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Metabolism of amyloid precursor protein APP in human platelets

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Abnormal metabolism of the amyloid precursor protein, APP, through the amyloidogenic pathway results in the accumulation of heterogeneous Aβ peptides in the central nervous system, causing the onset of Alzheimer's disease[1]. Aβ, as well as other different proteolytic fragments of APP are present in human plasma, and derive from circulating platelets. Platelets express APP isoforms similar to those found in neurons, and metabolise APP through α-secretase and β-secretase to produce soluble fragments sAPPα, sAPPβ and Aβ. Very little is known about the exact function of APP and of its soluble proteolytic fragments in normal cellular metabolism. In this study we investigated the metabolism of APP in human platelets.

We identified two different forms of APP expressed in human resting platelets. A 110-120 kDa soluble fragment (sAPPα and/or sAPPβ), derived from α/β secretase metabolism, was stored into platelets α-granules and was released upon platelet activation by several agonists. A 140 kDa full length intact protein, here named $APP_{FL,}$ was found expressed on the platelet surface, and represented about ten percent of total platelet APP. APP_{FL} underwent proteolysis upon stimulation of platelets. Agonist-induced proteolysis of APP_{FL} occurred independently of platelet aggregation or secretion, but was inhibited in the presence of EDTA. Interestingly, proteolysis of APP_{FL} was observed also upon incubation of platelets with the cell permeable calmodulin (CaM) antagonist W7. In platelets, shedding of the extracellular domain of several membrane glycoproteins, including GPIbα, GPV, GPVI, and PECAM1, represents a recently recognized mechanism for receptor down-regulation. In all these cases, shedding is constitutively inhibited by CaM binding to the intracellular regions of the receptors, and occurs upon CaM dissociation with W7 or with other antagonists[2]. We will next investigate the role of calmodulin in APP_{FL} regulation.

References

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