A GLANCE ON STRUCTURE AND ABNORMAL HYPERPHOSPHORYLATION OF TAU PROTEIN

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ABSTRACT:

Microtubule related protein (MAP) tau is anomalous hyperphosphorylated in Alzheimer's malady (AD) and related tauopathies; in this structure it is the significant protein subunit of combined helical fibers (PHF)/neurofibrillary tangles. Tau protein plays a role in microtubule assembly and dynamics that may regulate neuron morphology. This gene is transcribed into a nuclear RNA that yields six different isoforms, lacking or containing exons 2, 3, and 10 by alternative splicing. 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, frontotemporal dementia and other tauopathies. Mechanisms involved in hyperphosphorylation of tau are reduced level of protein *O*-GlcNAcylation, which reciprocally regulates phosphorylation , reduced activity of PP-2A in AD brain, increase in the activities of CaMKII, PKA and MAP kinases, inherited FTDP-17, tau mutations G272V, P301L, V337M and R406W, alterations in PP2A and PP2A regulatory proteins.

Key words: Tau, hyperphosphorylation, hexosamine, O-GlcNAcylation, CaMKII, PKA and MAP kinases, FTDP-17, PP2A and PP2A regulatory proteins.

INTRODUCTION

Alzheimer's sickness is notable to highlight neurofibrillary tangles that are made out of modified tau protein. Some other brain disorders related with anomalous tau protein are chronic traumatic encephalopathy, Pick disease, frontotemporal dementia with parkinsonism-17 (FTDP-17), dynamic supranuclear Palsy (PSP), and corticobasal degeneration (CBD). Albeit every one of these types of dementia is different, they are altogether chronic and progressive. Tau proteins in the cerebrums of individuals with Alzheimer's sickness are misfolded and unusually formed. The typical tau protein shapes some portion of a structure called a microtubule. One of the elements of the microtubule is to help transport supplements and other significant substances from one piece of the nerve cell to another.

STRUCTURE OF TAU:

The tau gene has 16 exons; exon 1, 4, 5, 7, 9, 11, 12and 13 (light blue) are constitutively transcribed in the CNS [5]. Exon 4A, 6 and 8 (orange) are often expressed in the brain but included in mRNA of most peripheral tissues, while exon 14 forms part of the 31untranslated region of the tau mRNA .

Exon 2, 3, 4A, 6, 8, 10 and 14 are spliced alternatively. Splicing of this gene might cede to [produce] 30 different variants of tau protein which creates an additional layer of complexity in distribution of tau at numerous tissues. Six widely known isoforms of tau in the CNS are generated through alternate splicing of exon 2, 3, and 10 with 352 to 441 amino acids in length and 60–74 kDa in weight on SDS-PAGE. **Foetal tau** is the smallest isoform of tau expressing three microtubule-binding repeats on its C-terminal (3R) and 0 N-terminal inserts, found in foetal brain and rest are found mostly in adult brains comprising either 3 or 4 [3R/4R] microtubule binding repeats and the presence or absence of 1 or 2 N-terminal inserts. The other five isoforms are bigger and predominantly found in the adult brain, having either three or four (3R/4R) microtubule binding repeats and the presence or absence of 1 or 2 N-terminal inserts [6].

Structurally, tau is subdivided into four regions; an N-terminal acidic region; a Proline-rich domain (PRD), repeat domain region and a C-terminal region, and the epitopes across these regions vary depending on the tau isoform [5, 6]. Isoform localization preference also exists between developmental stages, tissues, cell lines, brain regions and intracellular compartments.
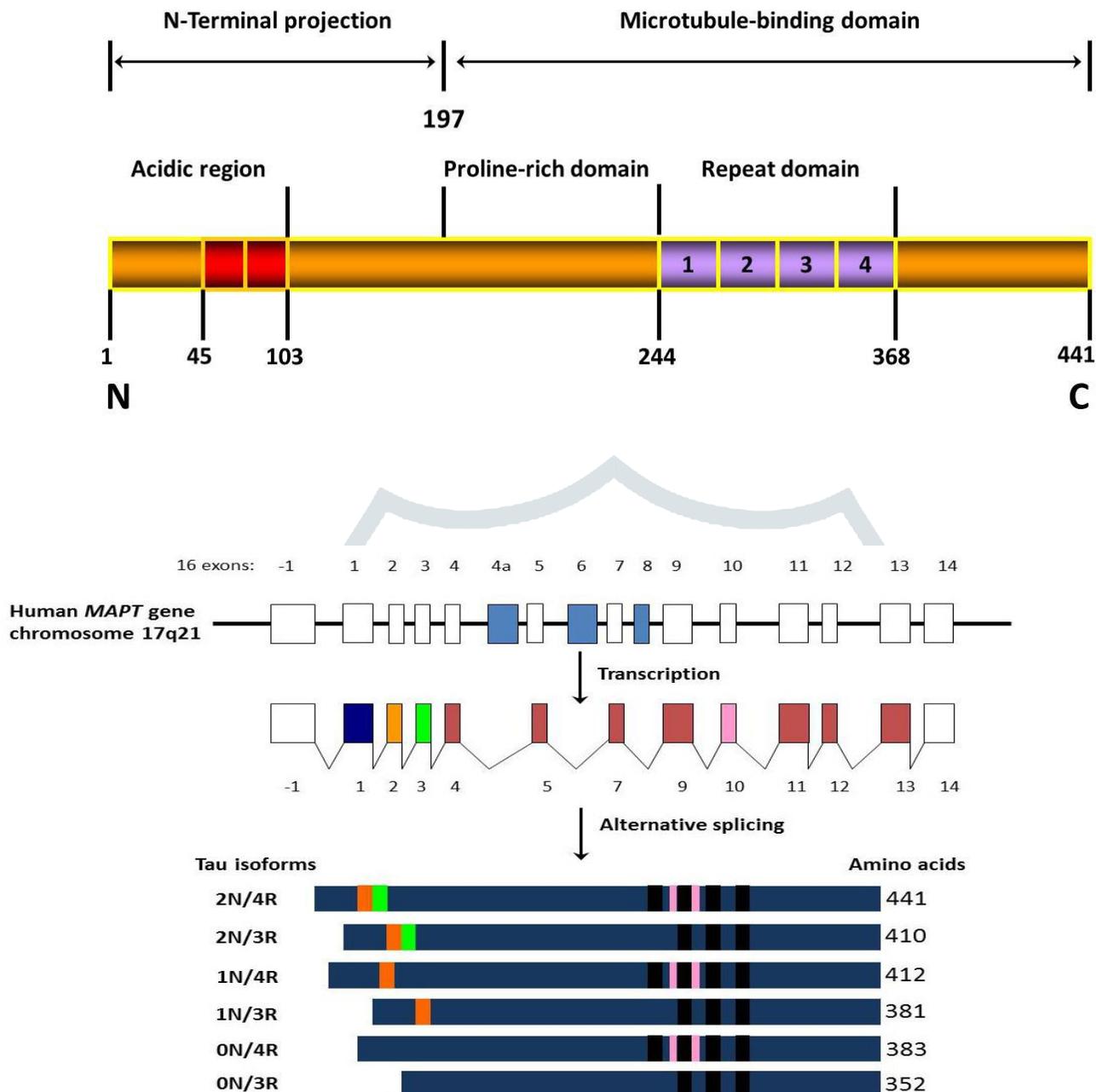
MECHANISMS UNDERLYING ABNORMAL HYPERPHOSPHORYLATION OF TAU:

Tau becomes abnormally hyper phosphorylated in AD and other tauopathies. Major mechanisms involved in the abnormal hyper phosphorylation of tau are:

- Reduced level of protein *O*-GlcNAcylation, which reciprocally regulates phosphorylation
- reduced activity of PP-2A in AD brain
- increase in the activities of CaMKII, PKA and MAP kinases
- inherited FTDP-17, tau mutations G272V, P301L, V337M and R406W
- Alterations in PP2A and PP2A regulatory proteins

1. O-GlcNACYLATION IN HYPERPHOSPHORYLATION OF TAU:

It is a novel type of protein O-glycosylation in which GlcNAc is transferred from UDP-GlcNAc donor onto the hydroxyl group of serine or threonine residues of proteins via an O-glycosidic bond by a cytosolic enzyme O-GlcNAc transferase (OGT). OGT activity as well as intracellular concentration of UDP-GlcNAc regulates protein O-GlcNAylation. Since UDP-GlcNAc is orchestrated from glucose through the hexosamine biosynthetic pathway, the intracellular UDP-GlcNAc focus relies upon glucose digestion. O-GlcNAc on proteins can likewise be evacuated with catalysis of β-N-acetyl-glucosaminidase (O-GlcNAcase). O-GlcNAcylation directed phosphorylation of tau in a site-

explicit way both in vitro and in vivo. At the greater part of the phosphorylation sites, O- GlcNAcylation inversely directed tau phosphorylation.

Fei Liu, et.al states that in an animal model of starved mice, diminished O-GlcNAcylation was produced by low glucose uptake/metabolism that mimicked those observed in AD brain resulting in the consequent hyperphosphorylation of tau at most of the phosphorylation sites. When contrasted with that in controls the O-GlcNAcylation level in AD brain was diminished. These outcomes uncover the pathway of regulation of tau phosphorylation and propose that abnormal hyperphosphorylation of tau could result from diminished tau O-GlcNAcylation, which presumably is initiated by insufficient brain glucose uptake/metabolism in AD and different tauopathies.

Restraint of the hexosamine biosynthesis pathway in rodent brain brought about diminished O-GlcNAcylation and expanded phosphorylation of tau, which resembled changes of O-GlcNAcylation and phosphorylation of tau in rat cerebrum, with diminished glucose metabolism initiated by fasting, however not those in rat brains when protein phosphatase 2A was repressed. Declined tau phosphorylation was observed at most of the phosphorylation sites at the point when Tau O-GlcNAcylation in separated PC12 cells was raised by inhibiting the OGlcNAcase activity in the presence of streptozocin (STZ) or O-(2-acetamido-2-deoxy-D-glucopyranosylidene)amino-Nphenylcarbanate (PUGNAc)

Comparable outcomes were additionally gotten in metabolically active rodent brain slices. Conversely, when the PC12 cells were cultured in medium containing 6-diazo-5-oxonorleucine (DON), an inhibitor of the hexosamine pathway, and, thusly, of protein O-GlcNAcylation, a decrease of protein O-GlcNAcylation and a rise of tau phosphorylation were observed. These outcomes unmistakably exhibit that O-GlcNAcylation contrarily directs phosphorylation of tau in cells. Such a reverse connection between O-GlcNAcylation and phosphorylation of tau is likewise observed in cerebellar granule neurons and tau-and OGT-transfected CHO cells.

In normal brain, both O-GlcNAcylation and phosphorylation can alter tau and these two adjustments keep harmony. In AD, diminished intracellular UDP-GlcNAc and tau O-GlcNAcylation (showed by more slender bolts) ceded by impeded glucose take-up/ metabolism which further initiated by numerous natural/metabolic/hereditary factors. Since O-GlcNAcylation regulates phosphorylation of tau contrarily, the diminished tau O-GlcNAcylation permits more phosphorylation of tau (i.e., hyperphosphorylation). The anomalous hyperphosphorylation not exclusively can't stimulate microtubule assembly or to balance out microtubule structures, yet additionally carries on as a toxic molecule to sequester typical MAPs and interrupt microtubules.
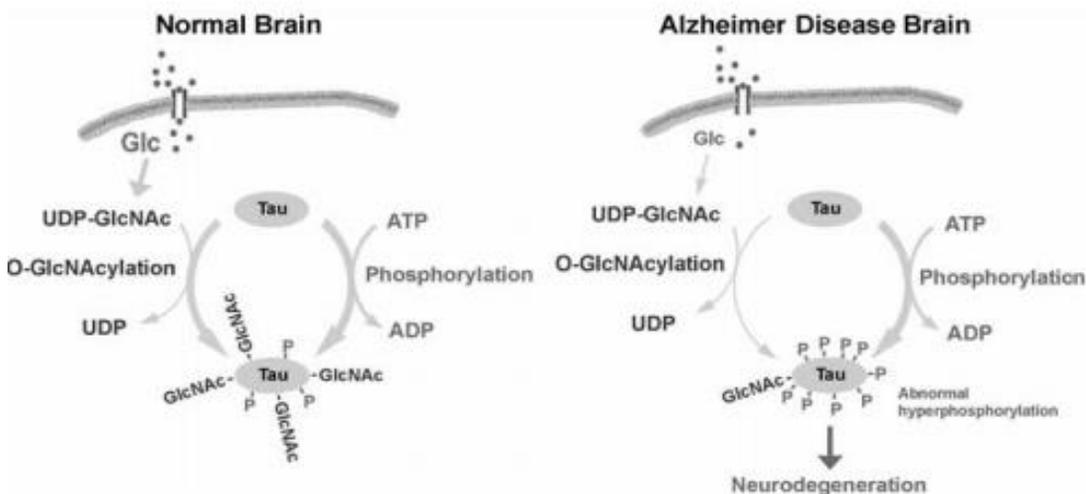
2. Reduced activity of PPA-2 IN AD brain:

Most of the brain Ser/Thr phosphatase activity is carried out by large family of enzymes namely Protein phosphatase 2A (PP2A). Specifically noteworthy to the Alzheimer's ailment (AD) field, adjustments in PP2A regulators and PP2A catalytic activity, subunit expression, methylation as well as phosphorylation, have been accounted for in AD-affected brain regions. The main pathological hallmarks of this neurodegenerative disorder like Hyper phosphorylation, amyloidogenesis and synaptic deficits has been connected to PP2A dysfunction which further affects the activity of Ser/Thr protein kinases implicated in AD.

The PP2A/Bα isoform is the primary tau phosphatase that binds to tau and expanded tau phosphorylation is correlated with its deregulation. Disruption of PP2A/Bα-tau protein interactions likely add to tau deregulation in

AD. Significantly, alterations in one-carbon metabolism that impair PP2A methylation are related to increased risk for sporadic AD, and enhanced AD-like pathology in animal models. Fundamentally, changes in one-carbon metabolism that hinder PP2A methylation are related with expanded hazard for sporadic AD, and improved AD-like pathology in animal models.

Post translational modifications of Tau:

Significantly, down-regulation of LCMT1 expression results in a big decrease of PP2A methylation and concomitant loss of PP2A holoenzymes containing the regulatory Bα (or PPP2R2A) subunit (PP2A/Bα).

Leucine carboxyl methyltransferase-1 (LCMT-1) catalyze the methylation of PP2A synergist subunit on Leu-309 and) and availability of the universal methyl donor, S-adenosylmethionine (SAM), regulates, the LCMT1 activity as similar to all methyl transferases and is inhibited by S-adenosylhomocysteine

On the other hand, the PP2A-explicit methylesterase PME-1 can straightforwardly bind to the active site of catalytic sub-unit, evacuate the methyl group and inactivate PP2A by removing manganese ions needed for phosphatase action. Protein complexes containing PME-1 coupled to demethylated, idle PP2A have been isolated in vivo

Biogenesis of PP2A holoenzymes mainly based on methylation. Substrate specificity as well as PP2A cellular sub unit composition is changed by altering the overall methylation status of PP2A catalytic subunit status.

Essentially, down-guideline of LCMT1 articulation prompts a huge diminishing of PP2A methylation and attendant loss of PP2A holoenzymes containing the administrative Bα (or PPP2R2A) subunit (PP2A/Bα; Lee and Pallas, 2007; Sontag et al., 2008; MacKay et al., 2013).

Changed PP2A subunit articulation, action and post-translational alterations have been portrayed in AD autopsy examination cerebrum tissue. A portion of these progressions might be intervened by modifications in explicit PP2A modulatory proteins (LCMT1, PTPA, alpha4) and endogenous PP2A inhibitors (I1PP2A and I2PP2A) that have additionally been accounted for in AD examination mind tissue. They likewise decline the cooperation of PP2A with tau. (B) The biogenesis of the PP2A/Bα holoenzyme, the essential Ser/Thr tau phosphatase in vivo, is accepted to be constrained by Leu-309 methylation of PP2A reactant subunit by LCMT1. This response requires the flexibly of SAM, the general methyl benefactor, and is hindered by SAH. The PP2A methylesterase, PME-1, can demethylate and inactivate PP2A through unmistakable systems, and structure a complex with inert PP2A catalysts. Those inert edifices could be-reactivated by means of the activity of the PP2A activator PTPA, taking into consideration ensuing methylation of PP2A C subunit. Many brain Ser/Thr protein kinases, including GSK3β, restrict the activity of PP2A/Bα and advance tau phosphorylation. Restraint or potentially down-regulation of PP2A can improve tau phosphorylation straightforwardly by forestalling its dephosphorylation or in a roundabout way by up-managing tau kinases.
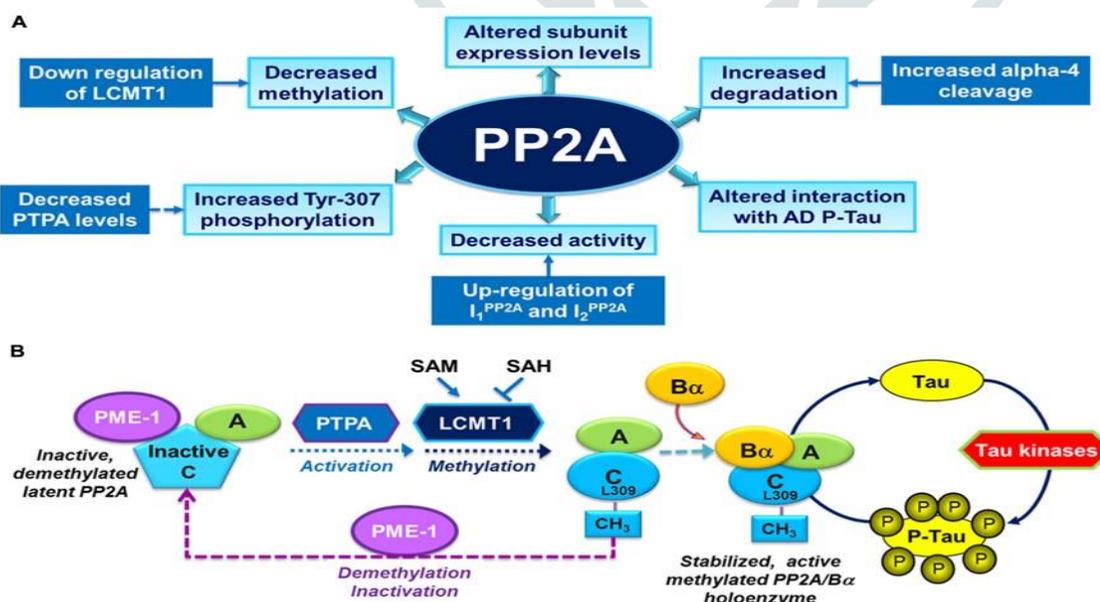
3. Alterations in PP2A and PP2A regulatory proteins:

There is a noteworthy reduction altogether PP2A activity estimated in AD cortical and hippocampal cerebrum homogenates. Shortages in PP2A action are in accordance with the detailed down- regulation of PP2A catalytic C subunit at the gene mRNA and protein articulation levels in AD. Conversely, "PP2A" articulation levels are expanded in AD astrocytes (Pei et al., 1997). All the more explicitly, diminished articulation levels of PP2A regulatory Bγ (or PPP2R2C) and B'ε (or PPP2R5E) subunit mRNAs in the hippocampus and cortical Bα subunit have been accounted for in AD. Quite, the loss of neuronal PP2A/Bα holoenzymes connects with the down-regulation of PP2A methylation and seriousness of phosphorylated tau (P-tau) pathology in AD-affected brain areas. Significantly, down-regulation of LCMT1 protein articulation matches the shortfalls in PP2A methylation saw in AD . Up-guideline of I1PP2A and I2PP2A, and mislocalization and cleavage of I2PP2A, could underlie the inactivation of PP2A in AD neocortical neurons. Diminished articulation levels of PTPA in AD cerebrum tissue may likewise prompt inactivation of PP2A by in a roundabout way expanding levels of PP2A phosphorylated at the Tyr-307 site. In conclusion, expanded calpain-interceded cleavage of alpha4, which basically regulates PP2A steadiness, could be answerable for increased degradation of PP2A catalytic subunit in AD.

4. FDTP- 17 mutations:

FTDP-17 is brought about by transformations in the MAPT gene. This gene is situated on chromosome 17, which is the way the illness got its name.

The MAPT gene gives directions to making a protein tau. Transformations in the MAPT gene disrupt the typical structure and function of tau. The imperfect protein structures unusual clusters inside neurons and other synapses. Notwithstanding, it is indistinct what impact these clusters have on cell capacity and endurance. FTDP-17 is portrayed by the continuous passing of cells in the frontal and temporal lobes of brain. The frontal projections are associated with thinking, arranging, judgment, and critical thinking, while the temporal flaps help process hearing, discourse, memory, and feeling. Lost cells in these brain locales prompts character changes, discourse challenges, and different highlights of FTDP-17.

FTDP-17 is one of a few related infections known as tauopathies, which are described by a strange development of tau in the mind.

5. Increase in the activities of CaMKII, PKA and MAP kinases:

Microtubule related protein (MAP) tau is anomalous hyperphosphorylated in Alzheimer's malady (AD) and related tauopathies; in this structure it is the significant protein subunit of combined helical fibers (PHF)/neurofibrillary tangles. In any case, the idea of protein kinases and phosphatases and tau destinations engaged with this injury has been tricky. self-assembly and microtubule assembly promoting activites of hyperphosphorylated tau detached from Alzheimer disease cerebrum cytosol, the AD strangely hyperphosphorylated tau (AD P-tau) when dephosphorylation by phosphoseryl/phosphothreonyl protein phosphatase-2A (PP-2A), and afterward rephosphorylation by cyclic AMP-subordinate protein kinase (PKA), calcium, calmodulin-subordinate protein kinase II (CaMKII), glycogen synthase kinase-3β (GSK-3β) and cyclin-subordinate protein kinase 5 (cdk5) in various kinase combinations.

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