Biomedicine & Diseases: Review

RNA and protein-dependent mechanisms in tauopathies: consequences for therapeutic strategies

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Abstract. Tauopathies are a group of neurodegenerative diseases characterised by intracellular deposits of the microtubule-associated protein tau. The most typical example of a tauopathy is Alzheimer’s disease. The importance of tau in neuronal dysfunction and degeneration has been demonstrated by the discovery of dominant mutations in the MAPT gene, encoding tau, in some rare dementias. Recent developments have shed light on the significance of tau phosphorylation and aggregation in pathogenesis. Furthermore, emerging evidence reveals the central role played by tau pre-mRNA processing in tauopathies. The present review focuses on the current understanding of tau-dependent pathogenic mechanisms and how realistic therapies for tauopathies can be developed.

Keywords. Tauopathies, neurodegeneration, Alzheimer’s disease, tau, alternative splicing, phosphorylation, glycogen synthase kinase, aggregation.

Introduction

Several major diseases of the central nervous system are characterised neuropathologically by prominent intracellular accumulations of abnormal filaments formed by the microtubule-associated protein tau in affected neurons and are collectively referred to as tauopathies [1]. Tauopathies include dementias such as Alzheimer’s disease (AD), Pick’s disease (PiD), some forms of frontotemporal dementia and cortico-basal degeneration (CBD) as well as movement disorders such as progressive supranuclear palsy (PSP) [2]. The most characteristic tau-containing lesions are the neurofibrillary tangles (NFTs) found in large number in AD, which are made of paired helical filaments (PHFs). Definitive evidence for the pathogenic importance of tau was provided in 1998 by the discovery of dominant mutations in the MAPT gene, the gene encoding tau, in the rare dementia, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) [3–5]. Tau is mainly expressed in neurons and predominantly localised in axons and promotes microtubule polymerisation and stabilisation [1, 6]. How tau causes neuronal dysfunction and death has been the subject on intense research and reviews of the field are published regularly (for recent examples, see [1, 6–10]). The present review focuses on the current understanding of tau-dependent pathogenic mechanisms and how realistic therapies for tauopathies can be developed.

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The MAPT gene

The human MAPT gene is a large gene of about 134 kb comprising 16 exons on chromosome 17q21.3 [11] (Fig. 1). Alternative splicing of exons 2, 3 and 10 (E2, E3 and E10) in the tau pre-mRNA results in the expression of six isoforms in adult human brain. E10 encodes the second of four imperfect 31–32-amino acid microtubule-binding repeats in the C-terminal half of the tau protein. Exclusion or inclusion of E10 gives rise to tau isoforms with three (tau3R, E10+) or four (tau4R, E10+) microtubule-binding repeats [12]. Furthermore, inclusion or exclusion of E2 and E3 produces tau isoforms with different N termini (Fig. 1). Tau isoforms can have either no N-terminal insert, E2 or E2+E3. E3 is never present without E2. The N terminus of tau regulates its interaction with the plasma membrane [13]. The six tau isoforms resulting from alternative splicing of E2, E3 and E10 have molecular masses ranging from 48 to 56 kDa. Tau3R and tau4R are expressed in approximately equal amounts in adult human brain, but only tau3R is expressed during embryogenesis. Exon 4a encodes a 254-amino acid sequence present in a high molecular weight form of tau expressed only in the peripheral nervous system [14, 15].

Two haplotypes of the MAPT gene, H1 and the less common H2, have been identified [16]. MAPT haplotypes are defined by a region of complete linkage disequilibrium that extends over the entire MAPT gene and contains a series of at least 16 single nucleotide polymorphisms in different exons and introns. Noticeably, H2 also contains a 238-bp deletion in intron 9 between positions –951 and –713 [16] (Fig. 1). H2 is invariant, but several variants of H1 have been identified. The MAPT gene is part of an ~900-kb inversion that prevents the recombination between the H1 and H2 haplotypes [17]. Stemming from the work of Conrad et al. [18], association between specific MAPT haplotypes and a number of tauopathies has now been shown. Homozygosity of H1 is associated with PSP and CBD [16, 19, 20], while H2 shows strong negative association with both diseases [16]. Furthermore, variants of H1, such as H1c and H1b have a high degree of association with PSP and CBD [21, 22]. The H1c sub-haplotype has also been shown to be associated with AD [23, 24] and the importance of the H1c haplotype in AD has been confirmed using quantitative trait analysis [25]. By contrast, no association between MAPT haplotypes and PiD has been found [26]. The association of MAPT haplotypes and tauopathies has been reviewed recently from a genetic standpoint [24]. A heterozygous deletion of 500–650 kb within the inverted region has been detected in three individuals with learning disability [27]. However, whether the clinical phenotype is caused by the loss of one copy of the MAPT gene is still to be determined.

MAPT mutations in FTDP-17

To date more than 35 mutations in the MAPT gene have been associated with FTDP-17. A comprehensive and up-to-date database of MAPT mutations and polymorphisms is available on the World Wide Web at: http://www.molgen.ua.ac.be/FTDmutations/. MAPT mutations are either missense, deletions and silent mutations in the coding region, or intronic mutations. Missense mutations outside E10, such as V337M and R406W, affect both tau3R and tau4R and lead to the development of tau filaments containing all six human tau isoforms, whereas missense mutations in E10, such as P301L and N279K affect tau4R only. The majority of missense MAPT mutations in FTDP-17 reduce the affinity of tau for microtubules and its ability to promote tubulin polymerisation and microtubule stability [28–32]. This is perhaps not surprising as a large proportion of the missense mutations are found in the C terminus of tau near or inside the microtubule-binding domain. In transfected cells, mutant tau binds to microtubules, but is displaced by co-expression of wild-type tau [33]. The G272V, Δ280K, or P301L mutations, but not the R406W mutation, reduce the ability of tau to regulate the dynamic instability behaviour of microtubules [34]. However, the I260V, Δ280K, P301L, V337M and R406W mutations do not affect the rate of translocation of tau in axons in cultured neurons [35]. Transgenic mice overexpressing the missense P301L mutation, the most common one, develop NFTs and Pick-body-like lesions in various areas of the brain from about 5 months of age and display motor and behavioural deficits [36]. These animals, referred to as JNPL3 mice, are widely used in investigating mechanism downstream of tau pathology and in the development of therapeutic strategies. Most intronic MAPT mutations are clustered near the 5′ end of intron 10 and increase the incorporation of E10 [3]. A mutation has also been identified at position –10 in intron 9 that also increased E10 incorporation in vitro [37]. Furthermore, with the exception of the P301L/S mutations, mutations within E10 also promote E10 inclusion. In turn, E10 retention results in a two- to six-fold excess of tau4R over tau3R, as opposed to both isoforms being in approximately equal proportions in normal adult brain [3, 5, 29, 38]. Fibrillar inclusions in neurons from patients carrying these mutations are mainly composed of tau4R. On the other hand, the Δ280K mutation