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Modeling Human Neurodegenerative Tauopathies in Animal Models: Focus on *Drosophila melanogaster*

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Introduction

Neuronal cells could not reproduce once damaged or eliminated, and therefore, loss of neuronal tissues above threshold limit may result in permanent impairment of nervous system. There are several fatal human disorders which manifest such conditions and termed as neurodegenerative disorders [1]. As neurons deteriorate, affected person experiences progressive loss of body coordination and memory. Such diseases mostly affect the elderly population and could be hereditary as well as sporadic in nature. The pathogenesis of several neurodegenerative disorders involves aberrant processing, misfolding, and deposition of aggregated proteins and other biological materials either extra-cellularly or within neurons. Progressive accumulations of such materials in neuronal cells adopt various dynamic shapes and ultimately lead to formation of aggregates of some pre-defined structures [2,3].

Neurodegenerative tauopathies

Neurodegenerative tauopathies are members of neurodegenerative disorders which develop due to intracellular and extracellular accumulation of the hyperphosphorylated microtubule associated tau protein [1,3]. Alzheimer's disease (AD), Parkinson's disease (PD) and FTDP-17 are most common forms of human tauopathies and being studied worldwide. Tau is an evolutionary conserved protein which expresses abundantly in both central and peripheral nervous system with little amount evident in some non-neuronal cells [1,3].

MAPT is a ~150 kb long single copy human Tau encoding gene with 16 exons and located on chromosome 17(17q21.3) [4]. Alternative splicing of exons 2, 3 and 10 results in generation of six different brain-specific tau isoforms ranging from 352-441 amino acids in size [5]. Splicing of exon 10 generates tau isoforms with either three (exon 10 missing) or four (exon 10 present) repeat domains, known as 3R and 4R tau, respectively [4,5]. Subsequently, splicing of exons 2 and 3 results in formation of 3R or 4R isoforms either without (0N) or with 29 amino acids (1N) or with 58 amino acids (2N) inserts. In adult human brain, 4R:3R ratio is approximately 1 and the 1N, 0N, and 2N tau isoforms comprise about 54%, 37%, and 9%, respectively [4,5]. Constant maintenance of the 4R:3R ratio at 1 is essential for neuronal functioning and any disruption from this normal ratio is indicative of neurodegenerative tauopathy disorder. Moreover, any deviation in equilibrium of alternative splicing also affects the phosphorylation status of tau protein, and therefore, alters the biological functions of tau isomers [4,5].

Tau protein regulates axonal transport and polymerization/stabilization of cellular microtubules [6]. Tau has also been found to localize in post and pre synapses and directly influences neuronal communication [6]. Synaptic tau directly modulates neuronal excitability by regulating trafficking or targeting ion channels. Tau acts as postsynaptic scaffold protein and target neurotransmitter receptors to the synapse and thereby regulates synaptic functions. Distribution pattern of tau in synapses changes during progression of tauopathies [7]. In neurodegenerative disorders such as AD, tangle-containing neurons shows low expression of the synaptic vesicle associated protein (synaptophysin) when compared with tangle-free neurons [1,3]. Tau proteins bind with spectrin and actin filaments and regulate cellular architecture, motility and flexibility of plasma membrane and other cytoskeletal proteins [1,3,5]. Moreover, tau protein interact with cellular organelles (mitochondria, neuronal plasma membrane), molecular chaperones and various proteins such as GSK-3β, PI3-k, GRB2, PLC-γ, FYN having Src homology 3 (SH3) domain (found in tyrosine kinases and adaptor proteins) [3,6]. Tau is known to modulate intracellular trafficking and in this capacity it also regulates various cellular signalling. For instance, tau-FYN interaction regulates N-methyl-D-aspartic acid (NMDA) receptor signalling which in turn triggers neuronal cell signalling and development [6].

Pathogenesis of Neurodegenerative Tauopathies

There are more than 40 different mutations reported to be associated with altered functioning of *MAPT* gene. The mutations associated with tauopathies could be divided in two categories. The first category includes missense and deletion mutations which alters the microtubule binding capacity of tau and finally results into protein aggregation. Second category of mutations affects splicing of exon 10 which in turn changes normal 4R:3R ratio of tau isoforms [7,8]. Majority of mutations have been found to affect the splicing pattern of exon 10 by various ways, and therefore, alter the normal ratio of tau isoforms [6,7].

Altered phosphorylation of tau protein has been postulated to be a major cause of tauopathies. Various studies have revealed that ~20% of total tau protein could be phosphorylated post-translationally [6]. So far, 80 putative serine or threonine phosphorylation sites have been identified on the longest CNS tau isoform (441 amino acids). Tau protein undergoes excessive phosphorylation during the pathogenesis of tauopathies. For instance, tau phosphorylation is tremendously increased in AD brain as 45 amino acid residues are phosphorylated compared to 17 residues in control brain [6,7]. Several kinases such as glycogen synthase kinase 3β (GSK3β), cdk5, p38, JNK, cdc2, PKA, PKC, calmodulin kinase II, MARK kinases, CKII etc. could phosphorylate various Ser or Thr residues of tau protein [4,8].

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Oligomerization and Aggregation of Tau Protein during Disease Pathogenesis

The molecular mechanisms leading to tau aggregation have been widely studied in various tauopathy disorders. In tauopathies, aggregated tau proteins are present in various morphologies such as Neurofibrillary Tangles (NFT), Paired Helical Filaments (PHF), Straight Filaments (SF) and Pick Body (PB) like inclusions [3]. The first step of tau aggregation includes formation of tau oligomers. There are certain hot spots on tau protein which facilitates tau interaction, self-assembly and formation of oligomers and β-sheets [8]. Formation of β-sheets alters the native conformation of tau and exaggerates the aggregation process [9,10]. In disease conditions, hyperphosphorylation and cytoplasmic accumulation of tau protein further increases the rate of oligomer formation [11]. Various tau mutations also facilitate aggregation of tau protein. For instance, intronic tau mutations alter normal 4R:3R ratio of tau isoforms which in turn enhances the aggregate formation. Interestingly, exonic missense tau mutations decrease microtubule binding capacity of tau which subsequently increases phosphorylation and cytoplasmic accumulation [9-11].

Modeling of Human Tauopathy Disorders in *Drosophila*

Identification of causative mutations facilitates development of transgenic systems to model the human diseases and to study various aspects of disease pathogenesis and screening of drugs and genetic modifiers. In spite of successful attempts in bacteria and plants, transgenic modeling of human neurodegenerative disorders has been mostly conducted in animal systems since the phenotypic manifestation has only been achieved in animals. *Drosophila melanogaster* has been used as prime model organism for neurobiology research since long time [12,13]. The major advantages of using *Drosophila* as a model system includes its short lifespan, economical and easy to maintain, availability of powerful genetic tools, large numbers of available transgenic/mutant lines and fully annotated genome database. It has been found that ~70% of human disease genes have evolutionary conserved fly homologues and lack of significant redundancy within the *Drosophila* genome further simplifies the genetic analysis of cellular processes. Tissue specific expression of both normal and pathogenic forms of human tau in *Drosophila* has been found to induce defects in axonal transport and neurodegeneration [14]. UAS/ Gal4 based binary system has been extensively utilized to achieve tissue specific expression of desired transgene. This system relies on the fact that yeast Gal4 transcriptional activator binds to the Upstream Activating Sequence (UAS) enhancer element in order to drive expression of the gene present immediately downstream of UAS [15]. In addition to transgenic approaches, forward genetic screens (from mutant phenotype to causative gene) using insertional mutagenesis, chemical mutagenesis or RNA Interference (RNAi) have also been used to identify mutations associated with human neurodegenerative disorders [16].

Power of *Drosophila* as human neurodegenerative disease models lies in its ability to decipher the cellular signalling pathways by performing large-scale unbiased genetic screening, with or without any prior assumption. Several genetic signalling cascades and genetic modifiers of human tauopathies such as *par-1*, tyrosine phosphatase *Ptp4E*, *Sgg/GSK3β*, *string*, *twine* etc. have been identified by utilizing *Drosophila* disease models [14,16].

Concluding Remarks

Given an excellent model of human tauopathies in the form of *Drosophila* and the wealth of tools available to study modified phenotypes, the precise molecular mechanism which causes disease toxicity still stands as a question mark. Moreover, lack of mechanism-based treatment strategies has been found to be incompetent in limiting the process of degeneration leaving no choice with the disease than to follow a fatal course. Hence, there is an urgent need for testing candidate molecules for their potential as possible modifiers of tauopathies. A combination of genetic, biochemical, bioinformatics and pharmacological approaches would help to develop better understanding about the molecular pathogenic mechanisms and development of novel and effective treatment strategies for such devastating neurodegenerative diseases.

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