Role of flotillins in the trafficking and processing of the Alzheimer Amyloid Precursor Protein

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Flotillins are highly conserved, ubiquitous proteins which are associated with cholesterol enriched membrane microdomains, known as rafts. The two members of the flotillin protein family have been recently recognized to regulate the cellular metabolism of the Alzheimer Amyloid precursor Protein (APP). Flotillin-1 was shown to directly bind to the cytoplasmic tail of APP and to be associated with the β-secretase BACE-1, whereas Flotillin-2 downregulation results in altered endocytosis and reduced amyloidogenic processing of APP. In addition, flotillins accumulate in the cortex of Alzheimer´s Disease (AD) patients. Amyloidogenic processing has been implicated to take place in lipid rafts, and the activities of both enzymes responsible for the amyloidogenic processing of APP, BACE-1 and γ-secretase, are concentrated in lipid rafts. So far, it has only been shown that APP directly interacts with flotillin-1. Our preliminary results implicate that the APP cytoplasmic tail directly interacts with both flotillin-1 and flotillin-2. Additionally, the substitution of the Tyrosine residues in the cytoplasmic domain of APP previously shown to reside in the canonical transport/endocytic signals and affecting the cellular trafficking (Y653, Y682, Y687) resulted in reduced interaction with flotillins. Our laboratory has recently developed a mouse line genetically ablated for the flotillin-2 gene. We found that the expression of APP in the brain of flotillin-2 knockout mice was reduced as compared to the wild type siblings. Therefore, these results support the hypothesis that flotillins play a significant role in the processing and/or trafficking of APP.