

**Seminar 1**

**Regulation of different isoform production of**

**tau protein in Alzheimer’s disease**

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**Microtubules (MTs) are essential components of the cytoskeleton in eukaryotic cells and have crucial functions in processes such as cell division and intracellular transportation. Many proteins interact with the MTs of the cellular cytoskeleton, with tau being one of the proteins associated with MTs. The abnormal aggregation of** **hyperphosphorylated tau, which results in neurofibrillary tangles (NFTs) and finally the death of neurons, is one of the pathological hallmarks of the most prevalent type of neurodegenerative disorders being Alzheimer’s disease (AD). At the molecular level, transcripts related to the tau gene on chromosome 17, which encounters a complex regulated splicing in the mammalian nervous system, results in the expression of human tau in six different isoforms or mis-spliced versions that may be more susceptible to hyperphosphorylation and subsequent aggregation into NFTs. To date, studies using molecular methods like RT-PCR, Western blotting and RNA-Seq analysis, have shown that Alternative Splicing (AS) is involved in the gene expression reprogramming associated with the functional changes observed in AD patients. More specifically, splicing abnormalities in AD tissues are associated with mutations in** **cis-acting regulatory sequences, alterations in the activity and sub-cellular localization of trans-acting splicing factors, and components of the spliceosome machinery, which may affect the onset and progression of the disease. The recognition of AS deregulation as a common feature of AD may help answer many questions, such as identifying genetic variants that affect specific splicing events associated with AD, to identify individuals at higher risk of developing the disease and allow those who do periodic brain imaging analyses to benefit from early stage AD detection.**

Keywords: hyperphosphorylated tau, Alternative splicing, Tau isoforms, cis-acting regulatory sequences, Tau mis-splicing.