Amyloid Precursor Protein processing modulates fast tau phosphorylation and compartimentalization during mitosis

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Alzheimer's disease is a heterogeneous neurodegenerative disorder with insidious onset and irreversible progression, genetically linked to few molecules: AßPP on chromosome 21, and the two presenilins (PSs) on chromosome 14 (PS1) and 1 (PS2), respectively(1). The molecular mechanisms causing sporadic and familial (FAD) forms of AD are not yet known and also the physiological functions of AßPP and PSs are unclear. AßPP is a type 1 transmembrane protein whose proteolytic processing generates long soluble N-terminal fragments (sAßPP), a family of short soluble amyloid-ß peptides (Aß)(2), and a second intracellular C-terminal fragment named AICD from 'AßPP intracellular domain' which is likely involved in gene regulation. Because mutations in AßPP or PSs or even the simple overexpression of AßPP (due to trisomy 21 or to mutations in the promoter region of AßPP) cause Aβ accumulation and dementia, the 'amyloid hypothesis' states that there is a clear cause-effect relationship between Aβ production and AD; hypothesizing that soluble Aβ are the toxic species responsible for neurodegeneration, while reactive gliosis and tangles of hyperphosphorylated tau protein (NFTs) represent secondary damaging events[3]. However, beside the formation of amyloid, AßPP and PSs are in the center of a network of protein-protein interactions whose significance for the regulation of Aß formation and generally for AD development is under extensive investigation. In particular, the C-terminal domain of AßPP is recognized by a plethora of adaptors and signaling molecules, the role of which for AD development is still unclear. We provided evidence for an involvement of AßPP in ERK1/2 and AKT activation, via Grb2 signalling, and more recently, we demonstreted that AßPP, when overexpressed, modulates the phosphorylation of tau. In particular, AßPP has the capability to influence the phosphorylation in mitotic phosphoepitopes on tau and its relative ratio between nuclear and cytoplasmic pools; an event observed also in AD brains(5). Here we show that the nuclear/cytoplamic ratio of phospho-tau during mitosis depends on AßPP processing also in DS fibroblasts, and that it is an immediate and fast event modulated by AßPP processing and upon mitotic stimuli in accordance to ERK1/2 and AKT1 kinetic.

It was proposed that neurons in AD brain re-enter the cell cycle before they die (6), and events associated to aneuploidy and cell cycle defects such as chromosome missegregation and trisomy 21 mosaicism have been associated to mutated AßPP and PSs. In this line, here we propose that the aberrant processing of AßPP may be linked to both amyloid formation and to signalling events that induce cell death in postmitotic cells (neuronal death), and cell proliferation in surrounding glia.

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