Tau and neurodegenerative disease: genetics and pathogenetic mechanisms

Gerard D. Schellenberg1-4, Ian D’Souza1,2, Parvoneh Poorkaj1,2 and Thomas D. Bird1-3

1 Geriatric Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA
2 Divisions of Gerontology and Geriatric Medicine, and Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, USA
3 Department of Neurology, 4 Department of Pharmacology, University of Washington, Seattle, WA, USA

Introduction

Neurodegenerative disease is often accompanied by abnormal tau aggregates in the form of neurofibrillary tangles (NFTs) and other intracellular structures. Diseases where tau pathology is found include Alzheimer’s disease (AD) [1], Down syndrome, frontotemporal dementia with parkinsonism-chromosome 17 type (FTDP-17), progressive supra-nuclear palsy (PSP) [2], Gerstmann-Straussler Scheinker disease [3], Pick’s disease [4], amyotrophic lateral sclerosis/parkinson dementia complex of Guam [5], Niemann-Pick type-C disease [6] and to a lesser degree in normal aging. In some disorders such as AD, Down syndrome and some forms of FTDP-17, tau aggregates are exclusively found in neuronal cell bodies as NFTs and as “ghost” tangles, the presumed remains of a dead neuron. In other disorders, such as in some forms of FTDP-17, tau aggregates are also in glial cells. The abnormal tau in these aggregates is highly phosphorylated.

The observation of tau neuropathology in a large number of different diseases suggested that tau aggregates were a consequence of neuronal death but not the cause. However, recently, mutations were identified in the gene (TAU) encoding tau protein in subjects from families with autosomal dominant FTDP-17 [7–9]. Thus altered TAU gene regulation and altered tau protein function can cause neurodegeneration and the process results in NFTs that in some cases are identical to those seen in AD. Thus, in disorders other than FTDP-17, tau must be considered to be an integral part of neurodegeneration and not just a by-product.

Structure and regulation of TAU

Tau is one of a number of homologous proteins belonging a group of proteins referred to as microtubule-associated proteins (MAPs). Though the normal function of tau is not completely understood, this protein is thought to promote microtubule (MT) polymerization and stabilize formed MTs, and possibly promote neurite extension and maintain neuronal integrity [10, 11]. In the central nervous system (CNS), TAU is expressed in high levels in neurons
but is also present in oligodendrocytes [12] and astrocytes. TAU is also expressed in non-neuronal tissues [13, 14].

TAU consists of 16 exons (E0, 1–4, 4a, 5–14; note E0 has also been called E-1) [15–19]. The structure of the gene is known and spans over 100 kb. Multiple protein products are produced and are the result of alternative splicing of exons 2, 3, 4A, 6, 8 and 10 (Fig. 1). The expression patterns of various tau transcripts are complex and depend on the developmental state, the organ, the cell type and the species examined [14]. In rodent and human fetal CNS, only a single transcript is produced (3R0, Fig. 1) and no alternatively spliced exons are included [17, 20]. In the rat, at 7 days after birth, E2+ and E2+/E3+ isoforms appear. E3 is only included when E2 is present, though transcripts with only E2 are observed. E2 and E3 are differentially regulated and appear at different but overlapping times in development [20]. In the human brain, 6 isoforms formed using E2, E3 and E10 (Fig. 1) are observed. In other organisms including rodents, brain isoforms containing E4a are found.

In the C-terminal end of tau there are either 3 or 4 repeated sequences, depending on the isoform, that are MT-binding domains. Three of these repeats are encoded by constitutively included exons. The fourth repeat is specified by alternatively spliced E10. Thus tau protein from transcripts that include E10 have 4 repeats and are called 4R tau, protein from transcripts that do not include E10 are 3-repeat or 3R tau.

Figure 1. TAU gene and cDNA structure (A) Adult human brain tau isoforms. Abbreviations on the left are the exon content for alternatively spliced exons E2, E3 and E10. 4R tau includes E10 and 3R tau does not. (B) Genomic structure of the TAU gene. Exons are indicated by boxes and splicing by lines connecting the boxes. The alternative splicing shown is for adult human brain.