Abstract

Alzheimer's disease (AD) is by far the most prevalent cause of dementia in the elderly and affects one out of three people after the age of 85. Because life expectancy is continuously increasing, there is an urgent need to find a way to stop or prevent it since more than 100 million people will be concerned by 2050. This devastating neurodegenerative disease was first described in 1906, by Alois Alzheimer a german neuropsychiatrist. This pathology affects the central nervous system and is characterized clinically by a progressive loss of memory and cognitive functions. The brain of individuals suffering with AD manifests a triad of neurological lesions: i) extracellular amyloid plaques (senile or neuritic plaques); ii) intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau protein; and iii) neuronal loss in the hippocampus and cerebral cortex. AD can be divided in two kinds, genetic (also called familial forms) and sporadic types. Although the exact etiology of Alzheimer's disease (AD) remains to be established, a network of evidence suggests that a set of peptides called amyloid beta peptides (Aβ) is intimately linked to the onset of the disease. The key role of Aβ peptides has therefore triggered a huge amount of studies aimed at elucidating the mechanisms involved in their genesis, catabolism, clearance and function. Aβ peptides are produced from βAPP via the so-called amyloidogenic pathway by the sequential cleavages by β- and γ-secretases. On the other hand, there exists a non-amyloidogenic α-secretase cleavage that occurs in the middle of the Aβ sequence**.** Therefore, the pharmacological regulation of these secretases represents one promising way to interfere with amyloidogenesis and the progression of Alzheimer's disease.

However, several other strategies have also been developed, one of the most promising being vaccination (aimed at specifically eliminating toxic Aβ species by means of antibodies). Very recently, stem cell technology has opened up new avenues for AD treatment since it offers the opportunity not only to model AD but also to examine whether βAPP and βAPP-cleaving secretases can control the fate (maintenance/differentiation) of adult stem cells and their decision to self-renew or differentiate into neurons. Sox2 (Sex determining region Y-box 2) is widely regarded as a key member of the transcription regulators that 1) controls pluripotency and self-renewal in embryonic stem cells and 2) maintains the stemness of neural stem cells. Very interestingly, two studies have established a link between Sox2 and AD/βAPP thereby suggesting a possible implication of Sox2 in the development of AD. Thus, Sox2 levels are up-regulated by the β-amyloid precursor protein (βAPP) and Sox2 deficiency induces neurodegeneration in mice.

As Sox2 plays a crucial role in the balance between stem cells maintenance and commitment to differentiate throughout the lifetime, we propose to investigate whether 1) Sox2 can functionally interact with βAPP, βAPP-derived metabolites and βAPP-cleaving secretases in human stem cells; 2) Sox2/βAPP functional cross-talk can control the equilibrium between proliferation and differentiation of neural human stem cells in neurodegeneration/AD; 3) Sox2 levels are altered in AD mouse model *in vivo*.

Keywords: Alzheimer' disease, Sox2, neural stem cells, βAPP, secretases
Research area/Sub area: Medical and health research/Neuroscience