


# The PH-like Domain of VPS13 Proteins - a Determinant of Localization to the Golgi Apparatus or to the Plasma Membrane

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## Abstract

Mutations in the four human genes *VPS13A-D*, encoding vacuolar protein sorting 13 (VPS13A-D) proteins, result in developmental or neurodegenerative diseases. Understanding the functioning of VPS13 proteins in physiology and pathology is a hot topic of research. Especially interesting is how VPS13 proteins are localized to specific membrane contact sites and function in lipid transport. Recently, the C-terminal Pleckstrin Homology (PH)-like domains of yeast Vps13 and human VPS13A were found to bind Arf1 GTPase and to phosphoinositol 4,5-bisphosphate. Here, hypotheses on the importance of the dual binding ability of the PH-like domain of VPS13A protein for cell physiology are presented. While yeast Vps13, together with Arf1 GTPase, is important for protein sorting in the Trans Golgi Network (TGN), the localization of VPS13A in TGN is speculated to restrict the binding of VPS13A to the plasma membrane.

## Keywords

VPS13 proteins, Arf1, Pleckstrin Homology (PH)-like domain, Trans Golgi Network, plasma membrane

The proteins belonging to the VPS13 (vacuolar protein sorting 13) family are large and are similar at the N- and C-termini. This family includes one yeast and four human (VPS13A-D) members, among others. Attention was drawn to this family when mutations in the *VPS13A-D* genes were linked to various developmental and neurodegenerative diseases, such as chorea acanthocytosis (*VPS13A*), Cohen syndrome (*VPS13B*), early-onset Parkinson's disease (*VPS13C*), and ataxia-paraplegia (*VPS13D*) (Dziurdzik and Conibear, 2021; Leonzino et al., 2021).

Although the individual VPS13 proteins are thought to perform the same function, i.e., transporting lipids, they localize to diverse sites of organelle contacts. Specifically, VPS13A was shown to be present between endoplasmic reticulum (ER) and mitochondria and between ER and lipid droplets; VPS13B in sites of contact between recycling endosomes and early endosomes; VPS13C between the ER and endosomes; and VPS13D between ER and mitochondria, ER and peroxisome, and lipid droplets and mitochondria. Additionally, VPS13B and VPS13D localize to the membranes of the Golgi apparatus. Interestingly, there is similarity not only between the N-termini of VPS13 proteins, but also between their C-termini (Dziurdzik and Conibear, 2021; Leonzino et al., 2021; Neuman et al., 2022). However, the localization of individual VPS13s appears to vary, which means that their interactions have to differ to

determine a specific localization. We are beginning to be able to identify specific partners of VPS13 proteins. To date, it was shown that the conserved C-termini of VPS13 proteins are involved in targeting to different membranes. For more information, read recent reviews (Dziurdzik and Conibear, 2021; Leonzino et al., 2021).

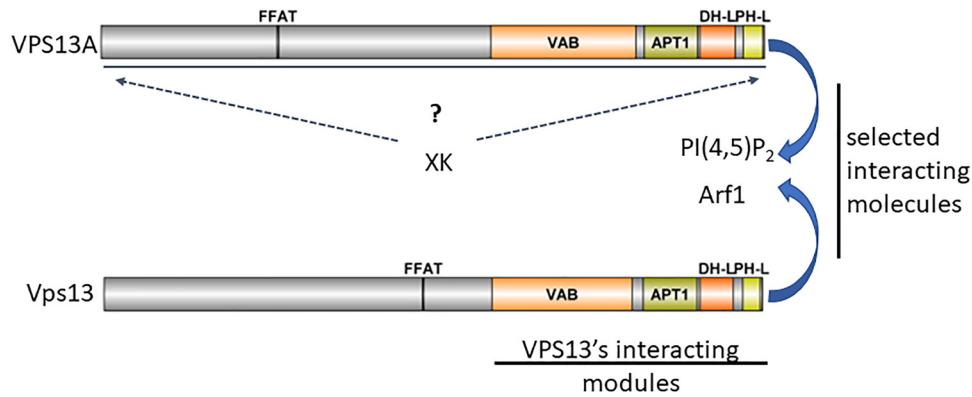
Knowledge about the determinants of VPS13 proteins localization is important. It is possible that the different clinical manifestation of mutations in individual *VPS13* genes could be the result of changes in the functioning/formation of different contacts between organelles, depending on which VPS13 protein is non-functional. Thus, several studies have aimed to find new interacting partners of VPS13 proteins. The publication by Kolakowski et al. (Kolakowski et al., 2021) identified the partners of the most C-terminal domains, the PH-like domains, from the yeast Vps13 and the human VPS13A. Both these PH-like domains are able to interact directly with both Arf1 GTPase, one of the main regulators of protein trafficking of endo-lysosomal membranes, and with phosphatidylinositol

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**Figure 1.** Schematic representation of human VPS13A and yeast Vps13 proteins. Domains and motifs are: FFAT motif; VAB, Vps13 Adaptor Binding; APT1 domain; DH-L, DH-like domain; and PH-L, Pleckstrin homology-like domain. Interacting molecules, proteins and lipids, relevant only to the text, are presented. Phosphatidylinositol 4,5-bisphosphate (PI(4,5)P<sub>2</sub>).

4,5-bisphosphate (PI(4,5)P<sub>2</sub>), plasma membrane (PM)-specific lipid in *in vitro* assays. As a result, the C-terminal part of Vps13 (239 amino acid residues long), previously described as an interacting with PI(4,5)P<sub>2</sub>-liposomes in the semi-*in vitro* assay (De et al., 2017), was shortened to the PH-like domain (108 amino acid residues long). Additionally, the yeast Vps13 was shown to interact with Arf1 *in vivo* in a PH-like, domain-dependent manner (Kolakowski et al., 2021). These findings have raised new questions: What is the physiological significance of this dual binding ability of the PH-like domain and at which membrane(s) does the interaction with Arf1 occur? The binding of the VPS13A PH-like domain to PI(4,5)P<sub>2</sub> suggests that VPS13A has the potential to localize to the PM. The same localization of VPS13A could be a result of the interaction with the X-Linked Kx Blood Group (XK) protein, which is a protein of PM. Therefore, the XK binding and the binding of the PH-like domain to PI(4,5)P<sub>2</sub> should confirm VPS13A's interaction with the PM. Surprisingly, when the biochemical interaction of these proteins is detected in the membrane fraction (Urata et al., 2019), microscopic studies do not demonstrate the localization of VPS13A on the PM. Instead VPS13A and XK proteins have been shown to co-localize at the ER or mitochondria (Park and Neiman, 2020). Is this because the localization of the VPS13A protein to the PM is transient since its permanent presence at this site is detrimental to the cell? This could be the case, as recent data show the importance of VPS13A-XK for phosphoserine (PS) exposure in the outer leaflet of the PM (Ryoden et al., 2022). PS in this localization regulates biochemical reactions but is also regarded as an apoptotic signal (Clarke et al., 2020). What is the dual binding affinity of the PH-like domain for? In the described scenario binding of VPS13A to Arf1 GTPase could regulate the level of VPS13A on the PM. This hypothesis should be tested. At least the binding of the PH-like domain of yeast Vps13 to Arf1 seems to occur at the Trans Golgi Network

(TGN) (Kolakowski et al., 2021), and binding of Vps13 C-terminal part to phosphatidylinositol 4-phosphate (PI4P) (De et al., 2017) could stabilize Vps13 on TGN membrane. Interestingly, the Vps13 function in sporulation process was recently shown to be regulated by PI4P (Nakamura et al., 2021). However, neither the presence of a small pool of Arf1 on the PM nor PI(4,5)P<sub>2</sub> on TGN can be ruled out. Notably, because the Arf1 protein is also found in other sub-cellular localizations, such as mitochondria or lipid droplets, the interaction can also occur there (Davis, 2018; Jackson and Bouvet, 2014).

There are also other questions regarding the significance of VPS13–Arf1 binding. Is this interaction only to retract VPS13 from PM or it is crucial for other reasons, i.e., does it affect other cellular processes? To confirm the importance of Arf1–Vps13 interaction, a genetic analysis was performed in yeast cells. In most cases, the additive effect of mutations is observed in genetic interaction when interacting genes encode proteins from two parallel pathways and contribute to the same process (Boone et al., 2007). This analysis of the interaction of *arf* and *vps13* mutations revealed that Arf1 and Vps13 work in parallel in maintaining mitochondrial morphology and in endocytosis, but together in the process of carboxypeptidase Y (CPY) sorting at TGN (Kolakowski et al., 2021). This indicates that the Vps13–Arf1 interaction may differ from just the regulation of the amount of Vps13 on the PM. How Arf1 and Vps13 participate together in CPY sorting remains to be studied. In particular, it is unknown whether the lipid transport ability of Vps13 is necessary for Golgi apparatus function. However, if such an ability is necessary, which membrane-contact sites must be formed? The most important question is about the clinical significance of the presence of VPS13A protein on the Golgi apparatus. The Golgi apparatus is vital for the neural development and neurotransmitter secretion, and its dysfunction is associated with several neurodegenerative disorders, including Cohen syndrome. Thus, further studies aimed at the characterization

of the Golgi-apparatus-specific processes in cells with mutations in *VPS13A*, *-C*, and *-D* are necessary. It is also interesting to note the relationship between the molecular function and localization of VPS13 proteins to the Golgi apparatus and the clinical manifestation of VPS13 protein dysfunction.

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