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Microtubule associated Tau squired by molecular chaperones in Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline. It accounts for 60%-70% of total dementia cases. The extracellular plaques of amyloid beta and the intracellular neurofibrillary tangles of Tau protein are the hallmarks of AD. Tau is a microtubule-associated protein, which stabilizes the microtubules and maintains neuronal structure as well as trafficking. It is amenable to various post-translational modifications (PTMs), which influence its microtubule binding affinity. The most exclusively studied PTM is hyperphosphorylation, which affects the microtubule binding and leads to Tau aggregation. Other PTMs include glycation, acetylation, methylation, nitration etc. Chaperones such as Hsp70 and Hsp90 tries to resolve the toxic conformations of Tau which is then either folded to its native form or in the downstream is degraded and eliminated from the cell. But in diseased conditions, the chaperones fail to remove the mutated or toxic Tau species. Chaperones are also involved in lysosomal degradation of Tau by a process called chaperone mediated autophagy (CMA) and helps in removal of modified Tau. The cellular machinery directs Tau degradation via UPS. In the other hand, inhibiting the chaperone activity would lead to degradation and elimination of toxic Tau species. Small molecules inhibitors against chaperone activity are known to be effective in clearance of the aberrant Tau from cell.

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