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Review On Alzheimer's Disease; A Neurodegenerative Tauopathy

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Abstract- Alzheimer's is a slowly progressive neurodegenerative disease and is one of the most common types of dementia, which causes, degeneration of the cells in the brain. It is a major concern in older people. Pathological characterization of Alzheimer's shows neurotic plaques and neurofibrillary tangles because of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain. Tau is an important microtubule-associated protein that stabilizes microtubules polymerization and regulates axonal stability thus contributing to the proper functioning of neurons. Alteration in tau, forms neurofibrillary tangles and amyloid plaques in intercellular space causing disruption in signal transmission. The molecular mechanism which causes tau aggregation is posttranslational modification. Abnormal phosphorylation is found in Alzheimer's disease. This review describes the role of tau in stabilization and destabilization and the molecular mechanism which causes Alzheimer's disease.

Keywords : Alzheimer's disease, Tau protein, Tauopathies.

INTRODUCTION - Alzheimer's disease is a neurodegenerative tauopathy characterized by the abnormal deposition of tau protein in the brain (Gabor G. Kovacs 2018)Tau protein is predominantly found in brain cells, a microtubule-associated protein that stabilizes microtubule bundle and is abundant in axons of neurons. Tau function is regulated by phosphorylation. Tau is the most studied MAPs because of its implication in the group of a neurodegenerative diseases called Tauopathies. Tau is customarily a "natively unfolded" protein with a major physiological role in the maintenance of microtubule stability (S. Muralidar et.al, 2020). This normal predominant unfolded conformation of tau expresses a very low tendency towards any kind of misfolding, aggregation, and accumulations in both intracellular and extracellular conditions (S. Muralidar et.al, 2020) Hence, if any deteriorative modification in tau such as "prion-like" dispersions leads to abnormal folding and aggregation results in neurodegenerative disorders referred generally as tauopathies. One of them is Alzheimer's disease. In this disease, tau is found in a hyperphosphorylated state (p-tau). Hyperphosphorylation of tau can potentially modulate the conformation and charge of the protein which ultimately leads to the exposure of the microtubule-binding domain enabling self-aggregation and oligomerization of tau.

The aggregated tau proteins eventually get converted into neurofibrillary tangles, hyperphosphorylation of tau at C- terminus induce self-assembly of tau protein and this conformation of tau leads to the loss of axonal transport and causes microtubule disassembly. In Alzheimer's disease, there is a higher amount of hyperphosphorylated tau protein is seen in comparison to the normal human being. This state of tau alters

the functioning of the microtubule and leads to improper axonal transport causing problems with memory, language, thinking, or judgment.

classification Of Tau protein

The MAP tau is physiologically associated with polymerization, stabilization, and spacing of microtubules. tau protein is encoded by the gene MAPT. This gene encodes six isoforms by alternative splicing of exons 2, 3, and 10, three isoforms each with either three or four tandem repeats within the microtubule-binding domain, called 3R or 4R-tau isoforms, respectively. Tau is the vital mediator of axonal growth, maintenance, adaptation, and function (F. Liu. Et. Al. 2008). Pathologically, Tauopathies are characterized by intracellular deposits of the protein tau. The different tau isoforms, 3R-tau, or 4R-tau, or mixed 3R-/4R-tau in Alzheimer's disease produce different ultrastructural aggregates and affect different regions of the brain (Marisol Espinoza. et.al.2008.

The TAU Gene- A cDNA for tau was first isolated from a mouse brain expression library, and subsequently, it was cloned from other species including goat, chicken, bovine, and human. recently, tau protein sequences have been identified in different species.

Human TAU Gene Expression- The human gene is located on chromosome 1, where it occupies over 100 kb and contains at least 16 exons (Following a GC-rich 5′-region, a single untranslated exon exists. Upstream of this exon there are several DNA sequences that contain consensus binding sites for promiscuous transcription factors such as AP2 or SP1. Tau is mainly expressed in neurons, and interaction with a neural-specific factor has been proposed. Nevertheless, the neural-specific expression of the protein could be also due to the presence of possible silencer elements in nonneural cells (Jesus. A, et.al.)

Tau protein localization- Tau is a microtubule (MT)-associated protein that is thought to be localized to the axon. However, its precise localization in developing neurons and mechanisms for the axonal localization of tau in cultured rat hippocampal neurons mainly occur during early neuronal development. Interestingly, transient expression of human tau in very immature neurons, but not in mature neurons, mimicked the developmental localization of endogenous tau to the axon. The tau-1 antibody has been widely wont to label the axons, as dephosphorylated tau at Ser-195, Ser-198, Ser-199, and Ser-202 (Szendrei et al., 1993) has been shown to highly accumulate within the axons of immature neurons in culture (Mandell and Banker, 1996). Although total tau has also been shown to be accumulated in distal axons (Mandell and Banker, 1996), its precise subcellular localization studied. The axonal accumulation in stage 3 neurons is not due to the increasing volume of the distal axon, as GFP did not exhibit such accumulation. Also, acetylated tubulin, which has also been shown to be accumulated in distal axons in immature neurons (Hammond et al., 2010), colocalized with tau at a high degree. These results suggest that the axonal localization process of tau starts already in stage 3 neurons.

Functions of normal tau

Neurons are the functional building blocks of the brain. Microtubules play an important role to maintain structural backbone and functions of neurons. MTs are stabilized in particular directions which give rise to two different cytoplasmic extensions like axon and dendrites. The primmest function of tau is providing stabilization of microtubules in distal portions of axons and dendrites. Recent studies revealed that tau also plays important role in other secondary functions like engaging to enzymes and structures like RNA and presenilin 1 (PS1) (S. Muralidar et.al, 2020)

Mts stabilization provides tau the ability to regulate MT- structure, and dynamics and thus can alter morphological l and regulatory functions of cells directly or indirectly. The microtubule network is responsible for axonal transport systems that allow the s transport of vital cellular components like cell organelles and signaling molecules. Thus, microtubule facilitated axonal transport systems and stabilization of MTs completely depends on tau. Furthermore, Tau is of prime importance in conserving the architecture of neuronal cells. Kurt R. Brunden 2014.

Tauopathy in Alzheimer's disease Pathological effects of tau

Tau is typically a "natively unfolded" protein that plays an important physiological role within the maintenance of microtubule stability. This normal predominant unfolded conformation of tau expresses a low tendency towards any misfolding, aggregation, and accumulation in both intracellular and extracellular conditions.

Hence, any deteriorative modification in tau like "prion-like" dispersions leads to abnormal folding and aggregation results in neurodegenerative disorders referred generally as tauopathies. even though phosphorylation has an important role in modifying tau under normal physiological conditions, an increased level of this modification results in self aggregated and hyperphosphorylated tau (p-tau. Hyperphosphorylation of tau can potentially modulate the conformation and charge of the protein which ultimately results in the exposure of the microtubule-binding domain enabling self-aggregation and oligomerization of tau. These aggregated tau proteins eventually get converted into neurofibrillary tangles (NFTs). Prior to the formation of NFTs, hyperphosphorylation at the C terminus of tau induces the self-assembly of tau protein resulting in the formation of paired helical filaments (PHFs). This conformation of the aggregated version of tau protein results in loss of axonal transport and also constantly covers way for microtubule destabilization]. Compared to the traditional controls, AD patients possess a relatively higher amount (4 fold increased) of abnormal or hyperphosphorylated tau proteins. Additionally, these misfolded tau proteins lose their primary function of MT stability alongside increased aggregation effects and are found to be potential neurotoxins. Ultimately, Tau-MT functioning is compromised resulting in synaptic plasticity and lack of proper axonal transport leading to cognitive insufficiencies. Further, p-tau also triggers the activation of MT- severing proteins like katanin to worsen the method of microtubule assembly .

Effects of Protein interactions on tau pathologies- From the above information, it can be concluded that abnormal phosphorylation and dephosphorylation could lead on to extreme pathological effects on the patients. Among them, Amyloid-β, Pin1, Fyn Kinase, Heat Shock Proteins, FKBP51 and FKBP52Immunophilins, α-Synuclein, PACSIN1 are the pivotal proteins that have direct effects on either phosphorylation or dephosphorylation of tau A. Mietelska et.al.Thus, tau's regulation depends on two crucial factors which include post-translation modification and protein interaction, and these crucial factors give us a lead to target tau proteins therapeutically.

Aβ and its interplay in tau-pathology- Developing research works suggests and proves that Aβ may potentially play an immediate or indirect interactive role with tau protein to hasten up the NFT formation. Recent evidence on Aβ's interplay with tau revealed the adverse effects of Aβ within the diverse molecular and cellular pathways of tau resulting in detrimental effects like tau aggregation, hyperphosphorylation, accumulation, and mislocalization.

Conclusion- Alzheimer's disease is the most ordinarily found tauopathy which is prevalent in elderly people. Tau protein with immense pathological effects in Alzheimer's disease acts as an important game-changer

within the progression of the disease. Tau's role in the stabilization of microtubule and enhancement of axonal transport is unquestionable proving its adequate need in message transfer inside the brain. Abnormalities within the functions of tau will ultimately cause instantaneous dysfunctional effects in microtubule assembly and axonal transport resulting in adverse neurodegeneration. Developing results proves the importance of tau in severing the disease pathology. These collective findings on tau protein's biology, pathological effects, and therapeutic strategies highlight the indispensable need for further understanding in various Tau mechanistic activities. Post-translation modifications and protein interactions on tau are often considered as pillars of targeting tau since modulating these two processes are often an efficient therapeutic step towards managing AD. [S. Muralidar et al.]. Even though different therapeutics with different approaches are emerging for the treatment of Alzheimer's disease , the challenge continues to exist awaiting proper evidence on their efficacies. With multiple roles within the development of Alzheimer's disease pathology, tau are often considered because the most promising candidate to develop better-targeted drugs to cure the incurable disease.

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