Tau protein

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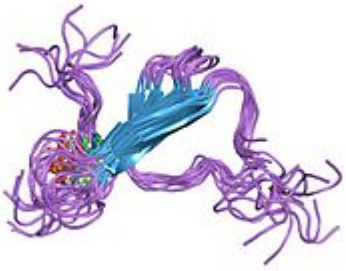

Microtubule-associated protein tau

Tau proteins are proteins that stabilize microtubules. They are abundant in neurons of the central nervous system and are less common elsewhere, but are also expressed at very low levels in CNS astrocytes and oligodendrocytes.[1] Pathologies and dementias of the nervous system such as Alzheimer's disease can result when tau proteins become defective and no longer stabilize microtubules properly.

The tau proteins are the product of alternative splicing from a single gene that in humans is designated **MAPT** (microtubule-associated protein tau).[2][3] They were discovered in 1975 in Marc Kirschner's laboratory at Princeton University.[4]

Function

Tau protein is a highly soluble microtubule-associated protein (MAP). In humans, these proteins are mostly found in neurons compared to non-neuronal cells. One of tau's main functions is to modulate the stability of axonal microtubules. Other nervous system MAPs may perform similar functions, as suggested by tau knockout mice, who did not show abnormalities in brain development - possibly because of compensation in tau deficiency by other MAPs.[5] Tau is not present in dendrites and is active primarily in the distal portions of axons where it provides microtubule stabilization but also flexibility as needed. This contrasts with MAP6 (STOP) proteins in the proximal portions of axons which essentially lock down the microtubules and MAP2 that stabilizes microtubules in dendrites.

Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules. Tau has two ways of controlling microtubule stability: isoforms and phosphorylation.

Structure

Six tau isoforms exist in human brain tissue, and they are distinguished by their number of binding domains. Three isoforms have three binding domains and the other three have four binding domains. The binding domains are located in the carboxy-terminus of the protein and are positively-charged (allowing it to bind to the negatively-charged microtubule). The isoforms with four binding domains are better at stabilizing microtubules than those with three binding domains. The isoforms are a result of alternative splicing in exons 2, 3, and 10 of the *tau* gene.

Tau is a phosphoprotein with 79 potential Serine (Ser) and Threonine (Thr) phosphorylation sites on the longest tau isoform. Phosphorylation has been reported on approximately 30 of these sites in normal tau proteins.[6]

Phosphorylation of tau is regulated by a host of kinases, including PKN, a serine/threonine kinase. When PKN is activated, it phosphorylates tau, resulting in disruption of microtubule organization.[7]

Phosphorylation of tau is also developmentally regulated. For example, fetal tau is more highly phosphorylated in the embryonic CNS than adult tau.[8] The degree of phosphorylation in all six isoforms decreases with age due to the activation of phosphatases.[9] Like kinases, phosphatases too play a role in regulating the phosphorylation of tau. For example, PP2A and PP2B are both present in human brain tissue and have the ability to dephosphorylate Ser396.[10] The binding of these phosphatases to tau affects tau's association with MTs.

Genetics

The MAPT gene for encoding tau protein is located on chromosome 17q21, containing 16 exons[*citation needed*]. The major tau protein in the human brain is encoded by 11 exons[*citation needed*]. Exons 2, 3 and 10 are alternatively spliced, allowing six combinations ($2^{-}3^{-}10^{-}$; $2^{+}3^{-}10^{-}$; $2^{+}3^{+}10^{-}$; $2^{-}3^{-}10^{+}$; $2^{+}3^{-}10^{+}$; $2^{+}3^{+}10^{+}$). Thus, in the human brain, the tau proteins constitute a family of six isoforms with the range from 352-441 amino acids. They differ in either zero, one or two inserts of 29 amino acids at the N-terminal part (exon 2 and 3), and three or four repeat-regions at the C-terminal part exon 10 missing. So, the longest isoform in the CNS has four repeats (R1, R2, R3 and R4) and two inserts (441 amino acids total), while the shortest isoform has three repeats (R1, R3 and R4) and no insert (352 amino acids total).

The MAPT gene has two haplogroups, H1 and H2, in which the gene appears in inverted orientations. Haplogroup H2 is common only in Europe and in people with European ancestry. Haplogroup H1 appears to be associated with increased probability of certain dementias, such as Alzheimer's disease. The presence of both haplogroups in Europe means that recombination between inverted haplotypes can result in the lack of one of the functioning copy of the gene, resulting in congenital defects.[11][12][13][14]

Role in disease

Further information: Tauopathy

Hyperphosphorylation of the tau protein (tau inclusions, pTau) can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of Alzheimer's disease and other tauopathies.[15]

All of the six tau isoforms are present in an often hyperphosphorylated state in paired helical filaments from Alzheimer's disease brain. In other neurodegenerative diseases, the deposition of aggregates enriched in certain tau isoforms has been reported. When misfolded, this otherwise very soluble protein can form extremely insoluble aggregates that contribute to a number of neurodegenerative diseases.

Recent research suggests that tau may be released extracellularly by an exosome based mechanism in Alzheimer's disease.[16][17]

Some aspects of how the disease functions also suggests that it has some similarities to prion proteins.[18]

Traumatic brain injury

High levels of tau protein in fluid bathing the brain are linked to poor recovery after head trauma.[19]