

## *The potential role of neuroinflammation and transcription factors in Parkinson disease*

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### Introduction

**P**arkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease and is characterized by progressive loss of dopaminergic neurons from the basal ganglia, which affects movement control. Bradykinesia, muscular rigidity, resting tremor, and sympathetic instability are primary symptoms of PD, whereas loss of dopaminergic neurons from the basal ganglia—which leads to the biochemical abnormality of low levels of dopamine—and Lewy bodies are the pathological characteristics of PD (*Figure 1*).<sup>1-5</sup> Researchers over the past decade have linked

*Parkinson disease (PD) is a neurodegenerative disorder characterized by dopaminergic neurons affected by inflammatory processes. Post-mortem analyses of brain and cerebrospinal fluid from PD patients show the accumulation of proinflammatory cytokines, confirming an ongoing neuroinflammation in the affected brain regions. These inflammatory mediators may activate transcription factors—notably nuclear factor  $\kappa$ B, Ying-Yang 1 (YY1), fibroblast growth factor 20 (FGF20), and mammalian target of rapamycin (mTOR)—which then regulate downstream signaling pathways that in turn promote death of dopaminergic neurons through death domain-containing receptors. Dopaminergic neurons are vulnerable to oxidative stress and inflammatory attack. An increased level of inducible nitric oxide synthase observed in the substantia nigra and striatum of PD patients suggests that both cytokine- and chemokine-induced toxicity and inflammation lead to oxidative stress that contributes to degeneration of dopaminergic neurons and to disease progression. Lipopolysaccharide activation of microglia in the proximity of dopaminergic neurons in the substantia nigra causes their degeneration, and this appears to be a selective vulnerability of dopaminergic neurons to inflammation. In this review, we will look at the role of various transcription factors and signaling pathways in the development of PD.*

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**Keywords:** apoptosis; autophagy; neuroinflammation; Parkinson disease; signaling pathway; transcription factor

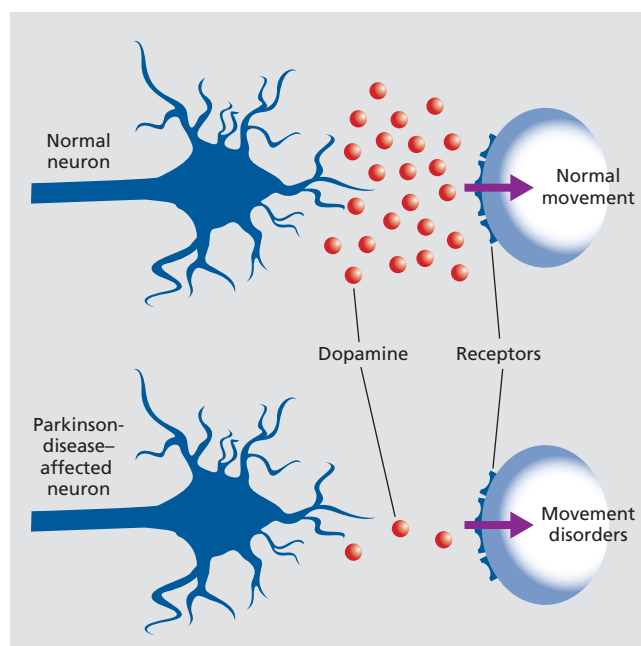
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## Selected abbreviations and acronyms

<b>IL</b>	<i>interleukin</i>
<b>SOCS</b>	<i>suppressor of cytokine signaling gene</i>
<b>PD</b>	<i>Parkinson disease</i>
<b>NF-<math>\kappa</math>B</b>	<i>nuclear factor <math>\kappa</math>B</i>
<b>mTOR</b>	<i>mammalian target of rapamycin</i>
<b>mTORC</b>	<i>mammalian target of rapamycin complex</i>
<b>TGF</b>	<i>transforming growth factor</i>
<b>SN</b>	<i>substantia nigra</i>
<b>SNpc</b>	<i>substantia nigra pars compacta</i>
<b>LPS</b>	<i>lipopolysaccharide</i>
<b>TNF</b>	<i>tumor necrosis factor</i>
<b>TLR</b>	<i>Toll-like receptor</i>
<b>AP-1</b>	<i>activator protein 1</i>
<b>MAPK</b>	<i>mitogen-activated protein kinase</i>
<b>FAF1</b>	<i>Fas-associated factor 1</i>

mutations in specific genes and familial PD, which accounts for nearly 15% of total cases of PD worldwide; familial PD is also called early-onset PD, as age of onset is under 40 years. Recessive familial PD is associated with mutations in Parkin, *DJ-1* (protein deglycase DJ-1), and *PINK1* (phosphatase and tensin homolog [PTEN]-induced putative kinase 1), whereas mutations



**Figure 1.** Dopamine levels in a normal and Parkinson disease-affected neuron.

in  $\alpha$ -synuclein and *LRRK2* (leucine-rich repeat kinase 2) are linked to a dominant form of familial PD.

A sporadic form of PD involves microglial activation by members of the signal transducer and activator of transcription family (STATs).<sup>6-10</sup> Briefly, STAT1 and STAT3, in concert with the *Jmjd3* gene (which encodes the histone H3 Lys 27 demethylase JMJD3), activate microglia, which then produce neurotoxic molecules, such as proinflammatory cytokines, chemokines, complement proteins, and nitric oxide. These cytokines activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and inducible nitric oxide synthase, resulting in the formation of reactive oxygen species and nitric oxide (NO).<sup>11,12</sup> Activated microglia also acquire phagocytic properties and develop neuroimmune interactions—involving expression of CD200/CD200R, CD47/CD172a, CX3C chemokine ligand 1 and its receptor (CX3CL1/CX3CR), along with regulatory proteins and components of the complement system (C1q and C3)—to eliminate cellular debris and damaged neurons.<sup>13</sup>

Transcription factors, such as nuclear factor  $\kappa$ B (NF- $\kappa$ B), STAT1, STAT3, and SMAD7 (SMADs are protein homologs of the *Drosophila* protein mothers against decapentaplegic and the *Caenorhabditis elegans* protein SMA), are upregulated in the chronic, self-sustaining environment of inflammation in the brain (neuroinflammation) and cause microglial activation, leading to PD through autophagy of dopaminergic neurons and various other mechanisms that are largely unknown. Autophagy-promoting gene *ULK1* (unc-51 like autophagy activating kinase 1) acts as a negative regulator of mammalian target of rapamycin (mTOR) complex 1 (mTORC1) by interacting with regulatory-associated protein of mTOR (RPTOR), which is implicated in cell survival.<sup>14</sup>

In this review, we aim to clarify the understanding of neuroinflammation and its relevance to PD with a discussion of various transcription factors such as NF- $\kappa$ B, STATs, SMAD7, and transforming growth factor (TGF)- $\beta$ , and mTOR signaling pathways.

## The role of neuroinflammation in Parkinson disease

Inflammatory components of PD involve deregulation of inflammatory pathways, probably resulting from genetic predispositions together with immune alterations

associated with aging and the primary activation of glia due to neuronal injury. Various researchers have associated aging with chronic mild inflammation in the substantia nigra (SN) pars compacta (SNpc), which makes dopaminergic neurons vulnerable to degeneration.<sup>15</sup> Active peripheral inflammation in PD contributes to the initiation and/or progression of the disease by exacerbating and synergizing with the central inflammatory response to promote dopaminergic neurodegeneration. Activation of microglia via lipopolysaccharide (LPS) in the proximity of dopaminergic neurons in SN causes its degeneration, whereas  $\gamma$ -aminobutyric-acid-ergic (GABAergic) and serotonergic neurons are spared, which suggests a selective vulnerability of dopaminergic neurons to inflammation.<sup>16</sup>

Several studies have shown inflammation and immune responses to be the determinant factor in disease progression and responsible for pathogenic processes in disease onset of both familial and sporadic PD.<sup>17-19</sup> A recent study reported the presence of activated microglia in the SN and putamen of patients with a PD diagnosis.<sup>20</sup> In a 2005 study, Ouchi et al suggested involvement of a microglial-mediated inflammatory process in an early stage of parkinsonism.<sup>21</sup> In another study, Gillardon et al, Moehle et al, and Harms et al suggested that different genetic mutations in genes, such as  $\alpha$ -synuclein (*SNCA*) or *LRRK2*, participate directly in the progression of chronic PD by stimulating inflammatory responses via microglia and astrocyte activation.<sup>22-24</sup> Both central and peripheral inflammation are responsible for sustained progression of PD.<sup>18,25</sup> Degeneration of dopaminergic neurons occurs with infiltration of T-cells and activation of microglia, along with increased production of inflammatory cytokines and chemokines due to a pathological accumulation of *SNCA* (Figure 2).<sup>24,26</sup>

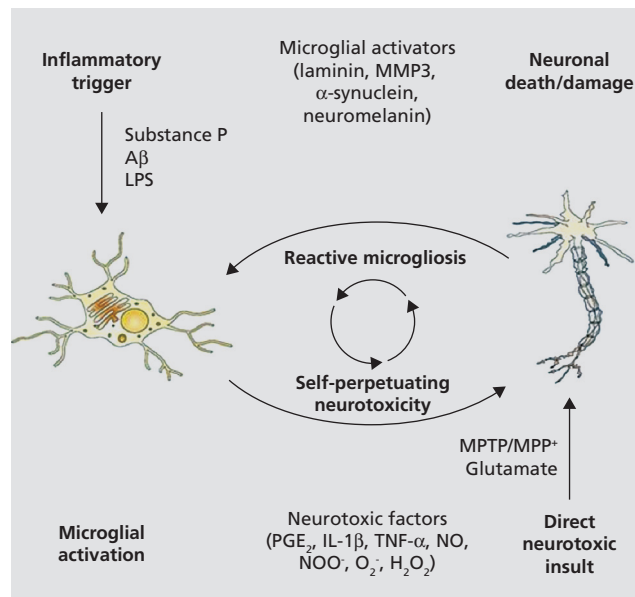
## Role of proinflammatory transcription factors in PD

### The role of NF- $\kappa$ B in Parkinson disease

NF- $\kappa$ B is a dimeric transcription factor, which includes c-Rel, RelA (p65), RelB, NF- $\kappa$ B1 (p50/p105), and NF- $\kappa$ B2 (p52/p100) proteins. c-Rel, RelA (p65), and RelB proteins have a transactivation domain in their carboxyl terminus; NF- $\kappa$ B1 and NF- $\kappa$ B2 are synthesized as large precursors, p105 and p100, which undergo ubiquitination to generate mature NF- $\kappa$ B subunits p50 and

p52. Ubiquitination of p105 and p100 proteins involves selective degradation of the carboxyl terminus region containing ankyrin repeats.

Studies have shown that gene expression in many of the proinflammatory responses is controlled by the transcription factor NF- $\kappa$ B. Indeed, researchers have described NF- $\kappa$ B as a “master switch” for gene expression of various inflammatory mediators.<sup>27</sup> The response to inflammatory mediators—such as tumor necrosis factor (TNF), IL-1 $\alpha$ , and IL-1 $\beta$ , along with the bacterial product LPS—and products of cell damage is mediated through NF- $\kappa$ B activation. Subsequently, NF- $\kappa$ B plays a crucial role in the inflammatory response by regulating genes that encode proinflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-12/23), chemokines (IL-8, macrophage inflammatory protein [MIP]-1 $\alpha$ , monocyte chemoattractant protein [MCP]-1),<sup>28,29</sup> inducible nitric oxide synthase, subunits p47 and p67 of NADPH oxidase,<sup>30,31</sup> and cell adhesion molecules (intercellular adhesion



**Figure 2.** Inflammatory triggers, such as lipopolysaccharide, generate a vicious cycle of neuroinflammation, which leads to degeneration of neurons. A $\beta$ ,  $\beta$ -amyloid; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; IL-1 $\beta$ , interleukin 1 $\beta$ ; LPS, lipopolysaccharide; MMP3, matrix metalloproteinase 3; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; ONOO<sup>-</sup>, peroxynitrite; O<sub>2</sub><sup>-</sup>, superoxide anion; PGE<sub>2</sub>, prostaglandin; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ . Adapted from reference 26: Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci.* 2007;8(1):57-69. Copyright © 2007, Nature Publishing Group.

molecule [ICAM]-1, vascular cell adhesion molecule [VCAM], and E-selectin).<sup>32,33</sup> Standard agents such as amino salicylates and corticosteroids used in the treatment of inflammatory conditions, as well as anti-inflammatory cytokines such as IL-10, exert their anti-inflammatory effects through NF- $\kappa$ B inhibition.<sup>30,34</sup> Various studies have shown that these compounds are potent inhibitors of microglia activation and have a neuroprotective effect on dopaminergic neurons both in vitro and in vivo. Thus, NF- $\kappa$ B activity has emerged as a key target for controlling chronic inflammation, and inhibition of NF- $\kappa$ B activity in microglia may lead to more effective treatment of PD.

### The role of STAT3 in Parkinson disease

A diverse range of proinflammatory and neurotoxic factors, such as superoxide, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and NO are secreted by activated microglia.<sup>35</sup> These proinflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ ) stimulate microglia to produce MCP-1, MIP-1 $\alpha$ , and MIP-1 $\beta$ , which also contribute to neuroinflammation.<sup>36</sup> Early cytokine expression is then stimulated (via messenger RNA stabilization) by binding of these inflammatory mediators to Toll-like receptor (TLR) 4. When released, these cytokines induce STAT1 and STAT3 activation.<sup>37</sup>

STAT3 thus activated in inflamed microglia drives dopaminergic neurons toward programmed cell death through transcriptional activation of cell death–mediating genes, such as those encoding B-cell lymphoma-extra-large (Bcl-xL), caspases, Fas, and TNF-related apoptosis-inducing ligand (TRAIL), along with genes regulating cell cycle progression, such as *p21waf1*. Thus, STAT3 activation of microglia causes functional changes such as dopaminergic neuron attenuation, which occurs in an IL-1–dependent manner because of autophagocytosis of dopaminergic neurons, and results in PD.<sup>38</sup>

### The role of TLRs in Parkinson disease

TLRs are type I transmembrane receptors characterized by extracellular leucine-rich repeats (LRRs) and an intracellular Toll/IL-1 receptor (TIR) signaling domain. TLRs are activated by molecules termed pathogen-associated molecular patterns (PAMPs), which include LPS, lipoproteins, and flagellin, along with viral and bacterial nucleic acids.<sup>39</sup> After exposure to these mol-

ecules, TLRs initiate signaling pathways that promote expression of inflammatory mediators, chemokines, and cell adhesion molecules.<sup>40</sup> Researchers have shown that TLRs are highly activated in activated microglia during degeneration of dopaminergic neurons. The canonical pathway of NF- $\kappa$ B is then activated by TLRs. NF- $\kappa$ B thus activated is translocated to the nucleus, which subsequently increases the expression of various proinflammatory molecules.<sup>41</sup> Release of these proinflammatory molecules from activated microglia into the local milieu enhances the oxidative stress of the SNpc, which results in degeneration of dopaminergic neurons.

### The role of AP-1 in Parkinson disease

Activator protein 1 (AP-1) is composed of heterodimers of Fos (*c-Fos*, *FosB*, *Fra1*, and *Fra2*) and Jun (*c-Jun*, Jun B, Jun D), along with activating transcription factors (ATFs). Activity of AP-1 is stimulated by the mitogen-activated protein kinase (MAPK) cascade, which results in c-Jun N-terminal kinase (JNK) activation, which then phosphorylates c-Jun.

TLRs activated in microglia of SNpc in turn cause activation of AP-1. AP-1 thus activated then promotes the vicious cycle of neuroinflammation in microglia of the SNpc, driving dopaminergic neurons toward apoptosis.<sup>42</sup> However, the exact role of AP-1 in PD pathology is yet to be elucidated.

### The role of FAF1 in Parkinson disease

Fas-associated factor 1 (FAF1) is a Fas-binding protein and product of a gene at the *PARK10* (Parkinson disease 10) locus on chromosome 1p32 and is associated with late-onset PD. FAF1 is a proapoptotic protein that drives cells toward the apoptotic pathway.<sup>43</sup> Researchers have shown that FAF1 is overexpressed in the SNpc of PD patients. Expression of endogenous FAF1 in SNpc is promoted by oxidative stress. Overexpression of FAF1 pushes dopaminergic neurons toward apoptosis by potentiating caspase-3–activated cell death.<sup>44</sup>

### The role of p38 MAPK in Parkinson disease

MAPKs make up a special class of serine/threonine kinases. There are four different types of MAPKs, including (i) extracellular signal–related kinases (ERKs); (ii) JNKs; (iii) atypical MAPKs, such as ERK3, ERK5, and

ERK8; and (iv) the p38 MAPKs.<sup>45</sup> The p38 MAPKs are activated by extracellular stress and cytokines, and are therefore described as stress-activated protein kinases. The p38 $\alpha/\beta$  isoforms of MAPK specifically bind to and activate MAPKAPK-2 (MK2) and MAPKAPK-3 (MK3) serine/threonine kinases, members of a MAPK-activated protein kinase subfamily.<sup>46,47</sup> Of all the kinases activated by p38 $\alpha/\beta$  isoforms of MAPK, MK2 is the most important because of its key role in mediating cellular stress and inflammatory responses. Extracellular stimuli, such as stress and proinflammatory cytokines, are known to activate p38 MAPK.<sup>48,49</sup>

The p38 MAPK-MK2 complex promotes the inflammatory process; this is evident in MK2-knockout mice, which are resistant to endotoxic shock when stimulated with LPS.<sup>50</sup> MK2 also regulates production of various inflammatory mediators, such as TNF- $\alpha$ , IL-6, and IL-8, along with other cytokines that play an important role in inflammatory processes.<sup>51,52</sup> Increased MK2 expression is observed in LPS- and interferon- $\gamma$ -stimulated microglial cells, which can release inflammatory mediators. In microglial cells cultured from MK2-knockout mice, a decreased release of various inflammatory mediators has been observed.<sup>53</sup> Researchers have documented that the activation of the p38 MAPK-MK2 pathway and the subsequent increase in the production of inflammatory cytokines play a significant role in neurodegenerative disorders such as PD.

### Role of prosurvival transcription factors in Parkinson disease

#### The role of TGF- $\beta$ in Parkinson disease

TGF- $\beta$ 1 is a multifunctional cytokine that regulates growth, differentiation, and functions of immune and nonimmune cells. Researchers have shown that TGF- $\beta$ 1 is a potent negative regulator of inflammation.<sup>54,55</sup>

Several mechanisms have been postulated for a neuroprotective effect from TGF- $\beta$  signaling. Various studies have shown that TGF- $\beta$ 1 inactivates Bad, a proapoptotic protein of the B-cell lymphoma 2 (Bcl2) family, by promoting its phosphorylation through activation of the Erk/MAP kinase pathway.<sup>56</sup> Increased TGF- $\beta$ 1 signaling also increases production of Bcl2 antiapoptotic protein.<sup>57</sup> TGF- $\beta$ 1 also synergizes with neurotrophins and is required for several important neuronal growth factors, such as neurotrophins, fibroblast growth

factor-2, and glial-cell-line-derived neurotrophic factor.<sup>58,59</sup> TGF- $\beta$ 1 signaling decreases inflammation in the infarcted area and attenuates secondary neuronal damage.<sup>60</sup> Thus, TGF- $\beta$  signaling plays an important role in progression of PD.

#### The role of mTOR in Parkinson disease

mTOR is a serine/threonine kinase present in two distinct complexes, mTORC1 and mTORC2. mTORC1 promotes cellular growth in response to various inputs, such as growth factors, along with hypoxia and energy stress, whereas mTORC2 promotes cell survival.<sup>61-66</sup>

Researchers have suggested that cell survival signaling of mTOR is inhibited in the SNpc in the brain of PD patients. REDD1, standing for regulated in development and DNA damage responses 1, is an mTOR-signaling inhibitor induced in activated microglia by inflammatory mediators such as IL-1 $\beta$ . REDD1 thus activated then binds with 14-3-3 protein and induces dissociation of the tuberlin (TSC2)/14-3-3 complex which results in inhibition of the cell survival signaling pathway of mTOR.<sup>67,68</sup>

#### The role of Wnt signaling in Parkinson disease

The Wnt signaling pathway plays an important role in the development of dopaminergic neurons in the midbrain. Wnt1 and Wnt3a induce dopaminergic precursors and are required for development of dopaminergic precursors into dopaminergic neurons.<sup>69</sup> It has been shown that induced expression of Wnt5a in ventral midbrain neural stem cells generates tenfold more dopaminergic neurons, and the transplantation of these cells in a mouse model of PD results in their recovery from parkinsonism.<sup>70,71</sup> Increased loss of dopaminergic neurons and *Nurr1*<sup>+</sup> (nuclear receptor related 1) cells is observed in *Wnt1*<sup>-/-</sup> and *Wnt5*<sup>-/-</sup> double-knockout mice as compared with single-knockout mice. Stabilization of  $\beta$ -catenin by *Wnt* increases its interaction with Nurr1 and disrupts the corepressor complex consisting of Nurr1 and lymphoid enhancer binding factor 1 (LEF1). This disruption of the corepressor complex then induces the expression of  $\beta$ -catenin-responsive genes.<sup>70</sup>

Downregulation of key components of the Wnt- $\beta$ -catenin pathway occurs in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).<sup>72</sup> Wnt1

expression increases in the midbrain of mice treated with MPTP, whereas expression of frizzled 1 (FZD-1) and  $\beta$ -catenin are deregulated, suggesting that the Wnt pathway may have a neuroprotective effect against MPTP-induced neurotoxicity. In mice, Wnt1 and  $\beta$ -catenin decrease with age. This may be related to failure of the mice to recover from MPTP-induced neurotoxicity.<sup>73</sup> Wnt signaling is also altered by treatment with pesticides, which induces sporadic PD.<sup>74</sup> In a 6-hydroxydopamine (6-OHDA) model of PD, Wnt signaling is inhibited by dickkopf-1 (Dkk1), which then promotes degeneration of dopaminergic neurons in these mice.<sup>75</sup> Wnt1, through its canonical pathway, has shown its protective effect in the human neuroblastoma cell line SH-SY5Y when these cells were treated with 6-OHDA.<sup>76</sup>

### The role of the SOCS pathway in Parkinson disease

The suppressor of cytokine signaling (SOCS) family proteins (SOCS1-7) and cytokine-inducible SH2-containing protein (CIS) are negative feedback regulators of inflammation.<sup>77,78</sup> SOCS3 and CIS expression is induced in brain microglia and astrocytes by thrombin via protein kinase C $\delta$  (PKC $\delta$ ) and reactive oxygen species.<sup>79,80</sup> Induction of SOCS1 and SOCS3 by the Janus kinase (JAK)/STAT pathway in turn inhibits the JAK/STAT pathway and curtails inflammation. However, cells deficient in SOCS1 are more prone to inflammation. DJ-1 protein exerts its anti-inflammatory effect by suppressing SOCS1 signaling.<sup>81</sup> Thus, in PD, SOCS signaling is inhibited, which leads to neuroinflammation and subsequent degeneration of dopaminergic neurons.

### The role of the transcription factor YY1 in Parkinson disease

The transcription factor Yin Yang 1 (YY1) plays an important role in the central nervous system during embryogenesis, differentiation, replication, and proliferation.<sup>82</sup>

YY1 has a neuroprotective effect, decreasing *SNCA* in SNpc, which would otherwise have a toxic effect on dopaminergic neurons. Thus, downregulation of YY1 signaling promotes degeneration of dopaminergic neurons; however, the exact mechanism through which YY1 signaling is downregulated/inhibited is not known.

### The role of MEF2 in Parkinson disease

Myocyte enhancer factor 2 (MEF2) was first identified in muscle cells. It is a member of the MCM1, agamous, *deficiens*, serum response factor (MADS) family of transcription factors.<sup>83</sup> *MEF2A* to *MEF2D* are members of the MEF2 gene family.

Loss of MEF2D-mediated neuronal survival is the key to loss of dopaminergic neurons in various models of PD.<sup>84,85</sup> In a 1997 study, it was reported that LPS increases transactivation activity of MEF2 by phosphorylating it through p38 MAPK.<sup>86</sup> Activation of MEF2 by p38 in neurons promotes their survival.<sup>87</sup> Along with MAPK, several other kinases also regulate MEF2 in neurons.<sup>84,88,89</sup> Activated MEF2 promotes the survival of neurons by inhibiting autophagy and mitophagy; the two processes that are promoted in PD due to mutations in the kinases *LRRK2* and *PINK1*.<sup>10,90,91</sup> Thus, dysregulation of MEF2 may promote degeneration of dopaminergic neurons due to increased autophagy and mitophagy of dopaminergic neurons. However, the exact cause of this dysregulation of MEF2 is not yet known.

### The role of FGF20 and Parkinson disease

Fibroblast growth factor (FGF) 20 has strong neurotrophic properties. Various researchers have suggested that expression of FGF20 in the SN of rat brain significantly increases the rate of survival of dopaminergic neurons. This neuroprotective effect of FGF20 is mediated by activation of FGF20 receptor-1c (a splice variant of FGF receptor 1).<sup>92-95</sup> Variation of FGF20 at the single-nucleotide polymorphism (SNP) rs1721100 and SNP rs12720208 has been associated with an increased risk for PD.<sup>96-99</sup>

## Conclusion and future prospects

Conventional therapy of PD solely addresses depleted dopamine levels in the basal ganglia, and levodopa is considered the gold standard for PD therapy. Currently, we understand a number of mechanisms involved in the death of dopaminergic neurons via activation of various transcription factors and regulatory proteins; however, it is also known that many transcription factors or signaling molecules prevent death of dopaminergic neurons. The inflammation of neurons causes release

of various inflammatory mediators (interferons, epidermal growth factor, IL-5, IL-6, hepatocyte growth factor, leukemia inhibitor factor, and bone-morphogenetic protein 2), with hallmarks of neuroinflammation including the presence of activated microglia and reactive astrocytes in the parenchyma of the central nervous system and increased production of cytokines. Proinflammatory transcription factors, such as NF- $\kappa$ B, STAT3, AP-1, TLRs, and FAF1, are constitutively upregulated in activated microglia. TLRs, when activated, promote NF- $\kappa$ B signaling and thus promote the vicious cycle of neuroinflammation. These transcription factors drive dopaminergic neurons toward apoptosis via p53 and other death-domain receptors. Neuroprotective signal-

ing pathways, such as mTOR, SOCS, and TGF- $\beta$ , are downregulated during development of PD, and YY1 signaling, which has a protective effect against *SNCA* toxicity, is significantly decreased in PD patients.

Going forward, focusing on these transcription factors and signal-regulated proteins would provide a better understanding of molecular mechanisms involved in the pathogenesis of PD. This may open the door for targeted therapy toward the prevention and cure of this currently incurable disease.  $\square$

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### **El papel potencial de la neuroinflamación y de los factores de transmisión en la Enfermedad de Parkinson**

La Enfermedad de Parkinson (EP) es un trastorno neurodegenerativo caracterizado por procesos inflamatorios en neuronas dopaminérgicas. El análisis post-mortem de cerebro y líquido céfalo raquídeo de pacientes con EP muestra la acumulación de citoquinas proinflamatorias, lo que confirma un proceso neuroinflamatorio en las regiones cerebrales afectadas. Estos mediadores inflamatorios pueden activar factores de transmisión –en especial el factor nuclear  $\kappa$ B, el Ying-Yang 1 (YY1), el factor de crecimiento de fibroblastos 20 (FGF20) y un blanco de rapamicina en los mamíferos (mTOR)- los que regulan las vías de señales descendentes y a la vez promueven la muerte de neuronas dopaminérgicas, a través de receptores que tienen un dominio de muerte. Las neuronas dopaminérgicas son vulnerables al estrés oxidativo y al ataque inflamatorio. En la sustancia nigra y el estriado de pacientes con EP se ha observado un aumento del nivel de sintetasa de óxido nítrico inducible, lo que sugiere que tanto la inflamación como la toxicidad inducidas por citoquinas y quimioquinas llevan al estrés oxidativo, lo que contribuye a la degeneración de las neuronas dopaminérgicas y al avance de la enfermedad. La activación de lipopolisacáridos de la microglía, en la proximidad de las neuronas dopaminérgicas en la sustancia nigra, provoca su degeneración y esto parece ser una vulnerabilidad selectiva de las neuronas dopaminérgicas a la inflamación. En este artículo se revisa el papel de varios factores de transcripción y vías de señales en el desarrollo de la EP.

### **Le rôle potentiel de la neuro-inflammation et des facteurs de transcription dans la maladie de Parkinson**

La maladie de Parkinson (MP) est un trouble dégénératif caractérisé par l'atteinte des neurones dopaminérgiques par des processus inflammatoires. Des analyses post-mortem du cerveau et du liquide céphalo-rachidien de patients parkinsoniens montrent l'accumulation de cytokines pro-inflammatoires, confirmant la présence d'une neuro-inflammation dans les régions cérébrales affectées. Ces médiateurs inflammatoires activent des facteurs de transcription, en particulier le facteur nucléaire  $\kappa$ B, le Ying-Yang 1 (YY1), le facteur 20 de croissance du fibroblaste (FGF20) et mTOR (cible de la rapamycine chez les mammifères), qui régulent ensuite les voies de signalisation en aval, qui à leur tour favorisent la mort des neurones dopaminérgiques à travers des récepteurs à domaine de mort. Les neurones dopaminérgiques sont vulnérables au stress oxydatif et à l'attaque inflammatoire. Une augmentation des taux de l'oxyde nitrique synthase inductible observée dans la substance grise et le striatum des patients MP suggère que l'inflammation et la toxicité induites par les chémokines et les cytokines conduisent à un stress oxydatif qui contribue à la dégénérescence des neurones dopaminérgiques et à la progression de la maladie. L'activation des lipopolysaccharides de la microglie proche des neurones dopaminérgiques dans le locus niger provoque leur dégénérescence, ce qui semble être dû à une vulnérabilité sélective des neurones dopaminérgiques à l'inflammation. Dans cet article, nous analysons le rôle de divers facteurs de transcription et voies de signalisation dans l'apparition de la MP.