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Tau degradation: The ubiquitin–proteasome system *versus* the autophagy-lysosome system

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ABSTRACT

The ubiquitin–proteasome system (UPS) and the autophagy-lysosome system are two major protein quality control mechanisms in eukaryotic cells. While the UPS has been considered for decades as the critical regulator in the degradation of various aggregate-prone proteins, autophagy has more recently been shown to be an important pathway implicated in neuronal health and disease. The two hallmark lesions of Alzheimer's disease (AD) are extracellular β-amyloid plaques and intracellular tau tangles. It has been suggested that tau accumulation is pathologically more relevant to the development of neurodegeneration and cognitive decline in AD patients than β-amyloid plaques. Here, we review the UPS and autophagy-mediated tau clearance mechanisms and outline the biochemical connections between these two processes. In addition, we discuss pharmacological methods that target these degradation systems for the treatment and prevention of AD.

Contents

Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer's disease; AMPK, adenosine monophosphate-activated protein kinase; ApoE4, apolipoprotein E4; APP, amyloid-β precursor protein; CHIP, Hsc70-interacting protein; CMA, chaperone-mediated autophagy; CP, core particle; DUB, deubiquitinating enzyme; FIP200, focal adhesion kinase (FAK) family interacting protein of 200 kD; JNK1, c-Jun NH_2-terminal kinase 1; LC3, microtubule-associated protein 1 light chain 3; MAPT, microtubule-associated protein tau; MBD, microtubule-binding domain; mTOR, mammalian target of rapamycin; NFT, neurofibrillary tangles; PAS, pre-autophagosomal structures; PE, phosphatidyethanolamine; PHF, paired helical filaments; PI3K, phosphatidylinositol-3-phosphate kinase; RNF182, RING finger protein 182; ROS, reactive oxygen species; RP, regulatory particle; Rpn, proteasome regulatory particle, non-ATPase-like; Rpt, proteasome regulatory particle, ATPase-like; Ub, ubiquitin; UBA, ubiquitin-activating enzyme; UPS, ubiquitin–proteasome system.

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1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, with more than 36 million newly diagnosed people per year worldwide (Prince and Jackson, 2009). The pathological changes in AD brains usually occur two to three decades prior to the onset of cognitive loss. Several genetic factors, including amyloid-β precursor protein (APP), presenilin 1 and presenilin 2 cause Mendelian forms of AD (Selkoe, 2001). Although familial AD account for only a minor portion of all AD cases, the general phenotypes of familial and sporadic AD are virtually identical, and it is believed that similar pathways may contribute to the development of late-onset AD. The various molecular origins that contribute to the etiology of non-familial forms of AD have been extensively studied. Among them, two major lesions in the AD brain which are thought to drive pathology are the amyloid-β peptide (Aβ)-derived extracellular senile plaques and the intraneuronal intracytoplasmic neurofibrillary tangles (NFTs) formed from hyperphosphorylated and aggregated tau. Accordingly, these proteins have been actively pursued as pharmacological targets for inhibiting the early molecular development of AD.

Initially, Aβ, a proteolytic product of APP was implicated as a key player in Alzheimer pathophysiology. Elevated levels of Aβ appear to act upstream of tau (Gotz et al., 2001; King et al., 2006). Because all known Mendelian causes of AD are related to the increase of APP production and/or amyloid fragment formation, the processing enzymes (β/γ-secretases) and related receptors have received much attention as targets of interest to reduce Aβ accumulation. The observation that a variant in APP that reduces Aβ formation is associated with decreased risk for AD provides yet further support for a key role for this pathway in disease (Jonsson et al., 2012). However, the mechanism of Aβ-mediated neurotoxicity still remains elusive. Various pharmacological interventions targeting Aβ, notably including tramiprosate and tarenflurbil, which were both in phase III clinical trials, showed no significant efficacy to reverse the cognitive decline of AD patients (Aisen, 2009). While these negative data do not preclude the strategy of targeting Aβ, this approach may have limited efficacy if given after a certain point in the disease course, and it may be worthwhile considering other complementary approaches. Increased accumulation of tau shows a stronger correlation with neurodegeneration and cognitive dysfunction, compared with soluble Aβ (Giannakopoulos et al., 2003), suggesting that tau may also be a critical mediator of neurodegeneration in AD (Ethell, 2010). Indeed, tau appears to act as an important effector of Aβ-mediated neurotoxicity. Reducing the levels of endogenous tau was shown to significantly reduce Aβ-induced cytotoxicity and consequent functional loss (Roberson et al., 2007; Vossel et al., 2010). The critical role of tau in AD pathogenesis is supported by a number of additional data. For example, the dual pathway hypothesis (Small and Duff, 2008) proposes that a common cause, such as apolipoprotein E4 (ApoE4), may trigger both abnormal Aβ level elevation and tau phosphorylation, which results in synergic effects in the onset of AD. There may also be close mechanistic links between Aβ and tau before they aggregate (Wray and Noble, 2009). It is also important to note that tau mutations and/or accumulation cause forms of other neurodegenerative diseases, termed tauopathies, including fronto-temporal dementia linked to chromosome 17 with Parkinsonism (FTDP-17), progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. This demonstrates that this protein is not a simple mediator of Aβ pathology but can directly mediate neurodegeneration (See et al., 2010).

Tau is an axonal cytosolic protein functioning in the stabilization of the microtubule network. Through its C-terminal 3 or 4 microtubule-binding domains (MBDs, Fig. 1A), each consisting of 18 amino acids, tau associates with and stabilizes microtubules. During embryogenesis, only the smallest 3R/0N isoform (352 residues) of tau is expressed, while in the adult brain six tau isoforms, generated by alternative splicing in the single MAPT (microtubule-associated protein tau) gene, are present. Various posttranslational modifications, including phosphorylation, glycosylation, and oxidation, occur in tau (Hernandez and Avila, 2007). Tau can also be acetylated, affecting the stability and pathological transformation of tau (Cohen et al., 2011; Min et al., 2010). The degree of tau phosphorylation decreases during embryogenesis, which might be related to increasing neuronal plasticity in the early developmental process. Tau, in its longest 4R/2N isoform (441 residues, Fig. 1A), contains ~80 serine and threonine residues. Among them, ~25 sites that are mainly clustered in the proline-rich domain (PRD) are phosphorylated in the AD disease state, weakening the interaction between tau and microtubules and destabilizing microtubules. Multiple kinases appear to cause tau hyperphosphorylation, including glycogen synthase 3β (GSK3β), cyclin-dependent kinase 5 (CDK5), protein kinase A (PKA), and extracellular signal-regulated kinase 2 (ERK2) (Fig. 1B). A number of pharmacological molecules inhibiting these kinases that may, as a consequence, enhance tau degradation and decrease its aggregation are currently being extensively studied as therapeutic targets in AD (Mazanetz and Fischer, 2007).

Accumulated hyperphosphorylated tau forms intraneuronal filamentous inclusions called paired helical filaments (PHFs), which are the principle constituent of NFT, and all tauopathies are characterized by phosphorylated tau-derived NFT. Although the *in vivo* initiator of tau fabrillization in pathological conditions has not been identified, hexapeptide motifs of tau (Fig. 1A) may function as a core to form β-sheet structures and, subsequently, to induce PHF formation (von Bergen et al., 2000). Notably, one of the hexapeptide motifs includes the ubiquitination site (Lys311) of tau, suggesting a possible link between tau aggregation through oligomerization and tau degradation through ubiquitination. This tau oligomerization process may be further facilitated as tau proteins are dissociated from microtubules, because the nucleation motifs are also located on the MBD and microtubule binding itself may effectively stabilize tau by masking its positively charged middle part (Fig. 1A). Along with insoluble PHFs, other major components of NFT are ubiquitin (Ub) and ApoE proteins, which may reflect cell's compensatory mechanisms for tau elimination and neuronal repair, respectively. Ub exists in NFTs as either a free form or as a protein-conjugate. Tau proteins also frequently undergo a stepwise fragmentation to generate cleaved forms of tau, some of which showed pro-aggregation properties and may induce neurodegeneration (Wang et al., 2010a) (Fig. 1B). The truncated forms of tau protein seem to be cleared by the autophagy system, while the degradation mechanism of the full-length tau is mainly via the ubiquitin–proteasome system (UPS) (Dolan and Johnson, 2010).

Abnormally high levels of intracellular total and phosphorylated tau are frequently observed in AD patients. Increased tau concentrations are directly implicated in its aggregation, PHF, NFT formation, and AD pathogenesis (Fig. 1B). For example, cerebrospinal fluid (CSF) tau levels correlate well with the formation of NFT and are used as a biomarker of Alzheimer-type pathological changes in the brain (Tapiola et al., 2009). The UPS and the autophagy-lysosome system (hereafter referred to as autophagy) are two major pathways that degrade intracellular proteins. Initially, the UPS received more attention as the primary clearance system of pathological tau, but the importance of autophagy-mediated tau degradation, especially at the late stage of NFT formation, is becoming more recognized. However, their relative contributions to normal and pathological tau clearance are still poorly understood. Moreover, it is unclear which system is