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Role of P38, a Kind of Signaling Molecules in CNS Diseases

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[**Abstract**] Currently, the researches of P38 and related signaling pathway have become a hotspot in various filed in medical science, due to its role in apoptosis. This review discussed the basic concept, biological function of P38 signaling pathway and its effect on the Central Nervous System (CNS) diseases. Moreover, the related signaling pathways of P38 were also explored. The researches for P38 and its related signaling pathway will contribute to the discovery of new drugs in various diseases in different system, ultimately shed a new light on some incurable diseases, including spinal cord injury (SCI) and Alzheimer's disease (AD).

[**Key words**] P38; Signaling pathway; Biological function; Effect; CNS diseases

P38– 一种信号分子在神经系统疾病中的作用

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[**摘要**] 因 P38 对凋亡的作用, 对 P38 信号分子及其相关信号通路的研究已成为目前医学科学界注目的焦点. 对 P38 的基本概念, 生物学功能及其对神经系统疾病的作用等进行综述. 另外, 与 P38 相关的信号通路也将在本文进行探讨. 对 P38 及其相关通路的研究将有助于不同系统多种疾病的治疗新药的发现, 最终给一些医学难治性疾病, 包括脊髓损伤和阿尔兹海默病等的治疗带来新的曙光.

[**关键词**] P38; 信号通路; 生物功能; 作用; 神经系统疾病
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P38, a crucial member of mitogen activated protein kinase (MAPK)[1], is one member of well known cell–death pathways, namely p38 mitogen – activated protein kinase (MAPK) pathways [2]. Researches[3] have demonstrated that p38 mitogen–activated protein kinase (MAPK) plays an important role in apoptosis and is also involved in the development of CNS diseases, such as cerebral vasospasm after subarachnoid hemorrhage (SAH).

1 Biological functions of P38

Researches [4] have demonstrated that oxidative stress trigger apoptotic pathways such as the c–jun N–terminal kinase (JNK) and p38–mitogen activated protein kinase (MAPK) are preferentially activated by pro – inflammatory cytokines and oxidative stress resulting in cell differentiation and apoptosis. Furthermore, the mitogen–activated protein kinase (MAPK) family of intracellular signal transducers includes ERK1/2, ERK5, JNK/SAPK, and p38 and has been shown to control survival, proliferation and differentiation of cells composing the central and peripheral nervous system. Some MAPKs preferably induce the differ–

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[**Brief introduction**] Li Jin–tao (1972~), male, born in Kunming, Yunnan Province, Doctor of medicine, Associate Professor, of tutor master degree is engaging in the researches involving in neural stem cells and CNS injury, neural stem cells and neurodegenerative diseases.
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entiation of neural precursor cells into the neuronal lineage, whereas others into the glial lineages, which comprises astrocytes, oligodendrocytes, and Schwann cells. Importantly, MAPKs and their upstream signalling receptors play also an important role in the development of neurodegenerative diseases due to their capacity to control neural cell apoptosis. It is therefore of vital importance to better define the processes controlled by MAPKs to design therapies aimed at preventing neurodegenerative disorders in future [5]. Mammalian p38 mitogen-activated protein kinases (MAPKs) are activated by various cellular stresses, as well as in response to inflammatory cytokines. In CNS, activation of the p38 MAPK pathway constitutes a key step in the development of several diseases, and the molecular mechanisms mediated by p38 MAPK signaling have been defined. Activation of this cascade releases pro-inflammatory cytokines that are known to be involved in cerebral ischemia, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), neuropathic pain and depression. In AD, stimulated p38 MAPK may trigger the hyperphosphorylation of a neural microtubule - associated protein, tau. In addition, Yasuda S et al[6] have recently revealed that activation of p38 MAPK signaling decreases dendritic spine number, which may be associated with memory impairment after epileptic seizures.

Thus, p38 MAPK can serve as a target for novel drug development for neural diseases. P38 MAPK inhibitors have been studied extensively in both preclinical experiments and clinical trials for inflammatory diseases. New p38 MAPK inhibitors are now being tested in phase II clinical trials for neuropathic pain and depression.

2 Relationship between P38 and restoration of nerve injury and underlying mechanism

Oxidative stress induced neuronal cell death by accumulation of β-amyloid (Aβ) is a critical pathological mechanism of Alzheimer's disease (AD). Lee YK et al[7] found that 4-O-MH, novel compound extracted from Magnolia officinalis might prevent the development and progression of AD through the reduction of oxidative stress and neuronal cell death via inactivation of p38 MAP kinase pathway. Cui L et al [8]revealed in their study that Oxymatrine, extracted from a traditional Chinese herb, Sophora flavescens Ait, protected the brain from damage caused by middle cerebral artery occlusion (MCAO); this effect may be through down-regulation of 12/15-LOX, phosphop38 MAPK, and cPLA2, but not through downregulation of p38 MAPK. Cyclin-dependent kinase (Cdk) 5 and p38 activities are significantly increased in Alzheimer's Disease (AD). It is well documented[9] that both p38 and Cdk5 promote neurodegeneration upon deregulation. Chang KH et al presented the first mechanism showing Cdk5 as a major regulator of p38 cascade in neurons and in transgenic mouse model of AD. Using beta-amyloid and glutamate as the neurotoxic stimuli, their results showed that deregulated Cdk5 induces p38 activation by increasing reactive oxygen species (ROS) in neuronal cells and in primary cortical neurons. Elimination of ROS inhibits p38 activation, revealing ROS as major stimuli of the p38 cascade. Importantly, Cdk5-mediated p38 activation increases c-Jun expression, thereby revealing a mechanistic link between deregulated Cdk5 and c-Jun level in AD brains. c-Jun is over-expressed in AD, and is believed to contribute significantly to neurodegeneration. Based on the proposed mechanism, Cdk5 inhibition is more neuroprotective relative to p38 and c-Jun, suggesting that Cdk5 is an upstream regulator of neurodegenerative pathways triggered by p38 and a preferable therapeutic target for AD. In another research [10], Abeta42 deposition in hippocampus was found to induce the brain inflammation and the over-expression of p-p38, p-JNK, p-MEK3/6. Inhibiting the over-expression of inflammatory cytokines and phosphorylated MAPK signaling molecules may be a major antagonistic mechanism of total glucosides of paeony (TGP) against AD. This supports the previous notion that in AD, p-p38 was over-expressed, and inhabitor of p38 may plays a critical role in the therapeutic strategy for AD.

Although oxidative stress is fundamental to the etiopathology of Parkinson disease, the signaling molecules involved in transduction after oxidant exposure to cell death are ill-defined, thus making it difficult to identify molecular targets of therapeutic relevance. Niso-Santano M et al [11] found that parkinsonian toxin paraquat (PQ) elicited a dose-dependent in-

crease in reactive oxygen species and cell death that correlated with activation of ASK1 and the stress kinases p38 and JNK. The relevance of these kinases in channeling PQ neurotoxicity was demonstrated with the use of interference RNA for ASK1 and two well-established pharmaceutical inhibitors for JNK and p38. Results showed that ASK1/JNK and ASK1/p38 are two critical pathways involved in the activation of cell death under oxidative stress conditions and identifies the Nrf2/Trx axis as a new target to block these pathways and protect from oxidant exposure such as that found in Parkinson and other neurodegenerative diseases. This suggests that inactivation of p38 played a crucial role in the recovery of impairment resulted from oxidative stress, such as PD, multiple sclerosis (MS) and AD. Cui L et al [8] found that 12/15-LOX, p38MAPK, phospho – p38MAPK and cPLA2 were up-regulated after cerebral ischemia in rats. Compared with MCAO group, atorvastatin, a kind of drug reducing blood cholesterol, dramatically reduced brain water content and infarct sizes, and the over-expressions of 12/15-LOX, p38MAPK, phospho-p38MAPK and cPLA2 were significantly decreased in high dose group (20 mg/kg, $P < 0.05$). Meanwhile, extra-vascular IgG was not only reduced, but blood brain barrier (BBB) permeability was also ameliorated. This suggests that Atorvastatin protected brain from damage caused by MCAO at the early stage; this effect may be through down-regulation of 12/15-LOX, p38MAPK and cPLA2 expressions, and ameliorating BBB permeability. Research [3]demonstrated that p38 MAPK was activated in cerebral vasospasm and associated with increased apoptosis in the basilar arteries and p38 MAPK inhibition suppressed apoptosis, suggesting that p38 MAPK could be a novel therapeutic target for cerebral vasospasm.

Yeghiazarians Y et al[12] found inhibition of the p38 mitogen-activated protein kinase (p38MAPK) directs the differentiation of human embryonic stem cell (hESC) -derived cardiomyocytes (hCM), which played a critical role in the prominent recovery of myocardial infarction in mice models

3 P38 associated signaling pathways

Though p38, JNK and AKT are three members of mitogen activated protein kinase (MAPK) pathway family [1], they exhibit different changes under various conditions.

Fong CC et al[13] proposed that Danshen-Gegen decoction has proliferative effect on myocardium cells via MAPK and insulin signaling pathways. The molecular mechanism of the action may include the up-regulation of IRS/AKT and JNK pathways as well as the inhibition of TNF and p38 pathways. This implys that p38 pathway is negatively correlated with IRS/AKT and JNK pathways. And although ERK, p38 and JNK are members of Mitogen activated protein kinase (MAPK)[1], their responses to a number of actors which contributed to the recovery in various types of injury are different. Researchers[14] also suggested that IL-32 may play a role in the regulation of neuroinflammatory responses in several neurological disease conditions such as ischemia and Alzheimer's disease in that increasing expression of inflammatory mediators accompanied by the increased mRNA expression encoding ERK1/2 and p38, two essential regulators of pro-inflammatory signaling in rat primary astrocytes, activated by IL-32 as evidenced by increased phosphorylation. This indicated that the overexpression of p38 was negatively related to neuroinflammatory impairment. Jin Z et al[15] evaluated the influence of stress on photothrombotic ischemic cortical injury in an animal model. They discovered that the activation of Erk1 and Erk2 were increased by restraint stress in sham operation group but decreased in stroke-stress group than stroke control group. The activation of p38MAPK was increased by stroke but this effect was decreased by restraint stress. This implies that the change of P38 in animal stroke model is adverse when compared with that of Erk1 and Erk2.However, the relationship between P38 and other signaling pathways remains to be elucidated.

4 Summary

P38, as a crucial member in signaling pathway, playing a crucial role in the process of apoptosis, is becoming an important molecule with which to search for novel drugs for many diseases, including cardiovascular diseases, CNS diseases, tumors in which damage of cells and tissues occurred, such as injury, is-

chemia, inflammation etc. Because accumulating evidence suggested that inhibition of P38 will contribut to the efficacy of therapy in some diseases as described before, this may shed a new light on new therapeutic strategies for incurable diseases in near future. However, the underlying mechanism of the action of P38 and the relationship between P38 and its related signaling pathway remain to be elucidated.

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