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Short Communication

Neuroinflammation in Parkinson's Disease (PD)

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Introduction

Neuroinflammation in PD

The inflammatory response helps to effectively remove the cause of the problem and speeds up tissue restoration. The coordinated interaction of immune and non-immune cells and the careful control of inflammatory mediators are essential for the beginning and development of inflammation. Primary inflammatory stimuli, including interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF), as well as aggregated or misfolded proteins, are known to cause inflammation. The Toll-Like Receptors (TLRs), IL-1 Receptor (IL-1R), IL-6 Receptor (IL-6R), and TNF receptor (TNFR) interact to cause it to be activated [1]. The Nuclear Factor Kappa-B (NF-B), the Janus Kinase Signal Transducer and Activator of Transcription (JAK-STAT), and other intracellular signal transduction cascades are all activated by the activated receptors. Effector lymphocytes and macrophages secrete pro- and anti-inflammatory cytokines that draw in additional leucocytes and control the inflammation itself through an intricate web of interactions, controlling both the process's expansion and its intensity. Neuroinflammation, the inflammatory response in the CNS, has been closely linked to bacterial and viral infections, autoimmune and neurodegenerative illnesses, trauma, vascular injury, and neuropsychiatric disorders. Neuroinflammation can cause cellular damage, increase blood-brain barrier permeability, and enhance neuronal excitability. Numerous studies have shown that neuroinflammation has a role in both neurodegenerative illnesses like Parkinson's Disease (PD) and usually inflammatory diseases such as viral encephalitis. Microglia and T lymphocytes are activated, and pro-inflammatory cytokines are expressed more frequently, as a result of neuroinflammation in PD. Neuroinflammation is extensively involved in neuronal cell death, although not its fundamental cause, according to studies with animal models of Parkinson's Disease (PD). According to the information that is now available, glucocorticoid receptors have a key role in controlling microglial reactivity and their severe dysregulation in inflammation-mediated neuronal degeneration.

Microglia in PD

The brain's indigenous macrophages are called microglial cells. They were first identified by Po del Ro Hortega and act as the CNS's principal innate immune cells, preserving the brain's homeostasis. Synaptogenesis, synaptic pruning, brain progenitor-cell development and differentiation, and myelinogenesis are all processes in which microglia take part. Microglial activation is a complex reaction to infection or injury that results in the M1 and M2 phenotypes, which function differently. Although substantially simplified, the overall concept proposes that M1 microglia generate pro-inflammatory cytokines (IL-1, IL-6, IL-12, and TNF) that promote neurodegeneration. The immunological response is widened by these mediators, which could also be a direct cause of neuronal death. TNF is well recognized for its pro-apoptotic activity, which requires on c-Rel, an NF-B homolog that prevents cell death and encourages neuronal survival, being downregulated in neurons. Additionally, M1 cells increase oxidative stress by upregulating enzymes that result in reactive oxygen species with antibacterial properties. Microglia can adjust to higher energy demands when their metabolism switches from oxidative phosphorylation (OXPHOS) to glycolysis simultaneously. The creation of ATP is accelerated by metabolic reprogramming, however, it is less effective in promoting cell growth, cytokine production, and ROS generation. Deoxy-D-glucose (2-DG), a glycolytic inhibitor, has been shown to reduce TNF and IL-6 in microglia through NF-B inhibition, leading to microglial death [2]. Additionally, an in vitro investigation of BV-2 microglial cells found that LPS activation increased lactate generation and decreased mitochondrial function. In contrast to M1 cells, M2 cells express molecules that promote tissue healing and suppress inflammation. To reduce the activity of pro-inflammatory cells, they produce chemicals like IL-10. High numbers of phagocytic receptors are also expressed by M2 microglia to aid in the removal of cell debris. However, high-throughput research has shown that microglial heterogeneity is much more complex, pointing to the possibility of a greater range of microglial phenotypes. The molecular causes of microglial heterogeneity remain mostly unknown. Studies using mouse models of PD caused by 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) have shown that microglial activation is a prominent and enduring aspect of PD. Even the fact that the substantia nigra is the area of the brain that is most commonly afflicted by PD is consistent with the higher density of microglial cells in this area of the brain. Microglia play a variety of roles in neuroinflammation and can be both harmful and beneficial. Infiltrating the region of neuroinflammation, activated microglial cells perform phagocytosis and release both pro- and anti-inflammatory cytokines [3]. As a component of the initial inflammatory response, microglial activation is characterized by the creation and secretion of cytokines, which continue as the disease progresses. Pro-inflammatory proteins include IL-1, IL-12, TNF, and inducible nitric oxide synthase that are secreted considerably to promote neuroinflammation, which frequently results in considerable neuronal death. On the other hand, microglial cells' release of anti-inflammatory cytokines such as IL-4, IL-10, IL-13, TGF-, and IGF-1 lowers inflammation and encourages neuroprotection [3]. This suggests that the release of -Syn is a significant element that may lead to microglial activation. It is a common neuronal protein that is found in the CNS's presynaptic terminals, where it controls vesicular recycling. The protein can also exist in abnormally aggregated forms such as oligomers, protofibrils, and fibrils in addition to its mainly unfolded natural shape. Lewy bodies' primary constituent, syn, makes up a large portion of PD's pathophysiology. Neurons in the extracellular interstitium frequently produce -Syn in the PD brain, allowing for its laboratory detection in the body fluids of PD patients. Rapid-Syn phagocytosis is therefore brought on by the microglial activation that is caused by -Syn. The FcR receptors on the activated microglial cells participate in the uptake of -Syn during this phase, which sets off a series of pro-inflammatory processes such as the translocation of NF-B and p65 and an increase in cytokine production. The loss of neurons and ongoing neurodegeneration in PD are the results of these neuroinflammatory consequences. In addition to -Syn, other PD risk factors like DJ-1 and LRRK2 can also play a role in the control of inflammation caused by microglia.

Astroglia in PD

The majority of glial cells in the brain, or astrocytes, undertake crucial tasks for the CNS's typical functioning. Mechanically, astrocytes assist the nearby capillaries and neurons. They protect the blood-brain barrier's structural stability and permeability. Numerous neurotrophic factors, such as Glial Cell Line-Derived Neurotrophic Factor (GDNF), brain-derived neurotrophic factor (BDNF), Nerve Growth Factor (NGF), and cerebral dopamine neurotrophic factor, are produced and secreted by astrocytes (CDNF). These neurogenic chemicals promote and regulate the survival, growth, and plasticity of neurons. Additionally, CDNF offers neuroprotection and aids in the restoration of dopaminergic neurons that have been injured. The astrocytes

that surround the synaptic cleft in the tripartite synapse interact with the pre-and post-synaptic neurons and take up too much glutamate. By transporting lactate for the Krebs cycle, astrocytes help the neurons metabolically. In addition to producing antioxidants, they can remove aggregated -Syn and damaged mitochondria from neural waste. The so-called astroglial scar is the result of astrocytes filling the spaces left following a neuronal loss, which completes the remodeling of the nervous tissue [4]. As with microglia, there are various functioning states for astrocytes. The production of pro-inflammatory substances such as IL-1, C1q, and TNF by the A1 astrocytic population increases inflammation and neuronal death. On the other hand, the A2 population encourages neuronal preservation and survival following injury. Microglia release the cytokines IL-1, TNF, and C1q to activate astrocytic cells, according to Liddelow et alresearch .'s from 2017 [4]. The scientists also showed that this activation led to increased production of pro-inflammatory cytokines such as TNF-, IL-1, and IL-1 in A1 astrocytes. Astrocytes no longer support neuronal survival in their pro-inflammatory condition; instead, they cause cell death by releasing neurotoxic chemicals. In turn, astrocytes can control microglial activation and inflammation caused by these cells. Different processes of PD development, including -Syn buildup, neuroinflammation, decreased mitochondrial metabolism, and oxidative stress, are influenced by altered astrocytic activity. The discovery that astrocytes express at least eight of the 17 known genes important in the causation of Parkinson's Disease (PD) is particularly intriguing. One of them, PARK7, is markedly upregulated in astrocytes from PD patients and is even more evident in astroglia than in neurons. The DJ-1 gene's product has a role in neuroprotection, glutamate absorption, and the response to oxidative stress. It has been demonstrated that removing extracellular -Syn, microglia, and astrocytes might have a protective effect on neurons. Glial cells use proteasomal and autophagic processes to ingest and break down complexes of accumulated -Syn. Not only do astrocytes and neurons exchange intracellular components, but neurons also exchange intact mitochondria and -Syn. Even though -Syn is mostly produced and accumulates in neurons, various investigations have shown that -synuclein also collects in astrocytes. Through mitochondrial malfunction and defective autophagy, accumulating -Syn can impair astrocyte function and hasten neurodegeneration. Sonnen et al. (2020) have shown that iPSC-derived astrocytes from PD patients expressing mutant versions of the LRRK2 gene undergo metabolic alterations. Atypical -Syn expression, metabolic changes, poor Ca2+ control, and increased cytokine production were all characteristics of these astrocytes. By disrupting the normal uptake and breakdown of glutamate, Ca2+-induced cell death, defective metabolism, and accumulation of ROS and toxic fatty acids, it has been suggested that mitochondrial dysfunction in astrocytes may cause neuronal toxicity.

Inflammatory cytokines

Numerous studies have shown a strong correlation between the degree of PD and the presence of immunological markers in plasma and serum. Patients with early PD have significantly increased serum levels of the proinflammatory cytokine IL-1. The clinical scales for PD assessment and the IL-1 levels, however, did not show any significant association. Elevated IL-6 was seen in the plasma of patients with early idiopathic PD, according to Selikhova et al. In PBMCs extracted from PD patients, pro-inflammatory cytokines IL-1, INF, and TNF were found in higher concentrations. TNF- levels are correlated with cognition and other non-motor symptoms of Parkinson's disease (but not IL-1 or IL-10) [5].

It is interesting to note that, in contrast to these results, a sizable downregulation of inflammatory cytokines has also been shown in PD patients. According to Rocha et al(2018) .'s study, the PD patient cohort had fewer T-lymphocytes overall, including activated T-lymphocytes, than healthy controls. The scientists also noted lower plasma levels of IL-4, IL-6, IL-10, TNF, IFN-, and IL-17A in the PD group in line with these findings. The soluble TNF-receptors, sTNFR1, and sTNFR2 were also found in the plasma of PD patients by the same authors in a prior study, indicating that inflammation may be the cause of PD. Another comparison study revealed that IL-6 levels in PD patients were considerably greater than in healthy controls. The levels of CRP, SIL-2R, and TNF-, on the other hand, were not significantly different between the two study groups, according to the investigators. Only TNF- was significantly overexpressed when Dufek et al. (2008) looked at a panel of inflammatory markers in serum samples from 29 PD patients. The PD group did not exhibit any aberrant alterations in any of the other interesting markers (IL-6, acute phase proteins, or components of the complement system). Additionally, there were no meaningful associations between the clinical status of the patients and the concentrations of the tested serum indicators.

Another cohort study found that PD patients' serum levels of IL-1 and IL-6 were considerably lower than those of their age-matched controls. In contrast, the control group's serum IL-1 levels looked to be much lower than those in the PD group. Once more, the scientists found no connection between the examined indicators and the severity of the condition.

Higher blood levels of TNF- and lower levels of IL-27 were found in patients with PD compared to healthy controls in a study of 83 PD patients and 83 healthy people (p 0.0001) [6].

Due to the very low enrollment, all of this research is severely constrained. In the first large-cohort study to assess serum cytokine indicators in the context of Parkinson's disease, 99 healthy controls, and 262 newly diagnosed PD patients were included. It proved that a panel of cytokines is strongly linked to PD's cognitive and motor characteristics. The experimental findings showed that PD patients had greater levels of TNF-, IL-1, IL-2, and IL-10 than healthy individuals. Using their results, the authors hypothesize that a more pro-inflammatory profile is linked to diminish cognition and quick motor regression, whereas a more anti-inflammatory profile is linked to improved cognition and preserved motor function. The extensive research into the intricate relationship between immunology and PD development has outlined the potential value of cytokines as indicators of neurodegeneration and inflammation. Future findings that incorporate clinical data, cellular, and molecular aspects are likely to be the most fruitful.

YKL-40 in PD-related neuroinflammation

It has been determined that the YKL-40 glycoprotein is a potential biomarker of neuroinflammation in neurodegenerative disorders. The role of YKL-40 as a biomarker in a variety of illnesses, such as toxoplasmosis, autoimmune diseases, and inflammation related to hemodialysis, has also been questioned. Several immune cells, particularly macrophages, release this protein as an acute-phase factor in response to pro-inflammatory signals such as IL-1, IL-6, IFN, and TNF. It's important to remember that YKL-40 comes from a variety of different cellular origins (chondrocytes, fibroblast-like synovial cells, vascular smooth muscle cells, and macrophages). Our earlier findings showed a relationship between the levels of YKL-40 and neuron-specific enolase and clinical ratings for determining the severity and prognosis of traumatic brain damage. We suggested that YKL-40 might represent some features of the brain's reaction to injury, namely neuroinflammation, and brain damage. YKL-40 levels may be correlated with glial activation and the number of cells responsible for neurodegeneration, according to several studies. Its levels in Cerebrospinal Fluid (CSF) have been linked to Parkinson's-related disorders' clinical phenotypes. Magdalinu et al. (2015), for instance, found that although YKL-40 levels were lower in PD patients compared to those with atypical Parkinson's symptoms, they were still greater than those in the control group. In this investigation, no associations with disease stages or severity were found. However, the YKL-40 expression results in PD are still debatable. There have also been reports of significantly elevated YKL-40 levels in PD patients. Two-year follow-up research found that, compared to baseline levels, the concentration of YKL-40 in the CSF of PD patients had significantly increased. Additionally, the consistent rise in YKL-40 levels was associated with a decline in cognitive function. However, some authors found that YKL-40 levels in PD patients were lower than in healthy individuals, those with multisystem atrophy, progressive supranuclear palsy, or people with corticobasal degeneration. Additionally, compared to tauopathies, the concentration of YKL-40 in CSF was lower in degenerative diseases known as synucleinopathies. Olsson et al. (2013) examined the levels of YKL-40 and soluble CD14 as indicators of astrocyte and microglial activation in that study. They looked at CNF and serum samples from 79 P+ patients, 50 PD patients, and 37 controls (with progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy). In comparison to healthy controls or those who had multiple system atrophy and tauopathies, the experimental results showed significantly reduced YKL-40 levels in the CNF of PD patients. In contrast to non-dementia controls, a more recent study found higher YKL-40 levels in Cerebrospinal Fluid (CSF) from individuals with AD dementia but not in those with PD and Lewy body dementia (LBD). The scientists also looked into any potential connections between other inflammatory markers and CSF YKL-40 dysregulation. The astrocytic markers glial-fibrillary acidic protein (GFAP), interleukin-8 (IL-8), Monocyte Chemoattractant Protein-1 (MCP-1), and interferon gamma-induced protein 10 were not correlated with YKL-40 levels (IP-10). Additionallythe

plasma levels of YKL-40 in the full range of neurodegenerative dementias have been examined. Creutzfeldt-Jakob Disease (CJD) was described by Villar-Piqué et al. (2019) as having considerably increased plasma YKL-40 levels, with a reasonable ability to distinguish CJD cases from controls. Furthermore, levels of YKL-40 were highly correlated with age but not with gender. At late stages of the disease in CJD, YKL-40 concentrations appear to be much greater. The protein YKL-40 may have a potential role as a promising biomarker that measures the intensity of inflammation in PD based on these extensive experimental results.

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