

Alzheimer's disease: a proteolytic problem?

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AD is characterized by the extracellular deposition of the amyloid β -peptide that derives from its precursor β APP by sequential actions of β -secretase and a high-molecular weight complex referred to as γ -secretase. Presenilins (PS), nicastrin, Aph-1 and Pen-2 have been characterized as the four necessary members of the γ -secretase complex. Mutations in PS that cause familial Alzheimer's disease (FAD) increase A β _{42/40} ratio and trigger p53-dependent cell death.

Once released, A β undergoes degradation by a zinc-metalloprotease called neprilysin. It is thought that the exacerbation of the A β load occurring in sporadic Alzheimer's disease cases is directly linked to impairment of A β degradation rather than on an altered production.

I will review the physical and functional characteristics of the β - and γ -secretases. I will document recent advances on the biology of the γ -secretase complex and I will describe our recent data showing that PS deficiency, catalytically inactive PS mutants, γ -secretase inhibitors and β APP or APLP2 depletion, all reduce the expression and activity of NEP, and lower the transactivation of its promoter and mRNA expression. NEP expressions were also diminished in the brains of PS- or β APP-deficient mice.

We will discuss advantages and pitfalls of strategies aimed at targeting γ -secretase and neprilysin to slow down or arrest Alzheimer's disease neuropathology.