Amyloid-β and tau in Alzheimer’s disease

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Alzheimer’s disease (AD) is a devastating neurodegenerative disorder with a relentless progression. AD pathogenesis is believed to be triggered by the accumulation of the amyloid-β peptide (Aβ), which is due to overproduction of Aβ and/or the failure of clearance mechanisms. Aβ self-aggregates into oligomers, which can be of various sizes, and forms diffuse and neuritic plaques in the parenchyma and blood vessels. Aβ oligomers and plaques are potent synaptotoxins, block postsynaptic function, inhibit mitochondrial activity, alter intracellular Ca²⁺ levels and stimulate inflammatory processes. Loss of the normal physiological functions of Aβ is also thought to contribute to neuronal dysfunction. Aβ interacts with the signalling pathways that regulate the phosphorylation of the microtubule-associated protein tau. Hyperphosphorylation of tau disrupts its normal function in regulating axonal transport and leads to the accumulation of neurofibrillary tangles and toxic species of soluble tau. Furthermore, degradation of hyperphosphorylated tau by the proteasome is inhibited by the actions of Aβ. These two proteins and their associated signalling pathways therefore represent important therapeutic targets for AD.

**APP and tau processing in neurons**

APP is processed by two pathways. In the non-amyloidogenic pathway, APP is cleaved by α-secretase (e.g., ADAM17, ADAM9 or ADAM10), to generate p3 and p3, which is localized to lipid rafts, BACE1 (a β-site APP C-terminal 99 cleaving enzyme, BACE1) and generates p5 and p5. Cleavage of p5 by γ-secretase yields p5 or p5 (not shown), which is associated with neuronal apoptosis. In functional neurons, Aβ and APP are degraded by IDE and TAU, respectively; TAU is degraded by Aβ and IDE in the formation of Aβ and TAU. Numerous kinases have been implicated in tau hyperphosphorylation, including GSK3β, which causes Aβ changes and APP oligomerization (not shown), and is associated with synaptic impairments. In functional neurons, Aβ and APP are degraded by IDE and TAU, respectively; TAU is degraded by Aβ and IDE in the formation of Aβ and TAU. Numerous kinases have been implicated in tau hyperphosphorylation, including GSK3β, which causes Aβ changes and APP oligomerization (not shown), and is associated with synaptic impairments. In functional neurons, Aβ and APP are degraded by IDE and TAU, respectively; TAU is degraded by Aβ and IDE in the formation of Aβ and TAU.