Canonical and Non-Canonical Roles of SNX1 and SNX2 in Endosomal Membrane Dynamics

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Abstract

Sorting nexins (SNXs) are a family of membrane-binding proteins known to play a critical role in regulating endocytic pathway sorting and endosomal membrane trafficking. Among them, SNX1 and SNX2 are members of the SNX–BAR subfamily and possess a membrane-curvature domain and a phosphoinositide-binding domain, which enables their stabilization at the phosphatidylinositol-3-phosphate (PI3P)-positive surface of endosomes. While their binding to PI3P-positive platforms facilitates interaction with endosomal partners and stabilization at the endosomal membrane, their SNX–BAR region is pivotal for generating membrane tubulation from endosomal compartments. In this context, their primary identified biological roles—and their partnership—are tightly associated with the retromer and endosomal SNX–BAR sorting complex for promoting exit 1 complex trafficking, facilitating the transport of cargoes from early endosomes to the secretory pathway. However, recent literature indicates that these proteins also possess biological functions in other aspects of endosomal features and sorting processes. Notably, SNX2 has been found to regulate endosome–endoplasmic reticulum (ER) contact sites through its interaction with VAP proteins at the ER membrane. Furthermore, data from our laboratory show that SNX1 and SNX2 are involved in the tubulation of early endosomes toward ER sites associated with autophagy initiation during starvation. These findings shed light on a novel role of SNXs in inter-organelle tethering and communication. In this concise review, we will explore the non-retromer functions of SNX1 and SNX2, specifically focusing on their involvement in endosomal membrane dynamics during stress sensing and autophagy-associated processes.

Keywords

sorting nexins, endosomes, membrane tubulation, autophagy, membrane dynamics

The endosomal system serves as a highly dynamic membrane network that connects the extracellular environment with intracellular trafficking stations, facilitating the exchange of information, nutrients, and growth factors (Scott et al., 2014). In mammals, this system is characterized by a vesiculo-tubular membrane maze that promotes the trafficking of proteins and lipids from the plasma membrane to endolysosomes. Early endosomes, also known as sorting endosomes, play a pivotal role as the initial sorting station, receiving membrane material from endocytic vesicles and orchestrating membrane and cargo trafficking through the generation of vesicles, tubules, and intraluminal vesicles (Solinger and Spang, 2022). As a central stage in early endocytosis, early endosomes require membrane-associated regulators to maintain their identity and regulate membrane dynamics processes such as fusion, budding, and tubulation.

In this context, lipids such as phosphatidylinositol-3-phosphate (PI3P) and phosphatidylinositol-4-phosphate (PI4P), along with small GTPases such as Rab5 and Rab11, are essential for setting up the endosomal dynamics stage. These molecules recruit specific membrane-related proteins that generate the necessary membrane remodeling associated with transport and cargo sorting. Additionally, endosomes form membrane-contact sites with the endoplasmic reticulum (ER), which have been shown to regulate both ER and endosomal functions (Audhya et al., 2007; Jang et al., 2022; Jean and Nassari, 2022; Wenzel et al., 2022). Besides their classical role in nutrient uptake, signaling molecule sorting, and transport, early endosomes are also involved in membrane dynamics processes triggered by stress responses, such as the autophagy program. Indeed, several proteins involved in autophagy regulation, autophagosome biogenesis, and lysosomal membrane turnover are present in endosomes (Molino et al., 2017; Melia et al., 2020). This suggests that besides their key role in endocytic

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sorting and recycling, endosomal membranes actively participate in autophagosome biogenesis and maturation.

The sorting nexins (SNXs) proteins, conserved from yeasts to mammals, form a family of peripheral proteins essential for shaping and maintaining endosomal membranes (Johannes and Wunder, 2011). SNXs primarily function as coat complexes and are characterized by a phosphoinositide-binding domain called phox homology, notably for PI3P and $PI3,5P_2$, which is crucial for their stabilization at the surface of endosomal membranes (Chandra et al., 2019). Among the SNXs, the SNX–BAR subfamily is particularly involved in endosome-associated membrane remodeling and tubulation. The C-terminus bin, amphiphysin, and Rvs (BAR) domain of SNX–BAR proteins play a significant role in sensing and generating membrane curvature.

Among the SNX–BAR proteins, SNX1 and SNX2, mammalian orthologs of yeast Vps5, exhibit high similarities and have been reported to function as an SNX1/SNX2 heterodimer (Haft et al., 1998) but are mainly described to form heterodimers with other SNX proteins including SNX5, SNX6, or SNX32 (Gallon and Cullen, 2015). The primary role of the SNX1/SNX2 partnership has been elucidated in the retromer machinery (Haft et al., 2000), which is located on a dedicated endosomal tubular network and is essential for coordinating endosome maturation and tubulation (van Weering et al., 2012; Gallon and Cullen, 2015). The retromer complex is involved in endosome-to-trans Golgi network (TGN) retrograde transport, a critical pathway responsible for the retrieval of cargoes, such as lysosomal hydrolases, from endosomes, as well as endosomes to plasma membrane recycling. The retromer machinery consists of a VPS26–VPS35–VPS29 subcomplex, and a heterodimeric subcomplex comprising SNX–BAR proteins, such as SNX5/SNX6/SNX32 and SNX1/SNX2, the latter being recognized as bona fide "retromer-SNXs". Within the retromer complex, SNX1 and SNX2 function as membrane shapers, promoting tubulation from PI3P-positive endosomes. These newly generated tubules facilitate the specific transport of retromer-associated cargoes, including the mannose-6-phosphate receptor (Mari et al., 2008; Figure 1). While SNX2 is present but not essential for retromer function (Carlton et al., 2005), SNX1 is required for proper cargo transport from endosomes to the TGN (Bujny et al., 2007; Rojas et al., 2007). Similarly, SNX1 and SNX2 are components of the endosomal SNX–BAR sorting complex for promoting exit 1 (ESCPE-1) complex (Kvainickas et al., 2017; Simonetti et al., 2019, 2023), which participates as well in cargo sorting in the endosomal system, either within or in parallel to the retromer pathway. The ESCPE-1 complex comprises the same heterodimeric SNX–BAR proteins but does not include VPS subunits. Importantly, it is widely accepted that among the SNXs involved in ESCPE-1/retromer, SNX1 and SNX2 are the primary contributors to endosomal membrane remodeling through tubulation (Carlton et al., 2004).

In addition to its implication in retrograde transport and endosomal cargo retrieval, recent data pointed out the requirement of retromer (including SNX1 and SNX2) in ciliogenesis during development, notably during turnover of mother centriole associated with primary cilium (Xie et al., 2022). Although the majority of retromer/ESCPE-1 SNX-related membrane dynamics regulatory functions have been identified by SNX1 dedicated investigations, a specific role of retromer/WASH associated SNX2 has been demonstrated in the regulation of endosomal budding via actin cytoskeleton local mobilization (Dong et al., 2016). Interestingly, this was shown to occur via PI4P-positive endosomal subdomains that engage with ER through membrane-contact sites, involving a VAP/SNX2 trans-interaction, suggesting that SNX2, via its FFAT-like motif (Di Mattia et al., 2020), could be considered as a bona-fide partner of membrane-contact sites machinery.

Beside SNX1 and SNX2 canonical roles (i.e., primarily identified) in above mentioned endosomal functions, these proteins have also been suggested to participate in non-retromer/ESCPE-1 endosomal functions (Figure 1). The first papers that described SNX1 targeting PI3P-positive endosomal membranes suggested that the endolysosomal transport of epidermal growth factor receptors was controlled by SNX1 (Cozier et al., 2002). Consistently, SNX1 was reported to participate in several trafficking pathways emerging from endosomes independently from the retromer complex. This includes the lysosomal transport of the G-protein-coupled protease-activated receptor-1 which occurs independently from SNX2 (Gullapalli et al., 2006) as well as the endosomal recycling trafficking of another G-protein-coupled protein, the P2Y1 receptor (Nisar et al., 2010). In parallel, SNX1 has been shown to participate in macropinosome formation (Wang et al., 2010) and was found associated with a specific recycling of junctional E-cadherin in epithelial cells under epidermal growth factor treatment during macropinocytosis process (Bryant et al., 2007). In parallel with their function in endosomal tubulation for the retromer/retrograde pathway, SNX1 and SNX2 have been also shown to play a role in modulating Kal7- and RhoG-dependent actin remodeling, independently of retromer (Prosser et al., 2010). Finally, SNX1 has been found to be required for the factors for endosome recycling and Rab interactions (FERARI) complex dedicated Rab11-dependent endosomal recycling via a kiss-and-run mechanism (Solinger et al., 2020).

SNX2 has been implicated in dedicated functions, particularly in autophagy during cellular response to starvation, specifically in lysosomal membrane maintenance and turnover (Nanayakkara et al., 2022). A recent study revealed that a pool of SNX2 associated with $PI3,5P_2$ was necessary for proper lysosomal membrane reformation through specific tubulation (Rodgers et al., 2022). This process is regulated by the turnover of phosphoinositides, which is facilitated by INPP4B and PIKFyve enzymes. Interestingly, this phenomenon appears to be distinct from cargo sorting or recycling mechanisms and bears resemblance to the autophagosomal components recycling (ACR) pathway. In the ACR pathway, SNX4, SNX5, and SNX17 proteins, collectively referred to as "the recycler," mediate the retrieval of autophagosomal membrane components from the autophagolysosome (Zhou et al., 2022).

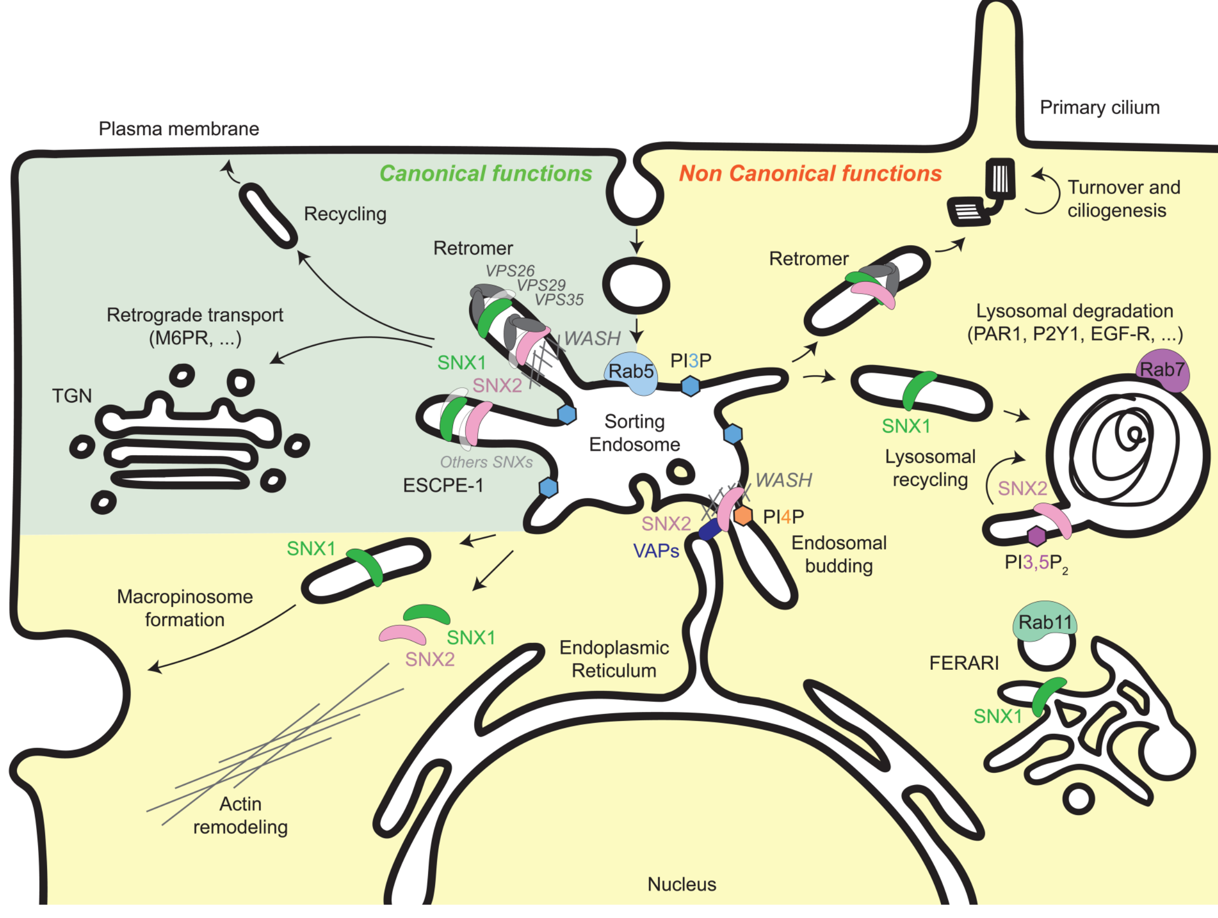

Figure 1. Overview of SNX1 and SNX2 endosomal functions. The green background represents canonical retromer/ESCPE-1 functions of SNX1 and SNX2 associated with VPS subunits (VPSS26/VPS29/VPS35; in dark grey) and other SNXs (SNX5/SNX6/SNX32; in light grey). The yellow background represents "non-canonical" functions of SNX1 and SNX2 such as macropinosome formation, endosomal budding with local actin remodeling, FERARI-dependent sorting, lysosomal degradation and recycling, and turnover of centrioles/ciliogenesis.
Note. ESCPE = endosomal SNX–BAR sorting complex for promoting exit 1; SNX = sorting nexin; FERARI = factors for endosome recycling and Rab interactions.

Relationships between autophagy regulation, especially early stages of autophagosome biogenesis, and SNXs have been already demonstrated (Hanley and Cooper, 2020). Autophagosome biogenesis sequence initiates at PI3P-enriched ER membrane subdomains termed omegasomes (Melia et al., 2020) where the confined presence of pre-autophagic regulators allow for the de novo formation of the phagophore, which will later expand and close to form a mature autophagosome (Lamb et al., 2013; Hu and Reggiori, 2022). These dynamic steps have been shown to be associated with ER membrane contact sites, such as ER-mitochondria (Hamasaki et al., 2013) and ER-plasma membrane contacts (Nascimbeni et al., 2017), and are necessarily related to membrane/lipid sources and specialized membrane trafficking and regulators local delivery. In this context, several SNXs have been directly or indirectly involved in the early steps of autophagosome biogenesis such as SNX18 (Knævelsrud et al., 2013; Søreng et al., 2018) or SNX4 and SNX7, in association with ATG9A vesicular trafficking (Antón et al., 2020).

By investigating the effects of starvation on endosomal morphology, our team recently showed that starvation-induced autophagy promotes a rapid and transient endosomal SNX1/SNX2 membrane rewiring of tubules toward sites of autophagosome biogenesis at ER subdomains (Da Graça et al., 2022). In this study, we reported that SNX1 overexpression increases autophagosome biogenesis while its knock-down leads to alteration of autophagic response. We show that a subset of endosomal membranes was generated within the very early stages of autophagic response. This endosomal rewiring was shown to be dependent on SNX1 and allow for the transient endosomal tubulation at the immediate vicinity of omegasomes. Importantly, our data also highlight the importance of SNX2, notably in the membrane tethering occurring between SNX1-positive tubules and the omegasome platform at the ER surface. This tethering is mediated by SNX2–VAPB interaction, as it was previously demonstrated in the context of endosomal membrane dynamics regulation by

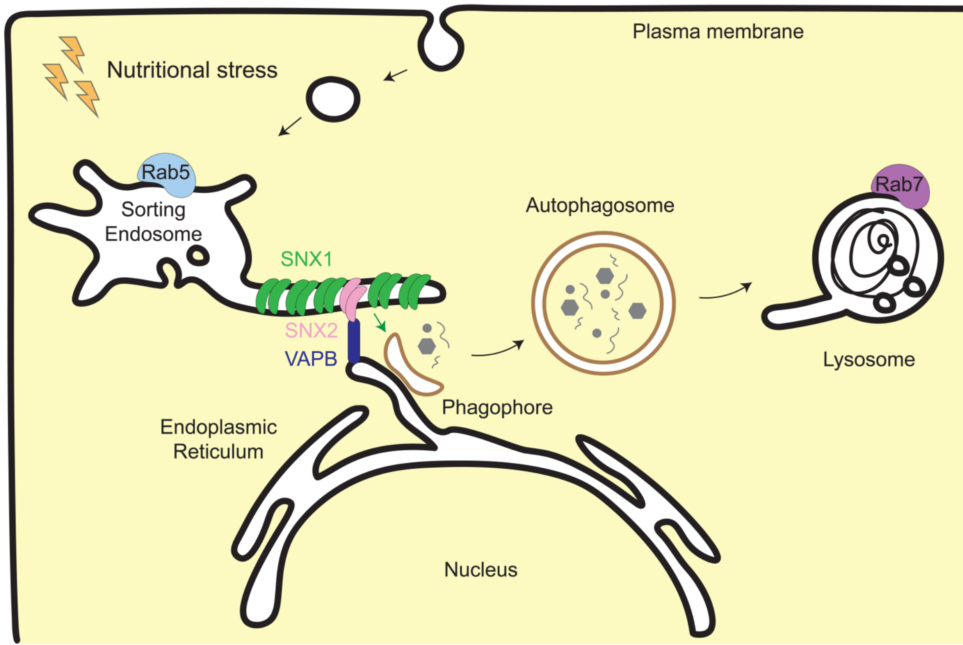

Figure 2. SNX1 and SNX2 mobilization during early stages of starvation. Nutritional stress induces rapid tubulation of SNX1-positive membranes from sorting endosomes. SNX2 localizes to specific regions along SNX1 tubules and binds to the endoplasmic reticulum (ER)-resident protein VAPB. The endosome/ER tethering occurs at sub-regions of the ER engaged in phagophore/autophagosome biogenesis formation. This process contributes to autophagosome biogenesis, the first step of the autophagic pathway. Autophagosome will close, resulting in a double membrane vesicle, and will fuse with the lysosome for degradation.

ER-PI4P-positive endosome contact sites (Dong et al., 2016). In this context, we show that the SNX2–VAPB interaction was transiently upregulated by starvation, highlighting the importance of endosome-ER dialog in the context of autophagy initiation, through mobilization of SNX1 and SNX2 proteins (Figure 2). These data demonstrate that SNX1 and SNX2 are well mobilized during autophagy, for very early endosomal rewiring associated with endosome–ER interface. Interestingly, we show that while SNX1 and SNX2 homogeneously colocalize on endosomal structures at steady state, SNX2 patterns along SNX1 tubules are generated by starvation, thus defining zones of SNX1 tubules that can engage with VAPB at the ER membrane. Without SNX2–VAPB interaction, SNX1 tubules are still generated but are no longer addressed to ER subdomains fostering autophagosome biogenesis sequence. Thus, this suggests that in this situation SNX1 and SNX2 act on similar processes and respond to the same stimuli, but not for the same membrane-related functions, since SNX1 is necessary for endosomal membrane elongation and SNX2 is required for tethering with ER. These observations also raise the question of SNXs non-exchangeable involvement in membrane dialog and coordination in response to stress. However, the direct involvement of SNX5/SNX6 and retromer partnership in stress-induced membrane tubulation was not assessed in this study, although preliminary and unpublished results suggested us to rule out this hypothesis.

The acute tubulation process in early endosomes, dependent on SNX1 and associated with SNX2-mediated ER tethering, occurs transiently during the initial stages of the starvation response. It operates on a different timescale than the established functions of SNX1 and SNX2 in retromer/ESCPE-1-mediated cargo trafficking to the TGN. Consequently, it would be intriguing to investigate whether retrograde transport is impaired or altered during the SNX1/SNX2 mobilization observed within minutes of starvation. Recent findings have also highlighted the role of SNX19 in promoting endosome–ER membrane tethering to regulate the intracellular mobility of endolysosomes (Saric et al., 2021). This, similar to our own data, suggests that SNXs may possess related functions in membrane dynamics, not solely dedicated to cargo transport.

In light of these observations, one could consider the existence of "side functions" of SNXs, wherein they act as membrane modulators to acutely redistribute pools of membranes, ensuring endomembrane homeostasis in specific situations such as the response to starvation. This response promotes endosomal rewiring, lysosomal membrane recycling, and autophagosome biogenesis from ER-mediated contact sites. It is thus tempting to postulate that SNXs act as local membrane modulators, necessary for fine-tuning the morphodynamics of endosomal compartments, particularly through their SNX–BAR domains and interaction with phosphoinositides in the case of SNX1 and SNX2. Importantly, these functions could be independent of their sorting and cargo-related roles.

Declaration of Conflicting Interests

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