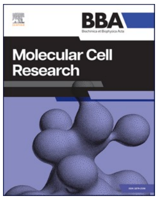
BBA - Molecular Cell Research 1872 (2025) 120031

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr



Review

SYT13: An underestimated synaptotagmin

Johannes Lehmann [a], Alberto Catanese [a,b,c,*]

[a] Institute of Anatomy and Cell Biology, Ulm University School of Medicine, 89081 Ulm, Germany
[b] German Center for Neurodegenerative Diseases (DZNE), Ulm Site, Germany
[c] Institute of Anatomy and Cell Biology, Neuroanatomy Department, Freiburg University, 79104 Freiburg, Germany

ARTICLE INFO

Keywords:
Synaptotagmin
Synaptotagmin13
SYT13
Syt XIII

ABSTRACT

Synaptotagmin-13 (SYT13) is a non-canonical member of the of synaptotagmin family that, canonical synaptotagmins, doesn't contain Ca^{2+} binding sites, but still appears to play a key role in the control of different cellular processes such as vesicle transport, cell migration, signaling and cell development. The recent findings associate SYT13 with neuronal survival and development, metabolic homeostasis (especially insulin secretion) and both oncogenic and tumor suppressive function in multiple cancers. And yet all this data is scattered in fields, with no systematic review covering SYT13's detailed biology. A comprehensive literature review is therefore needed to explain SYT13's multifaceted roles, uncover informational gaps and direct future studies to exploit SYT13 as a target for neurodegeneration, metabolic disease and cancer therapy.

1. Introduction

The synaptotagmin (SYT) protein family includes at least 17 distinct members in mammals. These proteins are broadly classified into two main groups: canonical and non-canonical synaptotagmins. This is based on their differing abilities to bind calcium ions (Ca^{2+}) and their specific roles in the cellular process of exocytosis [1,2]. Structurally, synaptotagmins typically share a common blueprint: they possess an N-terminal transmembrane segment that anchors the protein to either synaptic vesicle membranes or the plasma membrane, and they feature two variable C2 domains (C2A and C2B) situated in the cytoplasm [2].

Canonical synaptotagmins, which include isoforms like SYT1, SYT2, SYT3, SYT7, and SYT9, are characterized by C2 domains that contain functional Ca^{2+}-binding sites. These isoforms are vital for orchestrating several key neuronal processes, such as the release of neurotransmitters, the fusion of synaptic vesicles, and Ca^{2+} signaling [2–4]. Synaptotagmin 1 (SYT1) stands out as the principal Ca^{2+} sensor facilitating rapid, synchronized neurotransmitter release within the central nervous system [5]. A crucial function of these canonical SYTs is to connect Ca^{2+} signals with the exocytotic machinery, ensuring that neurotransmitter release is precisely coordinated with neuronal activity [6].

In contrast, non-canonical synaptotagmins lack the critical aspartate residues within one or both of their C2 domains, which are required for Ca^{2+} binding. This structural difference prevents them from functioning as conventional Ca^{2+} sensors [2]. Instead, it is proposed that these non-canonical variants may influence exocytosis and endocytosis through mechanisms that do not depend on calcium ions. For instance, synaptotagmin-12 (SYT12) has been shown to adjust the rate of spontaneous neurotransmitter release without directly interacting with Ca^{2+} [7]. Similarly, synaptotagmin-11 (SYT11) is believed to participate in the recycling of synaptic vesicles and has been linked to neurodegenerative disorders like Parkinson's disease [8]. Overall, the non-canonical synaptotagmins have been considerably less investigated than their Ca^{2+}-binding counterparts.

1.1. *Molecular characteristics of SYT13*

Synaptotagmin-13 (SYT13) was first identified in 2001 [9,10] and is encoded by the *SYT13* gene located on human chromosome 11p11.2. The gene spans approximately 46 kilobases and features six alternative-splicing exons, giving rise to at least three transcript variants that may encode distinct protein isoforms with potentially specialized functions [11–13]. The primary human SYT13 protein isoform consists of 426 amino acids, with a predicted molecular weight of around 47 kDa [12,13].

While SYT13 possesses the characteristic synaptotagmin architecture (an N-terminal transmembrane domain (TMD) followed by a linker region and tandem cytoplasmic C2 domains (C2A and C2B)), it exhibits several atypical features when compared to canonical synaptotagmins [9,10] (Fig. 1). For instance, SYT13 lacks a significant N-terminal

---

[*] Corresponding author at: Institute of Anatomy and Cell Biology, Neuroanatomy Department, Freiburg University, 79104 Freiburg, Germany.
E-mail addresses: johannes.lehmann@uni-ulm.de (J. Lehmann), alberto.catanese@uni-ulm.de (A. Catanese).

https://doi.org/10.1016/j.bbamcr.2025.120031
Received 28 March 2025; Received in revised form 25 July 2025; Accepted 29 July 2025

sequence preceding its TMD and possesses an unusually long, proline-rich linker region connecting the TMD to the C2 domains [10]. Crucially, both the C2A and C2B domains of SYT13 are considered degenerate for Ca^{2+} binding due to the absence of several conserved aspartate residues that are required for Ca^{2+} coordination [9,10]. This structural feature places SYT13 within the Ca^{2+}-independent subgroup of the synaptotagmin family, distinguishing its likely regulatory mechanisms from those of Ca^{2+}-sensors. (See Tables 1–4.)

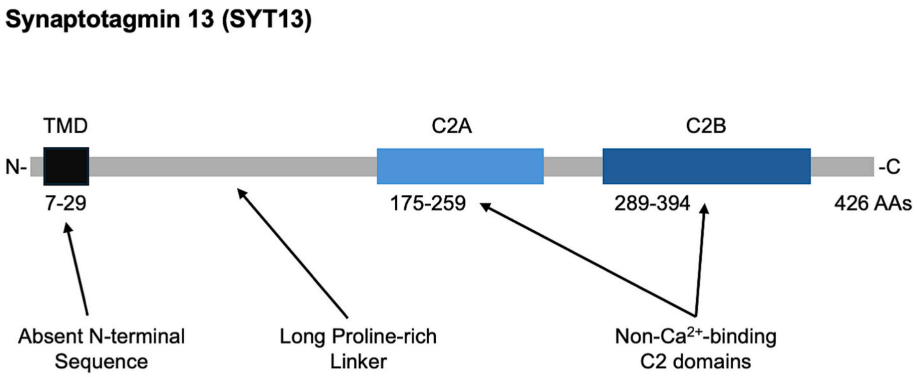
The distinct structural features of SYT13 are a product of its evolutionary trajectory within the synaptotagmin family, which exists in animal and plants [14,15]. Phylogenetic analyses indicates that SYT13 is conserved across vertebrate species, with orthologs identified in several genomes from mammals (e.g., mouse), amphibians (e.g., *Xenopus tropicalis*) and fish (e.g., zebrafish). This suggests strong selective pressure to maintain its specialized functions despite its different chromosomal linkage across species [14,15]. Based on its amino acid sequence, Wolfes and Dean (2020) grouped SYT13 with SYT15 and SYT17 [16], which are both known for lacking calcium-sensing capabilities (Fig. 2). While little is known about SYT15, SYT17 is thought to support endocytosis, thereby influencing synaptic strength and plasticity. Specifically, studies on SYT17 knockout models revealed its impact on AMPA receptor internalization and long-term depression. Although SYT17 might work with SYT3 to organize postsynaptic trafficking, its presence in axons also suggests a presynaptic function. Interestingly, SYT17 lacks a transmembrane domain but binds to membranes through N-terminal cysteine clusters and possesses protein kinase A consensus sequences, indicating potential involvement in cAMP-mediated signaling [16].

Regarding its expression, broad RNA sequencing analyses identified the expression of SYT13 mRNA in different human organs, with notable abundance in neuronal tissues, intestine, gallbladder, kidney, pancreas, and heart [17]. More detailed investigations by Tarquis-Medina et al. (2021), utilizing a SYT13-Venus fusion reporter mouse line, provided a more systematic examination of its expression. Their work confirmed high SYT13 protein abundancy in specific neuroendocrine cell populations within the brain (including tyrosine hydroxylase-expressing and oxytocin-producing cells), throughout the enteroendocrine cells of the intestine, and within the endocrine lineage of the pancreas. These findings solidify SYT13's status as a neuroendocrine marker and provide valuable context for understanding its diverse physiological roles [18].

1.2. *The SYT13 protein interactome: Experimental insights and functional implications*

Understanding the network of protein interactions in which SYT13 participates is essential for elucidating its diverse (and poorly understood) cellular functions. A significant step in this direction was provided by Bakhti et al. (2022), who used proximity-dependent biotin identification (BioID) labeling in Madin-Darby canine kidney (MDCK) cells overexpressing SYT13 [19]. This study yielded a dataset of high-confidence SYT13-interacting proteins, offering valuable molecular clues that support and expand on SYT13's observed functional roles. In fact, this experimentally-determined interactome revealed that SYT13 associates with a remarkable array of proteins involved in several key cellular processes:

1. **Endocytosis, Endosomal Sorting, and Vesicle Trafficking:** A prominent group of interactors strongly implicates SYT13 in the machinery of membrane uptake and intracellular trafficking. For example, **CLINT1 (Clathrin interactor 1)**, crucial for clathrin-mediated endocytosis and trafficking between the trans-Golgi Network (TGN) and endosomes [20,21], represented the top interactor in the dataset from Bakhti and colleagues. In addition, SYT13



Aliases	Synaptotagmin 13, SYT13, Synaptotagmin XIII, SytXIII, KIAA1427
Gen location	11p11.2
Gen size	46,040 bases
Molecular mass	46885 Da
# of splice variants	3 (described)
# of exons	6
Dimerization	unknown
Ca^{2+} binding	no
Expression (high to low)	brain, gall bladder, colon, small intestine, duodenum, kidney, stomach, heart, adrenal, appendix, thyroid, pancreas, prostate, testis, salivary gland

Fig. 1. Molecular characteristics of SYT13.

Table 1
Synaptotagmin 13 compared to canonical synaptotagmins.

Feature	Canonical Synaptotagmins (e.g., SYT1, SYT2, SYT7)	Synaptotagmin 13 (SYT13)	Possible Evolutionary/Functional Implication for SYT13
N-terminal Extracellular Sequence	Often present, variable length.	Almost absent	Altered membrane topology or interaction profile; potential impact on trafficking or localization.
Ca2 + −binding Motifs in C2 Domains	Conserved aspartate (and other) residues critical for Ca^{2+} coordination.	Key Ca^{2+}-coordinating residues are mutated/absent; C2 domains are degenerate for Ca^{2+} binding	Loss of direct Ca^{2+} sensing capability; enables Ca^{2+}-independent functions or regulation by other factors.
Proline-rich Linker	Variable, generally not as extensively proline-rich or as long as in SYT13.	Unusually long and proline-rich.	Potential for unique protein-protein interactions; may contribute to specific recruitment or scaffolding functions
Primary Mode of Regulation	Typically Ca^{2+}-dependent activation of membrane binding and/or SNARE interactions.	Likely Ca^{2+}-independent; regulation may involve other protein partners or lipid interactions.	Adaptation to cellular processes not directly gated by Ca^{2+} influx; allows for participation in constitutive or alternatively regulated trafficking pathways.
Primary Functional Roles	Ca^{2+}-triggered exocytosis (e.g., neurotransmitter release).	Vesicle trafficking, cell migration/ morphogenesis (e.g., pancreatic development), neuroprotection.	Diversification into roles beyond acute Ca^{2+}-regulated secretion; involvement in broader aspects of membrane dynamics and cellular organization.

Table 2
Metabolic and endocrine functions of SYT13.

Aspect	Details	References
Insulin Secretion Regulation	Associates with insulin secretory granules in beta cells; knockdown in in vitro models reduces secretion. Expression influenced by PDX1 and glucocorticoids. (In vivo impact & molecular mechanisms require further study).	[39–44]
Role in Diabetes & Complications	Expression reduced in pancreatic islets from type 2 diabetes donors, correlating with higher HbA1c. Elevated expression reported in retinal tissue during diabetic retinopathy.	[41,45]
Pancreatic Endocrine Cell Development	Crucial for endocrine cell egression/ delamination from pancreatic epithelium during islet morphogenesis. Localized to apical membrane and leading edge of egressing cells. Influences cell fate (β- vs α-cell differentiation).	[19]
Cell-Matrix Adhesion Remodeling (Pancreas)	Remodels cell-matrix adhesion by promoting α6β4 integrin internalization at the cell's leading domain, facilitating endocrine cell egression.	[19]
Selective Endocytosis	Enriched in Golgi; colocalizes with EEA1 & LAMP1. Augments Epidermal Growth Factor (EGF) uptake (but not Transferrin), suggesting a role in endocytosis of specific membrane proteins.	[19]
Intestinal Expression	Expressed in all enteroendocrine cells of the adult murine intestine. Specific physiological function in this context is currently unknown.	[18]

appears to interact with components of the ESCRT-0 complex such as **HGS (Hepatocyte growth factor-regulated tyrosine kinase substrate)** and **STAM2 (Signal transducing adapter molecule 2)**, both vital for the recognition and sorting of ubiquitinated membrane proteins into the endosomal pathway [22–24]. The interaction with **CAV1 (Caveolin-1)** suggests potential involvement in caveolae-mediated endocytosis as well [25]. Furthermore, proteins like **LRBA (Lipopolysaccharide-responsive and beige-like anchor protein)** and **DMXL1 (Rabconnectin-3 alpha)**, known for their roles in endosomal trafficking and receptor sorting, were also identified [26,27]. The association with **MYOF (Myoferlin)**, a protein involved in diverse membrane trafficking events including endo/ exocytosis [28], further underscores SYT13's deep integration into these pathways. These interactions provide a molecular basis for SYT13's role in the internalization of plasma membrane proteins such as α6β4 integrins and EGF receptors, as demonstrated by Bakhti et al. (2022) [19].

Table 3
SYT13 in neurological disorders.

Aspect	Details	Key References
Brain Expression & Localization	Highly expressed in the brain. Protein expression confirmed in forebrain, cerebellum, and specific neuroendocrine cells (e. g., TH-expressing, oxytocin-producing neurons).	[17,18]
Synaptic Plasticity & Memory	Elevated SYT13 mRNA in specific mouse brain regions (e. g., amygdala, cortex, thalamus) after contextual fear conditioning; suggests a potential role in memory-related synaptic remodeling.	[46]
Neuronal Development & Remodeling	Implicated in spontaneous activity-dependent neuronal circuit remodeling (e.g., murine retinal ganglion cells). Higher expression in immature neurons (e.g., bushy cells); linked to synaptic maturation and neurite growth.	[47,48,54]
Predicted Synaptic Interactions	Prediction databases suggest interactions with other synaptotagmins (SYT1, SYT4) and synaptic proteins (VAMP1, NRXN1, RAB3C), implying potential roles in vesicle dynamics (requires experimental validation).	Pathway Commons [Ref]; STRING database [Ref]
Neuroprotection in Motor Neuron Disease (ALS/SMA)	Overexpression in iPSC-derived MNs and in vivo in ALS/SMA mouse models improves MN survival, neurite length, motor function, delays disease onset, and extends survival.	[49]
Cellular Mechanisms of Neuroprotection	SYT13 overexpression reduces ER stress markers (e.g., BiP, pEIF2, ATF6, CASP3, BAX) and apoptosis, and may improve ER calcium homeostasis in affected MNs.	[49]
Pathophysiology of SYT13 Deficiency	Heterozygous SYT13 loss in human iPSC-derived MNs induces ALS-like phenotypes (reduced synapses, increases stress markers, protein aggregation). Transcriptomic changes include TP53 activation and dysregulation of key pathways.	[54]

Table 4
Dichotomous role of SYT13 in cancer.

Category	Aspect	Cancer Type(s)	Details	Key References
SYT13 as an Oncogenic Driver	Promotion of Invasion & Metastasis	Gastric	High expression correlates with peritoneal metastasis & poor prognosis. Inhibition reduces invasion/migration. ASO-4733 in clinical trial development.	[55–58]; Kanda et al., 2019
		Colorectal	Upregulation associated with increased migration and invasion.	[59]
		Cervical	Mediates ESM1-dependent migration/invasion via PI3K-Akt pathway.	[60]
		ER-positive Breast	Silencing reduces migration/invasion via FAK/AKT suppression and EMT modulation.	[61]; Ichikawa et al., 2021
		Small Bowel Neuroendocrine Tumors (SBNETs)	High expression associated with liver metastasis.	[62]
	Enhancement of Proliferation & Cell Survival (Anti-apoptotic)	Colorectal	Knockdown reduces proliferation, colony formation; induces G2 arrest & apoptosis. Decreases tumor growth in xenografts.	[59]
		ER-positive Breast	Knockdown inhibits proliferation, induces G1 arrest & apoptosis (via Cyclin D1, CDK4, Bcl-2, p21, Bax).	[61]
		Lung Adenocarcinoma	High expression correlates with poor prognosis. Knockdown reduces proliferation, colony formation; induces cell cycle arrest & apoptosis.	[63]
		Esophageal Squamous Cell Carcinoma (ESCC)	Upregulated; knockdown inhibits growth/migration, promotes apoptosis, potentially via ACRV1 regulation.	[64]
SYT13 as a Tumor Suppressor	Inhibition of Tumorigenicity & Promotion of Differentiation	Liver	Reduced expression linked to aggressive tumors. Restoration normalizes cell morphology, reduces neoplastic features, promotes MET (e.g., upregulates E-cadherin, WT1).	[65–67]
SYT13 as a Cancer Biomarker	Prognostic / Diagnostic Potential	Gastric	mRNA in peritoneal lavage may predict recurrence.	[56]
		Glioma	Identified as a potential diagnostic biomarker via bioinformatic analysis (AUC > 0.90).	[68]

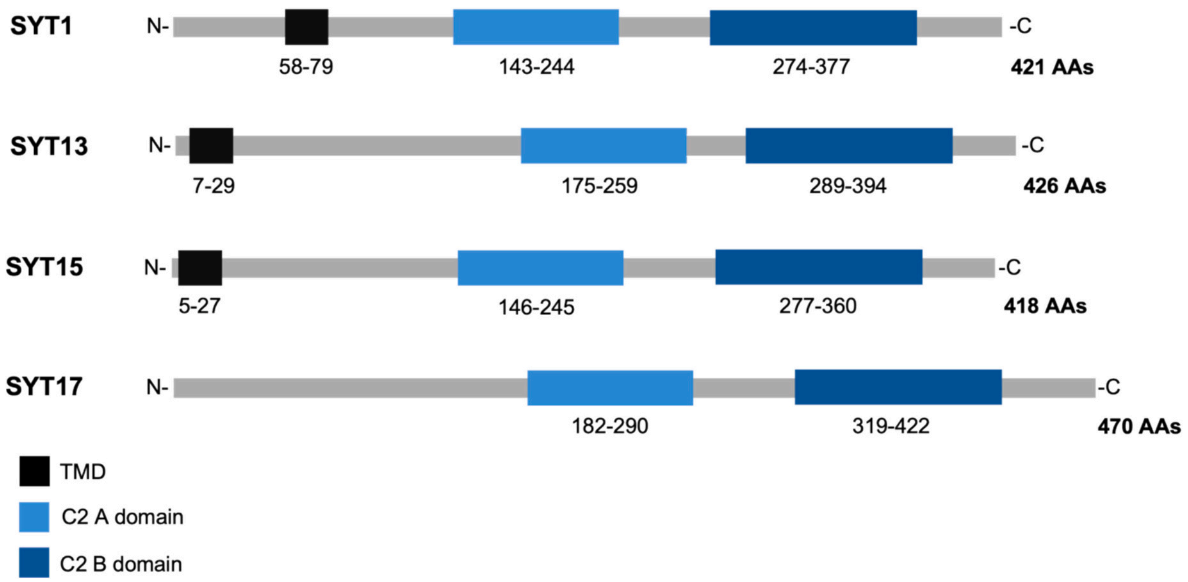


Fig. 2. Sequence localization of the protein domains of different synaptotagmins. SYT1 representing a canonical member of the synaptotagmin family with Ca^{2+} binding sequence in the C2A and C2B domain. SYT13, SYT15, SYT17 representing non-canonical members, with no such Ca^{2+} domains.

2. **Golgi/ER Dynamics and Protein Trafficking:** the localization of SYT13 at the Golgi is supported by its interactions with proteins resident in or trafficking through the ER-Golgi network. These include **ACBD3 (Golgi resident protein GCP60)**, involved in Golgi organization [29]; **COPG2 (Coatomer subunit gamma-2)**, a component of the COPI coat essential for intra-Golgi and Golgi-to-ER retrograde transport [30]; and **TFG (Protein TFG)**, which functions in organizing ER exit sites and ER-to-Golgi transport [31]. Interactions with ER-shaping proteins like **RTN4 (Reticulon-4)** and the ER-resident protein **TMEM33** further suggest a role for SYT13 in processes related to ER morphology or ER-Golgi communication [32,33]. **GOPC (Golgi-associated PDZ and coiled-coil motif-containing protein)**, involved in Golgi trafficking and receptor sorting [34], also features in the SYT13 interactome.
3. **Cytoskeletal Organization, Cell Adhesion, and Polarity:** several interaction partners link SYT13 to the regulation of cell structure and adhesion, which is critical for its function in processes like endocrine cell egression. Notable interactors include **ANK3 (Ankyrin-3)**, an adapter protein that connects the plasma membrane to the actin cytoskeleton and is involved in maintaining cell polarity [35], and **EFHD2 (EF-hand domain-containing protein D2)**, which influences actin dynamics and cell motility [36]. The association with subunits of the TRiC/CCT chaperonin complex (e.g., **CCT6A, CCT8**), responsible for folding actin and tubulin [37], suggests SYT13 may influence the availability or assembly of key cytoskeletal components. Myoferlin (MYOF) also contributes here, given its interactions with integrins and the actin cytoskeleton.
4. **ER Stress Response:** an intriguing finding from the interactome [19] is the identification of **EIF2AK3 (PERK)**, a primary sensor of ER

stress within the Unfolded Protein Response (UPR) [38]. While this interaction was identified in pancreatic cells, it offers a potential molecular link for SYT13's observed role in mitigating ER stress in neuronal models neurodegeneration, suggesting a conserved mechanism that warrants further investigation across different cell types.

While this experimental dataset from MIN6 cells provides robust insights, particularly in regard of SYT13's functions in epithelial and endocrine contexts, it is conceivable that SYT13 may engage with different sets of interactors in other cell types, such as neurons, to fulfill its specialized roles. Prediction databases like STRING and Pathway Commons may offer complementary hypotheses for SYT13's broader interaction landscape, but these require direct experimental validation. The experimentally defined interactome (Fig. 3) thus serves as a critical foundation for future mechanistic studies on SYT13.

1.3. *Metabolic and endocrine functions*

Different lines of evidence have highlighted SYT13 as a modulator of insulin secretion in pancreatic beta cells. Single-cell RNA sequencing has indeed revealed high SYT13 expression in newborn mouse beta cells and in human embryonic stem cell (hESC)-derived beta-like cells [39]. Supporting a role in the secretory pathway, immunolocalization studies have shown SYT13 colocalizing with insulin, suggesting its association with insulin secretory granules within beta cells [40]. Functional studies employing siRNA-mediated knockdown or knockout of SYT13 in in vitro models have demonstrated a significant reduction in insulin secretion, pointing towards its involvement in the exocytosis of insulin granules [40–42].

The expression of SYT13 appears to be under the regulation of PDX1, a key transcription factor for beta-cell development and function [43]. Furthermore, in human beta cells, glucocorticoid treatment, known to impair beta-cell function, has been shown to reduce both PDX1 and SYT13 levels, correlating with decreased insulin secretion. This suggests SYT13 may be a component of glucocorticoid-sensitive pathways impacting beta-cell function [44]. Clinically, SYT13 expression is significantly diminished in pancreatic islets from donors with type 2 diabetes. This reduced SYT13 level correlates with increased HbA1c, an

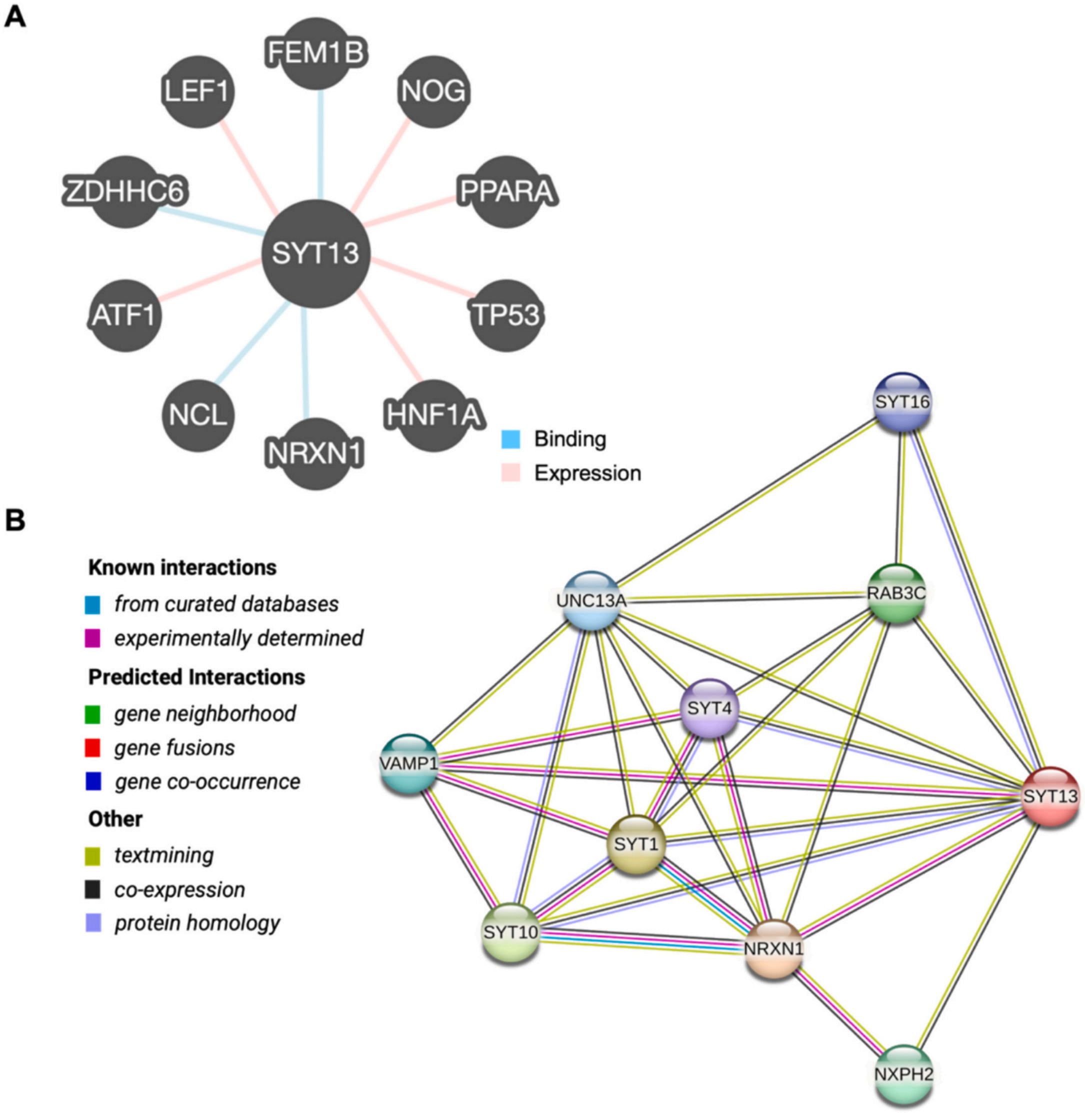


Fig. 3. Predicted interactions of SYT13
A Prediction of SYT13 interactions using the *Pathway Commons Interactions tool*
B Prediction of SYT13 interactions using the *STRING interaction network 12.0*, *textmining* up to August of 2022, minimum required interaction score: medium confidence (0.400)
Creative Commons Attribution license (CC BY 4.0).

indicator of impaired glycemic regulation, hinting that diminished SYT13 could contribute to the compromised insulin release observed in type 2 diabetes [41]. Interestingly, in the context of diabetic complications, high SYT13 expression has been reported in retinal tissue from patients with diabetic retinopathy [45], though the implications of this specific finding require further investigation.

While these findings are intriguing, it is important to note that most of the direct functional evidence for SYT13 role in insulin secretion was obtained with in vitro studies. The precise molecular mechanisms by which SYT13 participates in insulin granule exocytosis, and its overall impact on in vivo beta cell function and glucose homeostasis, remain areas requiring more extensive research.

A pivotal study by Bakhti et al. (2022) elucidated a critical role for SYT13 in pancreatic endocrine cell development, specifically in the process of endocrine cell egression or delamination from the pancreatic ductal epithelium during islet morphogenesis [19]. SYT13 was found to be upregulated in endocrine precursor cells and localized to the apical membrane and the leading edge of these cells as they egress. While this localization is associated with the profound cellular reorganization involved in egression, including changes in cell polarity, the study indicated that SYT13 is part of these polarity shifts rather than a primary regulator of the switch from apical-basal to a migratory front-rear polarity [19]. SYT13 expression in endocrine precursor cells also correlated with high levels of the transcription factor Neurogenin 3 (Ngn3). Subsequent knockout studies revealed that SYT13 influences endocrine cell fate, as its loss skewed differentiation from beta cells towards alpha cells, suggesting SYT13 acts downstream of Ngn3 in orchestrating proper endocrine lineage development [19].

Mechanistically, Bakhti et al. described SYT13 as a trafficking protein that utilizes the microtubule cytoskeleton for its transport and associates with phosphoinositides PIP2 and PIP3, primarily via its C2B domain. Additionally, it appears that SYT13 facilitates endocrine cell egression by impacting the cell-matrix adhesion through the internalization of plasma membrane proteins, such as α6β4 integrins, at the cell's leading domain. This controlled endocytosis of adhesion molecules is proposed to loosen the cell's attachment to the basement membrane, thereby enabling efficient egression of endocrine cells from the epithelium, rather than directly mediating sustained cell migration over long distances [19].

Further investigation into SYT13's subcellular localization and trafficking functions showed its enrichment in the Golgi apparatus and colocalization with the early endosome marker EEA1 and the lysosomal marker LAMP1 [19]. Moreover, SYT13 overexpression was found to specifically augment the uptake of epidermal growth factor (EGF) but not Transferrin (Tf), pointing to a role for SYT13 in the endocytosis of select plasma membrane proteins and receptor tyrosine kinases, which could be integral to its function in developmental processes like egression [19].

Beyond the pancreas, SYT13 is also prominently expressed in the intestine. Specifically, Tarquis-Medina et al. (2021) demonstrated SYT13 expression throughout all enteroendocrine cells in the adult murine intestine [18]. These cells play crucial roles in nutrient sensing and hormone secretion, contributing to metabolic regulation. However, despite its clear expression in this important endocrine cell population, the specific functions of SYT13 within intestinal enteroendocrine cells are currently unknown and represent an open area for future investigation.

2. SYT13 in neurological disorders

Since SYT13 is highly expressed in the brain [17], understanding its diverse neuronal functions is of considerable interest. Supporting its widespread presence, Tarquis-Medina et al. (2021), used a SYT13-Venus reporter mouse to demonstrate SYT13 protein expression in various brain regions, including high levels in the forebrain and cerebellum, and specifically within neuroendocrine cells such as tyrosine hydroxylase (TH)-expressing and oxytocin-producing neurons [18]. Early functional indications suggest SYT13 may be involved in processes like contextual fear memory, as increased SYT13 mRNA levels were observed in several murine brain areas (e.g., lateral amygdala, somatosensory cortex, piriform cortex, habenula, thalamus, hypothalamus) following contextual fear conditioning [46].

SYT13 also appears to play roles in neuronal development and activity-dependent refinement. A recent study identified SYT13 as an important Type I membrane protein involved in spontaneous activity-dependent neuronal remodeling in the developing murine visual system, based on transcriptomic analyses of retinal ganglion cells (RGCs) before eye-opening [47]. Furthermore, higher SYT13 expression has been noted in immature bushy cells of the cochlear nucleus during early auditory pathway development compared to their mature counterparts [48]. Bushy cells are characterized by their densely branched dendrites, and these observations collectively suggest a potential role for SYT13 in processes such as synaptic maturation, dendritic arborization and axonal branching during neuronal development.

Additional evidence highlighted a potential neuroprotective role for SYT13, particularly in the context of motor neuron diseases. Nizzardo et al. (2020) first showed that SYT13 is highly expressed in oculomotor neurons (OMNs) [49], which appear to be more resistant to degeneration than spinal motor neurons (MNs) in amyotrophic lateral sclerosis (ALS) [50]. In order to test whether SYT13 might be neuroprotective in ALS and spinal muscular atrophy (SMA), SYT13 was overexpressed in MNs derived from iPSCs of patients affected from these major neurodegenerative diseases. This upregulation improved MN survival and extended neurite length when compared with untreated cells [49].

Notably, both ALS and SMA are associated with increased ER stress and axonal degeneration [51–53], both pathways where SYT13 appears to play an important role. In fact, Nizzardo and colleagues demonstrated that SYT13 overexpression could rescue ER stress and MN loss in mouse models of ALS and SMA. In particular, ER stress markers including binding immunoglobulin protein (BiP), phosphorylated eukaryotic initiation factor 2 (pEIF2), cleaved activating transcription factor 6 (ATF6), cleaved caspase-3 (CASP3), and BAX were all downregulated suggesting that cellular stress had been decreased [49]. Moreover, SYT13 overexpression reversed ER calcium release changes, which might reflect better calcium homeostasis [49].

In order to investigate the potential therapeutic value of SYT13 in vivo, SYT13 was transfected into SOD1G93A ALS mice by an adeno-associated virus (AAV9) vector. This treatment induced higher levels of SYT13 in spinal MNs, which associated with increased neuromuscular function, delayed disease onset and 14 % increased survival. This was accompanied by reduced MN loss, greater axonal density, intact neuromuscular junctions (NMJs) and lower ER stress and apoptosis markers in the spinal cord when assessed by immunohistochemistry [49]. Similar to this, AAV9-mediated SYT13 transfected into SMAΔ7 mice led to notable motor function enhancements, 50 % survival extension, preserved MNs and NMJ integrity [49].

Complementing the overexpression studies, our team demonstrated that a heterozygous loss of SYT13 (SYT13+/−) in human iPSC-derived MNs is sufficient to trigger a neurodegenerative phenotype recapitulating features of ALS and SMA. These SYT13+/− MNs exhibited reduced synaptic contacts, increased cellular stress markers, reduced levels of the axonal marker neurofilament heavy chain and accumulation of protein aggregates [54]. RNA sequencing of human SYT13+/− MNs revealed widespread changes in gene expression, which included a downregulation of genes involved in spinal cord development, patterning, and neurotransmitter transport, as well as the upregulation of transcripts linked to extracellular matrix and myelination, ERK cascade, JNK signaling and toll-like receptor pathways [54]. Further analysis could show that the SYT13+/− transcriptome converges towards ALS and TDP53 signatures [54].

3. Role of SYT13 in cancer

SYT13 presents a complex and often paradoxical profile in the context of cancer, with studies reporting both oncogenic and tumor-suppressive functions depending on the specific malignancy and cellular context. This multifaceted behavior underscores the need for a deeper understanding of its tissue-specific mechanisms to evaluate its potential as a therapeutic target or biomarker.

3.1. *SYT13 as a promoter of malignancy in diverse cancers*

In several types of cancer, elevated SYT13 expression or activity has been linked to enhanced tumor progression, aggressive phenotypes, and poor patient prognosis.

3.1.1. *Promotion of invasion and metastasis*

A prominent oncogenic role for SYT13 is observed in **gastric cancer**, where higher expression correlates strongly with peritoneal metastasis and unfavorable outcomes [55,56]. Mechanistically, SYT13 inhibition was shown to reduce cancer cell invasion and migration in vitro and reduces the growth of peritoneal tumors in mouse models [55]. This has led to the promising development of SYT13-targeted amino-bridged nucleic acid (AmNA)-modified antisense oligonucleotides (ASOs), with ASO-4733 now ready for clinical trials in gastric cancer patients after successful preclinical toxicology testing [57,58]. Similarly, in **colorectal cancer**, SYT13 upregulation is associated with increased cell migration and invasion [59]. In **cervical cancer**, SYT13 acts downstream of endothelial cell-specific molecule 1 (ESM1) to promote cell migration and invasion, reportedly through activation of the PI3K-Akt signaling pathway [60]. Furthermore, in **estrogen receptor (ER)-positive breast cancer**, SYT13 silencing reduces cell migration and invasion, which is associated with suppression of FAK/AKT signaling and an increase in the epithelial marker E-cadherin alongside decreased vimentin, suggesting a role in modulating epithelial-mesenchymal transition (EMT) [61]. High SYT13 expression is also associated with liver metastasis in **small bowel neuroendocrine tumors (SBNETs)**, further highlighting its pro-metastatic potential in certain contexts [62].

3.1.2. *Enhancement of proliferation and cell survival*

Beyond metastasis, SYT13 often contributes to tumor growth by fostering proliferation and inhibiting apoptosis. In **colorectal cancer** cell lines (RKO and HCT116), SYT13 knockdown was shown to reduce proliferation and colony formation, induce G2 phase arrest, and promote apoptosis. These effects translated to decreased tumor growth in mouse xenograft models [59]. Similar pro-proliferative and anti-apoptotic roles are described in **ER-positive breast cancer**, where SYT13 knockdown inhibits proliferation and induces G1 cell cycle arrest by modulating proteins such as cyclin D1, CDK4, Bcl-2, p21, and Bax [61]. In **lung adenocarcinoma**, high SYT13 expression also correlates with worse outcomes, and its knockdown reduces proliferation, colony formation, and induces cell cycle arrest and apoptosis [63]. In **esophageal squamous cell carcinoma (ESCC)**, SYT13 is significantly upregulated, and its knockdown inhibits cell growth and migration while promoting apoptosis, potentially through regulation of the downstream protein acrosomal vesicular protein 1 (ACRV1) [64].

3.2. *SYT13 as a possible tumor suppressor: The case of liver cancer*

In stark contrast to its oncogenic roles elsewhere, SYT13 has been proposed to function as a tumor suppressor in **liver tumors**. Studies have indicated that reduced SYT13 expression is linked to more aggressive tumor characteristics in liver cancer [65–67]. In contrast, restoring SYT13 expression in a rat liver tumor cell line led to a normalization of cell morphology, a reduction in neoplastic features, and an increased expression of established tumor suppressor genes, such as Wilms tumor 1 (WT1), and the cell adhesion protein E-cadherin (CDH1). These findings suggest that in the liver context, SYT13 might promote epithelial differentiation, potentially through a mesenchymal-to-epithelial transition (MET)-like process, thereby counteracting tumor progression [66].

These contrasting roles of SYT13, which may act as an oncogene in many epithelial cancers while appearing as a tumor suppressor in liver cancer, highlight the critical importance of cellular context. Several factors could contribute to these discrepancies:

1. Tissue-Specific Interactome: SYT13 likely interacts with different sets of binding partners in various cell types. These context-specific interactomes could dictate which downstream signaling pathways are modulated by SYT13, leading to opposing cellular outcomes. For example, the pathways driving gastric or breast cancer progression may involve SYT13 in a manner distinct from its interactions in hepatocytes.
2. Differential Signaling Pathways: As evidenced, SYT13 is implicated in PI3K-Akt (cervical cancer) and FAK/AKT (breast cancer) pathways, both known for their complex and sometimes cell-type-specific roles in cancer. The specific upstream regulators and downstream effectors available in a given cell type could determine whether SYT13 activity ultimately promotes or inhibits malignancy.
3. Isoform Expression and Post-Translational Modifications: While not extensively studied for SYT13, the existence of transcript variants raises the possibility that different SYT13 isoforms with distinct functions or regulatory properties might be expressed in different tissues or cancer types. Post-translational modifications could also differentially regulate SYT13 activity.
4. Tumor Microenvironment and Cancer Subtype: The specific microenvironment of the tumor and the intrinsic molecular subtype of the cancer could also influence how SYT13 signaling is interpreted by the cell.

This highlights how further research focusing on identifying SYT13's interacting partners, function and expression patterns (also focusing on its potential isoforms) across a wider range of normal and cancerous tissues is essential to unravel this functional paradox.

3.3. *SYT13 as a potential cancer biomarker*

Beyond its functional roles, SYT13 expression levels show promise as a biomarker in certain cancers. For instance, SYT13 mRNA levels in peritoneal lavage fluid are being explored to improve the prediction of peritoneal recurrence in gastric cancer patients, even those with negative cytology [56]. More recently, bioinformatic analyses have suggested SYT13 as a potential diagnostic biomarker for glioma, with high precision reported from database mining [68]. These examples suggest that, with further validation, SYT13 could aid in diagnosis, prognosis, or prediction of treatment response in specific cancer types.

3.4. *Concluding remarks on SYT13 in cancer*

The role of SYT13 in cancer is clearly multifaceted and highly dependent on the specific neoplastic context. While its pro-oncogenic activities in cancers like gastric, colorectal, and breast cancer are paving the way for targeted therapies, its contrasting tumor-suppressive role in liver cancer warrants careful consideration. Resolving this “SYT13 paradox” by elucidating the molecular determinants of its context-specific actions will be important for effectively and safely implementing SYT13 as a therapeutic target or a reliable biomarker in oncology.

4. Conclusion and perspectives

This review has synthesized the literature on SYT13, revealing it as a highly versatile, yet atypical, member of the synaptotagmin family.

Initially overshadowed by its canonical Ca2 + −sensing relatives, SYT13 is now emerging as a critical modulator of diverse cellular processes, including pancreatic endocrine cell development, insulin secretion, neuronal survival, and tumorigenesis, often with context-dependent outcomes.

SYT13's involvement in pancreatic endocrine cell egression and its influence on endocrine cell fate underscore its importance in developmental biology. In the context of metabolic homeostasis, while studies suggest SYT13 influences insulin secretion, and its dysregulation is observed in type 2 diabetes, it is crucial to acknowledge that current functional evidence largely stems from in vitro models. The precise in vivo impact of SYT13 on beta-cell function and the underlying molecular mechanisms governing its role in insulin exocytosis require substantial further investigation before its therapeutic potential for enhancing glycemic regulation in disorders like diabetes can be fully assessed.

In the nervous system, the demonstrated neuroprotective effects of SYT13 overexpression in preclinical models of ALS and SMA (leading to preserved motor neurons, reduced ER stress, and improved functional outcomes) are particularly encouraging. These findings suggest that strategies aimed at modulating SYT13 activity or expression, possibly via AAV-mediated gene delivery, could hold therapeutic promise for motor neuron diseases, although significant translational work remains.

The role of SYT13 in cancer is notably complex, presenting a “SYT13 paradox.” In many malignancies, such as gastric, colorectal, and ER-positive breast cancer, SYT13 appears to function as an oncogene, promoting proliferation, invasion, and metastasis. The successful preclinical development of SYT13-targeted ASOs for gastric cancer highlights the potential of inhibitory strategies in these contexts. Conversely, in liver cancer, SYT13 exhibits tumor-suppressive characteristics. This striking dichotomy underscores that therapeutic approaches targeting SYT13 in cancer must be highly tailored to the specific malignancy.

Looking forward, a primary research imperative is to dissect the molecular determinants dictating SYT13's context-dependent functions. Understanding its tissue-specific and cancer-specific interactomes, the influence of different SYT13 isoforms, the impact of post-translational modifications, and its precise downstream signaling pathways will be critical. Such knowledge is essential not only for clarifying SYT13's contribution to other pathological conditions where its expression is altered (e.g., potentially sepsis [69] or atrial fibrillation [70]) but also for developing effective and safe precision therapeutic strategies. These strategies might aim to selectively enhance SYT13 activity in neurodegenerative scenarios or, conversely, inhibit its function in specific cancers.

In summary, while considerable mechanistic work is still required, SYT13 has evolved from an underestimated synaptotagmin to an intriguing therapeutic and biological focal point. Future research dedicated to unraveling its complex, context-specific biology holds the key to potentially exploiting SYT13 for more effective and personalized treatments across a spectrum of endocrine, neurodegenerative, and neoplastic diseases.

CRediT authorship contribution statement

Johannes Lehmann: Writing – original draft. **Alberto Catanese:** Writing – review & editing, Resources, Funding acquisition.

Declaration of Generative AI and AI–assisted technologies in the writing process

The authors used *Gemini 2.5 pro* grammar tool. Afterward, the authors reviewed and edited the manuscript and take full responsibility for the content of the published article.

Declaration of competing interest

The authors declare no competing interests. This work was supported by the German Research Foundation (DFG), project# CA2915/4-1 to AC.

References

[1] M. Craxton, Synaptotagmin gene content of the sequenced genomes, BMC Genomics 5 (2004) 43.

[2] T.C. Südhof, Synaptotagmins: why so many? *, J. Biol. Chem. 277 (2002) 7629–7632.

[3] N. Brose, A.G. Petrenko, T.C. Südhof, R. Jahn, Synaptotagmin: a calcium sensor on the synaptic vesicle surface, Science 256 (1992) 1021–1025.

[4] E.R. Chapman, How does synaptotagmin trigger neurotransmitter release? Annu. Rev. Biochem. 77 (2008) 615–641.

[5] W.C. Tucker, E.R. Chapman, Role of synaptotagmin in Ca2+−triggered exocytosis, Biochem. J. 366 (2002) 1–13.

[6] T.C. Südhof, Neurotransmitter release: the last millisecond in the life of a synaptic vesicle, Neuron 80 (2013) 675–690.

[7] A. Maximov, O.-H. Shin, X. Liu, T.C. Südhof, Synaptotagmin-12, a synaptic vesicle phosphoprotein that modulates spontaneous neurotransmitter release, J. Cell Biol. 176 (2006) 113–124.

[8] C. Wang, X. Kang, L. Zhou, Z. Chai, Q. Wu, R. Huang, H. Xu, M. Hu, X. Sun, S. Sun, J. Li, R. Jiao, P. Zuo, L. Zheng, Z. Yue, Z. Zhou, Synaptotagmin-11 is a critical mediator of parkin-linked neurotoxicity and Parkinson’s disease-like pathology, Nat. Commun. 9 (2018) 81.

[9] M. Fukuda, K. Mikoshiba, Characterization of KIAA1427 protein as an atypical synaptotagmin (Syt XIII), Biochem. J. 354 (2001) 249–257.

[10] C. Poser von, T.C. Südhof, Synaptotagmin 13: structure and expression of a novel synaptotagmin, Eur. J. Cell Biol. 80 (2001) 41–47.

[11] M. Craxton, Synaptotagmin gene content of the sequenced genomes, BMC Genomics 5 (2004) 43.

[12] SYT13 synaptotagmin 13 [*Homo sapiens* (human)] - Gene - NCBI, (n.d.).

[13] SYT13 - Synaptotagmin-13 - *Homo sapiens* (Human) | UniProtKB | UniProt, (n.d.).

[14] M. Craxton, Synaptotagmin gene content of the sequenced genomes, BMC Genomics 5 (2004) 43.

[15] GeneTree: ENSGT00940000160226 - Gene Tree Image - Homo_sapiens - Ensembl genome browser 114, (n.d.).

[16] A.C. Wolfes, C. Dean, The diversity of synaptotagmin isoforms, Curr. Opin. Neurobiol. 63 (2020) 198–209.

[17] L. Fagerberg, B.M. Hallström, P. Oksvold, C. Kampf, D. Djureinovic, J. Odeberg, M. Habuka, S. Tahmasebpoor, A. Danielsson, K. Edlund, A. Asplund, E. Sjöstedt, E. Lundberg, C.A.-K. Szigyarto, M. Skogs, J.O. Takanen, H. Berling, H. Tegel, J. Mulder, P. Nilsson, et al., Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics, Mol. Cell. Proteomics 13 (2014) 397–406.

[18] M. Tarquis-Medina, K. Scheibner, I. González-García, A. Bastidas-Ponce, M. Sterr, J. Jaki, S. Schirge, C. García-Cáceres, H. Lickert, M. Bakhti, Synaptotagmin-13 is a neuroendocrine marker in brain, Intestine and Pancreas, Int J Mol Sci 22 (2021) 12526.

[19] M. Bakhti, A. Bastidas-Ponce, S. Tritschler, O. Czarnecki, M. Tarquis-Medina, E. Nedvedova, J. Jaki, S.J. Willmann, K. Scheibner, P. Cota, C. Salinno, K. Boldt, N. Horn, M. Ueffing, I. Burtscher, F.J. Theis, Ü. Coskun, H. Lickert, Synaptotagmin-13 orchestrates pancreatic endocrine cell egression and islet morphogenesis, Nat. Commun. 13 (2022) 4540.

[20] PubChem, CLINT1 - clathrin interactor 1 (human), (n.d.).

[21] C. Kalthoff, S. Groos, R. Kohl, S. Mahrhold, E.J. Ungewickell, Clint: a novel Clathrin-binding ENTH-domain protein at the Golgi, Mol. Biol. Cell 13 (2002) 4060–4073.

[22] PubChem, STAM2 - signal transducing adaptor molecule 2 (human), (n.d.).

[23] PubChem, HGS - hepatocyte growth factor-regulated tyrosine kinase substrate (human), (n.d.).

[24] J.R. Mayers, I. Fyfe, A.L. Schuh, E.R. Chapman, J.M. Edwardson, A. Audhya, ESCRT-0 assembles as a heterotetrameric complex on membranes and binds multiple ubiquitinylated cargoes simultaneously, J. Biol. Chem. 286 (2011) 9636–9645.

[25] P.U. Le, G. Guay, Y. Altschuler, I.R. Nabi, Caveolin-1 is a negative regulator of caveolae-mediated endocytosis to the endoplasmic reticulum, J. Biol. Chem. 277 (2002) 3371–3379.

[26] M.C. Jaskolka, S.R. Winkley, P.M. Kane, RAVE and Rabconnectin-3 complexes as signal dependent regulators of organelle acidification, Front. Cell Dev. Biol. 9 (2021) 698190.

[27] C. Martínez Jaramillo, C.M. Trujillo-Vargas, LRBA in the endomembrane system, Colomb Med (Cali), 49 (n.d.) 236–243.

[28] Y. Dong, H. Kang, H. Liu, J. Wang, Q. Guo, C. Song, Y. Sun, Y. Zhang, H. Zhang, Z. Zhang, H. Guan, Z. Fang, F. Li, Myoferlin, a membrane protein with emerging oncogenic roles, Biomed. Res. Int. 2019 (2019) 7365913.

[29] X. Yue, Y. Qian, B. Gim, I. Lee, Acyl-CoA-binding domain-containing 3 (ACBD3; PAP7; GCP60): a multi-functional membrane domain organizer, Int. J. Mol. Sci. 20 (2019) 2028.

[30] V. Popoff, F. Adolf, B. Brügger, F. Wieland, COPI budding within the Golgi stack, Cold Spring Harb. Perspect. Biol. 3 (2011) a005231.

[31] A. Johnson, N. Bhattacharya, M. Hanna, J.G. Pennington, A.L. Schuh, L. Wang, M. S. Otegui, S.M. Stagg, A. Audhya, TFG clusters COPII-coated transport carriers and promotes early secretory pathway organization, EMBO J. 34 (2015) 811–827.

[32] PubChem, RTN4 - reticulon 4 (human), (n.d.).

[33] M. Kamil, U.Y. Kina, H.N. Atmaca, S. Unal, G. Deveci, P. Burak, A.S.I. Aly, Endoplasmic reticulum localized TMEM33 domain-containing protein is crucial for all life cycle stages of the malaria parasite, Mol. Microbiol. 121 (2024) 767–780.
[34] PubChem, GOPC - golgi associated PDZ and coiled-coil motif containing (human), (n.d.).
[35] S.R. Cunha, P.J. Mohler, Ankyrin protein networks in membrane formation and stabilization, J. Cell. Mol. Med. 13 (2009) 4364–4376.
[36] I.E. Vega, EFhd2, a protein linked to Alzheimer's disease and other neurological disorders, Front. Neurosci. 10 (2016).
[37] C. Zeng, S. Han, Y. Pan, Z. Huang, B. Zhang, B. Zhang, Revisiting the chaperonin T-complex protein-1 ring complex in human health and disease: a proteostasis modulator and beyond, Clin. Transl. Med. 14 (2024) e1592.
[38] B.F. Teske, S.A. Wek, P. Bunpo, J.K. Cundiff, J.N. McClintick, T.G. Anthony, R. C. Wek, The eIF2 kinase PERK and the integrated stress response facilitate activation of ATF6 during endoplasmic reticulum stress, Mol. Biol. Cell 22 (2011) 4390–4405.
[39] S. Sasaki, M.Y.Y. Lee, Y. Wakabayashi, L. Suzuki, H. Winata, M. Himuro, T. Matsuoka, I. Shimomura, H. Watada, F.C. Lynn, T. Miyatsuka, Spatial and transcriptional heterogeneity of pancreatic beta cell neogenesis revealed by a time-resolved reporter system, Diabetologia 65 (2022) 811–828.
[40] J.K. Ofori, A. Karagiannopoulos, M. Barghouth, M. Nagao, M.E. Andersson, V. A. Salunkhe, E. Zhang, A. Wendt, L. Eliasson, The highly expressed calcium-insensitive synaptotagmin-11 and synaptotagmin-13 modulate insulin secretion, Acta Physiol (Oxford) 236 (2022) e13857.
[41] S.A. Andersson, A.H. Olsson, J.L.S. Esguerra, E. Heimann, C. Ladenvall, A. Edlund, A. Salehi, J. Taneera, E. Degerman, L. Groop, C. Ling, L. Eliasson, Reduced insulin secretion correlates with decreased expression of exocytotic genes in pancreatic islets from patients with type 2 diabetes, Mol. Cell. Endocrinol. 364 (2012) 36–45.
[42] B.J. González, H. Zhao, J. Niu, D.J. Williams, J. Lee, C.N. Goulbourne, Y. Xing, Y. Wang, J. Oberholzer, M.H. Blumenkrantz, X. Chen, C.A. LeDuc, W.K. Chung, H. M. Colecraft, J. Gromada, Y. Shen, R.S. Goland, R.L. Leibel, D. Egli, Reduced calcium levels and accumulation of abnormal insulin granules in stem cell models of HNF1A deficiency, Communications Biology 5 (2022) 779.
[43] R. Sharma, S.K. Maity, P. Chakrabarti, M.R. Katika, S. Kapettu, K.V.L. Parsa, P. Misra, PIMT controls insulin synthesis and secretion through PDX1, Int. J. Mol. Sci. 24 (2023) 8084.
[44] J.L. Esguerra, J.K. Ofori, M. Nagao, Y. Shuto, A. Karagiannopoulos, J. Fadista, H. Sugihara, L. Groop, L. Eliasson, Glucocorticoid induces human beta cell dysfunction by involving riborepressor GAS5 LincRNA, Molecular Metabolism 32 (2019) 160.
[45] H. Xu, L.-B. Zhang, Y.-Y. Luo, L. Wang, Y.-P. Zhang, P.-Q. Chen, X.-Y. Ba, J. Han, H. Luo, Synaptotagmins family affect glucose transport in retinal pigment epithelial cells through their ubiquitination-mediated degradation and glucose transporter-1 regulation, World J. Diabetes 15 (2024) 958.
[46] S. Han, S. Hong, D. Lee, M. Lee, J. Choi, M.J. Koh, W. Sun, H. Kim, H.W. Lee, Altered expression of synaptotagmin 13 mRNA in adult mouse brain after contextual fear conditioning, Biochem. Biophys. Res. Commun. 425 (2012) 880–885.
[47] S. Negueruela, C. Morenilla-Palao, S. Sala, P. Ordoño, M. Herrera, Y. Coca, M. T. López-Cascales, D. Florez-Paz, A. Gomis, E. Herrera, Proper frequency of perinatal retinal waves is essential for the precise wiring of visual axons in nonimage-forming nuclei, J. Neurosci. 44 (2024) e1408232024.
[48] L. Xiao, Y. Han, H. Runne, H. Murray, O. Kochubey, R. Luthi-Carter, R. Schneggenburger, Developmental expression of Synaptotagmin isoforms in single calyx of held-generating neurons, Mol. Cell. Neurosci. 44 (2010) 374–385.
[49] M. Nizzardo, M. Taiana, F. Rizzo, J. Aguila Benitez, J. Nijssen, I. Allodi, V. Melzi, N. Bresolin, G.P. Comi, E. Hedlund, S. Corti, Synaptotagmin 13 is neuroprotective across motor neuron diseases, Acta Neuropathol. 139 (2020) 837–853.
[50] K.C. Kanning, A. Kaplan, C.E. Henderson, Motor neuron diversity in development and disease, Annu. Rev. Neurosci. 33 (2010) 409–440.
[51] S.-Y. Ng, B.S. Soh, N. Rodriguez-Muela, D.G. Hendrickson, F. Price, J.L. Rinn, L. L. Rubin, Genome-wide RNA-Seq of human motor neurons implicates selective ER stress activation in spinal muscular atrophy, Cell Stem Cell 17 (2015) 569–584.
[52] S. Saxena, C. E, C. P, A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice, Nat. Neurosci. 12 (2009).
[53] S. Saxena, R. F, S. K, L. K, J. Jp, G.-L. F, C. P, Neuroprotection through excitability and mTOR required in ALS motoneurons to delay disease and extend survival, Neuron 80 (2013).
[54] J. Lehmann, A. Aly, C. Steffke, L. Fabbio, V. Mayer, N. Dikwella, K. Halablab, F. Roselli, S. Seiffert, T.M. Boeckers, D. Brenner, E. Kabashi, M. Mulaw, R. Ho, A. Catanese, Heterozygous knockout of Synaptotagmin13 phenocopies ALS features and TP53 activation in human motor neurons, Cell Death Dis. 15 (2024) 1–12.
[55] M. Kanda, D. Shimizu, H. Tanaka, C. Tanaka, D. Kobayashi, M. Hayashi, H. Takami, Y. Niwa, S. Yamada, T. Fujii, H. Sugimoto, Y. Kodera, Synaptotagmin XIII expression and peritoneal metastasis in gastric cancer, Br. J. Surg. 105 (2018) 1349–1358.
[56] K. Nakanishi, M. Kanda, S. Umeda, C. Tanaka, D. Kobayashi, M. Hayashi, S. Yamada, Y. Kodera, The levels of SYT13 and CEA mRNAs in peritoneal lavages predict the peritoneal recurrence of gastric cancer, Gastric Cancer 22 (2019) 1143–1152.
[57] M. Kanda, Y. Kasahara, D. Shimizu, T. Miwa, S. Umeda, K. Sawaki, S. Nakamura, Y. Kodera, S. Obika, Amido-bridged nucleic acid-modified antisense oligonucleotides targeting SYT13 to treat peritoneal metastasis of gastric Cancer, Mol Ther Nucleic Acids 22 (2020) 791–802.
[58] M. Kanda, N. Takano, H. Miyauchi, K. Ueda, M. Mizuno, Y. Kasahara, Y. Kodera, S. Obika, Preclinical toxicological assessment of amido-bridged nucleic acid-modified antisense oligonucleotides targeting synaptotagmin XIII for intra-abdominal treatment of peritoneal metastasis of gastric cancer, Gastric Cancer 27 (6) (2024) 1229–1241.
[59] Q. Li, S. Zhang, M. Hu, M. Xu, X. Jiang, Silencing of synaptotagmin 13 inhibits tumor growth through suppressing proliferation and promoting apoptosis of colorectal cancer cells, Int. J. Mol. Med. 45 (1) (2019) 234–244.
[60] J. Lu, Q. Liu, L. Zhu, Y. Liu, X. Zhu, S. Peng, M. Chen, P. Li, Endothelial cell-specific molecule 1 drives cervical cancer progression, Cell Death Dis. 13 (2022) 1043.
[61] Y.-D. Zhang, R. Zhong, J.-Q. Liu, Z.-X. Sun, T. Wang, J.-T. Liu, Role of synaptotagmin 13 (SYT13) in promoting breast cancer and signaling pathways, Clin. Transl. Oncol. 25 (2023) 1629–1640.
[62] K.J. Keck, P. Breheny, T.A. Braun, B. Darbro, G. Li, J.S. Dillon, A.M. Bellizzi, T. M. O'Dorisio, J.R. Howe, Changes in gene expression in small bowel neuroendocrine tumors associated with progression to metastases, Surgery 163 (2018) 232–239.
[63] L. Zhang, B. Fan, Y. Zheng, Y. Lou, Y. Cui, K. Wang, T. Zhang, X. Tan, Identification SYT13 as a novel biomarker in lung adenocarcinoma, J. Cell. Biochem. 121 (2020) 963–973.
[64] L. Shao, B. Li, Synaptotagmin 13 could drive the progression of esophageal squamous cell carcinoma through upregulating ACRV1, DNA Cell Biol. 43 (2024) 452–462.
[65] J.E. Jahn, S.L. Ricketts, W.B. Coleman, Identification of candidate liver tumor suppressor genes from human 11p112 by transcription mapping of microcell hybrid cell lines, Int. J. Oncol. 22 (2003) 1303–1310.
[66] J.E. Jahn, D.H. Best, W.B. Coleman, Exogenous expression of synaptotagmin XIII suppresses the neoplastic phenotype of a rat liver tumor cell line through molecular pathways related to mesenchymal to epithelial transition, Exp. Mol. Pathol. 89 (2010) 209–216.
[67] J.E. Jahn, W.B. Coleman, Re-expression of tumorigenicity after attenuation of human synaptotagmin 13 in a suppressed microcell hybrid cell line, Int. J. Oncol. 32 (2008) 441–449.
[68] C. Jiang, B. Zhang, W. Jiang, P. Liu, Y. Kong, J. Zhang, W. Teng, Metal ion stimulation-related gene signatures correlate with clinical and immunologic characteristics of glioma, Heliyon 10 (2024) e27189.
[69] P. Papareddy, M. Selle, N. Partouche, V. Legros, B. Rieu, J. Olinder, C. Ryden, E. Bartakova, M. Holub, K. Jung, J. Pottecher, H. Herwald, Identifying biomarkers deciphering sepsis from trauma-induced sterile inflammation and trauma-induced sepsis, Front. Immunol. 14 (2024) 1310271.
[70] Q. Yang, Z. Xie, B. Lai, G. Cheng, B. Liao, J. Wan, M. Deng, Identification and verification of atrial fibrillation hub genes caused by primary mitral regurgitation, Medicine (Baltimore) 102 (2023) e35851.