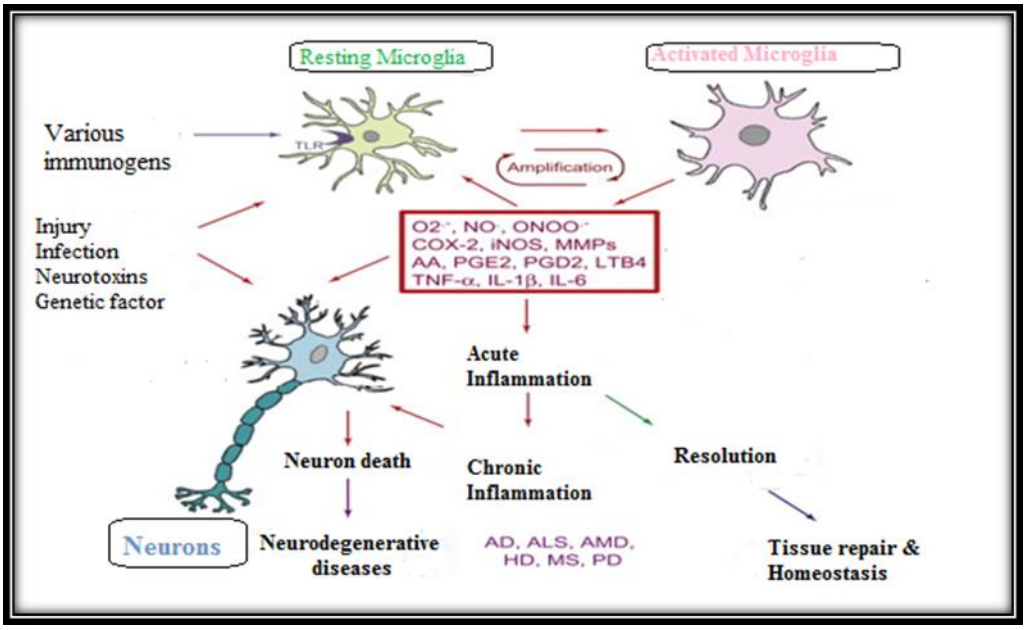

Figure 1. Neuroinflammation and neurodegeneration[1]

1. CELLS INVOLVED IN NEUROINFLAMMATION

Many studies interpret the mechanisms of immune cells in PD pathophysiology. Activation of pro-inflammatory processes through immune cells triggers damage to dopaminergic neurons. Experimental data enlighten that CNS glial cells activation, an increase of pro-inflammatory cytokines, and chemokines lead to neurodegeneration and contribute to disease pathology.[1]A glial reaction comprisingmicroglial cells, astrocytes, and lymphocytic infiltration has been accounted for in certain animal models of Parkinson's disease.[2]

1.1.Microglia in neuroinflammation in PD

- **Microglia**

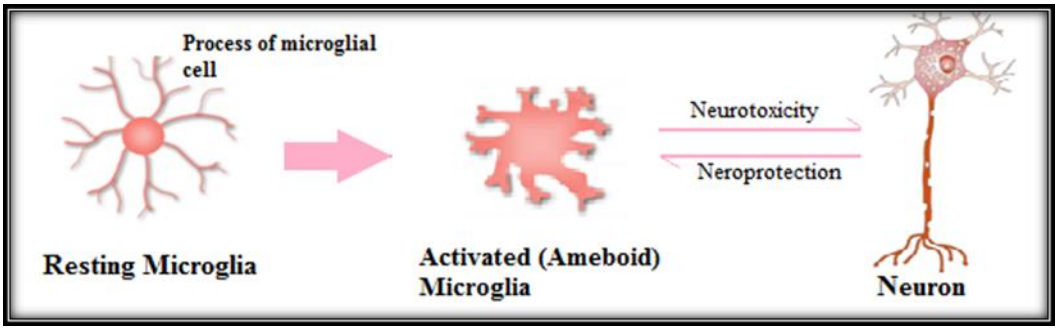

Figure 2 Microglial activation with neuronal injury

Microglia are the central players in neuroinflammation.[8]These innate immune cells carry out the primary immune protection and macrophage-like actions of the CNS, containing the production of chemokines and cytokines.[8]These glial cells act as the first line of defense in the brain and respond to pathological activities in the form of a cascade of inflammatory processes.[10]Microglia are the resident mononuclear phagocytes in the CNS, which comprise 10% of the total cell population. [12]Under normal circumstances, microglia display a ramified structure with many branches, which are known to recognize damaged neurons and abnormally aggregated proteins, which means these cells preserve brain homeostasis by monitoring nearby areas.[12]Microglia get activated in response to various pathogens, infection or injury, abnormal stimulation, tissue damage, and neurotoxins.[15] When activated by these stimuli, microglia go through a morphological change from the ramified to an amoeboid structure and then scavenge viral pathogens or dead cells like macrophages.[12]They are the key participants in neuronal inflammation and inflammatory neurodegenerative diseases. Hence the first sign of neuroinflammation is the activation of microglia.[15]Activated microglia is capable of phagocytes foreign materials or cellular debris. Simultaneously, they produce cytokines to attract more microglia, chemokines, and agents that cause microglia proliferation.[27]

During any brain injury, microglia round up, proliferate, migrate and accumulate around damaged tissue and change into the activated morphology and phenotype.[12]Activated microglia are capable of exhibiting pro-inflammatory as well as anti-inflammatory features according to their phenotypic activation. [1]While typically activated microglia (M1) is characterized by the production of pro-inflammatory cytokines for example interleukin (IL)-1β, tumor necrosis factor (TNF)-α, nitric oxide (NO), reactive oxygen species (ROS), and in addition to the activation of nuclear factor kappa B (NF-κB) signaling pathway, inducible nitric oxide synthase (iNOS); whereas the alternative activated phenotype, the M2 type, exhibit anti-inflammatory pathways, extracellular matrix reconstruction and debris clearance, tissue repair.[28]

- **Microglia in Neurodegeneration;**

Uncontrolled inflammation, which stimulates an increase in cytotoxic factors, if left unsupervised, could produce major damage to nearby healthy tissue.

In the form of chronic neuroinflammation, microglia may remain activated for extended periods, liberating neurotoxic molecules and cytokines that result in tin sustainable neurodegeneration.

Various pro-apoptotic pathways are facilitated by signaling molecules that are released in excess at the time of neuroinflammation, which means that neuroinflammation could straight away influence the apoptosis of neurons and activate microglia. The release of damaging intracellular elements is inhibited by microglial phagocytosis of dead or dying neurons. An organized, active process for the phagocytosis and clearance of excessive proteins is necessary for preserving the homeostatic balance of the protein in the brain and preventing the progression of neurodegeneration. Activated microglia can destroy neurons (neurodegenerative function). However, they may as well kill or eliminate pathogens (neuroprotective function).[15]Hence, preventing pro-inflammatory mediators triggered by microglia activation would be a beneficial therapeutic strategy in order to restrict the growth of neurodegenerative diseases.

- **Microglia in Parkinson's Disease;**

Neuroinflammatory mechanisms play a job in both normal brain development and neuropathological incidents. Neuroinflammation has remained repeatedly interlinked to neurodegeneration, especially in PD, but whether the neuroinflammatory incidents are a cause or a consequence of neuronal degeneration remains unresolved. Two promising pathological mechanisms liable for neuronal death exist in PD are cell-autonomous and non-cell-autonomous mechanisms. In a cell-autonomous mechanism, there's intrinsic damage within the degenerating neurons which results in their death. The second mechanism displays an indirect degeneration of the affected neurons resulting from pathological interactions with neighboring cells, like resident microglial cells or infiltrating immune cells from the periphery like lymphocytes and macrophages.
As dopaminergic neurons represent a good range of chemokine and cytokine receptors, it's been suggested that they're reactive to those inflammatory mediators which are derived from or activate microglia.[10] Mis-folded alpha-synuclein (α-syn) and environmental toxins are well known to stimulate the activation of M1 microglia in different animal models of PD. Activated microglia (M1) appeared to be assembled around α-syn-positive aggregates in particular regions of the PD brain. Persistent exposure to those microglia-derived pro-inflammatory cytokines is harmful to dopaminergic neurons. For instance, chronic expression

of low levels of TNF-α within the SN caused time-dependent neurodegeneration, motor symptoms, and microglia/macrophage activation in rats. Similarly, chronic systemic expression of IL-1 also aggravated neurodegeneration and microglial activation within the SN in 6-hydroxydopamine (6-OHDA) models of PD. [1]

1.2.Astrocytes in neuroinflammation in PD

- **Astrocytes**

Astrocytes are star-shaped cells with many processes and are the largest and most numerous of the neuroglia in the CNS. These are complex, supremely differentiated cells in the brain. They respond to various pathogens and neurodegenerative injuries by a process broadly known as reactive astrogliosis. [21]

The key role of astrocytes is to enable neurons with metabolites, thereby promoting neurotransmitter recycling and eventually the regulation of synaptic plasticity. In reaction to injury, astrocyte proliferates in, and then neuroinflammation induces two kinds of activated astrocytes, termed 'A1' and 'A2', respectively.[12] A1 astrocytes are characterized by the upregulations of proinflammatory factors such as cytokines, glutamate, chemokines, and reactive oxygen species (ROS).On the other hand, A2 astrocytes are referred to as trophic and have beneficial effects on neurons as they upregulate neurotrophic factors that promote neuron survival and growth and synapse repair under ischemic conditions or after acute trauma. Astrocytes support neuroinflammation by interacting completely with microglia and can carry out both pro-and anti-inflammatory effects.[12]

- **Astrocytes in Parkinson's Disease**:

PD patients are usually prone to reactive astrogliosis. In regards to PD patients, astrocytes release cytokines (pro-inflammatory type) along with some other harmful substances like NO which leads to dopaminergic neuronal death. Studies show that a rise in pro-inflammatory type cytokines, TNF-α & IFN-care is helpful in activating the astrocyte of a Parkinsonian. [12] It is found that responses from astrocytes are at a low pace as compared to microglial activation after stimulations. Astrocytes are activated due to many substances such as pro-inflammatory mediators secreted by microglia followed by amplification of immunosignals due to astrocytes. The collective activation of microglia & astrocytes leads to unconstrained

neuroinflammation which further contributes to intensified death of DA neurons in the SNpc during neurodegeneration [20]

The strange behavior of astrocytes failure in PD patients is usually due to PD genes like parkin and DJ-1. DJ-1 over-expressed astrocytes guard neurons from rotenone, whereas DJ-1 knock-down astrocytes make neurons unsafe from rotenone. Parkin in PD-related gene which triggered by unfolded protein stress in astrocytes except for neurons, recommending its particularity for astrocytes, along with the mouse model of PD, Parkin's mutation triggered astrocyte failure and increased neuronal death. [12] Hence, the studies show the significance of astrocytes in participation in handling the neuroinflammation in PD patients. [12]

In total, it is clear that microglia and astrocytes have significant roles in the maintenance of CNS homeostasis, and these neuroprotective roles are not found under brain injury. In the past, the main objectives of the treatment were to reduce the pace or halt CNS diseases with neurons. According to recent studies, it is becoming much more interesting to aim at microglia and astrocytes, provided that curbing the glia enablement has a positive impact on neuronal survival. [18]

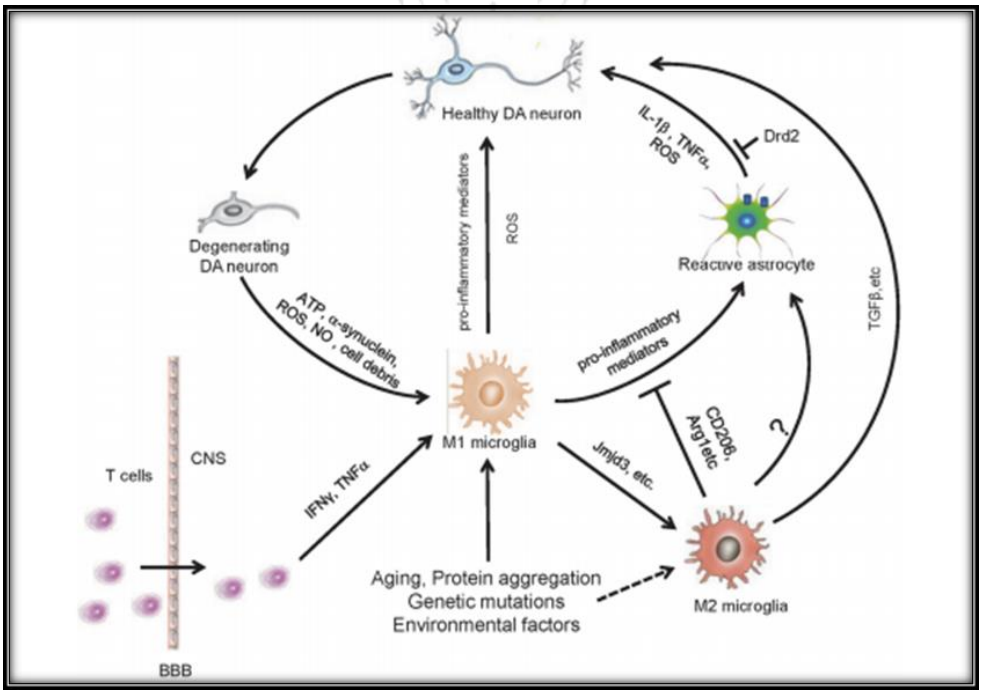

Figure 3 Diagrammatic depictions of inflammatory mechanisms involved in PD pathogenesis. [20]

Microglia become activated M1 phenotype in PD under pathological conditions such as protein aggregation, gene mutations, environmental factors, and cytokines released from infiltrated T cells. The pro-inflammatory mediators from M1 microglia trigger astrocytes leading to elevated production of proinflammatory factors, nitric oxide, and superoxide radical, contributing to the degeneration of DA neurons. The molecules released from degenerative DA neurons can further promote the activation of glia and enhanced inflammatory response. [20]

1.3 Peripheral immune cell

Brain-related immune cells (microglia and astrocyte) are important for brain stability whereas peripheral immune cells take part in CNS immune response. [5] During the process of neuroinflammation, T lymphocytes are triggered by M1 microglia while infiltrating the CNS, thus targeting and damaging dopaminergic neurons. Other studies have shown that stimulated leucocytes cause harmful inflammatory processes thus leading to dopaminergic neuronal cell death. [2] There are some T cell subtypes that possess anti-inflammatory properties in CNS. Controlling T cells (Treg) and Th2 cells have predominantly anti-inflammatory effects, whereby Treg cells stop MPTP- induced dopaminergic neuronal cell death and alter microglia to reduce ROS production. [12] Th2 cells guard motor neurons by discharging neurotrophic factors, such as IL-10 and IL-4, which might support activating M2 microglia. [22] These conclusions show that the peripheral immune cell supports CNS immune cells, particularly microglia.

1.4 Cytokines and Chemokines

The glycoproteins that are produced and discharged by animal cells are called Cytokines. Activated microglia discharge inflammatory mediators, such as chemokines and cytokines, and these inflammatory mediators can simulate microglial activation. [10] M1 microglia produce TNF-a, IL-1b, IL-23, IL-12 and IL-6 whereas M2 microglia produce IL-10, TGF-b, IL-4 and IL-3. [20] Moreover, increased levels of pro-inflammatory cytokines, such as TNF-a, IL-2, IL-6, IL-1b, and IFN-c, inside the brain is one of the main pathological properties of PD. [12] Chemokines react with G-protein coupled receptors on many cells and it was recently shown that they have the capability of inducing microglial migration at the site of injury. Chemokines are produced by microglia, astrocytes, and by immune and endothelial cells. IL-

4 has also been concluded to save against MPTP-induced dopaminergic neuronal degeneration in the In-vitro model. [12]

2 MOLECULAR PATHWAYS INVOLVED IN NEUROINFLAMMATION RELATEDWITHPD

Microglia and other immune cells get activated because of aging, injury, oxidative stress, and infection which cause the production of pro-inflammatory mediators like NO, iNOS, and COX-2. Furthermore, activated microglia produce excessive ROS, leading to NF-κB activation which triggers neuroinflammation to market neuronal damage and cell death. [15] Activated microglial cells play a vital role in immune and inflammatory responses in CNS and neurodegenerative diseases. The pro-apoptotic pathways are intervened by signaling molecules that are released at the time of neuroinflammation. [15] Excess production of pro-inflammatory components in over-activated microglia could be a risk factor to initiate neurodegeneration via many inflammatory pathways.

3.1Nf-κB activation in Neuroinflammation pathway

In glial cella, NF-κB, a transcription factor, triggered and handles the expression of various inflammatory processes during inflammation which is assigned to the pathology of the various neurodegenerative diseases.[15]

- **NF-κband Neuroinflammatory mediators**

NF-κB proteins are a cascade part that initiates outside the cells and ends in the nucleus. [15] Nuclear factor NF-κB is a family of inducible transcription factors that are shown in a wide variety of cells and tissues, containing astrocytes, microglia, and neurons.[23] In every eukaryotic cell, most extracellular signals, including inflammatory cytokines, infection and various stress scenarios can activate NF-κB. [15] NF-κB is a “master switch” for many inflammatory gene expressions. Inflammatory cytokines such as IL-1α and β and TNF, bacterial products such as lipopolysaccharide (LPS), strongly enable inflammatory responses by the simulation of NF-κB. NF-κB consequently plays a vital role in the inflammatory response by controlling genes encoding inflammatory cytokines, chemokines, adhesion molecules, nitric oxide production (iNOS), and NADPH oxidase. Activation of NF-κB is an important event in plenty of chronic inflammatory diseases. [23] NF-κB has been also shown as a major signal transducer responsible for cellular permeability, endocytosis, and intercellular trafficking at the level of the blood-brain barrier. [24] More curiously, the

simulation of NF-κB in neurons supports survival and plasticity. Moreover, NF-κB activation in glial cells holds a vital role in inflammatory processes which is neurodegenerative. [15]

- **Signaling Pathways of NF-κB**

TLRs are safeguarding against pathogens, and their simulations result in the death or disposal of the attacking pathogen. They identify particular ligands to start the inflammatory process, enabling signaling molecules such as NF-κB to support microglial phagocytosis and cytokine release. Microglia states a spread of TLRs that simulate these cells and start a neuroinflammatory reaction. Myeloid differentiating factor 88 (My88), which is an adaptor protein, binds to TLRs via their TIR domains, which simulates various signal transduction pathways and in the end leads to NF-κB activation and inflammation. [15] The NF-κB family comprises dimeric transcription factors which have five members: c-Rel, RelB, RelA (p65), NF-κB1 (p50/p105), and NF-κB2 (p52/p100). There are mainly two pathways of simulation: the classical or canonical pathway and the alternate or noncanonical pathway. [23]

The classical pathway, which is known to be controlling the generation of most pro-inflammatory mediators, is mediated by the simulation of a dimer of Rel proteins p50 and p65, complexed within the cytosol to the inhibitory complex IκBα. The stimulation of the classical NF-κB pathway relies on the phosphorylation, ubiquitination, and consequent proteasome-dependent degradation of IκBα. The phosphorylation of IκBα on serine residues is mediated by IκB kinase (IKK), which is a molecular complex of three proteins comprising a heterodimer of the two catalytic units IKKα and IKKβ, and also with IKKγ (the NF-κB essential modulator, NEMO). Simulation of the IKK in regards to inflammatory mediators like TNFα, LPS, and IL-1 β relies critically on the existence of the IKKγ (NEMO) subunit of the IKK complex and concludes in the phosphorylation of the IκB by the kinase activity of IKK β. An N-terminal zone of NEMO affiliates with a hexapeptide sequence within the C-terminus of both IKKα and IKKβ, known as the NEMO-binding (NBD), and interruption or mutation of this NEMO-NBD reaction site on either IKKβ or IKKγ concludes in a very loss of responsiveness of cells to pro-inflammatory signaling. [23]

However, the noncanonical pathway of NF-κB comprises heterodimers of Rel proteins p100/RelB that also possess transcriptional activity but appear to play more of a regulatory role in cellular stimulation and differentiation rather than in inflammation. In regards to a set of causes that consists of CD40L, B cell-activating factor, NFκB is simulated by an

alternative pathway independent of IKK. Rather, simulation initiates through the NF-κB-inducing kinase (NIK) that phosphorylates and enables IKKαα homodimers which, in turn, phosphorylate p100 in complex with RelB. This results in ubiquitin-dependent processing of p100 to p52 and translocation of p52/RelB to the nucleus. Cytokines-induced simulation of the noncanonical pathway of NF-κB is accompanied by an elevation in the concentration of nuclear IKKα that phosphorylates histone H3. In cells exposed to cytokines, the nuclear IKKα controls gene expression by promoter-associated histone phosphorylation and binding to promoter zones of NF-κB responsive genes.[23]

- **NF-κB and DA Neuroinflammation**

Moreover, the classical and alternative pathways are known to control distinct genes in regard to their various simulators.[23]

Relevant to PD, it has now been concluded that the canonical pathway is highly simulated within the SN of animals experiencing DA neurodegeneration, and after more in the brains of PD patients. On the contrary, the non-canonical NF-κB pathway is discovered to be simulated in regenerating DA-neurons from rats treated with glial-derived neurotrophic factor (GDNF), whereas the canonical p65/p50 pathway is simultaneously reduced, suggesting that this non-canonical NF-κB pathway is critical in neuron degeneration of DA neurons within the SN. Therefore, NFκB activity arises as a key target to manage the chronic inflammation in humans, and strategies for its use in PD. [23] Concluding to the point, all these studies show the potential of NF-κB to provide an excellent therapeutic aim in preventing DA neurodegeneration, and also research is necessary to govern the accurate approach and agent appropriate for the treatment of PD. [25]

3.2. ROS and neuroinflammation pathway

- **Reactive oxygen species**

Reactive oxygen species (ROS) are widely recognized as key mediators of cell survival, proliferation, differentiation, and apoptosis.[30] ROS are multi-potent, diffusible species of chemicals atom or molecules that possess an unpaired electron so they are capable of carrying out signal transduction processes in response to extracellular stimuli. [15]Excessive production of ROS (termed “oxidative stress”) by mitochondria and NADPH oxidase (Nox) is usually thought to be responsible for tissue injury associated with a range of brain injury,

inflammation, and degenerative diseases.[30] Oxidative stress is characterized by an increase in reactive species such as ROS and nitrogen reactive species (RNS).[32] These oxidative stresses (i.e., ROS/RNS)are essential for many physiological functions at low concentrations and for killing invading microorganisms.[30]

Reactive oxygen species (ROS) include molecules such as superoxide (O2−), hydroxyl radical (·OH), and hydrogen peroxide (H2O2). [29] In addition, H2O2 is associated with the generation of nitric oxide (NO), another reactive species. While ROS has some essential roles in normal cell functions, they are more associated with their pathological effects that ultimately lead to protein and cellular damage as well as cell death.[29]

Role of ROS in Neuroinflammation

Inflammation is a protective response of a multicellular organism to injury to localize, eliminate, and remove harmful stimuli as well as to recover (or replace) damaged tissues. There recently has been increasing evidence that reactive oxygen species (ROS) are involved in the initiation, progression, and resolution of the inflammatory response.[31]In a state of oxidative stress, there is an increase of reactive species, which induce altered intracellular signaling, leading to dysregulation of the inflammatory response.[32]In addition to ROS's direct toxic impact on biological macromolecules, they can trigger the inflammatory response by stimulating a number of genes which are regulating the inflammatory-signaling cascades. [15]

ROS acts as a critical signaling molecule to trigger inflammatory responses in central nervous systems (CNS) through the activation of the redox-sensitive transcription factors, including nuclear factor-κB (NF-κB) and activator protein-1 (AP-1).[30]Although ROS are important regulatory molecules in almost all stages of the inflammatory process, ROS overproduction by mitochondria and NADPH oxidase of leukocytes and endothelial cells, which is not compensated by the antioxidant systems, may result in serious cellular and tissue damage and promote chronic inflammation underlying many neurodegenerative diseases. [31]Brain cells, especially neuroglial cells, are susceptible to the injurious effects of oxidative stress. Several studies have shown that brain cells like microglia and astrocytes induce and release diverse inflammatory mediators in response to oxidative stress.[30]

Inflammation induces oxidative stress and DNA damage, which leads to the overproduction of ROS by macrophages and microglia. Oxidative stress-damaged cells produce larger

amounts of inflammatory mediators to promote microglia aging. [15]Since activated microglia is a part of the clearance phase of an inflammatory response and is additionally an important source of neurotrophins in neurodegeneration, microglial survival at moderate levels of ROS is crucial to their physiological function. [29] In microglial cells, ROS, as a major signaling molecule, mediates microglial activation induced by various pro-inflammatory mediators. [30]

- **ROS in Neurogenerative Disease**

Throughout life, the brain is exposed to oxidative stress and free radicals, which can be causes or consequences of a number of diseases. Acute, chronic inflammatory diseases and the aging process are some of the main reasons for excess production of ROS.[15]Neurodegenerative diseases are characterized by the presence of a state of chronic oxidative stress and dysregulation of the inflammatory response. Wide evidence shows that persistent oxidative stress and neuroinflammation are key factors in the development and maintenance of the progressive neurodegeneration process in these diseases. [32]Mitochondria are an important source of ROS leaked from the electron transport chain while they are susceptible to oxidative damage, leading to mitochondrial dysfunction and tissue injury. Mitochondrial dysfunction is commonly observed in many types of neurodegenerative diseases such as PD.[15]

At physiological concentrations in the organism, ROS and RNSare regulators of several physiological functions. In a chronic state of oxidative stress, reactive species can become injurious, because they oxidize proteins and lipids, and they can damage DNA. [32]

While ROS has some essential roles in normal cell functions, they are more associated with their pathological effects that ultimately lead to protein and cellular damage as well as cell death. [29]The main characteristics of the state of oxidative stress are an increase in the levels of reactive species and a decrease in, or incapability, of the antioxidant systems to counter free radicals. [32]Oxidative stress may be responsible for brain inflammatory disorders, which cause deleterious effects during CNS pathogenesis.[30]Different levels of oxidative stress induce disparate consequences for cellular function including proliferation, differentiation, and cell death. At high levels of ROS production, proteins become inactivated or damaged resulting in cellular degeneration and death. [29]

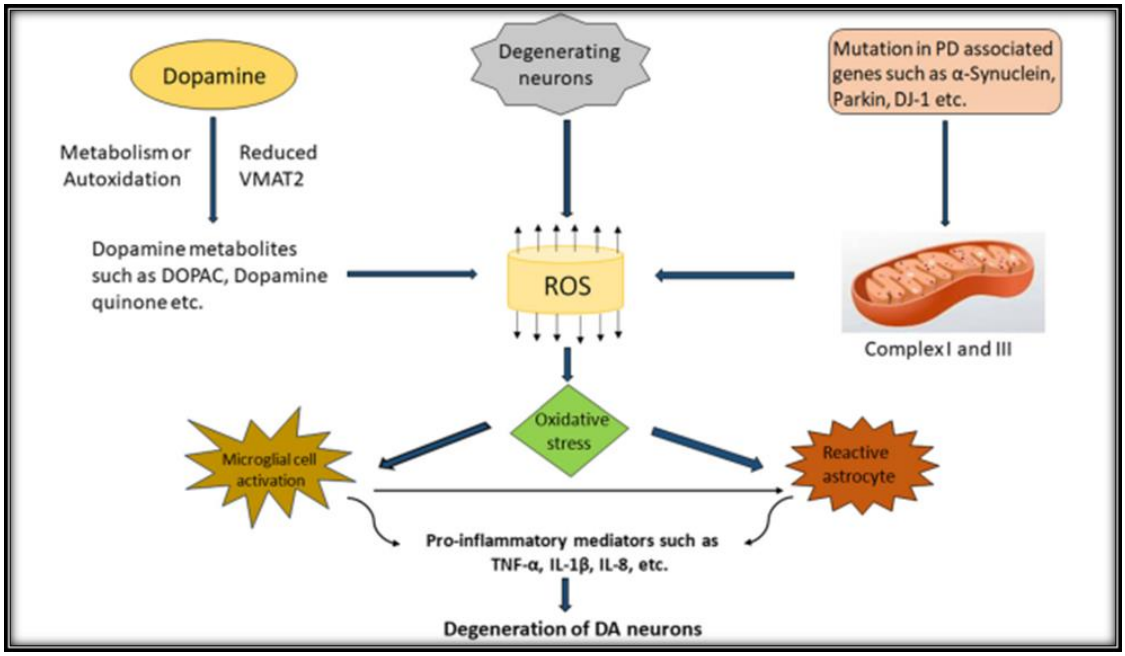

Figure 4. Oxidative stress and neuroinflammation in PD [25]

Degenerating neurons along with auto-oxidation of dopamine-generated dopamine metabolites like DOPAC, HVA, and dopamine quinines discover reactive oxygen species (ROS). Mutation in PD-associated genes like α-synuclein, Parkin, PINK1, and DJ-1 inhibits the complex I and complex III of the mitochondrial electron transport chain and triggers the development of ROS which further creates the oxidative stress inside the cell; neuroinflammation is the downstream event of oxidative stress. This oxidative stress causes the over-activation of microglia and astrocytes; these cells are the mediator of neuroinflammation and eventually cause the degeneration of the DA. [25]

3.3. Nitric oxide and neuroinflammation pathway

- **Nitric Oxide in Neuroinflammation**

NO is a free radical playing an important messenger role in a wide range of physiologic processes including vasodilatation, immune response, and neurotransmission. [33] In mammals, NO is mainly synthesized by nitric oxide synthases (NOS) through the conversion of L-arginine to NO and L-citrulline. Traditionally, three isoforms of NOS have been identified in the central nervous system (CNS): NOS1 or neuronal NOS (nNOS), NOS2, or inducible NOS (iNOS), and NOS3 or endothelial NOS. [34]nNOS is the predominant isoform in neurons, however, in the central nervous system, also eNOS and iNOS are expressed. In

particular, eNOS is present in cerebral vascular endothelial cells and in motor neurons; iNOS is expressed in astrocytes and microglia when these cells respond to inflammatory stimuli.[33]

Moreover, excessive NO synthesis under neuroinflammation ends up in the formation of reactive nitrogen species and neuronal death. There's a recognizable relation between microglial activation, NO, and neuroinflammation in the human brain. The part of NO in neuroinflammation has been defined in animal models where this neurotransmitter can balance the inflammatory process engaged on key regulatory pathways, like those associated with excitotoxicity processes produced by glutamate accumulation and microglial activation. Neuroinflammation-induced death is usually derived from the long-term impact caused by the rise of reactive oxygen and nitrogen species (RONS), which play a significant role in eliciting apoptotic death through irreversible oxidative or nitrosative injury to neuronal elements. Reactive glia express inducible NOS and produce NO that causes calcium mobilization from the endoplasmic reticulum, stimulating the release of vesicular glutamate from astroglial cells leading to neuronal death.[33]

- **Nitric Oxide and Neurodegenerative Diseases**

The physiological roles of NO depend on its local concentrations, similarly to its availability, and so on the character of downstream target molecules. [15] NO plays multiple roles within the nervous system and glial regulated pathways associated with neuroinflammation and neurodegenerative diseases.[34] Under pathological conditions and after exposure to neurotoxic agents, increased amounts of superoxide and NO is produced, resulting in net oxidative stress within the brain. Its double-edged sword action has been linked to neurodegenerative disorders. The generation of ROS leading to the induction of iNOS enhances gas production of glial and endothelial cells. An excessive amount of NO leads to inflammatory diseases like neurodegenerative diseases. [15] Excessive NO production, because evoked by inflammatory signals, has been identified collectively as the foremost important causative reason for the pathogenesis of several neurodegenerative diseases. [34] Increased NO levels can stimulate nitration of the various proteins which is reported within the neuronal tissues of patients with neurodegenerative diseases including AD, PD, HD, and amyotrophic lateral sclerosis (ALS).[15]

The augmented nitration of proteins will be initiated by a rise in the production of NO during neuroinflammation and therefore the generation of free radicals by dysfunctional

mitochondria, which are commonly observed in various neurodegenerative disorders. [34] The implication of high levels of neuronal NOS (nNOS) and inducible NOS (iNOS) expression was observed within the nigrostriatal region and basal ganglia within the post-mortem PD brains. NO has been also proposed to own a task within the inflammatory processes occurring in PD. [33] only if microglia is especially abundant within the neural structure which dopaminergic neurons are highly vulnerable to oxidative/ nitrosative stress, the resulting ROS/RNS overproduction severely damages their cellular structures and macromolecules mainly as a consequence of peroxynitrite formation. [33] Immunoreactivity for nNOS was also found consistently increased within the locus niger after treatment with PD-inducing drugs.

3.4. Pro-inflammatory cytokines and neuroinflammation pathway

Cytokines and chemokines are proteins that coordinate the response throughout the body. The dysregulation of cytokines and chemokines may be an essential feature within the progress of neuroinflammation, demyelination, and neurodegeneration both within the central and peripheral nervous systems and in circumstances of neuropathic pain. Pathological states within the system can cause the activation of microglia. The latter may mediate neuronal and vegetative cell injury and death through the production of pro-inflammatory factors like cytokines and chemokines. Although inflammation may induce beneficial effects like pathogen clearance and phagocytosis of apoptotic cells, uncontrolled inflammation may result in detrimental outcomes via the assembly of neurotoxic factors that exacerbate neurodegenerative pathology. In states of lengthy inflammation, persistent activation and recruitment of effecter cells can establish an assessment circuit that perpetuates inflammation and eventually leads to neuronal injury. A critical balance between repair and proinflammatory part determines the end result of a neurodegenerative process.[35]Proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, primarily mediate and facilitate neural activities and inflammatory processes. Particularly during the early period of development, activated proinflammatory cytokines may exert detrimental effects on the brain. [36]

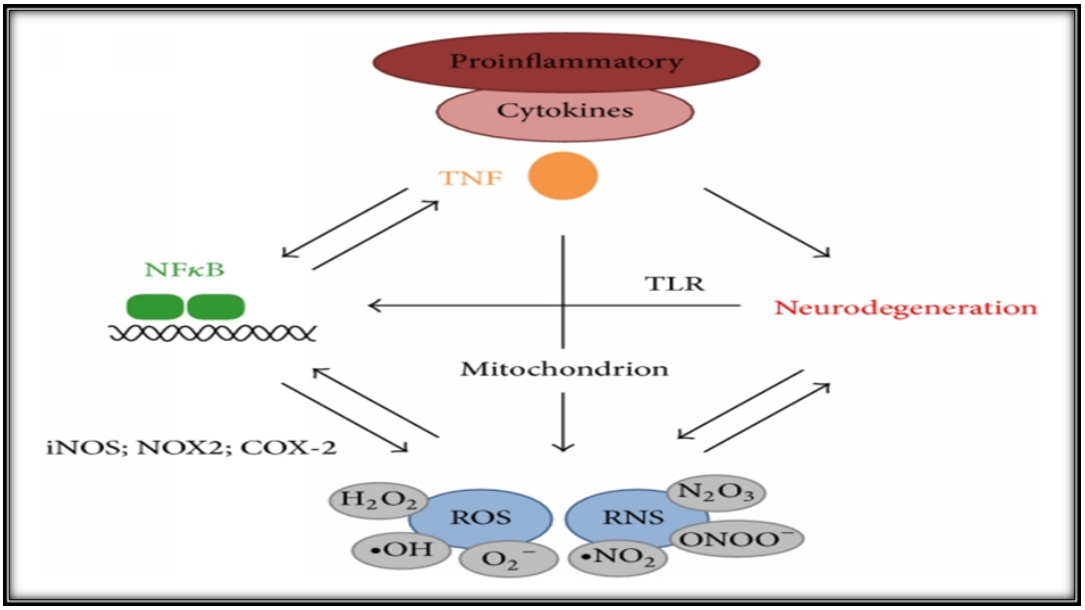

Figure 5 Interrelation of ROS and inflammatory cytokines in neurodegeneration [37]

A cytokine within the same cell looking at the functional context within which it acts can have paradoxical effects, inducing proliferation, necrobiosis, and survival. Microglia functions associated with an innate immunologic response are related to TNF-α signaling and its regulation of both inflammation and apoptosis. Increases in TNF-α and IL-1β are observed before neuronal death. In the beginning, inflammation is typically defined and determined by the discharge of proinflammatory cytokines, like TNF-α, and IL-1β in addition to adhesion molecules. IL-1β and TNF-α play an integral role in pathological inflammation and also the acceleration of disease. They'll cause blood-brain barrier (BBB) breakdown, up-regulate adhesion-molecule expression and stimulate the diffusion of toxic substances like gas (NO). IL-1β plays an important role in the progression of chronic neurodegenerative diseases like AD and PD. TNF-α could be a multi-potent, inflammatory cytokine that may induce apoptosis via activation of receptors containing a homologous cytoplasmic sequence identifying an intracellular death domain. This includes tumor necrosis factor receptor 1 (TNFR1) and CD95 (APO-1/Fas) with their corresponding death ligands, TNF-α, and therefore the structurally related type II transmembrane protein, FasL. For IL-1β, these effects are mediated primarily by the interleukin 1 receptor (IL-1R1). TNFR1 activation can cause quick apoptosis of neurons through a caspase 3-mediated pathway by providing a molecular mechanism. Membrane receptor mechanisms of apoptosis that are implicated in neuronal death involve intracellular death-signaling complexes, like activator protein 1 (AP-1), NF-κB, and caspases. [15]Top of Form.

4 PHARMACOLOGICAL APPROACHES TARGETING NEUROINFLAMMATION IN PD

The comprehensive, and still growing, the body of evidence discussed above indicates that neuroinflammatory processes are probably involved in the pathophysiology of Parkinson's disease. Neuroinflammation in Parkinson's disease may be a consequence of a primary neuronal alteration because of various causes within the different subtypes of the disease. Regardless of the origin of the neuroinflammatory processes in Parkinson's disease, a therapeutic intervention aimed toward the prevention or downregulation of those immune-associated mechanisms may be of great use to prevent disease progression or maybe halt the pathologic process. With the available knowledge of the cellular and molecular network implicated within the immune-associated damage to dopaminergic neurons, several immune therapeutic approaches are possible.[2]

Non-steroidal anti-inflammatory drugs

NSAIDs are generally used as analgesics and antipyretics amid inflammatory episodes. [2] NSAIDs share pharmacological properties with steroidal anti-inflammatory drugs. Both of them suppress eicosanoid production, however, NSAIDs mostly counter COX activity whereas steroidal anti-inflammatory drugs inhibit phospholipase A2, which decreases the amount of arachidonic-acid derived prostaglandins. The neuroprotective effect of NSAIDs was established experimentally in various animal models of PD and these beneficial effects were reported to be mediated through the decreasing NF-κB inhibition, ROS, and NO protection as well as COX inhibition. [1] Several non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, salicylic acid (SA), ibuprofen, and celecoxib, have also been shown to have protective effects on DA neurons in PD. [20] Acetylsalicylic acid and salicylic acid are neuroprotective against glutamate-induced neurotoxicity in vitro. This was because of the inhibition of NF-κB, the shared mechanism for acetylsalicylic acid and salicylic acid. Similarly, in an in vivo microdialysis study, aspirin showed neuroprotective effects with ROS scavenging activity. [1] Aspirin is also a potent inhibitor of COX2, which plays important role in the processes of neuroinflammation and neuronal degeneration. It promotes the resolution of inflammation and prevents dopamine depletion in the striatum in MPTP-induced mouse and 6-OHDA-induced rat PD models. SA is a metabolite product of aspirin, which is extensively used for the treatment of myocardial infarction, and cardiovascular diseases. SA administration in MPTP mice alleviates the neurotoxin-induced behavioral impairments as

well as dopamine depletion. Similarly, ibuprofen and celecoxib also show protective roles for DA neurons in MPTP and 6-OHDA-induced PD models. [20] Experimental findings also claimed mitochondria as a new molecular target of NSAIDs. In their study, acetylsalicylic acid and acetaminophen impeded the inhibition of the electron transport chain and complex I activity and of superoxide anion production by MPP+. These findings Suppose that mentioned NSAIDs protect mitochondria and block the generation of superoxide anion as well as scavenge hydroxyl radicals.[1] Long-term use of NSAIDs, especially the use of ibuprofen, decreased PD risk by 21 %, suggesting high therapeutic potentials of NSAIDs for PD.[20]

Drugs regulating glial-associated innate immunity

Strategies designed at suppressing the activation of glial cells and their inflammatory effects by the use of diverse drugs have been broadly tested in animal models. The use of drugs with a vast spectrum of action on inflammation would be more likely to safeguard dopaminergic neurons efficiently than higher selectively targeted drugs.[2] PPARs are a promising therapeutic target for neurodegenerative diseases since they involve the step back of major pathogenetic mechanisms that underlie these diseases such as mitochondrial and proteasomal dysfunction, oxidative stress, and neuroinflammation.[1] Preclinical studies have shown that pioglitazone, a PPARγ agonist that crosses the blood-brain barrier, can somewhat prevent dopaminergic cell loss induced by MPTP in mice and in the rotenone rat model of PD. [2] Recently, pioglitazone has been tested to identify the effects on neuroinflammation, cell proliferation, and hippocampal neurogenesis in the 6-OHDA model of PD.[1] In addition to the fact that pioglitazone is a drug approved by the US Food and Drug Administration, another major advantage of agonists of PPARγ is that these drugs have several mechanisms of action beyond their immunoregulatory properties. Plenty of evidence supports the role of agonism of this nuclear receptor in the regulation of mitochondrial bioenergetics, insulin signaling, glucose metabolism, and lactate production. The prospect that treatment with these compounds could together decrease the inflammatory concern and restore mitochondrial function and cellular metabolism within the damaged dopaminergic neurons is a novel therapeutic aspect for Parkinson's disease, in which mitochondrial dysfunction and disturbed metabolism are recognized as pathological mechanisms.[2] In a study with rosiglitazone, another PPAR-γ agonist, it was demonstrated that mitochondrial dysfunction and increase in production of free radicals by the complex I inhibitor rotenone were conversed by pre-

treatment of rosiglitazone in human differentiated SHSY-5Y cells and PINK1 knockdown cells. Moreover, rosiglitazone was found to inhibit the remarkably activated morphology of microglia and invert the increased levels of TNF-α. [1] Minocycline is a semi-synthetic, second-generation tetracycline analog, which, as a lipophilic molecule, can efficiently get through the BBB and has been expressed to have anti-inflammatory and neuroprotective properties in multiple inflammation-related neurological diseases. Minocycline treatment capably protects DA neurons from degeneration and downturn glial cell stimulation in the SNpc of LPS and 6-OHDA challenged mice. [20] In a study with MPTP and maneb-paraquat mice models of PD, which induce mitochondrial dysfunction and microglial activation, minocycline repaired the altered expression of some mitochondrial proteins involved in the neurodegeneration process, especially in maneb-paraquat mice models of PD.[1] Other approaches aimed at preventing microglial cell activation that uses more specific targeting compounds have recently emerged and would merit further assessment in preclinical settings.[2]

5 CONCLUSION

Neuroinflammation is now recognized as a crucial pathophysiological feature of neurodegenerative disorder. Animal experiments and clinical studies have generated an array of evidence encouraging the involvement of neuroinflammation in the progression of PD. However, the definite role of inflammation in PD is still not fully understood. The emerging demonstration of both protective and pathogenic roles of microglia and astrocytes and the activation of familiar inflammation pathways in these cells in several neurodegenerative diseases supports the theory that glia mediated inflammation is an amplifier of pathology. So far, many candidate drugs aiming at inflammation in PD have been developed and tested. Although some of them have been described to attenuate the behavior deficits and loss of DA neurons in PD animal models, the clinical investigations of these candidates only show moderate effects. Although suppression of neuroinflammation may not alter the underlying origin of disease, it may reduce the production of elements that contribute to neurotoxicity, thereby concluding in clinical benefit. Conducting trials on populations of individuals prone to developing PD, will allow us to discover whether anti-inflammatory and other drugs can delay or even hinder the progression of PD. In addition, identifying other drug targets in PD associated with neuroinflammation can probably yield an effective way of slowing down this as yet incurable disease.

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