The structural biology of the amyloid precursor protein APP - a complex puzzle reveals its multi-domain architecture.

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Abstract

The amyloid precursor protein (APP) and its processing are widely believed to be central for the etiology of Alzheimer's disease (AD) and appear essential for neuronal development and cell homeostasis in mammals. Many studies show the proteolysis of APP by the proteases α-, β- and γ-secretase, functional aspects of the protein and the structure of individual domains. It is, however, largely unclear and currently also widely debated of how the structures of individual domains and their interactions determine the observed functionalities of APP and how they are arranged within the three-dimensional architecture of the entire protein. Further unanswered questions relate to the physiologic function of APP, the regulation of its proteolytic processing and the structural and functional effect of its cellular trafficking and processing. In this review, we summarize our current understanding of the structure-function-relationship of the multi-domain protein APP. This type-I transmembrane protein consists of the two folded E1 and E2 segments that are connected to one another and to the single transmembrane helix by flexible segments and likely fulfills several independent functions.

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