Review Article • DOI: 10.1515/tnsci-2018-0022 • Translational Neuroscience • 9 • 2018 • 147-153

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P38 MITOGEN-ACTIVATED PROTEIN KINASE AND PARKINSON'S DISEASE

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Received 11 July 2018
accepted 08 August 2018

Abstract

Parkinson's disease, the second major neurodegenerative disease, has created a great impact on the elder people. Although the mechanisms underlying Parkinson's disease are not fully understood, considerable evidence suggests that neuro-inflammation, oxidative stress, mitochondrial dysfunction, cell proliferation, differentiation and apoptosis are involved in the disease. p38MAPK, an important member of the mitogen-activated protein family, controls several important functions in the cell, suggesting a potential pathogenic role in PD. This review provides a brief description of the role and mechanism of p38MAPK in Parkinson's disease.

Keywords

Parkinson's disease • p38MAPK • neuro-inflammation • oxidative stress • mitochondrial dysfunction

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease following Alzheimer's disease, has created a great impact on the elderly, the family and society. The average age of onset is about 60 years old, and the prevalence of Parkinson's disease in older people over 65 increases with age[1]. It is estimated that approximately 10 million individuals worldwide suffer from this disease, though many cases may go undiagnosed. With the growth of aging populations, the number will double over the next 25 years, which causes enormous social and economic problems.

The major pathological features of PD include progressive loss of dopaminergic (DA) neurons and formation of intracellular Lewy bodies (LBs) in the survival neurons of substantia nigra (SN). Its clinical manifestations include rest tremor, bradykinesia, muscle rigidity, posture gait abnormalities and other movement disorders, as well as cognitive disabilities, sleep disorders and other non-motor barrier [2, 3], some of the symptoms of non-motor symptoms can occur prior to motor symptoms, and neurodegenerative neuropathies are not limited to SNc but have a broader impact[4, 5]. The etiology and pathogenesis of PD are complex and not yet fully understood. More studies suggest that genetic mutations in proteins play major role for the development and progression of PD[3, 6]. Neuro-inflammatory [7], oxidative stress[8], mitochondrial dysfunction[9] and cell proliferation, differentiation, apoptosis involve in the pathogenesis of both familial and idiopathic PD [10].

The MAPK cascade is a major intracellular signaling system that transmits extracellular information to the nucleus and mediates various cell responses and plays an significant role in cell proliferation, differentiation and apoptosis[11], it is one of the important signal-regulated enzymes that connect the cell surface receptors with the decisive gene expression. p38 Mitogen-activated protein kinase (p38MAPK) is an important member of the mitogen-activated protein kinase family. The p38MAPK signaling cascade is a major signaling pathway for endogenous and endogenous stimulation (including growth factors, stress and cytokines) in respond to endothelial cell function and accordingly mediating a wide range of cellular effects, which provides cells with mechanisms to responding to external mitogenic signals[12-14]. p38MAPK play an important role in the pathogenesis of PD.

2. p38MAPK involves in neuro-inflammation in PD progression

The PD patients showed accumulation of pro-inflammatory cytokines in the brain and cerebrospinal fluid, which demonstrates that neuro-inflammation is occurring in the affected brain area[15, 16]. In vivo evidence of neuropathic inflammation in PD patients includes cytokines and other molecular mediators expression disorders[17-19], microglia activation[20], peripheral immune cell invasion and changes around the composition and performance in Substantia nigra pars compacta (SNpc) [21]. Neuro-inflammation is thought to be an prominent pathological factor

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that contributes towards the development and progression of PD[22].

The development of neuro-inflammation plays an important role in the immune system of the central nervous system, which includes microglia and astrocytes[23]. The neuro-inflammation process begins with the activation of glial cells, producing many neurotoxic components including reactive oxygen species (ROS), nitric oxide synthase (NOS), cytokines and other inflammatory mediators, all of which can lead to neurodegeneration[24, 25]. Inflammatory triggers such as Aβ, lipopolysaccharide (LPS) and MPTP can trigger inflammation and activate microglial cells. In addition to the generation of large amounts of free radicals after microglial activation, a large number of pro-inflammatory cytokines are released, such as IL-1β, TNF-α, TNF-γ.[26, 27]. These inflammatory mediators can damage neurons and further activate microglial cells resulting in a vicious circle that aggravates neuro-inflammation and degeneration[28].

Activated microglia is observed in various degenerative neurological conditions such as PD and amyotrophic lateral sclerosis (ALS). Activated microglia can also increase ROS such as NO, superoxide Etc. As a result, these reactive substances can pass directly through the dopaminergic neurons against the endogenous antioxidant system and eventually cause oxidative stress and degeneration of dopaminergic neurons[29]. In addition, a series of enzymes, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX) 1 and 2 can be produced, which can cause some damage to dopaminergic neurons[30-32].

p38MAPK plays an important role in neuro-inflammation and degeneration. Microglia reaction is the core of dopamine neuron degeneration, and recent studies have shown that p38MAPK signaling pathway plays a key role in microglial activation and response impact[33, 34]. Rotenone, dexmedetomidine and paraquat can all activate microglial cells by directly activating p38MAPK, which release large amounts of cytokines and thus damaging dopamine neurons[22, 35, 36]. These toxins can also induce NF-κB activation by directly activating p38MAPK, and iNOS expression is up-regulated. In glial cells, p38MAPK induces iNOS to catalyze the production of nitric oxide (NO) in a large amount, excessive NO can cause lipid peroxidation and other nerve damage[37, 38], inhibiting the synthesis of DNA, leading to neuron death. It can also react with superoxide radicals to generate peroxynitrite and initiate a series of cytotoxicity, eventually leading to neuron loss [39].

In the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) induced Parkinson's disease model mice, MPTP can induce the activation of p38 MAPK in the midbrain substantia nigra[40-42]. The activation of p38 leads to the phosphorylation of p38 and the increase of p-p38 leads to the up-regulation of cyclooxygenase-2 (COX-2), and the up-regulation of COX-2 increases prostaglandin E2 (PGE2)[31, 40]. COX-2 overexpression, COX-2-mediated inflammatory response will further activate caspase-3, which results in dopaminergic neuron degeneration[43]. In addition, the high expression of COX-2 can induce inflammatory response, make reactive glial cell proliferation, increase the release of collagen damage[43, 44]. COX-2 overexpression and its mediated inflammatory response involve in the oxidative stress response in the substantia nigra and cause damage to dopaminergic neurons [45, 46].

Lipopolysaccharide (LPS) is a major component of gram-negative bacterial cell walls and is now known to be an effective stimulator of macrophages in the brain. In vitro and in vivo studies have shown that LPS induced the activation of microglial cells leading to ROS, NOS and pro-inflammatory factors such as IL-1β, IL-6, TNF-α,IFNs production[47, 48]. p38 signaling cascade contributes to immune-related cytotoxicity and neurodegenerative disease sequelae, in the LPS-induced PD model, LPS induces activation of the p38 and JNK pathways, which can increase IL-1β, TNF-α and the production of iNOS, which eventually leads to midbrain neuronal death. [24].

3. p38MAPK acts in oxidative stress in PD development

Oxygen is essential for all human life activities, and is crucial for all living cells. Oxidative stress exerts a causative role of in loss of dopamine neurons, which has been considered to be the pathological hallmark of PD. Genetic, environmental, drugs and other factors can induce oxidative stress response, triggering the body's redox reaction imbalance, resulting in dopamine neuron loss[49-51].

Oxidative stress triggers the p38 MAPK pathway, activating mitochondria and other mitochondrial apoptotic pathways in dopamine neurons. Paraquat, rotenone and MPTP all can directly or indirectly activate the p38MAPK pathway, resulting in increased accumulation of ROS [35, 52]. On the other hand, activated p38MAPK can enhance the oxidative stress, making neurodegeneration[39].

Oxidative stress increases the steady-state levels of ROS and the ROS can regulate the activation of MAPKs in various stimuli-triggered apoptosis[53, 54], the production of ROS activates JNK and p38 MAPK[55], which can induce the production of ROS increased.

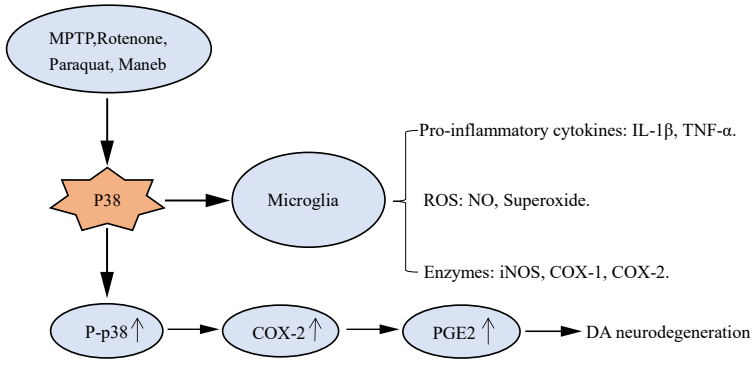

Fig 1. p38MAPK involves in neuro-inflammation in PD progression

Too much ROS can in turn affect the activation of p38MAPK, the formation of a feedback loop play an important role in the development of PD.

4. p38MAPK makes an important role in mitochondrial dysfunction in PD occurrence

Mitochondria play a vital role in energy metabolism. They provide a large amount of available energy in the form of mitochondrial ATP for intracellular metabolic pathways[56, 57]. Mitochondria are highly dynamic, multifunctional organelles, in addition to their primary role in energy metabolism, they are also essential for many cellular processes including neurotransmission, synaptic maintenance, calcium homeostasis, cell death and neuronal survival[58, 59].

Mitochondrial dysfunction is a common feature of sporadic and familial PD. The main manifestations of mitochondrial dysfunction include ROS production, mitochondrial electron transport complex enzymatic activity defection, ATP depletion, caspase-3 release and mitochondrial DNA consumption[60, 61]. Inhibition of mitochondrial complex I or blockade of normal electron transfer may lead to ROS increase and ATP decrease[58], which may damage mitochondrial DNA, destroy respiratory chain and triggering a vicious cycle between mitochondrial damage and oxidation[4].

Energy failure, oxidative stress, genetic mutations and environmental toxicants in PD are closely linked to mitochondrial dysfunction[61]. Neurotoxins such as MPTP, rotenone and paraquat induce the death of dopamine neurons directly related to the mitochondrial complex I activity inhibition, which in turn may cause different mitochondrial disorders and subsequently neuronal degeneration[60, 62].

Mitochondria metabolism is the major sources for ROS that may contribute to intracellular oxidative stress, mitochondrial respiratory chain disorder, particularly complex I deficiency, and the increase of ROS may directly or indirectly lead to the production of sporadic PD[63-65]. Existing research shows that ROS can regulate intracellular signal cascades. Excessive ROS production can lead to intracellular stimulation and mitochondrial damage, eventually leading to apoptosis and necrosis.

MPTP, rotenone and paraquat can cause mitochondrial dysfunction, triggering other stimuli in neurons[42, 66]. MPTP is selectively toxic to dopaminergic neurons, it can cross the blood-brain barrier in minutes and is rapidly metabolized by monoamine oxidase B (MAOB) to the active metabolite MPP+ in the brain, which is selectively transported to dopaminergic neurons[67], then accumulates in the mitochondria[68, 69]. MPP+, an active metabolite in mitochondria, suppresses mitochondrial complex I in the electron transport chain, thereby disrupting the flow of electrons, leading to a decrease in ATP production and an increase in ROS production[68-70]. The expression of MAOB is regulated by the activation of p38 MAPK, and the activation of p38 MAPK is accompanied by astrocyte proliferation, and then causes astrocytes and neuron loss. The activation of MAOB can be prevented by inhibiting the p38 MAPK pathway[67, 71, 72].

One possibility that cytoplasmic p38 affects mitochondria is that p38 activation induces the translocation of its substrate (p53) into mitochondria, which in turn eliminates unhealthy mitochondrial proteins and thereby protect mitochondrial dysfunction[73, 74].

On the other hand, activating the p38MAPK pathway may indirectly induce the mitochondrial pro-apoptotic protein Bax to produce CytC by activating p53, and CytC can activate caspase-3 and cause apoptosis of dopamine neurons[49, 58, 75]. In the study done by Fengsen Duan, ROS was found to regulate the expression of p38MAPK, eventually resulting in mitochondrial damage, which fed back each other and formed a vicious circle[55].

Mitochondrial dysfunction splays an important role in PD occurrence, progression and development. Currently there are many substances against mitochondrial damage used in PD treatment, such as antioxidant enzymes (SOD, CAT), α-lipoic acid, green tea polyphenols, melatonin, ginseng water extract, all showed an improved effect against PD[76, 77].

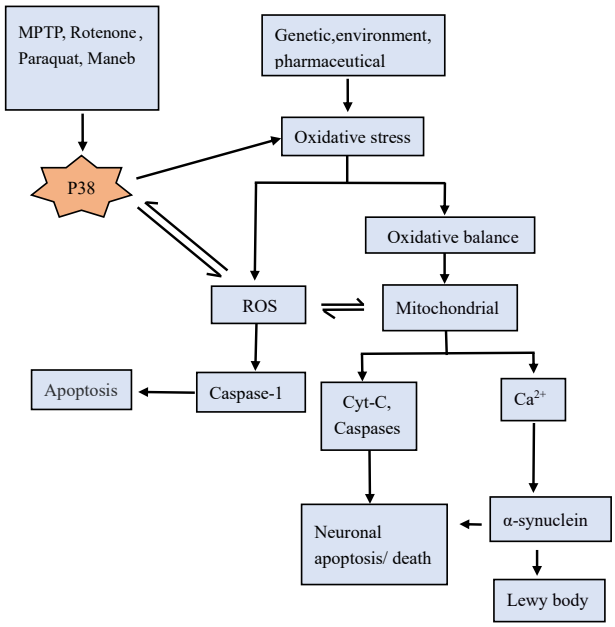

Fig 2. p38MAPK acts in oxidative stress in PD development

5. Conclusion

Parkinson's disease affects approximately 1–2% of the population over 65 years of age, and up to 5% of the population by age 85. Though efforts have been made to elucidate

the PD pathogenesis, the mechanisms are still not understood clearly. Neuro-inflammation, oxidative stress can accelerate the progress and development of Parkinson's disease. Mitochondrial dysfunction plays an important role in the occurrence of PD[39].

p38, as a key member of the signal transduction pathways, plays a crucial role during the process of apoptosis. More and more evidence has shown that the activation of p38 MAPK signal pathway has a vital role in promoting the development of PD and the inhibitory effect of p38 can appropriately improve the therapeutic effect of PD, which may provide a new medicinal strategy for the treatment of PD, this pathway can be used as a breakthrough in the study of Parkinson's disease, and then find effective control disease treatment. In vitro experimental studies showed that minocycline could prevent NO-induced phosphorylation of p38 and cell death associated with NO-induced toxicity, which was neuroprotective in many neurodegenerative models, such as the 1-methyl-4-phenyl-1, 2,3,6-hydrogen pyridine (MPTP) model of PD[78, 79].

Although there are many researches and some medicines have a therapeutic effect on Parkinson's disease, none of them cure the disease fundamentally. Neuro-inflammation, oxidative stress and mitochondrial dysfunction in PD are closely liked to p38MAPK, it may be a target to PD. So for best understanding this signal pathway in PD occurrence progress and development is essential[80].

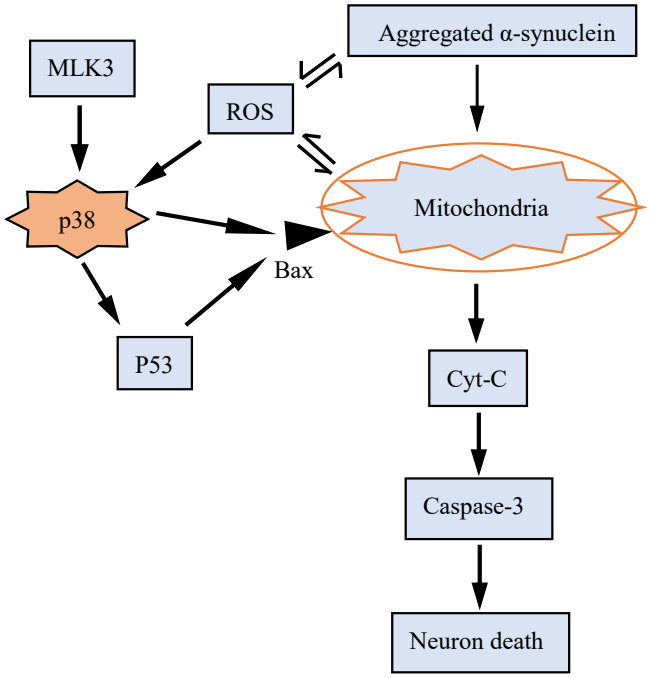

Fig 3. p38MAPK makes an important role in mitochondrial in PD occurrence

Acknowledgements

This work was supported by the fund of Yunnan key program of Science and Technology (2014FA031), National Natural Science Foundation of China (81460593) and Yunnan program of Science and Technology (2015FB006).

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