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Shifting the balance: Soluble ADAM10 as a potential treatment for Alzheimer's disease

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PURPOSE OF THE ABSTRACT

Accumulation of amyloid β in the brain is regarded as a key initiator of Alzheimer's disease pathology. Processing of the amyloid precursor protein (APP) in the amyloidogenic pathway yields neurotoxic amyloid β species. In the non-amyloidogenic pathway, APP is processed by membrane-bound ADAM10, the main α-secretase in the nervous system. Here we present a new enzymatic approach for potential treatment of Alzheimer's disease using a soluble form of ADAM10. The ability of the soluble ADAM10 to shed overexpressed and endogenous APP was determined with an ADAM10 knockout cell line and a human neuroblastoma cell line, respectively. The soluble enzyme hydrolyzes APP and releases the neuroprotective soluble APPα when exogenously added to cell cultures. We further demonstrated by thioflavin T fluorescence, HPLC and confocal microscopy its ability to degrade different amyloid β species inhibiting the formation and aggregation of characteristic amyloid β extracellular neuronal plaques. Using N-terminal and C-terminal enrichment proteomic approaches we investigated its substrates, identifying new and verifying others, such as VGF and N-cadherin, respectively. Lastly, a truncated soluble ADAM10, based on the catalytic domain, was expressed in E. coli for the first time and its activity evaluated. The truncated variant also exhibited α-secretase capacity as shown with a specific ADAM10 fluorescent substrate in addition to shedding overexpressed and endogenous APP. Our in vitro work demonstrates that exogenous treatment with a soluble variant of ADAM10 would shift the balance towards the non-amyloidogenic pathway. The potential of such a treatment for Alzheimer's disease needs to be further evaluated in vivo.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

Alzheimer's disease | ADAM10 | Proteomics | Amyloid beta

BIBLIOGRAPHY