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Sommario/riassunto	<p>The amyloid precursor protein APP plays a key role in the pathogenesis of Alzheimer's disease (AD), as proteolytical cleavage of APP gives rise to the Aβ peptide which is deposited in the brains of Alzheimer patients. Despite this, our knowledge of the normal cell biological and physiological functions of APP and the closely related APLPs is limited. This may have hampered our understanding of AD, since evidence has accumulated that not only the production of the Aβ peptide but also the loss of APP-mediated functions may contribute to AD pathogenesis. Thus, it appears timely and highly relevant to elucidate the functions of the APP gene family from the molecular level to their role in the intact organism, i.e. in the context of nervous system development, synapse formation and adult synapse function, as well as neural homeostasis and aging. Why is our understanding of the APP functions so limited? APP and the APLPs are multifunctional proteins that undergo complex proteolytical processing. They give rise to an almost bewildering array of different fragments that may each subserve specific functions. While Aβ is aggregation prone and neurotoxic, the large secreted ectodomain APP_s - produced in the non-amyloidogenic α-secretase pathway - has been shown to be neurotrophic, neuroprotective and relevant for synaptic plasticity, learning and memory. Recently, novel APP cleavage pathways and enzymes have been discovered that have gained much attention not only with respect to AD but also regarding their role in normal brain physiology. In addition to the various cleavage products,</p>

there is also solid evidence that APP family proteins mediate important functions as transmembrane cell surface molecules, most notably in synaptic adhesion and cell surface signaling. Elucidating in more detail the molecular mechanisms underlying these diverse functions thus calls for an interdisciplinary approach ranging from the structural level to the analysis in model organisms. Thus, in this research topic of Frontiers we compile reviews and original studies, covering our current knowledge of the physiological functions of this intriguing and medically important protein family.
