

P012 The FAPP proteins control sphingolipid metabolism and post Golgi carrier formation.

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We have reported the identification of two phosphatidylinositol 4-phosphate (PtdIns4P) effectors in mammals: four-phosphate-adaptor protein 1 and 2 (FAPP1 and FAPP2). Both of these proteins localize to specific domains of the Trans Golgi Network (TGN) due to the dual interactions of their PH domains with PtdIns4P and the small GTPase ARF1. Knock-down of the FAPPs inhibits cargo transfer to the plasma membrane. The FAPPs are members of a larger family of proteins, which includes OSBP1 and CERT. FAPP2, OSBP1 and CERT share two interesting features: an N-terminal PH domain that has a high affinity for PtdIns4P; and a C-terminal lipid-transfer domain that shows glycolipid specificity with FAPP2, oxysterol/ cholesterol specificity with OSBP, and ceramide specificity with CERT.

Here, we show that all of the FAPP family members localize to the TGN and that the over-expression of the FAPP-PH domain displaces all of them from the TGN membranes. As all of the members of this family appear to have roles in the sensing, binding and transferring of lipids that are enriched in detergent resistant domains, we speculated that the FAPP family members are involved in microdomain formation at the TGN. Through their control of the formation of such membrane domains, the FAPPs could have a role in cargo sorting and carrier formation, as well as having an influence on the tubular structure of the TGN. Consistent with this hypothesis, we show that the FAPP2 knock-down impairs post-Golgi-carrier formation and results in a significant reduction in the TGN area, as determined by electron microscopy.