Neurochemistry International 158 (2022) 105376

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

The role of Tumour Necrosis Factor in neuroinflammation associated with Parkinson's disease and targeted therapies

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ARTICLE INFO

Keywords:
TNF-α
Inflammation
Microglia
Neurodegeneration
Neuroinflammation
TNF-α inhibitors
Parkinson's disease

ABSTRACT

Neurodegenerative disorders Parkinson's disease is a progressive neurodegenerative disorder associated with neuroinflammatory responses that lead to the neurodegeneration of the dopaminergic neurons. These neuroinflammatory mechanisms involve various cytokines produced by the activated glial cells. Tumour Necrosis factor α (TNF α) is one of the major mediators of the neuroinflammation associated with neurodegeneration. TNF α has a dual role of neuroprotection and neurotoxicity in the brain. The effective pathways of TNF involve various signalling pathways transduced by the receptors TNFR1 and TNFR2. Effective therapeutic strategies have been produced targeting the neurotoxic behaviour of the Tumour Necrosis Factor and the associated neurodegeneration which includes the use of Dominant Negative Tumour Necrosis Factor (DN-TNF) inhibitors like XENP 345 and XPro®1595 and peroxisome proliferator receptor gamma (PPAR-γ) agonists.

1. Introduction

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease affecting 1–2% of the population above the age of 65 (Rizek et al., 2016). It's a slowly progressing disease with a development that lasts for 20 years (Stoker and Barker, 2020). It is majorly characterized by motor symptoms which are a result of a deficiency in dopamine due to the neurodegeneration of substantia nigra pars compacta of the basal ganglia region of the brain (which usually helps control voluntary movement of the brain). It has been shown that the degeneration of these neurons leads to a substantial loss of dopamine which is mostly responsible for the symptoms of the disease (Ali et al., 2022).

Parkinson's disease is majorly characterized by motor symptoms which are a result of a dopamine deficiency (Emamzadeh and Surguchov, 2018). Motor symptoms include bradykinesia (slowness in movement), resting tremor, hypokinesia, akinesia, uncontrolled facial expression (hypomimia), posture instability and so on. Other motor symptoms include primitive reflexes, neuro-ophthalmologic abnormalities, bulbar dysfunction, respiratory disturbances, dystonia and skeletal

Abbreviations: TNFα, Tumour Necrosis factorα; DN-TNF, Dominant Negative Tumour Necrosis Factor; PPAR-γ, Peroxisome proliferator receptor gamma; PD, Parkinson's disease; MTPT, 1-methyl-1,4-phenyl-1,2,3,6-tetrahydropyridine; ROS, reactive oxygen species; RNS, reactive nitrogen species; CNS, Central nervous system; DA, Dopaminergic; LBD, Lewy body dementia; ATP, **Adenosine triphosphate**; IL, Interleukin; GFAP, Glial fibrillary acidic protein; INFγ, Interferon-gamma; TGFβ, transforming growth factor-beta; TNFR1, Tumor necrosis factor receptor 1; TNFR2, Tumor necrosis factor receptor 2; TRADD, TNFR associated death domain; TRAF, TNFR associated factors; MHC, **major histocompatibility complex**; NO, nitric oxide.

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https://doi.org/10.1016/j.neuint.2022.105376
Received 6 March 2022; Received in revised form 29 May 2022; Accepted 30 May 2022
Available online 3 June 2022

abnormalities and gait abnormalities. Most dopaminergic treatments target the motor symptoms of the disease. It is also associated with various non-motor symptoms. Non-motor symptoms of PD include neuropsychiatric symptoms (depression, attention deficit, dementia, hallucinations), sleep disorders (Rapid eye movement disorder, insomnia), autonomic symptoms (bladder disturbances, sexual dysfunction, sweating), gastrointestinal symptoms (constipation, dribbling of saliva, nausea) sensory symptoms (pain, paraesthesia, olfactory disturbances) (Chaudhuri et al., 2005). These non-motor symptoms are ignored by most clinicians more than half of the time (Bonnet et al., 2012; Nussbaum et al., 2017).

A study of 101 PD patients showed that only 12% of these patients were devoid of any non-motor symptoms (Engels et al., 2019). Depression is the most common non-motor symptom along with cognitive impairment and autonomic dysfunction (Tibar et al., 2018). The prevalence of depression in PD patients varies from 10- to 45%. The occurrences of anxiety, fatigue, sleep disturbance, and sensory symptoms in PD patients were 33%, 40%, 47%, and 63% (Grover et al., 2015). Non-motor disease also contributes to the severity of the disease. Non-motor symptoms usually increase with the severity of the disease and the age of the patient. However, Symptoms like depression, olfactory problems, and sleeping disorders can commence in the early stages of the disease(Tibar et al., 2018). Dopaminergic treatments have been known to show no profound effect on most of the non-motor symptoms even though dopamine agonists like pramipexole indicated a role in the treatment of depression (Weiss and Marsh, 2012). Several non-dopaminergic treatments like rivastigmine helped in the treatment of dementia associated with Parkinson's disease (Reingold et al., 2007). However, there are not many effective treatments for the non-motor symptoms of Parkinson's disease.

The oral consumption of drug-like Levodopa, a precursor of dopamine, is the most common treatment for the disease and alleviated the symptoms of the disease (Sit, 2000). This provided substantial evidence for the loss of dopaminergic neurons in the substantia nigra pars compacta to be the major cause of the disease. For this reason, most of the treatments for Parkinson's disease target the neurodegeneration of the substantia nigra pars compacta neurons. Before the discovery of Levodopa the mortality rate of Parkinson's disease was a lot more in number (Goetz, 2011). Levodopa was shown to improve the quality of life in the patients. People administered with Levodopa showed increased longevity (Schapira et al., 2009). Since Parkinson's disease was first mentioned in Essay on the Shaking Palsy in 1817 (Parkinson, 1817) and into the late 1990s, neurodegeneration was the only known cause of Parkinson's disease due to decreased dopaminergic neurons. The symptoms of the disease begin to appear when there is at least 60% the death of dopamine-producing neurons in the substance nigra pars compacta (Zafar and Yaddanapudi, 2020).

Most neurodegenerative disorders are seen to be associated with neuroinflammation (Padureanu et al., 2019; Sharifi-Rad et al., 2022). Even though the MTPT and other animal models of Parkinson's disease did not completely replicate the pathological condition of the disease, some evidence reported inflammation in a few of the animal models (Duty and Jenner, 2011). It was believed for a very long time that the brain is devoid of any immune response because of the presence of the blood-brain barrier. However, in the presence of any neurotoxin or any pathogen (disease conditions), there is dysregulation of the blood-brain barrier and hence the immune cells have access to the brain in disease conditions. Inflammation in the brain can be due to various reasons like protein aggregates, injury of the neurons and disrupted synapses. (Chao et al., 2014).

This review focuses on the role of TNF α in the progress of Parkinson's disease and its potential as a target for providing novel therapeutic strategies for Parkinson's disease.

2. Review methodology

To gather up-to-date scientific evidence on the role of neuroinflammation in Parkinson's disease, a search was conducted in the following databases: PubMed, Web of Science, TRIP Database, Science Direct, and Google Scholar using the following MeSH terms: "Brain/pathology", "Cytokines/antagonists & inhibitors", "Cytokines/immunology", "Humans", "Inflammation/immunology", "Inflammation/pathology", "Microglia/metabolism", "Microglia/pathology", "Neurons/metabolism", "Neurons/pathology", "Parkinson Disease/physiopathology", "Parkinson's disease/etiology", "Tumor Necrosis Factor-alpha/physiology", "Parkinson Disease/drug therapy", "Tumor Necrosis Factor-alpha inhibitors/therapeutic use", "Tumor Necrosis Factor-alpha/antagonists & inhibitors".

Inclusion criteria: article written in English that provided evidence on the dual role of neuroinflammation in the pathogenesis or progression of PD; studies evaluating TNFα inhibitors in PD; studies describing molecular mechanisms of TNFα inhibitors.

Exclusion criteria: studies with other topics than Parkinson's disease and neuroinflammation, duplicate data and abstracts were not included in this review.

The most important data on the molecular mechanisms of action were highlighted in suggestive figures.

3. Epidemiology of PD

PD is the most common cause of Parkinson's syndrome and the second leading cause of motor impairment of neurological origin (after stroke) in the elderly (Bloem et al., 2021). The diagnosis of Parkinson's disease is a clinical one and is based on a set of internationally accepted criteria, and the definitive diagnosis is the histological one that highlights the characteristic morphological changes (Váradi, 2020).

PD is the second most common degenerative disease after Alzheimer's disease, with an overall incidence rate of 4.5–19 per 100,000 people per year. This variation is probably determined by methodological differences and case definition, as well as by the age distribution of the study population. Differences in prevalence figures may be related to environmental risk factors or differences in the genetic basis of the study population (Cacabelos, 2017). Although the disease usually manifests itself in the fifth or sixth decade of life, recent data show information about the increased incidence with advancing age, even at an earlier age (Ball et al., 2019). Patients with the onset of the disease before the age of 40 years are considered to have an early onset, in the case of onset between 21 and 40 years of age - with onset at a young age, and up to the age of twenty-one years - with juvenile-onset (Post et al., 2020). Contributions in the field of genetics have shown that a large part of patients with the onset of the disease at a young or juvenile age has a genetic etiology (Billingsley et al., 2018).

The most important risk factors for Parkinson's disease are:

Age: PD is a condition which starts at maturity or later, and the risk increases with age. People usually develop the disease around the age of 60 or later (Belvisi et al., 2022).

Heredity: The chances of getting the disease increase if there is a person in the family who has been diagnosed with Parkinson's. However, the risks are lower if there are not more family members with this disease (Lunati et al., 2018).

Gender: Men are more likely to develop Parkinson's disease than women (Cerri et al., 2019).

Exposure to toxins: Prolonged exposure to herbicides and pesticides may slightly increase the risk of Parkinson's disease (Shrestha et al., 2020).

4. Pathophysiology of Parkinson's disease: a brief overview

Parkinson's disease is caused due to the neurodegeneration of the dopaminergic neurons present in the substantia nigra pars compacta

(Tsoukalas et al., 2021; Zheng and Zhang, 2021). These neurons are known to be rich in the pigment called neuromelanin and hence loss of these neurons is associated with the depigmentation of the substantia nigra pars compacta (Siokas et al., 2021). (Fig. 1).

The two major pathological hallmarks of the disease are the loss of these dopaminergic neurons at the substantia nigra pars compacta and the formation of protein aggregates called Lewy bodies (Calina et al., 2020). Any pathogenic stimulus leads to downstream pathological hallmarks mentioned above that are either the death of the dopaminergic neurons or the formation of Lewy bodies. There has also been evidence that disease manifestations can also occur due to mitochondrial dysfunction that leads to oxidative stress resulting in the oxidation of dopamine which is toxic (Hossain et al., 2022). All these mechanisms are however not independent of each other. Accumulation of all these leads to the disease, they interact with each other. For instance, the oxidation of the α synuclein enhanced the misfolding of the protein and lead to the aggravation of the protein aggregates responsible for Lewy bodies (Giasson et al., 2000).

Aggregation of proteins is a pathological symptom seen in most neurodegenerative disorders. The aggregated protein can lead to deformed neurons or intracellular trafficking between neurons affecting the normal functions of the protein (Sharifi-Rad et al., 2020c). Overexpression of a protein can also lead to the sequestration of various other proteins required for the normal functioning of the brain (Salehi et al., 2020). The formation and aggregation of misfolded proteins in the central nervous system (CNS) is a hallmark of neurodegenerative diseases. Recent studies indicate that α-synuclein spreads to many regions of the brain and may cause α-synuclein to aggregate in these regions in a "prion-like" manner. α-synuclein undergoes conformational changes, thus propagating from the site of formation in other regions of the brain, causing the degeneration of neurons in the substantia nigra and striatum (Ma et al., 2019; Suzuki et al., 2018).

In the case of inherited Parkinson's disease, there are missense mutations that might lead to the accumulation of the misfolded proteins whereas, in the case of sporadic cases, there is a direct modification of the protein or dysregulation of the protein processing pathway like the chaperones and the proteasomal pathway which takes care of the misfolded proteins (Konya et al., 2011). Oxidative stress can also be one of the reasons that could render a protein toxic by the action of reactive oxygen species (Docea et al., 2020; Sharifi-Rad et al., 2020a). Dopaminergic neurons produce reactive oxygen species as the metabolism of dopamine involves the production of superoxide radicals and hydrogen peroxide. Auto-oxidation of dopamine also produces DA-quinone which damages proteins by reacting with the cysteine residues (Graham, 1978).

4.1. Genetic etiology

Until the late 20th century, there were not many pieces of evidence for the genetic basis of the disease. Hence several studies were conducted to study the pathophysiology of the disease. One such study involved the use of MTPT which is a neurotoxin namely 1-methyl-1,4-phenyl-1,2,3,6-tetrahydropyridine which replicated the same effects as that of Parkinson's disease. This induced the death of the substantia nigra pars compacta neurons and lead to the depletion of dopamine. MTPT is hence used to design animal models that replicated the condition similar or more or less identical to that of Parkinson's disease and help study the symptoms of the disease as they also successfully replicated the symptoms in various vertebrates and primates (Obeso et al., 2017; Kasahara et al., 2017; Da Cunha et al., 2002). In 1997 it was discovered that mutations in the α-synuclein gene caused an inherited form of the disease (Polymeropoulos et al., 1997). With the onset of this

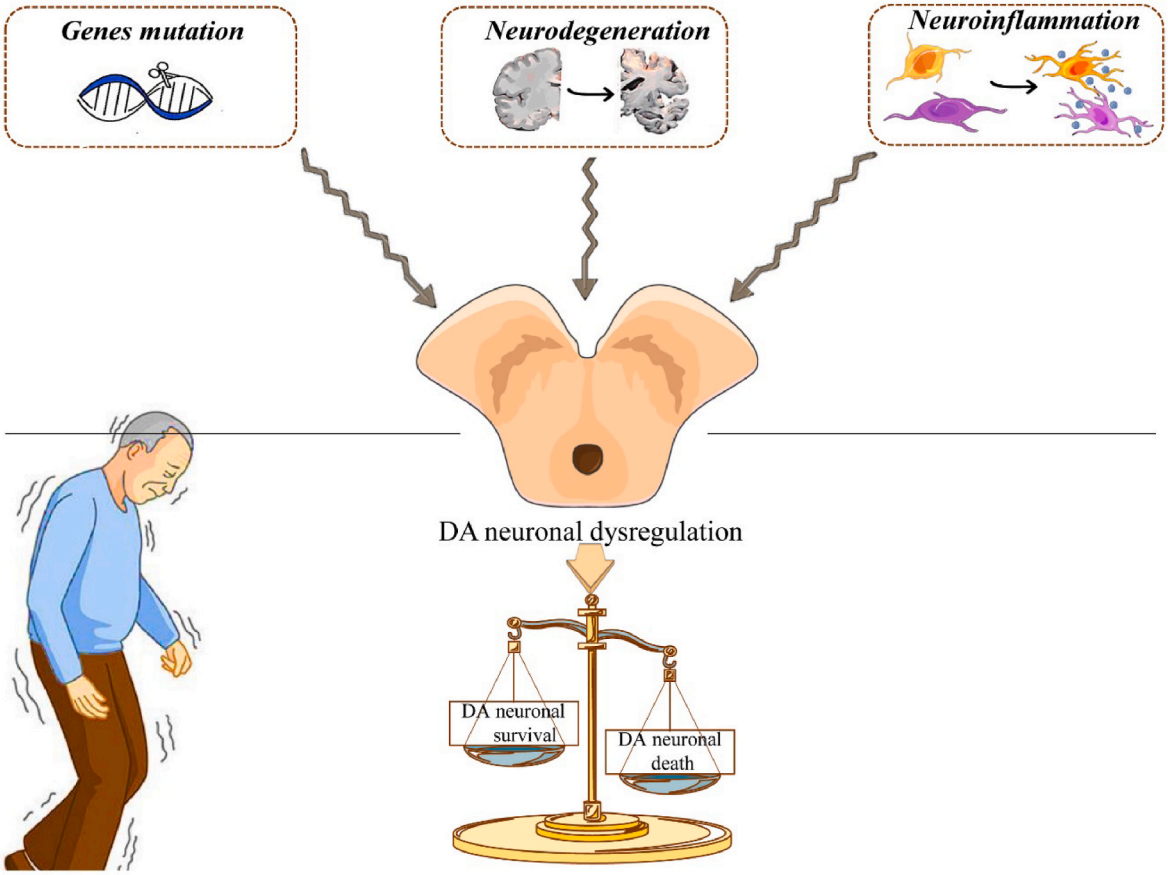

Fig. 1. Summarized scheme of the most important etiologies of Parkinson's disease. Abbreviation: DA (dopaminergic).

discovery, there were numerous studies conducted to study the genetic basis of the disease. (Uwishema et al., 2022).

Parkinson's disease is usually a sporadic disorder. Earlier, very little was known about the genetic association in the manifestation of the disease. In recent years, several cases of inherited forms of the disease were reported and the different loci associated with the disease were identified (Siokas et al., 2021). About 16 genetic loci and 11 genes have been identified to be associated with PD. Among these genes, 5 have been studied extensively: α-synuclein (also known as SNCA), parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and LRRK2 (PARK8) (Klein and Westenberger, 2012). Mutation in the synuclein gene (SNCA) causes Parkinson's disease. This one faulty gene is enough to cause the disease by itself. This suggests that high concentrations of a-synuclein can be toxic.

Normally synuclein gene is believed to modulate synaptic plasticity and neurotransmitter release. Pathogenic mutations and elevated concentrations lead to the misfolding of the protein and the formation of a b-sheet structure that readily polymerizes into oligomers and forms higher-order aggregates such as fibrils (Lee and Trojanowski, 2006). The insoluble synuclein fibrils are known to be the hallmark of Parkinson's disease and are called Lewy bodies. The mutations seen in the SNCA gene are missense mutations, A53T, A30P, and E46K (Polymeropoulos et al., 1997; Athanassiadou et al., 1999; Zarranz et al., 2004), with A53T being the most common one. α-synuclein gene is involved in the inherited autosomal dominant form of Parkinson's disease. α-synuclein gene exerts a toxic effect on the necessary cellular activities of the dopaminergic neurons.

Mutation in another gene called Leucine-rich repeat kinase 2 or LRRK2 is also associated with the autosomal dominant form of PD. LRRK2 is a large gene 144 Kb in size with 51 exons that codes for a protein, 2527 amino acids in length. Mutations in this gene associated with PD are seen in the catalytic regions of GTPase and kinase domains which resulted in an increased kinase activity in-vitro (West et al., 2002). Increased kinase activity subsequently leads to cell death. Expressing both the mutant forms of the genes resulted in an additive effect. A lower lever of mutant LRRK2 limits the toxic effects of synuclein. Hence both the proteins are seen to be interacting with each other. Mutant LRRK2 neurotoxicity can be blocked by LRRK2 kinase inhibitors GW5074 and indirubin-3′-monoxime (Lin et al., 2009). This suggests that LRRK2 kinase inhibitors could potentially be a treatment for PD.

Mutations underlying the three genes namely parkin, DJ-1, and PINK1 form the basis of the autosomal recessive form of Parkinson's disease. Patients homozygous for loss-of-function parkin mutations or having compound heterozygous parkin mutations account for about 50% of all familial early-onset cases of Parkinson's disease(Mata et al., 2010). Mutations in PINK1, the second most common autosomal recessive mutation (following parkin) contribute between 1% and 7% of early-onset Parkinson's disease(Gasser, 1998)whereas mutations in DJ-1 are a rare cause of Parkinson's disease (Bonifati et al., 2003). Most associated genes discussed above like the SNCA gene, and LRRK2 are mostly seen to be associated with the early onset of familial Parkinson's disease. The later-onset form of the disease is seen to be associated with more than 25 loci according to a study conducted on individuals of European ancestry (Nalls et al., 2014). Another study showed an additional 17 novel loci associated with the disease (Chang et al., 2017).

As a novelty, a recent study identified five genes involved in the development of PD, after sequencing the genome of patients diagnosed with Lewy body dementia(Chia et al., 2021):

- BIN1 and TMEM175 - are two genes involved for the first time in dementia with Lewy bodies;
- SNCA, APOE and GBA - are three other genes that have been reported as involved in disease and previous studies, reinforcing the importance of the results.

The study also supports the link between Lewy body dementia and Parkinson's disease, while suggesting that the genetic profile of Lewy body dementia may be similar to that involved in Alzheimer's disease (Chia et al., 2021). Evaluation of the genetic profile of Lewy body dementia (LBD) involved sequencing the entire genome of 2981 patients diagnosed with the disease, as well as 4931 healthy participants in the control group. The study was multicenter, with biological samples taken from 44 centres, 17 in Europe and 27 in North America.

The results of the study were as follows:

- the sequences of the five genes were often different in patients with LBD, compared to the control group, which indicated their potential role in pathology;
- differences in the same five genes were also identified when the DNA sequences of another 970 patients with LBD were compared with a new control group comprising 8928 participants;
- additional analyses have suggested that altering the activity of these genes may lead to dementia and that the GBA gene may have a particular influence on the development of the disease.

The researchers also investigated previous scientific data on Alzheimer's disease and Parkinson's disease, reporting that, based on the genetic profiles of LBD patients in this study, they were more likely to suffer from either Alzheimer's disease or Parkinson's disease, compared to participants in the control group. Moreover, the genetic risk profiles of LBD patients for each of the two neurodegenerative diseases did not overlap. Thus, although clinically and etiopathogenetic these two neurodegenerative diseases are fundamentally distinct, the changes in each of them seem to occur in dementia with Lewy bodies (Chia et al., 2021).

4.2. Neurodegeneration

PD is caused by neurodegeneration of dopaminergic neurons in the Substantia nigra pars compacta of the brain (Stoker and Barker, 2020; Khan et al., 2021). The subpopulations of the dopaminergic neurons are selectively affected. But it is also been suggested that the loss of dopaminergic neurons is heterogeneous across the catecholaminergic neurons (Demaagd and Philip, 2015). The most severe neuronal selective vulnerability is found in the substantia nigra, moderate in the ventral tegmental area, the A8 catecholaminergic cell group and the lowest in the Central Gray substance. A recent study analyzed how genetic risk is implicated in the etiopathogenesis of Parkinson's disease. The researchers found that molecular processes related to cell death in other neurodegenerative diseases were intensified in this particular group of dopaminergic neurons and identified exactly where the cells are usually located, in the lower part of the substance nigra pars compacta. (Soreq et al., 2017).

Three types of dopaminergic neurons are identified in the Parkinsonian Substantia nigra.

- Type 1 – "Healthy" neurons, which are located in the Matrix and are unaffected by the pathological processes.
- Type 2 – "Apoptotic" neurons are dopaminergic neurons that are already involved in the degenerative processes and they display typical features of apoptosis and autophagy.
- Type 3 – "Suffering" neurons, are those which may not function properly but have not yet reached the irreversible final degeneration step.

The type 3 neurons suggest that the neurodegeneration in Parkinson's disease is not spontaneous but a subsequent loss in the functional activity of the dopaminergic neurons. Some of these neurons may contain Lewy bodies which is the histopathological hallmark of PD.

The SNCA gene is involved to cause neurodegeneration of the dopaminergic neuron by several mechanisms (Mcclymont et al., 2018):

i. The protein aggregate forms a doughnut-like structure that penetrates the plasma membrane to form a pore which allows the passage of calcium ions into the cell causing an increase in the calcium ion concentration which is toxic to the cell.
ii. the synuclein protein aggregate leads to mitochondrial dysfunction that leads to the death of neuronal cells. α synuclein protein also leads to intracellular trafficking which results in blocking of the release of dopamine by the dopaminergic neurons due to which the dopamine concentration in the cell increases.
ii i.With the increase in dopamine concentration, there is an increase in the production of dopamine quinone which leads to the damage of the neurons.
iv. The deregulation of the proteasomal degradation of the misfolded α synuclein which also leads to neurodegeneration.

4.3. Neuroinflammation

Neuroinflammation in the CNS is associated with an innate immune response where there is an activation of the resident cells of the brain called the glial cells and the production of cytokines (Buga et al., 2019; Sharifi-Rad et al., 2022). Immune response in the brain is also associated with the production of reactive oxygen species(ROS), reactive nitrogen species(RNS) and complement proteins (Salehi et al., 2019; Mititelu et al., 2020).

Microglia are resident cells present in the CNS. These cells are derived from blood monocytes. Microglial cells once activated by the various stimuli change their morphology (Tsatsakis et al., 2019; Yeni et al., 2022). They form amoeboid structures and release neurotoxic factors that lead to chronic inflammation that leads to the neurodegeneration of the dopaminergic neurons (Glass et al., 2010). Immunohistochemical analysis of the animal models of Parkinson's disease showed that microglia are present in substantia nigra pars compacta when treated with the neurotoxin. (Yokoyama et al., 2011; Kohutnicka et al., 1998). Various studies show that neurodegeneration of the substantia nigra pars compacta dopaminergic neurons are due to the oxidative stress and proinflammatory cytokines produced by the glial cells(Farooqui and Farooqui, 2011; Ojha et al., 2016). Several other studies showed that anti-inflammatory drugs can lower the incidence of Parkinson's disease by 46 percent (Moore et al., 2010). Post mortem examination of the brain and cerebrospinal fluid of the patients with Parkinson's disease showed that there is an increased level of Tumour Necrosis Factor α (Mogi et al., 1994). Various animal models like the MTPT also showed an increased level of TNF α mRNA and protein level (Ciesielska et al., 2002).

Other than the mechanisms like oxidative stress, protein aggregation, and dysregulated proteasomal pathways, neurodegeneration is also known to be caused due to neuroinflammatory responses (Singh et al., 2021).. (Fig. 2)

Some studies have shown that neuroinflammatory responses are also seen before a significant level of neuronal loss which suggests that the neuroinflammatory responses may rely on genetic and environmental factors(Sharifi-Rad et al., 2020b) (Sharifi-Rad et al., 2020b). It has been shown in one of the studies that there is oxidative stress due to the inflammatory responses (Hald and Lotharius, 2005) and this in combination with the cytokine-dependent neurotoxicity is responsible for the deregulation of the nigrostriatal pathway and leads to the neurodegeneration of the dopaminergic neurons in Parkinson's disease.

One of the first pieces of evidence for inflammation associated with Parkinson's disease was the presence of increased expression of MHC II molecules on the substantia nigra pars compacta (Mcgeer et al., 1988)in patients with Parkinson's disease. There were an increased expression of class I MHC molecules in the striatum in patients with Parkinson's disease (Mogi et al., 1995). Another major evidence is the increase in the cytokine levels in the CSF (Cerebrospinal fluid) and the striatum of the brain in the patients with Parkinson's disease when compared to the control subjects (Nagatsu et al., 2000). The two major cells involved in

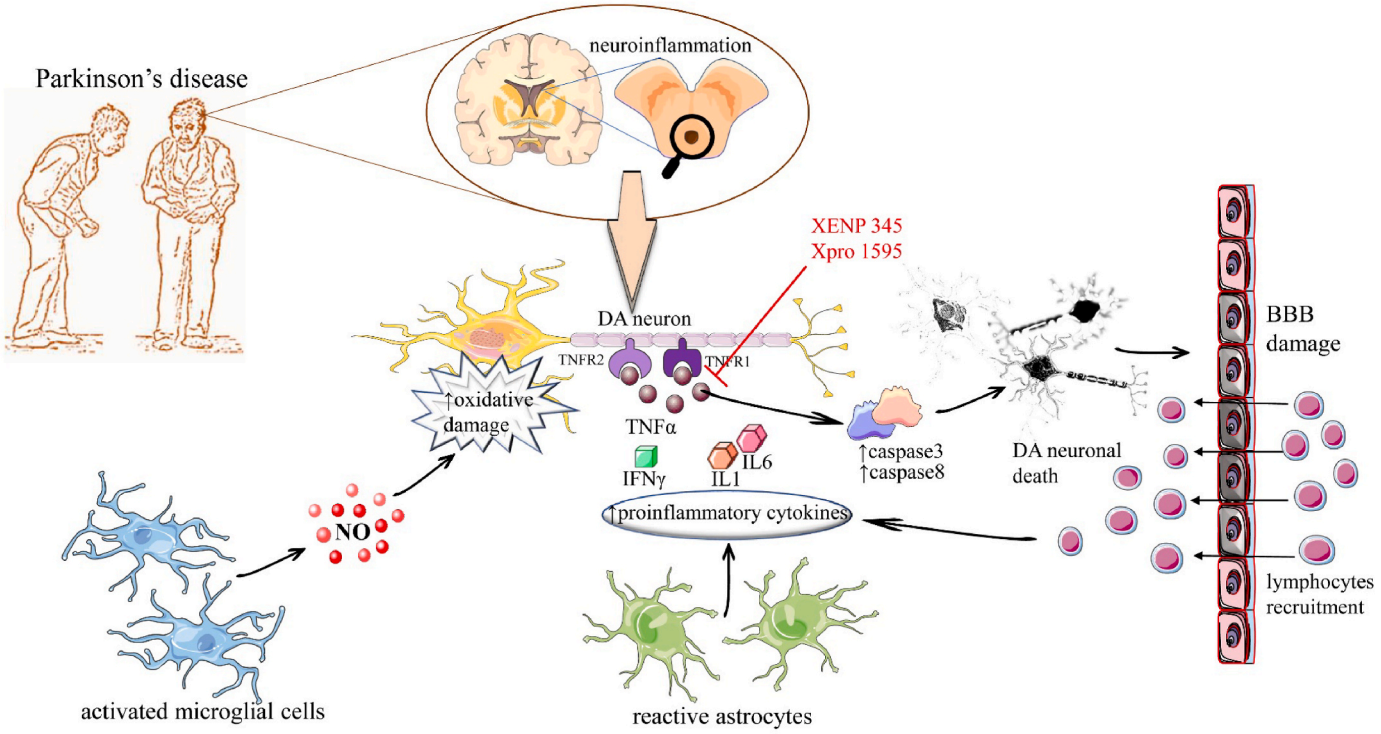

Fig. 2. Schematic diagram with the role of neuroinflammation in the pathogenesis of Parkinson's diseases. The activated microglial cells and reactive astrocytes present in the CNS are the hallmarks of the neuroinflammation caused in the brain. The neuroinflammatory responses involve the breakdown of the blood-brain barrier and infiltration of the lymphocytes in response to neuronal loss. Abbreviations and symbols: ↑ (increased), ↓ (decreased), DA (dopamine), TNFα (tumour necrosis alpha), IL (interleukins), NO (nitric oxide), BBB (blood-brain-barrier).

the neuroinflammatory mechanisms associated with neurodegenerative disorders are the microglial cells and the astrocytes (Sharifi-Rad et al., 2021). The primary role of immune surveillance is performed by microglial cells hence they are neuroprotective when regulated (Islam et al., 2021).

In normal conditions, the resident microglial cells of the brain usually show a ramified morphology but when it is exposed to any insult like a misfolded CNS protein, a gram-negative bacterial cell wall component like LPS, or various complexes of biomolecules like ATP, cAMP, Interleukins(IL6, IL10), the glial cell takes up an amoeboid cell morphology (Fig. 2). The activated glial cells release pro-inflammatory cytokine-like TNF alpha and IL-1 which are neurotoxic. Other than the proinflammatory cytokines the activated glial cells also produce chemokines, prostaglandins, reactive oxygen species, and reactive nitrogen species which in excess amounts are neurotoxic (Joe et al., 2018). During chronic inflammation conditions, the cytokines produced affect the gene expression of the cells of the glia, both microglia and the astrocytes (Aloizou et al., 2021; Takahashi et al., 2015). Astrocytes are cells of the glia that tightly regulates the functioning of oligodendrocytes and neurons. It maintains the homeostatic environment of the neuronal network. Astrocytes secrete certain neurotrophic factors that are neuroprotective (Sanchez et al., 2021).

As mentioned above, astrocytes and microglia produce cytokines most importantly tumor necrosis factor-alpha (TNFα), IL6, Interferon-gamma (INFγ), and transforming growth factor-beta (TGFβ), Interleukins 1 and 6 (IL1, IL6). The cytokines show neuroprotective effects and some, the TNFα, are shown to modulate synaptic plasticity. However, it can also lead to the death of oligodendrocytes, astrocytes, and neurons. Hence cytokines could also contribute to nigrostriatal degeneration. A piece of evidence for this is that when activated with LPS, the proinflammatory cytokines produced killed dopaminergic neurons in mixed neuron-glial cultures and they do not kill the dopaminergic neurons in pure neuron cultures. This indicated that glial cells are responsible for the production of cytokines that lead to the subsequent death of dopaminergic neurons (Gundersen, 2021).

4.3.1. Role of proinflammatory cytokines

The production of cytokines in Parkinson's disease is integral to the neuroinflammatory response associated with the disease. Various cytokines produced are known to show a profound effect on the survival of the dopaminergic neurons of the substantia nigra pars compacta (Kouli et al., 2020). The involvement of the cytokines in neurodegeneration is explained by two different mechanisms (Fig. 2).

In one of the mechanisms, the cytokines produce nitric oxide in the glial cells. Studies show that the inducible form of nitric oxide causes neurotoxicity in the substantia nigra pars compacta neurons and leads to their neurodegeneration in Parkinson's disease when compared to an age match control group (Hunot et al., 1999).

In the second mechanism, the dopaminergic neurons express several cell surface receptors for the cytokines, for instance, TNFR1 and TNFR2 are receptors for the cytokine TNFα, which trigger signalling pathway that causes deleterious events in the dopaminergic neurons. TNFα binds to the TNFR1 receptor which leads to downstream activation of caspase 8 and caspase 3 (Hunot et al., 1999). Hence TNFR1 can lead to apoptosis of the dopaminergic neuron. A postmortem study was conducted using antibodies against the activated caspase 3 and caspase 8 and the results showed that there was a higher concentration of caspase 3 (Hartmann et al., 2000) and caspase 8 in the parkinsonian patients than in the control(Hartmann et al., 2001).

4.3.2. Dual role of TNFα in neuroinflammation

TNFα is a 26 kDa protein which is later cleft by an enzyme, TNFα converting enzyme to produce a 17 functional kDa protein. It carries out its function in an autocrine or paracrine fashion by binding to TNFR1 and TNFR2 receptors. Based on the downstream effector molecules these receptors activate, TNFα shows either neuroprotective or neurotoxic behaviour. TNFα has various deleterious effects on dopaminergic neurons (Kwon and Koh, 2020). TNFα is produced by the activated microglial cells in response to any conditions like brain injury, infections, or in case of neurodegenerative diseases like Parkinson's and Alzheimer's disease. As discussed above TNFα is one of the mediators of the neuroinflammation seen in Parkinson's disease that leads to the neurodegeneration of the dopaminergic neurons by mechanisms like apoptosis (Kwon and Koh, 2020; Jayaram and Krishnamurthy, 2021).

The level of TNFα is elevated in conditions of infections, brain injury, and neurodegeneration. The level of TNFα is also seen to be increased in the case of Parkinson's disease (Zhao and Yang, 2021). A polymorphism is found to be associated with Parkinson's disease in the TNFα gene. −1031C allele of the gene causes an increased level of TNFα (Nishimura et al., 2001). Upon activation of the TNFR, the adapter proteins are recruited namely TNFR associated death domain (TRADD) which binds to the death domains followed by recruitment of the Fas-associated death domain (FADD) and TNFR associated factors (TRAF) that brings out neuroprotective or neurotoxic responses accordingly.

TNFα has a dual role in Parkinson's disease: it is both neurotoxic and neuroprotective. (Table 1 and Fig. 3).

↓ (decreased), TNFα (tumour necrosis alfa), NO (nitric oxide), NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells).

The neuroprotective and neurotoxic behaviour of TNFα is region-specific. From various studies conducted by knocking out the genes for TNFα, TNFR1 and TNFR2, it has been shown that the absence of TNFα and both the receptors lead to hippocampus injury whereas it leads to a decrease in the loss of dopaminergic neurons in the striatum. Hence TNFα was seen to be having a neurotoxic role in the striatum and a neuroprotective role in the hippocampus.

The difference in the expression of both the receptors TNFR1 and

Table 1
The most important mechanisms of neurotoxicity and neuroprotective mechanisms of TNFα.

TNFα neurotoxicity mechanisms	Ref	TNFα neuroprotective mechanisms	Ref
↓integrity of the blood-brain barrier ↑infiltration of the immune cells	Su and Zhou (2021)	↑survival, ↑growth, ↑maintenance of the neurons ↑remyelination of demyelinated cells	(Mcwilliams et al., 2017)
↑ activation of the caspases ↑apoptosis	Pajares et al. (2020)	protects the hippocampus from excitotoxic injury lack of TNFα in the hippocampus may lead to structural damage	Olmos and Lladó (2014)
↑activation of the resting microglial cells ↑release of proinflammatory cytokines ↑oxidative stress	Kam et al. (2020)	protects the brain from nitric oxide excitotoxicity	Tansey and Goldberg (2010)
regulates the expression of MHC molecules on the surface of the astrocytes, oligodendrocytes, and neurons which in turn presents the cells to the lymphocytes	(Macmahon Copas et al., 2021)	↑astrocytes ↑release of neurotrophic factor	Palasz et al. (2020)
↓reuptake of glutamate ↑glutamate toxicity	Iovino et al. (2020)	↑repair processes of the peripheral neurons	Ma et al. (2021)
brain edema	Ugalde-Muñiz et al. (2020)	↑synaptic plasticity ↑ Ca^{2+} level ↓NF-kB ↓peroxide	Beckhauser et al. (2016)

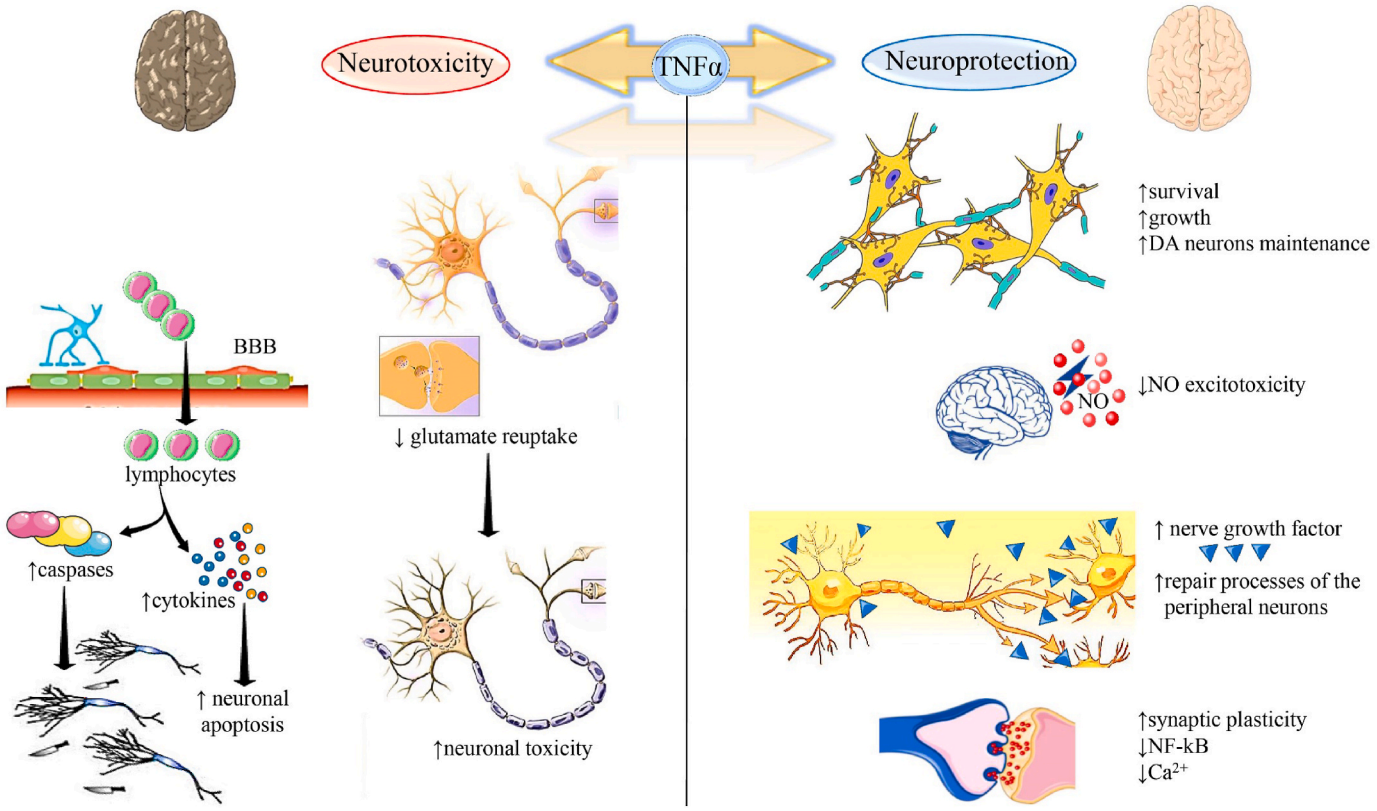

Fig. 3. The dual role (neurotoxic and neuroprotective) of TNF-α in Parkinson's disease. Abbreviations and symbols: ↑ (increased).

TNFR2 decides if it is going to have a neurotoxic role or a neuroprotective role (Dopp et al., 1997). It was shown that INFγ increased the expression level of TNFR2 mRNA in all the glial cells and by TNFα in the oligodendrocytes and the TNFR2 mRNA was upregulated by TNFα in all the microglial cells. The distribution and the morphology of the microglial cells are not even throughout the brain (Lawson et al., 1990). This explains the variation in cytokine production throughout the brain. Hence the distribution of the microglial cells and their morphology is one factor that decides the role of TNFα and the other aspect is the differential expression of both the TNFR receptors and the signalling pathways it transduces.

5. Emerging role of TNFα inhibitors in pharmacotherapeutic management of PD

Neuroinflammation caused by the proinflammatory cytokines in neurodegenerative disorders like Parkinson's disease can lead to further loss of dopaminergic neurons in the substantia nigra pars compacta. TNFα being one of the most abundant proinflammatory cytokines secreted by the glial cells plays a major role in the modification of the nigrostriatal pathway and promotes apoptosis of the dopaminergic neurons in conditions like chronic inflammation. Hence by targeting TNFα, the loss of the dopaminergic neurons can be halted but it should be taken care of the microglial cells are not affected at the same time because the immunosurveillance is important (Olmos and Lladó, 2014).

Anti-TNFα drugs selectively block necrosis (TNF α), an essential mediator of the inflammatory process (Peter et al., 2018). Their effect is quite fast and, so far, their safety has proven to be good. However, more clinical studies are still needed for the long-term follow-up of potential side effects (Li et al., 2017). A few years ago, the US Food and Drug Administration issued a warning about the possible growth of tumors (especially lymphomas) associated with longer use of these drugs (Calip et al., 2018). There is no scientific evidence that this risk is real, although it has also been suggested that autoimmune disease itself is associated with a small increase in the rate of malignancy (as it occurs in adults). Physicians need to discuss with families the risk and benefit profiles associated with the use of these drugs. Because experience with TNF inhibitors is recent in the pharmacotherapy of Parkinson's disease, reliable long-term data are not yet available (Zhou et al., 2020).

Several studies have shown that the risks of developing Parkinson's disease can be reduced by 46% by the use of anti-inflammatory drugs (Chen et al., 2003). As TNFα causes neurotoxicity by various signalling pathways, one of the approaches to treat Parkinson's disease is to inhibit the TNFα signalling pathways by using TNFα inhibitors and hence inhibit neurodegeneration. Hence targeting TNFα in the early stages of the disease can be an effective therapeutic strategy (Kang et al., 2021).

Dominant Negative TNF inhibitors (DN- TNF) are used in inhibiting the binding of the soluble TNFα monomers to the TNF receptors for the effective signalling that leads to neurodegeneration by forming heterotrimers. The heterotrimers cannot bind effectively to the TNFR receptors and hence blocks the signalling (Kang et al., 2021).

a) XENP 345

XENP 345 is one of the first dominant-negative inhibitors that was used. It inhibits the binding of the TNFα to the TNFR receptors. It attenuates the neurotoxic effect of TNFα (Mccoy et al., 2006). It also showed a decrease in the neurodegeneration in the Parkinson's disease animal models. XENP345 showed neuroprotection only in the nigral region and not in the striata. Lentivirus mediated gene transfer of the Dominant-negative TNFα inhibitor showed more efficacy than the chronic infusion of the inhibitor (Mccoy et al., 2008).

a) XPro®1595

XPro®1595 is also a DN-TNF inhibitor and it is very similar to the

soluble TNFα. It has a two amino acid substitution which prevents it from binding to the TNFR receptors. The XPro®1595 binds to the soluble TNF monomers and prevents downstream signalling by forming heterotrimers with them. XPro®1595 binds only to the soluble TNF and not the transmembrane TNF Hence the immunological function of the transmembrane TNF against any infection is maintained (Barnum et al., 2014).

b) Thiazolidinedione (TZD)

Thiazolidinedione (TZD) are peroxisome proliferator receptor gamma (PPAR-γ) agonists. PPAR-γ agonists show neuroprotection and decrease neurodegeneration (Wang et al., 2020).

6. Conclusion

The connection between inflammation, oxidative stress and the pathogenesis of PD has become better known as a result of an impressive number of studies published in the last decade on the role of inflammation in the progressive loss of dopaminergic neurons. Neuroinflammation is an important component of the pathogenic puzzle of Parkinson's disease.

Current evidence suggests that the physiological role of microglial and astrocytic cells may be compromised by age, thus contributing to the onset and progression of Parkinson's disease. Tumour necrosis factor (TNF) is a powerful pro-inflammatory cytokine that triggers intracellular signalling by binding to its receptors and exerting a range of biological effects. Targeting TNFα signaling for PD prevention or therapy, exploiting genetic variation in or near the gene encoding TNF receptor 1 (TNFR1), which is suggestive of the inhibition of pro-inflammatory TNF signalling through this receptor, may play a significant role in PD. Its importance has been highlighted in different synucleinopathy models.

Although preclinical experimental pharmacology studies in animals have shown promising neuroprotective results of compounds with anti-inflammatory properties, it is not known exactly whether anti-inflammatory therapy in humans could have a beneficial effect in preventing and slowing the progression of PD. Possible causes of failure of clinical trials with anti-inflammatory compounds in PD therapy may be the following: incorrect dosing regimens; advanced degraded clinical condition of patients included in the study; improper or incorrect choice of the tested anti-inflammatory compound. Therefore, further clinical trials in this area are needed before approving long-term pharmacotherapy with anti-inflammatory drugs in PD. On the other hand, other promising candidates with small molecules that can easily cross the blood-brain barrier or incorporate into nanocarrier target transport systems will also need to be developed/formulated. If successful in these studies, then these anti-inflammatory compounds may offer new clinical benefits in the management of PD in the future, and TNFα inhibition with widely accessible medicines may be a potential disease-modifying therapy for this historically incurable illness.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the review. All authors have read and agreed to the final version of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Availability of data and materials

Not applicable.

Declaration of competing interest

There is no conflict of interest.

Acknowledgements

Not applicable.

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