



## **Title: The amyloid hypothesis**

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Several lines of anatomical and genetic evidence suggest that the amyloid peptides (A $\beta$ ) that accumulate in senile plaques of Alzheimer's disease-affected brains predominantly contribute to the neurodegenerative process taking place in this pathology. Thus, all mutations responsible for early-onset aggressive forms of the disease have in common to modify the levels and/or the nature of the amyloid peptides produced in vitro and in vivo. A $\beta$  peptides are generated from a transmembrane protein precursor  $\beta$ -APP by subsequent cleavages by two proteolytic activities referred to as  $\beta$ - and  $\gamma$ -secretases<sup>1</sup>. An alternative pathway implying another secretase called  $\beta$ -secretase results in a cleavage located inside A $\beta$  domain of  $\beta$ -APP, thereby precluding A $\beta$  production<sup>1</sup>. Once produced, A $\beta$  peptides are either mainly proteolytically degraded by various endoproteases<sup>2</sup> and/or N-terminally truncated by aminopeptidase A3. We will rapidly describe the various secretases activities and we will document the advantages and drawbacks of thereapeutic strategies aimed at either inhibiting  $\beta$ - and  $\gamma$ -secretase or activating  $\beta$ -secretase or A $\beta$ -degrading enzymes.

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