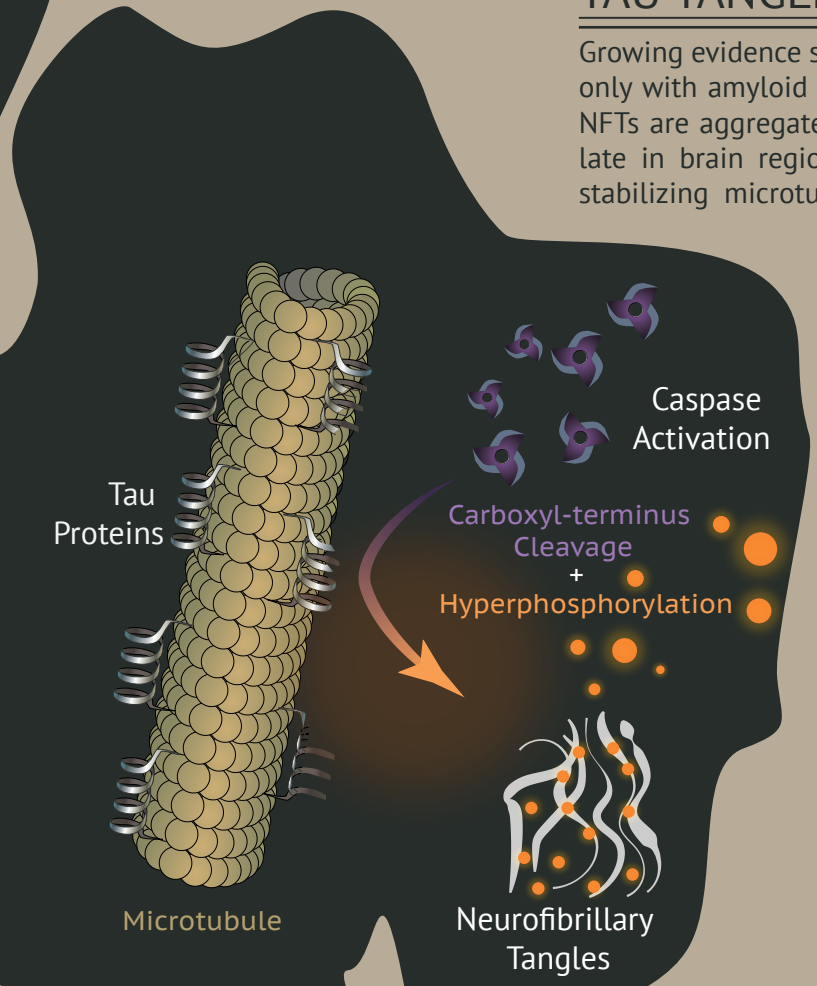
Recent studies have demonstrated that certain presenilin (Ps) mutations can alter the site of APP cleavage and subsequently increase the Aβ42/Aβ40 ratio.[6] These mutations additionally reduce the catalytic efficiency of γ-secretase, favouring the production of peptides of longer lengths, such as Aβ42.[6] Because of their key role in APP cleavage, γ-secretase and its catalytic core, presenilin, have become attractive therapeutic targets for Alzheimer's disease.[6,8]

TAU TANGLES

Growing evidence suggests that APP and Ps mutations are associated not only with amyloid plaques, but also with neurofibrillary tangles (NFTs).[9] NFTs are aggregates of hyperphosphorylated tau proteins that accumulate in brain regions critical to cognitive function.[9,10] Responsible for stabilizing microtubules, tau supports the neuronal cytoskeleton and facilitates axonal transport.[7] However, following aberrant modifications, tau triggers the synaptic loss and neuronal death characteristic of Alzheimer's. According to recent research, the Aβ peptides comprising amyloid plaques may also contribute to the formation of NFTs.[9,10] In particular, Aβ activates caspases involved in programmed cell death, or apoptosis.[9,10] Caspase activation induces cleavage of tau at its carboxy-terminus, and the resulting tau fragments assemble more rapidly into filaments.[9,10] Further conformational changes initiate and accelerate tau phosphorylation and aggregation.[9,10] Tangled and twisted, the filaments impede axonal transport and impair neuronal function, ultimately leading to the potentiation of caspase-mediated apoptotis.[10] Given the significant role of NFTs in neurodegeneration, studies continue to investigate the therapeutic potential of inhibiting abnormal hyperphosphorylation and disassembling filament aggregates.[11]



REFERENCES

1. Alzheimer's Statistics [Internet]. Alzheimers.net. 2016 [cited 2016Oct10]. Available from: http://www.alzheimers.net/resources/alzheimers-statistics/
2. 15 per cent of people with dementia under 65: Alzheimer society - Technology & Science - CBC News [Internet]. CBC News. CBC/Radio Canada; 2009 [cited 2016Oct10]. Available from: http://www.cbc.ca/news/technology/15-per-cent-of-people-with-dementia-under-65-alzheimer-society-1.779540
3. Jeong YH, Park CH, Yoo J, Shin KY, Ahn SM, Kim HS, Lee SH, Emson PC, Suh YH. Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model. The FASEB journal. 2006 Apr 1;20(6):729-31.
4. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, Vollset SE, Ozgoren AA, Abdalla S, Abd-Allah F, Aziz MI. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
5. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzherimer disease. Cold Spring Harbor Perspectives in Medicine. 2011 Sep;1(1):a006189.
6. Selkoe DJ, Wolfe MS. Presenilin: running with scissors in the membrane. Cell. 2007 Oct 19;131(2):215-21.
7. Bonner JM, Boulianne GL. Drosophila as a model to study age-related neurodegenerative disorders: Alzheimer's disease. Experimental gerontology. 2011 May 31;46(5):335-9.
8. De Strooper B. Loss-of-function presenilin mutations in Alzheimer disease. EMBO reports. 2007 Feb 1;8(2):141-6.
9. Cotman CW, Poon WW, Rissman RA, Blurton-Jones M. The role of caspase cleavage of tau in Alzheimer disease neuropathology. Journal of neuropathology & experimental neurology. 2005 Feb 1;64(2):104-112.
10. Gamblin TC, Chen F, Zambrano A, Abraha A, Lagalwar S, Guillozet AL, et al. Caspase cleavage of tau: Linking amyloid and neurofibrillary tangles in Alzheimer's disease. Proceedings of the national academy of sciences. 2003 Aug 19;100(17):10032-37.
11. Medeiros R, Baglietto-Vargas D, LaFerla FM. The role of tau in Alzheimer's disease and related disorders. CNS neuroscience & therapeutics. 2011 Oct;17(5):514-24.