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Review

Tau protein phosphatases in Alzheimer's disease: The leading role of PP2A

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ABSTRACT

Tau phosphorylation is regulated by a balance between tau kinase and phosphatase activities. Disruption of this equilibrium was suggested to be at the origin of abnormal tau phosphorylation and thereby that might contributes to tau aggregation. Thus, understanding the regulation modes of tau dephosphorylation is of high interest in determining the possible causes at the origin of the formation of tau aggregates and to elaborate protection strategies to cope with these lesions in AD. Among the possible and relatively specific interventions that reverse tau phosphorylation is the stimulation of certain tau phosphatases. Here, we reviewed tau protein phosphatases, their physiological roles and regulation, their involvement in tau phosphorylation and the relevance to AD. We also reviewed the most common compounds acting on each tau phosphatase including PP2A.

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1. Introduction

Alzheimer's disease (AD) (Alzheimer, 1907) is a neurodegenerative process characterized by two neuropathological hallmarks: neurofibrillary tangles (NFT) and senile plaques (SP) (Kidd, 1963). A feature of AD is the intraneuronal accumulation of tau proteins in phosphorylated form termed NFT or paired helical filaments (PHF) (Kidd, 1963). The abnormally tau phosphorylated proteins interact with neurofilaments and microtubules disrupting the stability of the neuronal cytoskeleton. SP are the other neuropathological features of AD. These plaques are extracellular and constituted of insoluble aggregates of Aβ42/43 peptides, due to proteolytic processing of amyloid precursor protein (APP) that could be regulated by a specific phosphorylation of APP at T668. This phosphorylation could be lead to APP cleavage into peptides Aβ42/43. In this review, we focus on the cytoskeleton microtubule-associated protein tau, the main element involved in PHF formation.

In AD context, abnormal tau phosphorylation conducts to intracellular aggregates under NFT form. SP are formed from amyloid β-peptide (Aβ) in the extracellular compartment. Molecular and cellular mechanisms responsible for the formation of these lesions are unsolved and their role in AD is still controversial. It remains to be determined whether these lesions are the main causal factor of AD or if there are just markers of the etiologic process.

Several tau post-translational modifications were proposed to play a prominent role in tau aggregation linked to AD. Among them, phosphorylation is the major tau post-translational modification with 85 putative phosphorylation sites (Martin et al., 2011a). Disruption of this equilibrium between tau kinase and phosphatase activities was suggested to be at the origin of abnormal tau phosphorylation and thereby to contribute to tau aggregation.

Phosphatases downregulation has been suggested to be implicated in the abnormal tau phosphorylation and aggregation linked to AD (Gong et al., 1995; Tanimukai et al., 2005; Chen et al., 2008; Gong and Iqbal, 2008; Iqbal et al., 2009). Activity and/or expression of protein phosphatases-1 (PP1), -2A (PP2A), -2B (PP2B), -5 (PP5) and phosphatase and tensin homolog deleted on chromosome 10

Abbreviations: AD, Alzheimer's disease; NFT, neurofibrillary tangles; PHF, paired helical filaments; SP, senile plaques; APP, apolipoprotein; PP1, protein phosphatase-1; PP2A, protein phosphatase-2A; PP2B, protein phosphatase-2B; PP5, protein phosphatase-5; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PDPK, proline-directed protein kinases; TPK, tyrosine protein kinases; GSK3, glycogen synthase kinase-3; CDK5, cyclin-dependent kinase-5; MAPK, mitogen activated protein kinases; TTBK1/2, tau-tubulin kinase 1/2; CK1α/1δ/1ε/2, casein kinase 1α/1δ/1ε/2; DYRK1A/2, dual specificity tyrosine-phosphorylation-regulated kinase 1A/2; MARK, microtubule affinity-regulating kinases; PhK, phosphorylase kinase; PKA, cAMP-dependent protein kinase; PKB, protein kinase B/Akt; PKC, protein kinase C; PKN, protein kinase N; CaMKII, $Ca2^{+}$/CalModulin-dependent protein kinase II; SFK, Src family kinase; c-Abl, c-Abelson; Arg, Abl-related gene; AGE, advanced glycation end products; PPP, phosphoprotein phosphatase; PTP, protein tyrosine phosphatases; I_1^{PP2A}, inhibitor-1 of PP2A; I_2^{PP2A}, inhibitor-2 of PP2A; NLS, nuclear localization sequence; LCMT-1, leucine carboxyl methyltransferase-1; PME-1, phosphatase methylesterase-1; OKA, okadaic acid.

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(PTEN) are disrupted in AD brains (Chung, 2009). Thus, understanding the regulation modes of tau phosphorylation is of high interest in determining the possible causes at the origin of the formation of tau aggregates and to elaborate protection strategies to cope with these lesions in AD. The possible and relatively specific intervention that could abrogate tau phosphorylation is the stimulation of a specific tau phosphatase.

In this review, we succinctly summarize the main tau kinases involved in both balance of tau phosphorylation and AD course. We also describe and discuss the roles and implications of tau protein phosphatases in NFT formation and their relationship to AD. The most relevant compounds activating tau phosphatase(s) are reviewed in order to propose original therapeutic strategies against tau hyperphosphorylation.

2. Tau kinases: a brief overview

Tau phosphorylation is dependent on three classes of protein kinases:

(i) proline-directed protein kinases (PDPK) including glycogen synthase kinase-3 (GSK3) (Hooper et al., 2008; Hanger et al., 2009; Hernandez et al., 2010), cyclin-dependent protein kinase-5 (CDK5) (Patrick et al., 1999) and mitogen activated protein kinases (MAPK) such as p38, Erk1/2 and JNK1/2/3) (Atzori et al., 2001; Ferrer et al., 2001);
(ii) non-PDPK including tau-tubulin kinase 1/2 (TTBK1/2) (Sato et al., 2006), casein kinase 1α/1δ/1ε/2 (CK1α/1δ/1ε/2) (Greenwood et al., 1994; Hanger et al., 2007), dual specificity tyrosine-phosphorylation-regulated kinase 1A/2 (DYRK1A/2) (Woods et al., 2001; Ryoo et al., 2007), microtubule affinity-regulating kinases (MARK) (Biernat et al., 1993; Augustinack et al., 2002), phosphorylase kinase (PhK) (Morishima-Kawashima et al., 1995; Seubert et al., 1995; Paudel, 1997), cAMP-dependent protein kinase (PKA) (Hanger et al., 2007; Tian et al., 2009), protein kinase B/Akt (PKB/Akt) (Zhou et al., 2009), protein kinase C (PKC) (Taniguchi et al., 2001), protein kinase N (PKN) (Kawamata et al., 1998; Taniguchi et al., 2001) and $Ca2^{+}$/CalModulin-dependent protein kinase II (CaMKII) (Litersky et al., 1996; Singh et al., 1996; Yoshimura et al., 2003; Yamamoto et al., 2005);
(iii) and tyrosine protein kinases (TPK) including Src family kinase (SFK) members, *e.g.* Src, Lck, Syk and Fyn (Lee et al., 2004; Lebouvier et al., 2008) and c-Abelson (c-Abl) kinase or Abl-related gene (Arg) kinase (Derkinderen et al., 2005; Vega et al., 2005; Tremblay et al., 2010).

Additionally to their direct phosphorylation, certain tau kinases can also indirectly act on phosphorylation of tau proteins. Kinases such as CDK5 (Sengupta et al., 1997) or PKA (Liu et al., 2004) make tau a better substrate for GSK3β, and consequently promotes excessive tau phosphorylation while others such as PKB (Hajduch et al., 2001), PKC (Isagawa et al., 2000; Li et al., 2006; Wang et al., 2006) or PKN (Isagawa et al., 2000) would instead inhibit, by phosphorylation, GSK3 activity. Interestingly, GSK3β inhibition by neuroglobin attenuates tau hyperphosphorylation through Akt signaling pathway (Chen et al., 2012). Other kinases such as MARK are known to phosphorylate tau aggregates (Chin et al., 2000). During ageing, the increase of advanced glycation end products (AGE) induces tau hyperphosphorylation, memory deterioration, decline of synaptic proteins, and impairment of long-term potentiation in rats by activation of three tau protein kinases, *i.e.* GSK-3, Erk1/2, and p38 (Li et al., 2011).

In AD brains, GSK3β (Yamaguchi et al., 1996; Pei et al., 1997), p38 active form (Zhu et al., 2000), JNK (Zhu et al., 2001; Ferrer et al., 2002), CK1 (Kuret et al., 1997; Schwab et al., 2000), PKA (Layfield et al., 1996; Jicha et al., 1999; Umahara et al., 2004), PKN (Kawamata et al., 1998), Fyn (Shirazi and Wood, 1993; Ho et al., 2005) and c-Abl (Lee et al., 2004; Derkinderen et al., 2005; Lebouvier et al., 2009) co-localize with NFT. In these pathological brains, CK1δ and DYRK1A mRNA levels (Ghoshal et al., 1999; Yasojima et al., 2000; Kimura et al., 2007) as well as expression levels of p38, Erk1/2 and JNK1/2/3 are increased (Hensley et al., 1999; Perry et al., 1999; Shoji et al., 2000; Pei et al., 2002; Swatton et al., 2004). These data suggest that the dysregulation of these protein kinases could be in part responsible of the tau hyperphosphorylation.

Reducing phosphorylation through a specific kinase inhibition has therefore emerged as a target for drug development. Despite considerable efforts to develop therapeutic kinases inhibitors, success has been possible but, so far, insufficient. An alternative approach is to develop pharmacological compounds which enhance the activity of a specific tau phosphatase.

3. Tau phosphatases

Phosphatases are generally classified into three groups according to their amino acids sequences, the structure of their catalytic site and their sensitivity to inhibitors: phosphoprotein phosphatase (PPP), the metal-dependent protein phosphatase and the protein tyrosine phosphatase (PTP). Tau phosphatases belong to PPP group (PP1, PP2A, PP2B and PP5) and PTP group (PTEN).

Physiologically, in human brains without neurodegenerative pathology, analysis of phosphatase activities shows a predominance of PP2A activity (≈71%) compared to other phosphatases like PP2B (≈7%), PP5 (≈11%) or other phosphatases (≈11%, PP1 predominantly) (Millward et al., 1999; Liu et al., 2005a).

In AD brains, total phosphatase activity is reduced by half (Liu et al., 2005a) with PP2A, PP1 and PP5 activities are decreased by 50%, 20%, and 20%, respectively, suggesting that certain tau phosphatases play a crucial role in the AD process (Gong et al., 1993, 1995; Liu et al., 2005a,b; Rahman et al., 2005).

3.1. PP2A: a central role in tau (de)phosphorylation linked to Alzheimer's disease

PP2A is a heterotrimeric phosphatase comprising of a structural A subunit (α and β isoforms), a highly variable regulatory subunit B and a catalytic C subunit (α and β isoforms) (Jones et al., 1993; Ruteshouser et al., 2001; Janssens et al., 2008). The A subunit crescent shape coordinates the assembly of PP2A subunits whereas the B subunit regulates substrate specificity and complex formation with the other subunits (Westermarck and Hahn, 2008). So far, 4 families of B subunits have been identified and called B′/B55/PR55 (α, β, γ and δ isoforms), B′/B56/PR61 (α, β, γ, δ and ε isoforms), B″/PR72 (PR48, PR59, PR72 and PR130 isoforms) and B‴ (PR93/SG2NA and PR110/striatin isoforms). Diversity of each PP2A subunits leads to a multiple combination of more than 200 PP2A heterocomplexes (Xu et al., 2006; Cho and Xu, 2007), increasing the possibilities of action at various phosphorylation sites.

PP2A activity is regulated by three processes: phosphorylation, methylation and the binding of endogenous inhibitors such as inhibitor-1 and -2 of PP2A (I_1^{PP2A} and I_2^{PP2A}) (Li et al., 1995, 1996; Li and Damuni, 1998; Tsujio et al., 2005; Chen et al., 2008). Nuclear I_1^{PP2A} and cytoplasmic I_2^{PP2A} activities are increased by 20% in AD brains (Tanimukai et al., 2005; Chen et al., 2008), suggesting that decrease of PP2A could be at the origin of AD. I_1^{PP2A} activation induces tau hyperphosphorylation at T231, S235, S262, S356 and S404 sites in cultured neuronal cells and disrupts the neuronal cytoskeleton and neuritic growth (Saito et al., 1995; Chen et al., 2008). Abnormal I_2^{PP2A} cleavage in its nuclear localization

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