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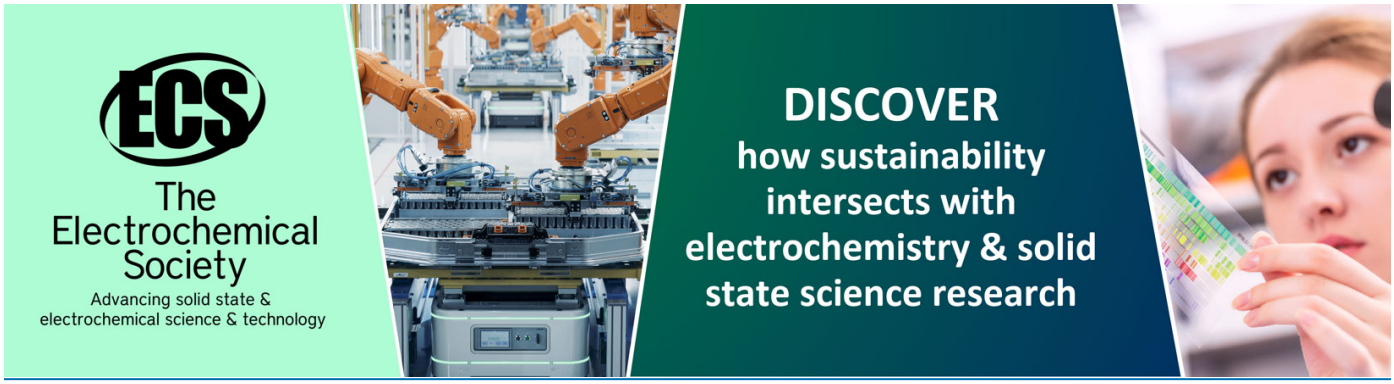

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Phosphorylation of microtubule-associated protein tau by mitogen-activated protein kinase in Alzheimer's disease

Tingting Li, Huahua Shi and Yan Zhao*

Department of Bioengineering, Harbin Institute of Technology, Weihai, Shandong, P. R., 264209 China.

*Corresponding author e-mail: zhaoyan@hitwh.edu.cn

Abstract. Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly. The presence of neurofibrillary tangles (NFTs), which primarily contain self-aggregated hyper phosphorylated tau protein, is one of the major pathological characteristics of AD brains. Tau is a microtubule-associated protein important for regulating microtubule assembly and stability. Abnormal hyper phosphorylation of tau decreases its microtubule-binding capacity and disrupts microtubule stability. A number of protein kinases have been implicated in the abnormal phosphorylation of tau including mitogen-activated protein kinases (MAPKs). This article reviews the hyper phosphorylation of tau in the pathogenesis of AD and discusses the role of MAPKs in the phosphorylation of tau.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly. Patients with AD suffer progressive brain tissue damage and cognitive dysfunction [1, 2]. As the aging population increases, the prevalence of AD has increased remarkably worldwide and AD has become one of the leading causes of disability and death among the elderly [3, 4].

The major pathological characteristics of AD brains are senile plaques, neurofibrillary tangles (NFTs) and neuronal loss [5]. The main components of the NFTs are paired helical filaments and straight filaments, which primarily contain self-aggregated hyper phosphorylated tau [6]. Tau is a microtubule-associated protein important for regulating microtubule assembly and stability [7]. Abnormal hyper phosphorylation of tau decreases its microtubule-binding capacity and disrupts microtubule stability [8]. The disintegration of the microtubules system causes the decline of the axonal transport, resulting in the loss of the axon function [9]. The mechanism of abnormal hyper phosphorylation of tau that leads to neuronal dysfunction is still not totally understood. A number of protein kinases, including mitogen-activated protein kinase (MAPK), have been implicated in the abnormal phosphorylation of tau [10]. This article reviews the hyper phosphorylation of tau in the pathogenesis of AD and discusses the role of MAPK in the phosphorylation of tau.

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2. Microtubule-associated tau protein

The human tau gene is located on chromosome 17q21 [11], containing 16 exons [12]. Tau protein is mainly expressed in neurons. In human adult brain, alternative splicing of exons 2, 3 and 10 generates 6 major isoforms of tau protein, ranging in length from 352 to 441 amino acids, and size from 45 to 65 kDa [13, 14]. The primary structure of full-length tau protein can be divided into four regions: N-terminal acidic domain, proline-rich basic domain, microtubule binding domain and C-terminal domain. Tau associates with microtubules primarily through the microtubule binding domain, comprising either three or four repeats sequences of 31 amino acids, separated by flanking regions [15]. The microtubule binding domain of tau also interacts with actin, providing an important link between the actin filament and microtubule cytoskeletons [16]. The main function of tau is promoting microtubule stabilization, which is essential for cytoskeleton maintenance and intracellular transport [17]. Thus, tau dysfunction decreases microtubule stability and impairs the axonal transport. Tau has also been shown to interact with Src homology-3 (SH3)-containing proteins including the Src family protein kinases, suggesting tau has additional functions such as modulation of cell signaling pathways [18]. The association of amino-terminal domain of tau with the plasma membrane indicates that tau maybe a mediator of microtubule-plasma membrane interaction [19, 20].

Tau is extensively posttranslational modified by phosphorylation. There are about 45 serine and 35 threonine phosphorylation sites in the longest brain tau protein isoform which contains 441 amino acids [21, 22]. At least thirty phosphorylation sites have been described, using the phosphorylation dependent monoclonal antibodies of tau, mass spectrometry and sequencing [23]. Most of the phosphorylation sites of tau are located in the proline-rich regions [24].

3. Abnormal phosphorylation of tau protein in AD

Under normal physiological conditions, the phosphorylation and dephosphorylation of tau is in a dynamic balance [25]. However, the phosphorylation of tau in the brains of AD patients is 2-3 times more than that in the normal individuals [26]. Abnormal hyper phosphorylation of tau decreases its microtubule-binding capacity and disrupts microtubule stability [8]. The disintegration of the microtubules system causes the decline of the axonal transport, resulting in the loss of the axon function [9] and even neuronal death, which can lead to a series of neurodegenerative conditions [27]. The hyper phosphorylated tau aggregated into straight filaments and paired helical filaments, which form NFTs in the neurons of patients with neurodegenerative diseases including AD [28]. It has been shown that the number of NFTs correlates with the presence and the degree of dementia in AD [29].

4. Tau phosphorylation by MAPKs

MAPKs are important cell pathways that regulate many cell activities including gene expression, mitosis, metabolism, apoptosis, proliferation, differentiation and movement [30]. Three major MAPK family kinases identified in mammals are extracellular signal regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase 1 and 2 (JNK1/2) and p38 MAPKs [31]. These MAPKs are sequentially activated by MAPK kinase (MAPKK or MKK) and MAPK kinase kinase (MAPKKK or MEK) [32, 33]. The diversified functions of MAPKs are achieved by the phosphorylation of a wide variety of substrates by MAPKs, such as phospholipase, transcription factors and cytoskeleton proteins [30]. Studies have shown that MAPKs also participate in tau phosphorylation. The serine and threonine sites of tau protein phosphorylated by MAPKs in vitro are consistent with the phosphorylation sites of PHF-tau found in AD brains [34]. Moreover, it is found that MAPKs are localized in AD brain region where axonal dystrophy is developed [35], close to the area of senile plaques and NFTs [36]. Further evidence suggests that p38 MAPKs, ERK1/2 and JNK1/2 are all involved in the phosphorylation of tau in AD.

P38 MAPKs are serine/threonine protein kinases with six isoforms, namely p38α1, p38α2, p38β1, p38β2, p38γ and p38δ, which can be activated by upstream kianses MKK3, MKK4, and MKK6 in response to external stress, inflammatory cytokines or UV radiation [37]. Activation of p38 MAPK is an early event in pathological process of AD [38]. Both in vitro and in vivo results suggest that tau can

be phosphorylated by p38 MAPKs [39]. The activated p38 MAPK colocalized with the epitope of AT8 antibody in AD brains [38].

In response to growth factors, cytokines, osmotic stress and microtubule disorders, ERK1/2 are activated as the downstream kinases of Raf and MEK1/2 [40]. The activated ERK1/2 can phosphorylate many substrates including transcription factors, membrane proteins and cytoskeleton proteins like tau [30]. In PC12 cells, the activation of ERKs is associated with manganese-induced phosphorylation of tau at S199, S202, T205 and S404 [41]. The phosphorylation of tau by ERK may be closely linked to oxidative stress [42]. The basal levels of phosphorylated tau are not reduced by pharmacologic inhibition of ERK1/2 in mice and SH-SY5Y cells [43]. Thus, further studies are needed to determine if ERK directly phosphorylates tau under pathologic conditions.

There are mainly three different isoforms of JNKs, JNK1, JNK2 and JNK3 coded by jnk1, jnk2 and jnk3 respectively [44]. JNKs can be activated by many factors including cytokines, growth factors, oxidative damage, osmotic pressure and heat shock. When inhibit the activity of JNKs, the phosphorylation of tau at S202, T205, and S422 is also significantly decreased [45]. In hippocampal and cortical regions of AD brains, the localization of activated JNK is overlapped with tau-positive NFTs [46]. It has also been shown that the phosphorylation of tau by JNK isoforms reduces the ability of tau to promote microtubule assembly, suggesting an important role of JNK in tau pathology [47].

5. Conclusion

AD is one of the most common neurodegenerative diseases seen in the elderly [1]. With the aging of the population, the number of people with AD has increased remarkably and AD has become a major public health problem globally [3]. Tau protein is a major microtubule-associated protein in neurons [7]. Its normal phosphorylation is necessary for tau to perform its functions. However, the abnormal hyper phosphorylated tau falls off microtubules, disrupting microtubule stability and forming NFTs, a major pathological characteristic found in AD brains [1, 8]. MAPKs are important cell signal pathways that lead to the hyper phosphorylation of tau [34, 38, 46]. It is also reported that hyper phosphorylated tau can induces the activation of MAPK, which may further promote the hyper phosphorylation of tau and tau pathology [48]. Therefore, the activation of MAPKs and the hyper phosphorylation of tau by MAPK are important events contributing to the development of AD.

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