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ENDOSOMAL AND PHAGOSOMAL SNAREs

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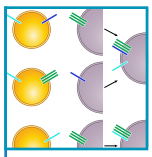

Dingjan I, Linders PT, Verboogen DR, Revelo NH, ter Beest M, van den Bogaart G. Endosomal and Phagosomal SNAREs. *Physiol Rev* 98: 1465–1492, 2018. Published May 23, 2018; doi:10.1152/physrev.00037.2017.—The soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein family is of vital importance for organelle communication. The complexing of cognate SNARE members present in both the donor and target organellar membranes drives the membrane fusion required for intracellular transport. In the endocytic route, SNARE proteins mediate trafficking between endosomes and phagosomes with other endosomes, lysosomes, the Golgi apparatus, the plasma membrane, and the endoplasmic reticulum. The goal of this review is to provide an overview of the SNAREs involved in endosomal and phagosomal trafficking. Of the 38 SNAREs present in humans, 30 have been identified at endosomes and/or phagosomes. Many of these SNAREs are targeted by viruses and intracellular pathogens, which thereby reroute intracellular transport for gaining access to nutrients, preventing their degradation, and avoiding their detection by the immune system. A fascinating picture is emerging of a complex transport network with multiple SNAREs being involved in consecutive trafficking routes.

I. INTRODUCTION

Eukaryotic cells rely on the ingestion of foreign material by endocytosis and phagocytosis, as this is required for the uptake of nutrients, the clearance of infections, and the removal of apoptotic and necrotic cells from the body (92). Solutes and small particles (<1 μm sized) are taken up by a process called endocytosis, whereas larger particles (>1 μm), such as microbial pathogens or tumor cells, are ingested by phagocytosis. There are many pathways for endocytosis and phagocytosis that depend on the cell type and the receptors engaged, and differ in the uptake machinery, downstream signaling, and processing of the ingested material within the cell (92). Endocytosis often (but not always) relies on specific cage proteins, most notably clathrin and caveolin, whereas phagocytosis is dependent on the formation of the F-actin cytoskeleton for particle engulfment (22). Moreover, phagocytosis can be accompanied by fusion of vesicles at the plasma membrane site of uptake, and this allows growing of the nascent phagosome and serves to compensate for the loss of plasma membrane surface area. After uptake, endosomes and phagosomes undergo a transition process called maturation, where early endosomes and phagosomes first convert into late endo/phagosomes and then into acidic lysosomes for the degradation of the ingested cargo (86, 92, 144, 237). The maturation of endosomes and phagosomes is mechanistically similar (23, 86) and driven by vesicular transport between early and late endo/phagosomes, lysosomes, the plasma membrane, the Golgi apparatus, and recycling endosomes. Recycling endosomes are dynamic and heterogeneous compartments that function as a sorting station, where proteins and lipids are recycled back to the plasma membrane or routed to late endosomes and eventually to lysosomes for degradation (144, 196). In addition to this degradation of internalized material, both early and late endosomes have important roles in the biogenesis and recycling of specialized secretory granules and vesicles, such as synaptic vesicles in neurons (144, 150, 189). Moreover, both late endosomes and lysosomes can fuse with autophagosomes, leading to the formation of amphisomes and autolysosomes, respectively, and this is necessary for the degradation of autophagosomal cargo (90, 147, 342). Finally, the endoplasmic reticulum (ER) and the ER-Golgi intermediate compartment (ERGIC) might contribute to phagosome formation via direct vesicular trafficking between ER/ERGIC and (nascent) phagosomes (25, 51, 102, 130), although this is controversial (136, 267, 304).

The identity of organelles is determined by the presence of specific Rab-GTPases, soluble NSF attachment protein receptor (SNARE) proteins, and phosphoinositide lipids (86,

92, 144, 235, 237). Rab-GTPases, SNAREs, and phosphoinositides interact with large multi-subunit tethering complexes, such as the homotypic fusion and vacuole protein sorting (HOPS) and class C core vacuole/endosome tethering (CORVET) complexes, that bridge opposing membranes (45, 176, 189, 226, 235, 280, 328). SNARE proteins are the central catalysts of intracellular membrane fusion and are involved in nearly all organellar trafficking steps, except mitochondrial fusion (139, 149). The human SNARE family consists of 38 known members **(FIGURE 1)** and is conserved from yeast **(FIGURE 2)**. The fusion of membranes starts with the complexing of cognate sets of SNARE proteins present in both the target and acceptor membranes. Together, these contribute four different SNARE motifs to a so-called *trans*-SNARE complex **(FIGURE 3)**. This complex "zippers up" from the NH_2- to the COOH-terminal end of the SNARE motifs, forming a four α-helical coiled-coil bundle called a *cis*-SNARE complex. This *trans* to *cis* conformation change brings the two opposing fusing membranes in close apposition and provides sufficient energy to drive membrane fusion (32). SNARE proteins are classified according to the central residue in their SNARE motifs into R- (from arginine) and Q- (glutamine) SNAREs. A SNARE complex requires one R-SNARE and three Q-SNARE motifs, called Qa-, Qb-, and Qc-SNAREs **(FIGURE 4)**. Although members of the SNARE family often have overlapping functions and are involved in multiple organellar trafficking pathways, SNARE proteins contribute to the specificity of organellar trafficking as they preferentially complex with their cognate binding partners, and different trafficking steps are catalyzed by specific sets of SNARE proteins (60, 139, 140, 149, 169). After completion of membrane fusion, the individual SNARE molecules are released from the *cis*-SNARE complex by the triple-A ATPase *N*-ethylmaleimide-sensitive factor (NSF) (reviews, Refs. 35, 270). NSF is recruited to the *cis*-SNARE complex by the adaptor soluble NSF-attachment protein α (α-SNAP), although in endosomal trafficking this function can also be performed by its homolog γ-SNAP (145).

The goal of this review is to provide an in-depth overview of the mammalian SNAREs involved in endosomal and phagosomal transport. From numerous studies employing subcellular fractionation combined with Western blot or proteomics analysis, as well as from microscopy of immunolabeled or overexpressed SNARE proteins, by far most of the members of the SNARE family have currently been identified at endosomes and/or phagosomes (30 out of 38; **FIGURE 1**). Many of these SNAREs are targeted by viruses and intracellular pathogens, which thereby actively delay endo/phagosomal maturation or reroute intracellular trafficking to gain access to nutrients, avoid their degradation in lysosomes, and avert recognition by the immune system (48, 92, 236, 237, 240, 284). Moreover, mutations in genes coding for SNAREs or their regulating proteins can lead to disease (60, 192, 257, 290). In the next sections, we discuss the roles of each SNARE identified at endosomal and phagosomal membranes, and their roles in disease.

II. Qa-SNAREs

A. Stx1A and Stx1B

The Qa-SNARE syntaxin-1 (Stx1) is one of the most studied SNARE proteins, as it forms the plasmalemmal Q-SNARE complex, together with synaptosomal-associated protein 25 (SNAP25) (Qbc) for the release of neurotransmitter-containing synaptic vesicles, mainly by complexing with vesicle-associated membrane protein 2 (VAMP2; R) (139, 148, 149, 294). It is present in two 84% identical isoforms from gene duplication, Stx1A and Stx1B, that have a similar function in neurotransmitter release. Because of compensation by Stx1B, Stx1A knockout mice develop normally with only mild neurological disorders caused by impaired synaptic plasticity (98). In contrast, Stx1A cannot sufficiently compensate for lack of Stx1B, as Stx1B knockout mice die within several weeks from neurological disorders (98, 168). Stx1A also has secretory roles outside the neurological system, for instance in secretion of the hormone glucagon-like peptide 1 from intestinal enteroendocrine L cells (327). Both Stx1 isoforms have the hallmark topology of the syntaxin subfamily of SNAREs and contain a short NH_2-terminal regulatory peptide, followed by a regulatory Habc-domain connected to the SNARE motif via a linker and a COOH-terminal transmembrane helix **(FIGURE 1)**. The Habc-domain can fold back onto the SNARE motif, and this prevents its engagement in a SNARE complex, thereby auto-inhibiting membrane fusion **(FIGURE 4)** (197). Regulation of Stx1 is well understood and is mediated by binding to numerous regulatory proteins, including the Sec1/Munc18-like (S/M) protein syntaxin-binding protein 1 (STXBP1; Munc18a), complexin, and the calcium-sensor synaptotagmin-1, as reviewed elsewhere (148, 294).

Like all other exocytic SNAREs (see below), Stx1A and/or B are found at endosomes (39), and, at least in a *Drosophila* macrophage cell line, the single fly isoform of Stx1 has been found by proteomics at phagosomes (293). The functional roles of endosomal and phagosomal Stx1 are unclear, and it might play a role in the transport of Stx1 to the plasma membrane or in the routing of unneeded Stx1 to lysosomes for degradation. At the plasma membrane, Stx1 and other SNAREs are not randomly distributed, but are clustered in discrete sub-micrometer-sized membrane domains that have well-understood roles in vesicle tethering, defining the sites of secretion, and regulating membrane fusion (review, Ref. 34). Similarly, endocytic trafficking of Stx1 might also be facilitated by its localization in membrane domains, as superresolution microscopy revealed clustering of Stx1 in endosomal membranes (107).

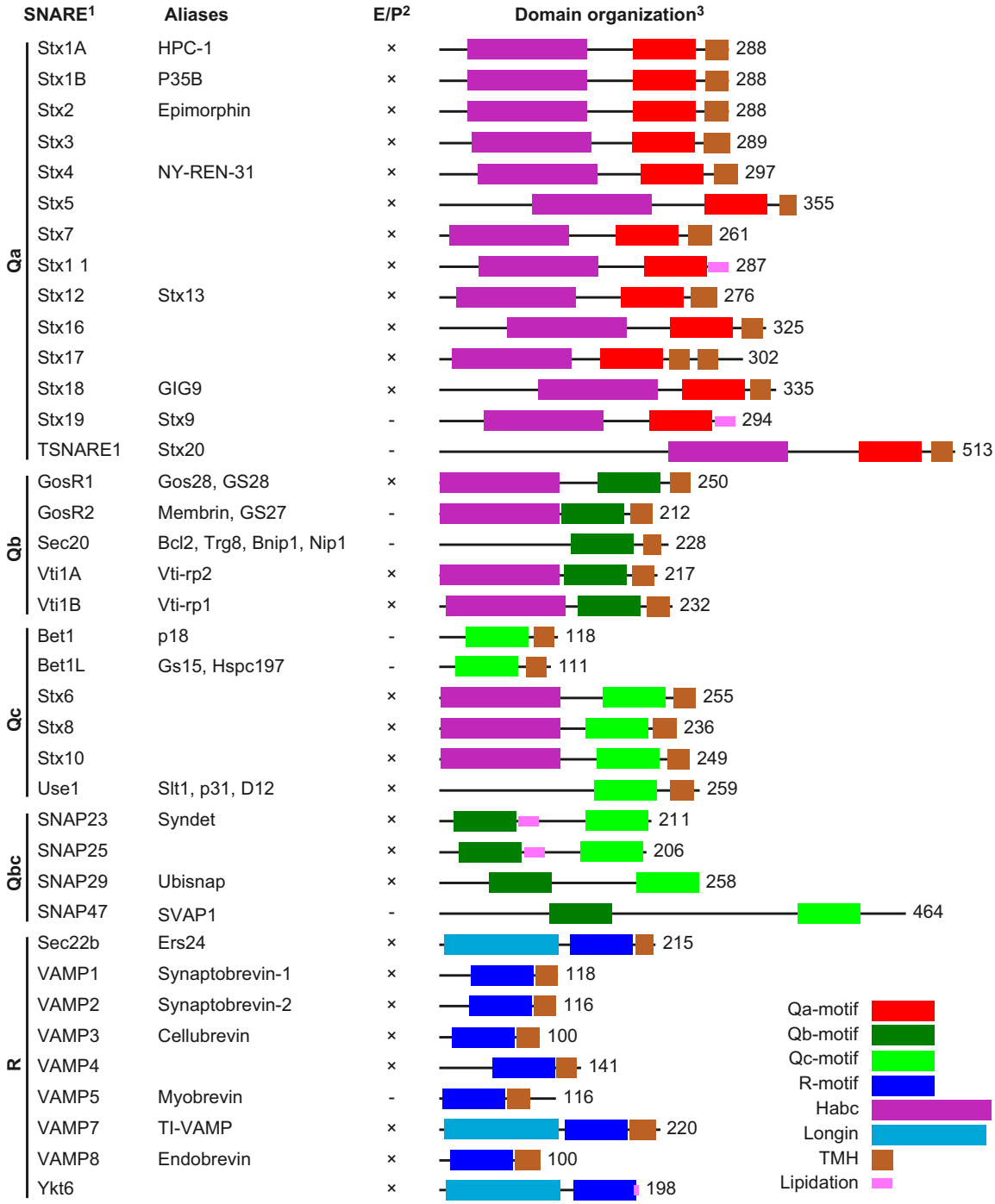

FIGURE 1. Domain topology of human soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs). [1]Missing in the table are amisyn (STXB6), tomosyn-1 (STXBP5), and tomosyn-2 (STXBP5L) that all contain an R-SNARE motif, but are considered incapable of fusing membranes (129, 139, 277). [2]An × indicates that the SNARE has been reported to locate at endosomes and/or phagosomes as discussed in this review. [3]Domain topology of the SNAREs showing the Qa-SNARE motif (red), Qb-motif (dark green), Qc-motif (light green), R-motif (blue), transmembrane helix (TMH; brown), Habc-domain (purple), Longin-domain (cyan), and lipidation sites (pink). The number of residues is indicated. E/P, endosome/phagosome; Stx, syntaxin; SNAP, soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein; VAMP, vesicle-associated membrane protein.

B. Stx2

The exocytic Qa-SNARE Stx2 is required for epithelial morphogenesis, and Stx2 knockout mice are male sterile due to defective spermatogenesis (321). Although Stx2 predominantly locates at the cell membrane, it is also present at intracellular compartments (94), including early/recycling endosomes (88) and phagosomes [by proteomics (FIGURE

	Yeast	Human[1]	Identity[2]	E-value[3]
Qa	Pep12p	Stx2	31%	8×10^{-14}
	Sed5p	Stx5	32%	7×10^{-33}
	Sso1p	Stx1A	29%	1×10^{-22}
	Sso2p	Stx1A	30%	4×10^{-25}
	Tlg2p	Stx16	26%	5×10^{-17}
	Ufe1p	Stx18	27%	2.4×10^{-1}
	Vam3p	Stx7	27%	1×10^{-7}
Qb	Bos1p	GosR2	25%	4.7×10^{-2}
	Gos1p	GosR1	26%	8×10^{-18}
	Sec20p	Sec20	16%	2×10^{-4}
	Vti1p	Vti1A	32%	4×10^{-25}
Qbc	Sec9p	SNAP23	28%	1×10^{-6}
	Spo20p	SNAP23	23%	3.8×10^{-1}
Qc	Bet1p	Bet1	24%	5×10^{-7}
	Sft1p	Bet1	27%	4×10^{-4}
	Syx8p	Stx8	28%	4
	Tlg1p	Stx10	24%	3.2×10^{-1}
	Use1p	Use1	24%	1×10^{-3}
	Vam7p	Stx6	27%	2×10^{-1}
R	Nyv1p	VAMP1	28%	9×10^{-8}
	Sec22p	Sec22b	38%	4×10^{-48}
	Snc1p	VAMP2	38%	6×10^{-14}
	Snc2p	VAMP2	36%	2×10^{-12}
	Ykt6p	Ykt6	47%	2×10^{-62}

FIGURE 2. Yeast soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) with closest human SNARE orthologs. [1]Closest human SNARE ortholog predicted by protein sequence alignment with PSI-BLAST. [2]Percentage protein sequence identity. A higher value indicates stronger homology. [3]Expect value (E-value) from BLAST. A lower value indicates stronger homology. Stx, syntaxin; SNAP, soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein; VAMP, vesicle-associated membrane protein.

5) and Western blot (122)]. Most quantitative proteomics studies report a decreased phagosomal presence of Stx2 at later time points after antigen uptake (>1 h) compared with earlier time points (<0.5 h; FIGURE 5).

Like Stx1, it is unknown whether Stx2 has endosomal and/or phagosomal trafficking roles or is merely a bystander that is taken up during invagination of the plasma membrane.

C. Stx3

The Qa-SNARE Stx3 is essential (170), and its abolishment leads to defects in secretion (61, 94) and endosomal trafficking (52). Stx3 is present at the plasma membrane (94, 104, 109, 122, 312) and at various intracellular compartments (88, 108, 109, 313, 341). Stx3 locates at phagosomes, as shown by Western blot, microscopy (51, 122), and proteomics (Refs. 38, 182, 286 and FIGURE 5). Stx3 can interact with various R-SNAREs, including VAMP3 for fusion events at the plasma membrane and VAMP8 for intracellular fusion events (313). Plasmalemmal and intracellular pools of Stx3 also interact with VAMP7, and this facilitates the secretion and biogenesis of lysosomes and lysosome-related organelles (52, 53, 339). In epithelial cells, Stx3 regulates apical secretion by forming a Q-SNARE acceptor complex with SNAP23 (Qbc) (87, 178, 185), where it cycles via Rab11a-recycling endosomes (167) in a manner regulated by mono-ubiquitination of Stx3 (108). In addition, Stx3 is regulated by interactions of its Habc-domain with the S/M-protein Munc-18b (STXBP2) (302) and with the ERM protein ezrin (341). Endocytic trafficking of Stx3 is targeted by human cytomegalovirus (HCMV), as plasmalemmal Stx3 is required for virus assembly (52) and its downregulation by viral micro-RNAs likely aids in immune evasion (120).

D. Stx4

The essential Qa-SNARE Stx4 is highly studied as it is required for many exocytic pathways (87, 109, 243, 289, 312, 313), such as insulin-stimulated delivery of the glucose transporter GLUT-4 to the plasma membrane in

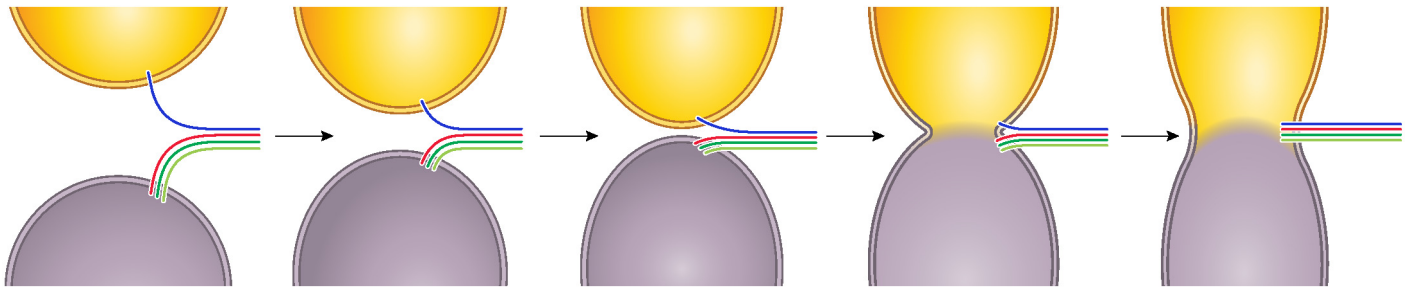

FIGURE 3. Scheme of membrane fusion by soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes. Cognate R- (blue), Qa- (red), Qb- (dark green), and Qc-SNARE (light green) proteins engage with the NH_2-terminal ends of their SNARE motifs and form an α-helical coiled-coil SNARE helix. A single SNARE complex suffices for membrane fusion (33), although multiple complexes may result in faster fusion dynamics (283). In the scheme, the R-SNARE is present in the *top* and the Q-SNAREs in the *bottom* compartment, but this does not necessarily have to be the case, and other distributions can also lead to membrane fusion (348).

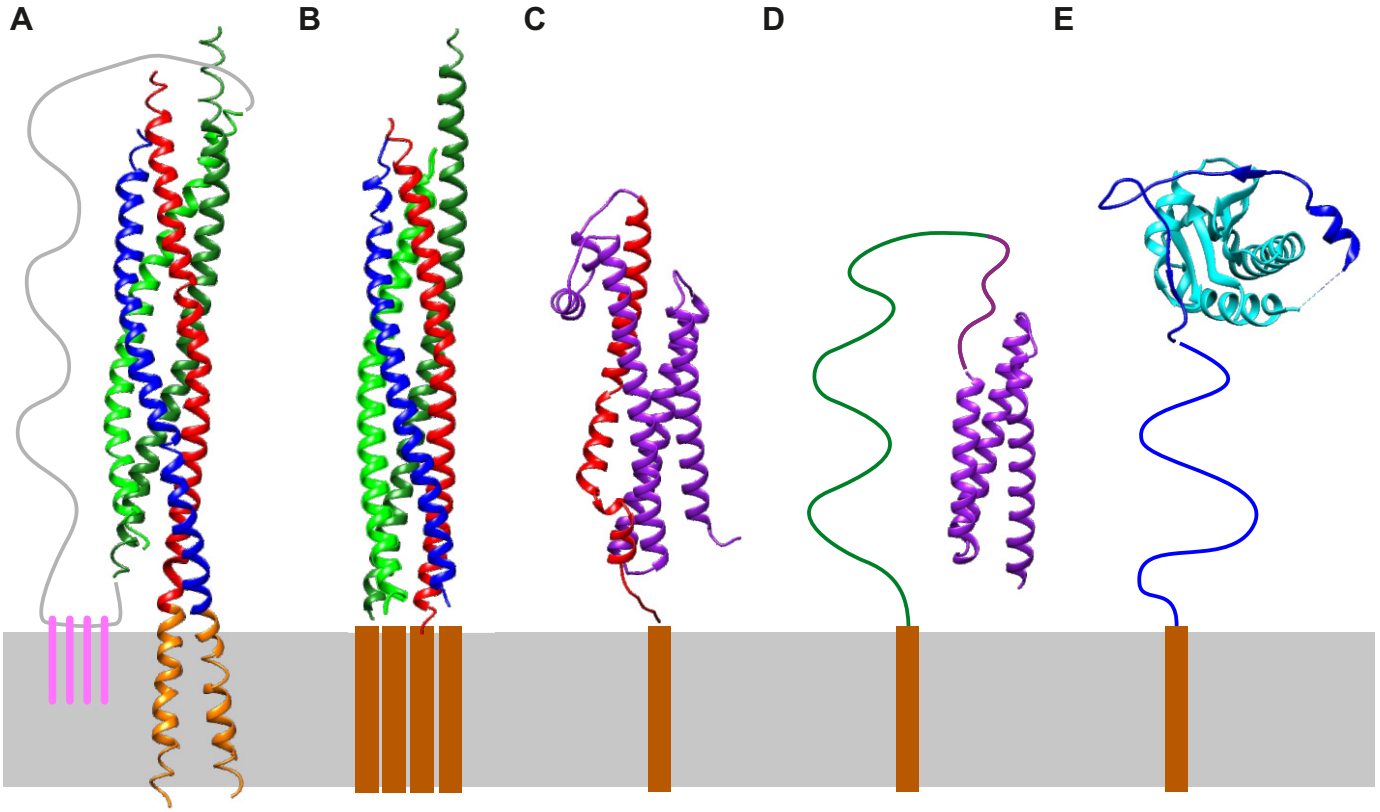

FIGURE 4. Structures of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins. *A*: crystal structure of the neuronal SNARE complex consisting of vesicle-associated membrane protein 2 (VAMP2) (R-SNARE; blue), syntaxin (Stx) 1A (Qa-SNARE; red), and soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein (SNAP) 25 (Qbc-SNARE; Qb-motif: dark green; Qc-motif: light green) [protein database (PDB) accession number 3IPD (292)]. Transmembrane helices are brown. Palmitoylation of SNAP25 is pink. Not shown is the NH_2-terminal Habc-domain of Stx1 (see *C* and *D*). The shaded gray area depicts the position of the membrane. *B*: crystal structure of an endosomal SNARE complex consisting of VAMP4 (R; blue), Stx12 (Qa; red), Vti1a (Qb; dark green), and Stx6 (Qc; light green) [PDB accession number 2NPS (348)]. Not shown are the NH_2-terminal regulatory domain of VAMP4 and the NH_2-terminal Habc-domains of Stx12, Vti1a, and Stx6. *C*: crystal structure of Stx1A with its Habc-domain (purple) interacting with its Qa-SNARE motif [red; PDB accession number 4JEH (59)]. *D*: crystal structure of the Habc-domain of Vti1b (Qb; purple), which does not interact with its SNARE motif (10) [PDB accession number 2QYW (206)]. *E*: crystal structure of VAMP7 (R) with its longin domain (cyan) interacting with the NH_2-terminal end of its SNARE motif [blue; PDB accession number 4B93 (278)].

adipocytes (302). Moreover, Stx4 is the basolateral counterpart of the apical Stx3 in epithelial cells (185). Although most Stx4 localizes at the plasma membrane (94, 213, 275, 289, 312), intracellular pools of Stx4 are reported in various cell types (83, 88, 258, 315). Stx4 is found at early and recycling endosomes (20) and at phagosomes (51, 122, 156, 271), with quantitative proteomics revealing a decreased presence of Stx4 at phagosomes over time of uptake **(FIGURE 5)**. Stx4 is clustered at the plasma membrane site of phagocytosis, where it mediates the polarized delivery of VAMP3 (R) positive early/recycling endosomes to facilitate phagosome formation (219). Except for exocytosis, other trafficking roles of Stx4 are unknown, and, although it was proposed to mediate trafficking from the ERGIC to phagosomes by pairing with Sec22b (R) (51), direct evidence for this is lacking.

Endocytic trafficking of Stx4 is regulated by interactions with the GTP-bound form of the early endosomal small-GTPase Rab5 (240) and with the S/M-protein Vps45, which in turn interacts with the Rab5 effector rabenosyn-5 (106). Stx4 is further regulated by interactions with the S/M-protein Munc18c (STXBP3) (234, 302), the F-actin cytoskeleton (20, 152, 332), the coiled-coil protein α-taxilin (258), and the calcium-sensor synaptotagmin VII (256). Stx4 is targeted by mycobacterial parasites that retain Stx4 at their intracellular habitat (240, 314). This prolonged presence of Stx4 at mycobacterial phagosomes promotes fusion with early endosomes and results in a maturation arrest that allows the intracellular pathogen to avert its degradation (314). Moreover, Stx4 is essential for the release of hepatitis C virus (HCV) via exocytosis of multivesicular bodies, and HCV-infected cells possess increased levels of Stx4 and reduced levels of α-taxilin (258).

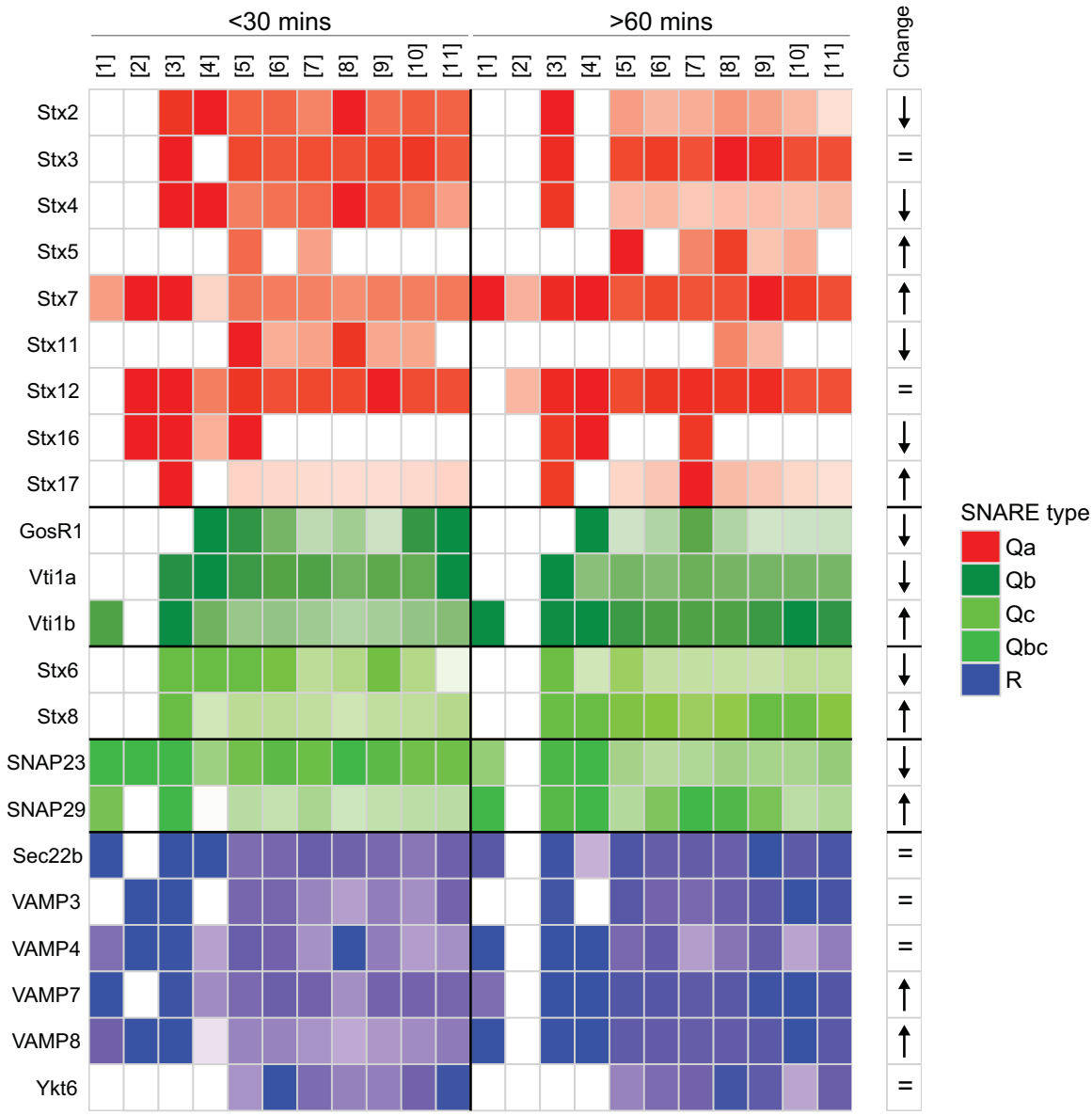

FIGURE 5. Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) identified at early and late phagosomes by quantitative proteomics. For each quantitative proteomics study and for each SNARE, all conditions were compared with the condition with the maximum abundance. The intensity of the color indicates the relative abundance of the SNAREs at early and late phagosomes. "Change" indicates whether most studies report that a SNARE is present at higher (↑), lower (↓), or similar (=) levels at late (>60 min after uptake) compared with early (<30 min) phagosomes. [1], Ref. 267; phagosomes with IgG-opsonized 0.8-μm-sized latex beads for 10–30 min (early) and 60–120 min (late) purified from RAW264.7 macrophages. [2], Ref. 82; endosomes with 100-nm-sized latex beads for 15 min (early) and 60 min (late) purified from J774 macrophages. [3], Ref. 46; phagosomes with 0.8-μm-sized latex beads for 15 min (early) and 60 min (late) purified from J774 macrophages. [4], Ref. 113; phagosomes with 0.8-μm-sized latex beads for 30 min (early) and 270 min (late) from J774 macrophages. [5–11], Ref. 77; phagosomes with 0.8-μm-sized latex beads for 30 min (early) and 180 min (late) from mouse bone-marrow-derived macrophages. Beads were coated with avidin alone [5], or with avidin coupled to the apoptotic marker calreticulin [6], complement cleavage fragment iC3b [7], Fc-antibody region [8], lipopolysaccharide [9], mannan [10], or phosphatidylserine [11]. Stx, syntaxin; SNAP, soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein; VAMP, vesicle-associated membrane protein.

E. Stx5

The essential (170) Qa-SNARE Stx5 has well-understood roles in ER-Golgi trafficking (194). Stx5 is present in two isoforms that arise from two alternative starting methionines (142). Whereas the short isoform of Stx5 predominantly localizes at the Golgi apparatus (26, 49, 158), the long isoform contains an ER-retention signal and is mainly

located at the ER (142, 210, 295). Stx5 is responsible for both antero- and retrograde intra-Golgi transport by pairing with GosR2 (Qb), Bet1 (Qc), and Sec22b (R), or GosR1 (Qb), Bet1L (Qc), and Ykt6 (R), respectively (139, 194). The latter Stx5-GosR1-Bet1L-Ykt6 SNARE complex also mediates retrograde trafficking from early/recycling endosomes to the Golgi complex (9, 299), although this trafficking may also be mediated by a Stx6-Stx16-Vti1a-VAMP4 SNARE complex (193). Stx5 has been found at phagosomes by proteomics (Ref. 38 and **FIGURE 5**), where, given the role of Stx5 in Golgi trafficking, it seems possible that it mediates trafficking from phagosomes to the *trans*-Golgi network for recycling of Golgi components. The NH_2-terminus of Stx5 binds to the S/M-protein Sly1 and interacts with the conserved oligomeric Golgi (COG) complex, a multisubunit tethering complex that regulates retrograde Golgi transport (181, 194). In addition to its role in Golgi trafficking, Stx5 is required for formation of lipid droplets, which are storage compartments of excess fats, together with SNAP23 (Qbc) and VAMP4 (R) (37).

Stx5 plays a role in infectious disease, as it is recruited to the cytoplasmic viral assembly compartment of HCMV, where it promotes the efficient production of infectious virus (66). Moreover, retrograde trafficking to the *trans*-Golgi by Stx5 is required for adeno-associated virus transduction (228). Finally, Stx5 is recruited to vacuoles containing the intracellular pathogen *Leishmania* and is essential for the development of this compartment (49).

F. Stx7

The Qa-SNARE Stx7 mainly locates at late endosomes and lysosomes (17, 24, 62, 88, 217), but is also found at early and recycling endosomes (29, 88, 158, 247) and the plasma membrane (134, 158). In addition, Stx7 locates at phagosomes, as found by imaging (62, 79), Western blot (271), and proteomics (38, 43, 156, 286, 293). Although Stx7 can be recruited to phagosomes in multiple phases (267), several studies showed a rapid increase in phagosomal Stx7 over time after uptake (Refs. 62, 79 and **FIGURE 5**). Stx7 mediates homotypic fusion of late endosomes by forming a complex with Vti1b (Qb), Stx8 (Qc), and VAMP8 (R) (12, 217, 251), and the structure of this SNARE bundle has been solved by X-ray crystallography (11) **(FIGURE 4)**. The Stx7-Vti1b-Stx8 SNARE complex with VAMP7 (R) instead of VAMP8 mediates fusion of late endosomes with lysosomes and homotypic fusion of lysosomes (251, 322). Stx7 also mediates fusion of lysosomes with phagosomes (24, 79) and plays a role in trafficking from the *trans*-Golgi network to endosomes (57).

Stx7 is involved in the selection of cargo proteins for vesicular transport by direct interactions, as shown for the chloride channel cystic fibrosis transmembrane conductance regulator (CFTR) in epithelial cells (29), and by indirect interactions via the epsin NH_2-terminal homology domain protein EpsinR, which is a cargo adaptor involved in Golgi-endosome transport (57). The regulation of the activity and subcellular localization of Stx7 are well characterized. Similar to Stx1 and Stx4, the Habc-domain of Stx7 can prevent SNARE complex formation by folding back on its SNARE region (10). Cycling of Stx7 between endosomes and the plasma membrane is regulated by a dileucine-based internalization motif located at its cytoplasmic domain (158). Stx7 is also regulated by various posttranslational modifications: Stx7 is palmitoylated on a cysteine at the cytoplasmic face of the transmembrane domain, and this is important for its internalization at the plasma membrane (134). Stx7 can be phosphorylated by the kinase colony-stimulating factor 1 and this phosphorylation promotes formation of the Stx7-Vti1b-Stx8-VAMP8 SNARE complex (3). This complex is stabilized by interactions with the calcium-sensor protein unc-13 homolog D (Munc13-4; UNC13D) (331), which locates together with Stx7 at lysosomes and lysosome-related organelles (133).

Stx7 further interacts with the HOPS and CORVET tethering complexes (164) and with the positive regulator of these complexes, UV radiation resistance-associated gene (UVRAG) (242). These interactions are hijacked by various negative-strand RNA viruses, such as influenza A and vesicular stomatitis virus (VSV), which thereby facilitate viral entry and propagation by promoting assembly of the Stx7-Vti1b-Stx8 SNARE complex and recruitment of VAMP8 endosomes to virus-containing endosomes (242). Stx7-mediated trafficking pathways are also targeted by the intracellular pathogen *Helicobacter pylori*, resulting in the formation of a hybrid late endosomal-lysosomal vacuole supporting bacterial survival (298).

G. Stx11

The Qa-SNARE Stx11 lacks the typical COOH-terminal transmembrane domain present in most other SNAREs **(FIGURE 1)**, but, similar to Ykt6 (and possibly Stx19), it is anchored to membranes by lipids covalently attached to cysteines located near its COOH-terminus (231, 309). Stx11 is located at the plasma membrane, early/recycling endosomes, late endosomes, lysosomes, and the *trans*-Golgi network (124, 231, 309, 343) and has been identified at mostly early phagosomes by proteomics **(FIGURE 5)**. Stx11 is strongly expressed by immune cells (246), and genetic mutations of Stx11 are the cause of the autosomal recessive disorder familial hemophagocytic lymphohistiocytosis type-4 (FHL-4). FHL-4 patients (and Stx11 knockout mice) display immune dysregulation and high blood levels of inflammatory cytokines (60). These symptoms are caused by secretory defects, as Stx11 is required for exocytosis in many immune cells, including cytolytic T cells, natural killer cells, and platelets (68, 124, 131, 340). Exocytosis is mediated by formation of a Stx11-SNAP23-VAMP8 com-

plex, and this is regulated by binding to the S/M-protein Munc18b (131, 340). Stx11 also has intracellular trafficking roles, as it regulates transport from late endosomes to lysosomes (231). Here, Stx11 can act as a nonfusogenic SNARE that interacts with Vti1b (Qb), but does not result in membrane fusion. This negatively regulates the availability of Vti1b to pair with other SNAREs (231). In line with such a role for Stx11 as a negative regulator of membrane fusion, silencing of Stx11 in macrophages led to increased phagocytosis and TNF-α secretion, while overexpression resulted in the opposite effect (343), although this was not observed in a later study (68).

H. Stx12

Stx12 (called Stx13 in rat) is located at early and recycling endosomes and cycles via the plasma membrane (24, 39, 62, 88, 217, 247), although it is also found at the Golgi apparatus (88) and autophagophores (the precursors of autophagosomes) (187). Superresolution-stimulated emission depletion microscopy revealed that Stx12 can organize in membrane domains at endosomal membranes (107). Stx12 also locates at phagosomes (38, 43, 62, 79, 96, 156, 271, 286), and, although one study showed that Stx12 was rapidly cleared from phagosomes after uptake (62), most studies report no or only a slow clearance of Stx12 from phagosomes (Refs. 79, 96, 271 and **FIGURE 5**). Stx12 has well-characterized, but apparently nonessential (28, 106), trafficking roles. It mediates homotypic fusion of early endosomes by complexing with Vti1a (Qb), Stx6 (Qc), and VAMP4 (R) (39, 203, 208, 297). The complexing of Stx12 with Vti1a is also involved in homotypic fusion of autophagophores to form autophagosomes (187). In addition, Stx12 mediates transport from early and recycling endosomes to the plasma membrane, in a manner regulated by the protein hepatocyte growth factor-regulated tyrosine kinase substrate Hgs (also called Hrs) (297, 337). Finally, Stx12 has cell-type specific roles in the recycling and biogenesis of secretory compartments, such as neurotransmitter vesicles and melanosomes (151, 266). Endosomal localization and activity of Stx12 is regulated by interactions with adapter protein 3 (AP3) (151), early endosomal antigen 1 (EEA1) (203, 208), and, at least in *Caenorhabditis elegans*, with the S/M-protein Vps45 (106).

I. Stx16

The Qa-SNARE Stx16 locates at the Golgi apparatus (88, 155, 239, 282) and in membrane domains (107) at recycling endosomes (39, 155). Stx16 has also been detected at phagosomes by proteomics (Ref. 38 and **FIGURE 5**), but it does not seem to be enriched here (138). Although Stx16 is required for structural integrity of the Golgi apparatus (285), its role is apparently not essential, as Stx16 knockout mice display only minor phenotypic abnormalities (97, 170). Stx16 mediates retrograde trafficking from late endosomes to the Golgi by Rab9-dependent complexing with Vti1a (Qb), Stx10 (Qc), and VAMP3 (R) (105, 193). In contrast, Rab6A- and Rab11-dependent (105, 193) transport from early/recycling endosomes to the Golgi apparatus is mediated by complexing of Stx16 with Vti1a (Qb), Stx6 (Qc), and VAMP3 or VAMP4 (R) (9, 193, 248, 282, 299, 307). Endosome to Golgi transport is further regulated by interactions of Stx16 with the tethering protein Golgi-associated retrograde transport protein (GARP) (239), the putative tethering protein GCC185 (105), and the S/M-protein Vps45 (106, 255). Finally, at least in *Drosophila*, Stx16 interacts with the S/M-protein Vps33, a component of the HOPS and CORVET tethering complexes (6).

J. Stx17

The COOH-terminal region of the Qa-SNARE Stx17 consists of two relatively short hydrophobic domains and a glycine zipper that can form a hairpin-type structure for insertion of free (nonmembrane bound) Stx17 into membranes (139). Although Stx17 plays a role in ER-Golgi transport, and knockdown of Stx17 causes fragmentation of the Golgi complex (147, 218), it is especially well studied in autophagy. Stx17 is required for the degradation of autophagosomal cargo (1, 147, 165, 300), and its insertion in autophagosomes allows for the fusion with lysosomes (reviews, Refs. 73, 135, 171, 342). Several proteomics studies identified Stx17 at phagosomes **(FIGURE 5)**, and, although still unclear, the insertion of Stx17 in phagosomal membranes might be important for the degradation of phagosomal cargo by autophagy-related processes. Insertion of Stx17 in autophagosomal membranes requires lysosome-associated membrane protein 2 (141), and this insertion is regulated by the NH_2-terminal regulatory domain of Stx17 (306). Autophagosome-lysosome fusion is the result of a SNARE complex composed of Stx17, SNAP29 (Qbc), and VAMP8 (R) (119, 147). The Stx17-SNAP29 Q-SNARE acceptor complex is stabilized on autophagosomes by binding of Stx17 to the Beclin-1-associated autophagy-related key regulator ATG14 (75), although this interaction may also play a role already upstream in autophagosome formation (1, 125). In *Drosophila*, Stx17 interacts with the HOPS tethering complex, which, in addition to endosomal maturation, regulates the fusion of lysosomes with autophagosomes (301). Enterovirus A71 exploits this pathway to facilitate its replication, as the nonstructural viral protein 2BC promotes autolysosome formation by interacting with Stx17 and SNAP29 (179). In contrast, the intracellular pathogen *Legionella* suppresses this pathway by secreting a serine protease that cleaves Stx17, and thereby prevents its degradation by autophagy (15).

K. Stx18

Stx18 is an essential Qa-SNARE (170) with well-known roles in ER transport, but Western blot and microscopy

revealed that it also locates at phagosomes (130). Although controversial (136, 267, 304), Stx18 is proposed to promote phagocytosis by mediating fusion of ER-derived vesicles to nascent phagosomes (25, 51, 102, 118, 130) by complexing with Use1 (Qc) and/or a plasmalemmal Qa-SNARE (which would result in a complex with two Qa-SNAREs) (128, 130). The availability of Stx18 for phagocytosis is proposed to be negatively regulated by the R-SNARE Sec22b, which might sequester Stx18 by forming a nonfusogenic SNARE complex (128).

III. Qb-SNAREs

A. GosR1

The Qb-SNARE GosR1 mediates retrograde trafficking from early and recycling endosomes to the *trans*-Golgi network by complexing with Stx5 (Qa), Bet1L (Qc), and Ykt6 (R) (299). GosR1 potentially could have a similar role in phagosome-to-Golgi transport, as it is found on phagosomes by proteomics (Ref. 293 and **FIGURE 5**).

B. Vti1a

The Qb-SNARE Vti1a, which is weakly homologous to Vti1b (28% sequence identity), locates at the Golgi network (172, 335) and endosomes (39). Vti1a also locates at phagosomes (38, 44, 286), with quantitative proteomics showing a decreased phagosomal presence over time of uptake **(FIGURE 5)**. Although Vti1a knockout mice are viable (177), they show behavioral, metabolic, and growth defects (170). Vti1a not only plays a role in Golgi trafficking, with depletion of Vti1a resulting in a disruption of the ribbon structure of the Golgi apparatus (285), but can also act as a negative regulator of phagocytosis (44). Vti1a mediates retrograde trafficking from late endosomes to the *trans*-Golgi network by complexing with Stx16 (Qa), Stx10 (Qc), and VAMP3 (R) and trafficking from early/recycling endosomes with Stx16, Stx6 (Qc), and VAMP4 (R) (105, 172, 193, 305). Assembly of this latter Vti1a-Stx16-Stx6-VAMP4 SNARE complex is mediated by the GARP tethering complex (239). The intracellular pathogen *Coxiella burnetii* hijacks retrograde endosome-Golgi trafficking by actively recruiting Vti1a to its vacuolar habitat, thereby facilitating the interaction with endosomes (47). In addition to retrograde endosome-Golgi trafficking, Vti1a also mediates anterograde trafficking (335) by complexing with VAMP7 (R) (93) and autophagosome formation by pairing with Stx12 (Qa) (187). Finally, neurons and neuroendocrine cells express a splice variant of Vti1a, called Vti1a-β, which contains an insertion of seven amino acids next to its SNARE motif (14). This isoform mediates homotypic fusion of early endosomes (with Stx12, Stx6, and VAMP4) (39) and is involved in the recycling of neurotransmitter vesicles (14, 172, 266, 318).

C. Vti1b

The Qb-SNARE Vti1b localizes at the Golgi apparatus, late endosomes, lysosomes (17, 24, 39, 88, 172, 186, 206, 231), and less at early endosomes (29, 206). Vti1b is also found at phagosomes (38, 44, 286) where, opposite to Vti1a, it becomes more abundant during phagosomal maturation (Ref. 79 and **FIGURE 5**). Although Vti1b-deficient mice are viable and fertile, they are smaller than wild-type mice and display minor trafficking defects, such as delayed lysosomal degradation (16). In contrast, mice lacking both Vti1a and Vti1b (but not the single knockouts) display severe neuronal defects, suggesting that these Qb-SNAREs can substitute for each other (177). Vti1b mediates fusion of late endosomes with other endosomes and lysosomes by complexing with Stx7 (Qa), Stx8 (Qc), and VAMP7 or VAMP8 (R) (12, 251). These SNARE complexes with Stx6 (Qc) instead of Stx8 can mediate biogenesis of lysosome-related organelles, such as melanosomes (317). Vti1b also has roles in Golgi-endosome trafficking [with Stx7, Stx6, and VAMP3 (R)] (219, 220) and is required for the fusion of autophagosomes with lysosomes (101) that mediates degradation of intracellular pathogens (229). Finally, Vti1b is proposed to have a nonfusogenic tethering role, as it promotes release of cytolytic granules from cytolytic T lymphocytes at the immune synapse (81) by linking cytolytic granules to endosomes (254). This nonfusogenic role might explain how Vti1b could act as a negative regulator of phagocytosis (similar to Vti1a, VAMP8, and Sec22b) (44), as it would allow to sequester other SNAREs by forming nonfusogenic complexes.

Vti1b contains an NH_2-terminal Habc domain which, in contrast to some Qa-SNAREs, cannot interact with its own SNARE motif (10), but regulates its localization at late endosomes and the *trans*-Golgi network by binding to the clathrin adapter EpsinR (56, 206). The subcellular localization of Vti1b further depends on Stx6 (175), whereas Vti1b in turn affects the stability of Stx8 (16). The endocytic trafficking role of Vti1b with Stx7 is regulated by binding to UVRAG and viruses, such as influenza A and VSV, use this pathway for their escape from endosomes (242). Like Vti1a, the bacterial-driven recruitment of Vti1b to intracellular vacuoles containing the pathogen *Coxiella burnetii* has been shown to promote bacterial survival and proliferation (47).

IV. Qc-SNAREs

A. Stx6

The Qc-SNARE Stx6 mainly localizes at the Golgi apparatus (31, 55, 58, 158, 239, 247, 265, 325), but also at early and recycling endosomes, the plasma membrane, and secretory vesicles, and it plays a role in trafficking between these

compartments and from these compartments to lysosomes (39, 55, 88, 94, 154, 158, 175, 287, 325). Stx6 is detected by proteomics on phagosomes (38), where most quantitative studies report a lower presence of Stx6 at late phagosomes (>1 h after uptake) compared with earlier timepoints (<0.5 h; **FIGURE 5**). However, Stx6 is best understood in both retrograde and anterograde Golgi-endosome trafficking (219, 220, 261, 265), and depletion of Stx6 results in a disruption of the Golgi ribbon structure (285). For retrograde trafficking, Stx6 forms a SNARE complex with Stx16 (Qa), Vti1a (Qb), and VAMP4 (R) (193, 282, 291, 305).

Stx6 is important for endosomal trafficking of cholesterol, and Stx6 senses cholesterol levels by direct binding (143) at the interface between endosomes and the *trans*-Golgi network (261). The altered cellular cholesterol levels in Niemann-Pick type C1 syndrome cause a redistribution of Stx6 from the Golgi to early/recycling endosomes (261, 307). Stx6 is also involved in the transport of lipids to the plasma membrane (58), where it cycles by means of a tyrosine-based internalization motif located between its Habc domain and SNARE motif (158). In addition to lipid trafficking, Stx6 mediates homotypic fusion of early/recycling endosomes [with Vti1a, VAMP4, and Stx16 or Stx12 (Qa)] (39, 172, 208), as well as the fusion of endo/phagosomes with autophagosomes [with Vti1b (Qb) and VAMP3 (R)] for clearance of intracellular pathogens (229). Finally, in many cell types, Stx6 is found at specialized secretory granules (172, 266) where it can be involved in their biogenesis, as shown for melanosomes (317).

The regulation of Stx6 in retrograde endosome-Golgi trafficking in well understood and is mediated by binding of its Habc domain, which does not interact with its SNARE motif (209), to the S/M-protein Vps45 (31, 255), the COG complex (180), and the Stx6 Habc-interacting protein of 164 kDa (SHIP164) (239). Following binding of SHIP164 to Stx6, it can interact with the GARP tethering complex (233), and this promotes the assembly of the Stx6-Stx16-Vti1a-VAMP4 SNARE complex (239). Anterograde Golgi-to-endosome transport is regulated by interactions of Stx6 with the mammalian E3 ubiquitin ligase family members MARCH-II and MARCH-III (222), whereas its endocytic trafficking roles are regulated by direct interactions with the Rab5-effector EEA1 (208, 287). Stx6 is targeted by the intracellular pathogen *Mycobacterium tuberculosis* that promotes its proliferation by preventing Stx6 recruitment to pathogen-containing phagosomes (96). In contrast, the intracellular pathogens *Salmonella* and *Chlamydia* promote Stx6 recruitment to their intracellular vacuoles, and this aids their survival (191, 213).

B. Stx8

The Qc-SNARE Stx8 localizes at early and recycling endosomes (30, 88, 158, 247, 260), late endosomes, lysosomes (17, 24, 88, 134, 158, 186, 247), and the *trans*-Golgi network (247). Stx8 is also detected at phagosomes (38, 43, 96, 156, 286), with most quantitative studies showing an increased phagosomal presence of Stx8 over time after uptake (Ref. 79 and **FIGURE 5**). Although Stx8 is nonessential, and knockout mice show no significant abnormalities (170), its endocytic trafficking functions are well studied. SNARE complex formation of Stx8, Stx7 (Qa), and Vti1b (Qc) with VAMP8 (R) mediates homotypic fusion of late endosomes (12, 251), whereas the same SNARE complex with VAMP7 (R) mediates fusion between late endosomes and lysosomes (251). The formation of these SNARE complexes and late endosomal localization of Stx8 are regulated by interactions of Stx8 with the SNARE-associated protein SNAPIN (186). The late endosomal localization of Stx8 is further mediated by interactions of its Habc domain, which does not bind back on the SNARE motif (10), with EpsinR (57) and UVRAG (242), and by a dileucine motif of Stx8 (159). Another dileucine motif mediates internalization of Stx8 at the plasma membrane (158, 260). Stx8 is stabilized by Vti1b (16) and is palmitoylated, although this does not seem to be important for its trafficking in contrast to Stx7 (134). Stx8 mediates trafficking of several key cargo molecules by direct interactions, as shown for the internalization of the K^+ channel TASK-1 (260), surface-delivery of the Cl^- channel CFTR (29, 30), and surface-delivery of the nerve growth factor receptor TrkA (54). Finally, endosomal trafficking of Stx8 is targeted by several pathogens. *Mycobacterium* delays Stx8 recruitment to its intracellular habitat, which could promote pathogen survival by blocking acquisition of lysosomal constituents (96). Moreover, VSV and other viruses promote their cellular entry by rerouting trafficking of Stx8 with Stx7, Vti1b, and VAMP8 (242).

C. Stx10

Stx10 is a Qc-SNARE, which is structurally closely homologous to Stx6 (61% sequence identity) (2). Stx10 is not much studied because it is absent in mouse (but present in humans), but it is believed to be involved in retrograde transport from endosomes to the *trans*-Golgi network (105, 193). Whereas Stx6 mediates transport from early/recycling endosomes to the Golgi apparatus (see above), Stx10 mediates transport from late endosomes by pairing with Stx16 (Qa), Vti1a (Qb), and VAMP3 (R) (105, 193). This retrograde trafficking by Stx10 depends on the small GTPase Rab9 (105). Stx10 is not found at phagosomes by proteomics, but most of these studies are conducted with mouse cells that do not have Stx10. Stx10 locates at intracellular vacuoles bearing the intracellular pathogen *Chlamydia trachomatis*, and this is required for the creation and maintenance of these vacuoles (188).

D. Use1

The Qc-SNARE Use1 locates at the ER and Golgi apparatus and is involved in trafficking to lysosomes, presumably by

complexing with VAMP7 (R) (232). By microscopy and Western blot, Use1 was found to locate at phagosomes (130). Although controversial (136, 267, 304), Use1 is proposed to mediate transport from the ER to phagosomes by complexing with Stx18 (Qa), and these Q-SNAREs might be negatively regulated by forming a nonfusogenic complex with Sec22b (R) (128, 130).

V. Qbc-SNAREs

A. SNAP23

The essential (161) Qbc-SNARE SNAP23 is best known for its role in plasma membrane trafficking. SNAP23 mediates exocytosis in many cell types (109, 110, 174, 178, 219, 234, 256, 312, 346), for instance in neurons where it mediates the post-synaptic surface delivery of the glutamate receptor at dendritic spines (296). The Qb- and Qc-SNARE-motifs of SNAP23 are connected by a linker region containing five palmitoylated cysteines (272) that anchor it at the plasma membrane, recycling and late endosomes, and the *trans*-Golgi network (88, 94, 104, 109, 166, 223, 275, 309, 312, 346). SNAP23 is also found at phagosomes (38, 51, 79, 215, 221, 271, 286), and, although it might be recruited at several stages during phagosomal maturation (267), most quantitative proteomics show an overall decrease of phagosomal SNAP23 following uptake **(FIGURE 5)**. Although best understood for its role in plasma membrane trafficking, SNAP23 also catalyzes endosomal fusion events (166, 309), such as for the biogenesis of lysosome-relate organelles (e.g., melanosomes) (339). The intracellular trafficking roles of SNAP23 are characterized for phagosomes, where SNAP23 is responsible for the recruitment of several proteins with key roles in phagosomal maturation from recycling endosomes (221) and lysosomes (79, 271, 308): the V-ATPase (271), MHC class I (221), and the NADPH oxidase NOX2 [with Stx7 (Qa) and VAMP8 (R)] (79, 271, 308).

The subcellular localization of SNAP23 is regulated by phosphorylation by the serine IkB kinase-β (157, 221), and this promotes SNARE complex formation and membrane fusion (157, 221, 223, 323). In cancer cells, SNAP23 can also be phosphorylated by pyruvate kinase type M2, a metabolic enzyme (323), but whether this occurs in healthy cells is unknown. SNAP23 is further regulated by interactions with the calcium-sensor synaptotagmin-7 (256) and the Sec6 and Sec8 subunits of the exocyst complex (174).

B. SNAP25

The Qbc-SNARE SNAP25 is anchored by four palmitoylated cysteines (one less than SNAP23) (115, 272) at the plasma membrane, early/recycling endosomes, and the *trans*-Golgi network (4, 5, 39, 115, 174, 245, 272). Although SNAP25 is expressed by nonneuronal cells (174), it is best known for its role in neurotransmitter release from neurons and neuroendocrine cells by complexing with Stx1 (Qa) and VAMP2 (R) (139, 148, 149, 294, 296). These SNAREs can also mediate the subsequent recycling of synaptic vesicles, thereby directly coupling exocytosis with endocytosis (334, 344). Another role of SNAP25 is the homotypic fusion of early endosomes by complexing with Stx12 (Qa) and VAMP2 regulated by Hgs in a calcium-dependent manner (297, 337). SNAP25 has been detected at phagosomes from macrophages and from *Drosophila melanogaster* (286, 293), but its functional roles here are unclear. Finally, SNAP25 may have a role in autophagy, as its upregulation in cancer promotes autophagy-mediated tumor progression (216).

Endocytic trafficking of SNAP25 is regulated by phosphorylation within its Qc-SNARE motif by the serine kinase protein kinase C (160). Trafficking of SNAP25 is further regulated by ADP-ribosylation factor 6 (ARF6) (5) and interactions with the Sec6 and Sec8 subunits of the exocyst complex (174). The protein cytoplasmic LEK1 regulates endosomal transport by linking SNAP25-positive early/recycling endosomal vesicles to the microtubule network (245).

C. SNAP29

Loss of the Qbc-SNARE SNAP29 results in CEDNIK syndrome (cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma), characterized by a wide range of symptoms, including severe psychomotor retardation and generalized ichthyosis (257, 290). In mice, SNAP29 might even be essential, as no homozygous knockout mice for SNAP29 were obtained (170). In contrast to SNAP23 and SNAP25, the linker between the Qb- and Qc-SNARE motifs of SNAP29 contains no palmitoylation sites. This lack of palmitoylation makes SNAP29 a cytosolic protein, although it can locate at the plasma membrane, early/recycling endosomes, and other organelles by interacting with other (membrane-anchored) SNAREs (88, 268, 279, 326), such as Stx6 (Qc) (325). Proteomics studies identified SNAP29 at phagosomes (Refs. 156, 293 and **FIGURE 5**), where it can be recruited at multiple stages following phagocytosis (267).

Although SNAP29 might be involved in Golgi trafficking, and cells from CEDNIK patients have a disrupted Golgi morphology (257), it is best characterized in endocytic trafficking. SNAP29 mediates recycling of transferrin and integrins from recycling endosomes (257) and the fusion of these compartments with phagosomes (326). The endocytic role of SNAP29 is regulated by interactions with EH-domain containing protein 1, the subunit α-adaptin of AP-2, and the small-GTPase Rab3A (268, 279). In addition, SNAP29 mediates the fusion of autophagosomes with lysosomes by complexing with Stx17 (Qa) and VAMP8 (R) (75,

119, 147) or VAMP7 (R) (300) in a manner dependent on O-GlcNAcylation of SNAP29 (119). This pathway is blocked by human parainfluenza virus type 3, which thereby prevents its lysosomal degradation and promotes virus replication (78). In contrast, enterovirus A71 facilitates its replication by promoting this pathway, and binding of the viral protein 2BC to SNAP29 and Stx17 promotes fusion of autophagosomes with lysosomes (179).

VI. R-SNAREs

A. Sec22b

The nonessential (170) R-SNARE Sec22b plays a role in ER-Golgi trafficking and mainly locates at the ER, the ER-GIC, and *cis*-Golgi compartments (51, 241), but it is also found at phagosomes (Refs. 25, 38, 43, 51, 130, 182, 221 and **FIGURE 5**). Although controversial (212, 333), Sec22b regulates trafficking from the ERGIC to phagosomes in dendritic cells (8, 41, 51). Sec22b might also be responsible for transport from the ER to phagosomes by complexing with Stx18 (Qa) and Use1 (Qc) (25, 130), although this is also debated (136, 267, 304). This route is used by intracellular parasites, such as *Leishmania*, *Toxoplasma*, and *Legionella*, that redirect Sec22b-mediated transport from the ER to parasite-containing phagosomes to promote their survival (48, 51).

In addition to the controversial roles in ER/ERGIC-phagosome trafficking, Sec22b locates at autophagosomes where it performs two functions. First, Sec22b coordinates the recruitment of autophagic secretory cargo, such as IL-1β, by interaction with the cargo receptor TRIM16. Second, Sec22b mediates the fusion of autophagosomes with the plasma membrane by complexing with Stx3 or Stx4 (Qa) and SNAP23 or SNAP29 (Qbc) (165). Moreover, Sec22b has been shown to form nonfusogenic SNARE complexes, for instance with Stx1 (Qa) for tethering of the ER to the plasma membrane (241). Such nonfusogenic SNARE complex formation might explain how Sec22b sequesters other SNAREs [such as Stx18 (Qa)] and thereby negatively regulate phagocytosis (128), although this is also controversial (51, 286). Finally, Sec22b trafficking is regulated by its NH_2-terminal longin domain (139), which can interact with its SNARE motif to prevent complex formation (similar to VAMP7 and Ykt6) (195).

B. VAMP1

The R-SNAREs VAMP1 and VAMP2 are highly homologous (78% sequence identity), both locate at secretory vesicles and endosomes (146, 204), and both mediate neuronal secretion by complexing with Stx1 (Qa) and SNAP25 (Qbc) (139, 148, 149, 204, 294). Despite this high structural and functional similarity, VAMP1 and VAMP2 are expressed in discrete but partially overlapping areas of the brain (184, 347) and have unique trafficking functions, as VAMP1 (but not VAMP2) mediates TNF-α-induced surface trafficking of the transient receptor potential (TRP) A1 and V1 channels in trigeminal ganglion neurons (204). Mice carrying a VAMP1 null mutation display the so-called lethal-wasting (*lew*) phenotype, characterized by severe neurological defects and premature death (230).

C. VAMP2

VAMP2 is the main R-SNARE for neuronal secretion by complexing with Stx1 (Qa) and SNAP25 (Qbc) (139, 148, 149, 294) and is also involved in the subsequent recycling of synaptic vesicles (74, 344). VAMP2 knockout mice die immediately after birth, because of the absence of neurotransmitter release from neurons (which do not contain compensatory VAMP3) (36). Although VAMP2 is predominantly expressed in neurons and neuroendocrine cells, it also mediates exocytosis in nonneuronal cell types (110, 162, 174, 202), mainly by complexing with Stx4 (Qa) and SNAP23 (Qbc) (110, 162, 174, 202, 205, 211, 308). In addition, VAMP2 facilitates the membrane growth for phagocytosis by mediating local fusion of endosomes with the plasma membrane at the site of uptake (123). Besides being located at secretory vesicles, VAMP2 also locates at the plasma membrane (207, 313), early/recycling endosomes (39, 117), and lysosomes (17). VAMP2 is organized in membrane domains of early endosomes (107) and mediates homotypic fusion of these compartments by complexing with Stx12 (Qa) and SNAP25 (297). VAMP2 does not contain a regulatory NH_2-terminal domain, but reaches secretory granules by trafficking signals located within its SNARE motif (117). These signals likely interact with the cargo adaptor protein AP3 and the endocytic clathrin adaptor CALM/PICALM, which are known to mediate intracellular sorting of VAMP2 (207, 273). Interaction with AP3 is required for trafficking to synaptic vesicles (273), whereas interaction with CALM/PICALM is necessary for VAMP2 retrieval from the plasma membrane (207).

D. VAMP3

The R-SNARE VAMP3 is structurally and functionally closely related to VAMP2 (63% sequence identity), but is ubiquitously expressed. VAMP3 mainly locates at early and recycling endosomes and regulates transport to other endosomes, autophagosomes, the Golgi apparatus, and the plasma membrane (27, 55, 72, 87, 89, 103, 174, 207, 219, 221, 312, 313, 330, 336). VAMP3 also locates at phagosomes (38, 138, 201, 221) with quantitative immunofluorescence microscopy showing that VAMP3 is more abundant at early (<1 h after uptake) compared with late (>1 h) phagosomes (138), although this is opposite to the findings from most quantitative proteomics studies **(FIGURE 5)**.

VAMP3 mediates exocytosis mainly by complexing with Stx4 (Qa) and SNAP23 (Qbc) (87, 91, 112, 153, 219, 243, 312, 313, 346). In addition, trafficking from early/recycling endosomes to the Golgi apparatus is mediated by complexing of VAMP3 with Stx16 (Qa), Vti1a (Qb), and Stx6 or Stx10 (Qc) (105, 193, 265), whereas trafficking in the reverse direction is mediated by complexing with Stx7 (Qa), Vti1b (Qb), and Stx6 (196, 219, 220). VAMP3 has also been described to mediate fusion between autophagosomes and multivesicular bodies to generate autophagosomal vacuoles called amphisomes (85), and this may play a role in the degradation of pathogen-containing endo/phagosomes (229).

Endocytic trafficking of VAMP3 is required for many cellular processes, including the recycling of the transferrin receptor (72, 103), insulin-stimulated trafficking of GLUT-4 (281), the recycling of integrins in migrating cells (21, 249), and fibrinogen uptake by platelets (21). Nevertheless, VAMP3 knockout mice have no (338) or only a very mild phenotype (170), and this is probably caused by compensation by other R-SNAREs, as shown for VAMP3 in phagocytosis. Here, VAMP3 mediates ARF6-dependent fusion of recycling/early endosomes with the plasma membrane at the site of phagocytosis by complexing with Stx4 (18, 219, 227), but ablation of VAMP3 does not affect phagocytosis (7, 138, 338). Since phagocytosis is blocked by tetanus neurotoxin (123), which cleaves and inactivates both VAMP2 and VAMP3, it is suggested that VAMP2 can compensate for VAMP3. Compensation in the reverse direction (i.e., VAMP3 for VAMP2) has been shown in chromaffin cells, where VAMP2 knockout cells have no secretory defect due to full compensation by VAMP3 (36).

Like VAMP2, VAMP3 contains no NH_2-terminal regulatory domain, but its subcellular sorting is mediated by signals located within its SNARE motif (117). Retrieval of VAMP3 from the plasma membrane is governed by interactions with the endocytic clathrin adaptor CALM/PICALM (207), and, at least in *Drosophila*, trafficking of VAMP3 to early/recycling endosomes is regulated by ubiquitination (336). Endosomal sorting of VAMP3 is further regulated by two enzymes involved in phosphoinositide metabolism: phosphatidylinositol 4-kinase IIa, which regulates its pairing with Vti1a (Qb) (153), and the phosphoinositide lipid 3-phosphatase myotubularin-related protein 4 (224). Finally, VAMP3 is involved in the formation and maintenance of vacuoles supporting survival of several intracellular pathogens (23, 47, 95), as, for example, VAMP3-positive vesicles are selectively recruited to the infection sites of *Salmonella typhimurium* and *Trypanosoma cruzi* to facilitate their survival (64, 67).

E. VAMP4

The R-SNARE VAMP4 predominantly locates at the Golgi apparatus (88, 193, 238, 239, 291, 305, 329), but is also present at the plasma membrane, in membrane domains of early/recycling endosomes (39, 88, 107, 193, 291, 305), and at lysosome-related secretory compartments, such as synaptic vesicles from neurons (266, 291) and cytolytic granules in natural killer cells (173). Moreover, VAMP4 has been found at phagosomes by proteomics (Refs. 38, 286 and **FIGURE 5**), and Western blot experiments revealed that VAMP4 is recruited to phagosomes in consecutive phases following uptake (267). VAMP4 functions in retrograde trafficking from early and recycling endosomes to the *trans*-Golgi network by complexing with Stx16 (Qa), Vti1a (Qb), and Stx6 (Qc) (193, 305) and loss of VAMP4 results in disruption of the ribbon structure of the Golgi (285). VAMP4 also participates in anterograde transport from the Golgi to endosomes (291), which is important for distributing cholesterol at the Golgi-endosome interface by pairing with Stx6 (261, 307). Moreover, VAMP4 plays a role in the homeostasis of other lipids as well, because it is involved in the formation of lipid droplets, storage compartments of excess lipids, together with Stx5 (Qa) and SNAP23 (Qbc) (37). Other endocytic functions of VAMP4 are the clathrin-independent bulk endocytosis in neurons (225) and the homotypic fusion of early endosomes by forming a SNARE complex with Stx12 (Qa), Vti1a, and Stx6 (39).

The well-conserved NH_2-terminal domain of VAMP4 contains a dileucine motif and an acidic cluster that regulate its localization to the *trans*-Golgi network by interacting with the cargo adaptor protein AP1 (139, 238) and the GARP complex (239). The NH_2-terminal domain also regulates clathrin-dependent endocytosis of VAMP4 (305). Endosomal trafficking of VAMP4 is hijacked by the intracellular pathogen *Legionella pneumophila*. This pathogen expresses three proteins that resemble Q-SNAREs and forms a SNARE-like complex with VAMP4 (284), which results in fusion of VAMP4-containing vesicles with the pathogen-containing vacuoles, and thereby it enables growth of these vacuoles, promoting proliferation of the pathogen (284).

F. VAMP7

The R-SNARE VAMP7, also known as tetanus neurotoxin-insensitive VAMP (review, Ref. 53), mainly locates at late endosomes and lysosomes (24, 40, 55, 67, 84, 85, 87, 88, 101, 200, 244, 250, 251, 256, 329), although it is also found at the plasma membrane (104), early endosomes (151), and autophagosomes (84, 101, 214). VAMP7 is detected already at the nascent cup (40) of phagosomes (38, 43, 156), and its phagosomal presence increases in the time following uptake **(FIGURE 5)**. VAMP7 knockout mice only have a mild behavioral phenotype (71), possibly related to a reduced neurite outgrowth (276). By complexing with Stx7 (Qa), Vti1b (Qb), and Stx8 (Qc), VAMP7 mediates fusion of late endosomes with lysosomes and homotypic fusion of lysosomes (251, 322) and is proposed to mediate fusion of lysosomes with phagosomes (24). VAMP7 is also involved

in Golgi-to-late endosome trafficking (244), the biogenesis of lysosome-related secretory compartments, such as melanosomes (150, 339), the formation of autophagophores (the precursors of autophagosomes) (214), and the fusion of autophagosomes with lysosomes (85, 101). However, these roles of VAMP7 in late endosomal and lysosomal trafficking were recently questioned, and it was argued that VAMP7 primarily acts as a SNARE for exocytosis of lysosomes and lysosome-related secretory compartments (53). Indeed, a role for VAMP7 in exocytosis has been reported for many cell types, mainly by complexing with plasmalemmal Stx3 or Stx4 (Qa) and SNAP23 (Qbc) (55, 70, 84, 87, 104, 173, 178, 211, 275, 329). This exocytic role of VAMP7 is important for efficient uptake of some phagocytic cargoes (40), because VAMP7-mediated fusion of vesicles with the plasma membrane at the site of phagocytosis can promote phagosome formation (40, 274), although VAMP7 has also been reported to act as a negative regulator of phagocytosis (138).

The regulation of VAMP7 is well understood. Like Ykt6 (R) and Sec22b (R), VAMP7 contains an NH_2-terminal longin domain that can bind back on its SNARE motif and thereby prevents formation of a SNARE complex **(FIGURE 4)** (199, 200). This closed conformation of VAMP7 is stabilized by interactions with the guanine exchange factor (GEF) ankyrin repeat domain-containing protein 27 (VARP), a GEF for Rab21, which interacts with the retromer complex and regulates the endosomal localization of VAMP7 (reviews, Refs. 53, 100). VARP also interacts with GolginA4 and the kinesin 1 Kif5A (42), and this promotes the directed movement of VAMP7 vesicles from the cell center to the cell periphery (42, 67, 84). In contrast, the AP2 binding protein Hrb (HIV Rev-binding protein) only binds to the longin domain in an open conformation of VAMP7, thereby allowing for specific recycling of *cis*-SNARE complexes by clathrin-mediated endocytosis (190, 250). Hrb binding to VAMP7 plays an additional role in autophagosome formation (214). The longin domain of VAMP7 also binds to AP3, and this binding is responsible for targeting VAMP7 from early and recycling endosomes to late endosomes and lysosomes (163, 200). Other proteins regulating VAMP7 are Stx12 (Qa), with a loss of Stx12 resulting in mislocalization of VAMP7 to lysosomes (151), and the calcium-binding protein synaptotagmin-7 (256).

VAMP7 plays a role in the pathogenesis of at least two intracellular pathogens. First, *Coxiella burnetii* promotes its survival and proliferation by actively recruiting VAMP7 to bacteria-containing phagosomes (47). Second, VAMP7 is required for efficient host cell infection by *Trypanosoma cruzi*, and VAMP7-positive lysosomes are recruited to the infection site at the plasma membrane (67).

G. VAMP8

VAMP8 locates at early/recycling endosomes (29, 39, 174, 198, 207, 221, 330), late endosomes, lysosomes (17, 24, 76, 101, 147, 217, 330), the plasma membrane, the *trans*-Golgi network (13, 207), and phagosomes (38, 79, 138, 156, 182, 201, 221, 286). Quantitative imaging (79) and most quantitative proteomics studies **(FIGURE 5)** revealed an increased presence of VAMP8 following phagosome maturation, although the phagosomal recruitment of VAMP8 can occur in multiple phases after uptake (267). VAMP8 is best understood as a general SNARE for regulating exocytosis of the exocrine system, and VAMP8 knockout mice have secretory defects in exocrine tissues (205, 253, 303, 319, 320). VAMP8 mediates exocytosis mainly by interacting with plasmalemmal Stx4 (Qa) and SNAP23 (Qbc) (243), and this is, for instance, required for granule secretion from mast cells (183, 253, 275, 303, 331) and platelets (114, 243, 259). Moreover, the secretory role of VAMP8 is required for host defense to *Entamoeba histolytica* as it mediates the intestinal mucin secretion triggered by this pathogen (65). In addition to these secretory roles, VAMP8 mediates fusion between early/recycling endosomes, late endosomes, and lysosomes [with Stx7 (Qa), Vti1b (Qb), and Stx8 (Qc)] (11–13, 217, 251) and is responsible for biogenesis of lysosome-related secretory compartments, such as melanosomes [with Stx7, Vti1b, and Stx6 (Qc)] (317). VAMP8 also mediates the trafficking from lysosomes to phagosomes (24, 79), although some studies show that it might actually act as a negative regulator of phagocytosis (137, 138). Finally, VAMP8 is involved in autophagosomal fusion by complexing with Stx17 (Qa) and SNAP29 (Qbc) (101, 119, 147).

Although VAMP8 contains no NH_2-terminal regulatory domain, its function is regulated by binding to the calcium-sensor Munc13-4 (133), the lipid phosphatidylinositol 3-phosphate (69), the endocytic clathrin adaptor CALM/PICALM (207), the human trypanolytic factor APOL1 (192), and the small GTPase Rab17 (76). Rab17 stabilizes VAMP8 at late endosomes (76), whereas Munc13-4 stabilizes the Stx7-Vti1b-Stx8-VAMP8 SNARE complex to promote homotypic endosome fusion and exocytosis (331). Mutations in APOL1 that affect binding to VAMP8 are the cause of kidney disease (192). The phagocytic activity of VAMP8 is regulated by caspase-dependent cleavage of VAMP8 in its SNARE motif (137). This pathway is hijacked by the intracellular pathogen *Leishmania*, which averts its detection by the immune system by cleaving VAMP8 with a bacteria-produced protease and thereby blocks NOX2 recruitment to the phagosome (201). On the other hand, VAMP8 can also facilitate pathogen invasion, as *Salmonella typhimurium*-generated phosphatidylinositol 3-phosphate promotes the recruitment of VAMP8 to the bacterial invasion site to allow pathogen uptake (69). Moreover, VAMP8 selectively traffics to at least a subset of

vacuoles containing *Coxiella burnetii*, suggesting a role in the survival of this intracellular pathogen (47).

H. Ykt6

The R-SNARE Ykt6 does not contain a transmembrane domain, but is attached to the membrane by prenylation and palmitoylation of cysteine residues at its COOH-terminus (99, 127, 139). The reversible palmitoylation allows Ykt6 to actively cycle on and off membranes (324), and, therefore, Ykt6 is present as both a free cytosolic pool and a membrane-associated pool at the Golgi apparatus (99, 316), late endosomes, and lysosomes (127). Ykt6 has also been identified at phagosomes by proteomics (Ref. 38 and **FIGURE 5**), although it could not be detected by Western blot (51, 221). Like VAMP7 (R), Ykt6 contains an NH_2-terminal longin domain (139) that can adopt a closed conformation to prevent SNARE complexing (99). In case Ykt6 is only prenylated but not tethered to membranes by palmitoylation, the prenyl moiety stabilizes this closed conformation of Ykt6, thereby inactivating the soluble form of Ykt6 (324). Ykt6 mediates retrograde transport from early/recycling endosomes to the *trans*-Golgi network by complexing with Stx5 (Qa), GosR1 (Qb), and Bet1L (Qc) (299), and it has secretory roles (111, 112), such as exosome production and release (116, 269).

VII. DISCUSSION AND CONCLUSIONS

To date, a vast majority of the human members of the SNARE protein family (30 out of 38) have been identified at endosomes and/or phagosomes **(FIGURE 1)**, and, given the increased sensitivity of detection methods, we expect that more SNAREs will be found at these organelles in the future. Although its localization at endo/phagosomes does not automatically mean that a SNARE has active trafficking roles, and it could be merely present as a cargo molecule en route to its target organelle, almost all 30 SNAREs have currently been assigned functions in endosomal and/or phagosomal trafficking. In fact, most SNAREs are not implied in a single transport route, but function in multiple and frequently consecutive pathways between endo/phagosomes with other endosomes, lysosomes, the plasma membrane, autophagosomes, the Golgi apparatus, the ER, and the ERGIC **(FIGURE 6)**. Moreover, the functions of many of these SNARE proteins overlap, and there are often no well-definable single sets of SNAREs mediating a certain endosomal/phagosomal transport route.

At first glance, it does not seem surprising that by far most SNAREs participate in multiple endosomal and/or phagosomal trafficking routes. Many other membrane trafficking components are involved in multiple and overlapping trafficking steps as well, such as phosphoinositides, Rab-GTPases, and cage proteins (19, 45, 113, 121). Although SNARE proteins contribute to the identity of organellar membranes (139, 140, 149), the specificity of organellar trafficking requires the combined presence of SNAREs and several other components, thus the synergistic recognition of specific SNAREs, Rab-GTPases, cage proteins, tethering complexes, and phosphoinositides, in a process called coincidence detection (50, 235). This coincidence detection is facilitated by direct interactions between SNAREs with phosphoinositides, adapter proteins, the cytoskeleton, multisubunit tethering complexes, and Rab-GTPases (45, 76, 176, 189, 240, 279, 280, 328). As described in this review, these interactions are important for the specific trafficking roles of SNAREs, as they allow control over the selection of cargo, the formation of trafficking vesicles, and the tethering and docking of these vesicles to the target organelles. Moreover, coincidence detection is an efficient way to increase the number of different trafficking routes with only a limited number of components, i.e., 38 SNAREs, ~70 Rab-GTPases, and 7 phosphoinositides. Nevertheless, the requirement for coincidence detection for organellar identity was put to question in a recent study employing microinjection of artificial liposomes carrying reconstituted Stx12 (Qa), Vti1a (Qb), Stx6 (Qc), and VAMP4 (R) in mammalian cell lines (169). These liposomes specifically fused to early endosomes within the cells, demonstrating that, at least for early endosomes, SNAREs alone suffice for organellar targeting (169). This finding raises the question of how these SNAREs can have other trafficking roles as described in this review (e.g., endosome-Golgi, endosome-plasma membrane trafficking).

Perhaps the answer to the question how SNAREs can be involved in multiple trafficking pathways lies in the trafficking of the SNARE proteins themselves. Most SNAREs are stably membrane-anchored by their COOH-terminal transmembrane domain and rely on intracellular membrane transport for reaching their subcellular location. There are, in principle, two ways by which a SNARE protein can reach its target organelle **(FIGURE 7)**: *1*) by the action of other SNAREs (i.e., the cargo SNARE being transported by other R- and Q-SNAREs); and *2*) by its direct complexing with SNAREs that are already present at the target membrane (i.e., the cargo SNARE trafficking itself), followed by disassembly of the SNARE complex by NSF with α-SNAP. There is evidence in literature supporting both mechanisms. First, for example, VAMP8 (R) does not directly mediate exocytosis of cytolytic granules from CD8+ killer T cells, but rather is responsible for bringing Stx11 (Qa) from recycling endosomes to the immunological synapse, which, in turn, mediates lytic granule release by complexing with VAMP2 (R) on the granules (198, 202). Second, in macrophages, VAMP3 (R) transports TNF-α from the Golgi apparatus to early/recycling endosomes by complexing with endosomal Stx7 (Qa), Vti1b (Qb), and Stx6 (Qc), but is also involved in the subsequent exocytosis of TNF-α by pairing with plasmalemmal Stx4 (Qa) and SNAP23 (Qbc) (196, 219, 220).

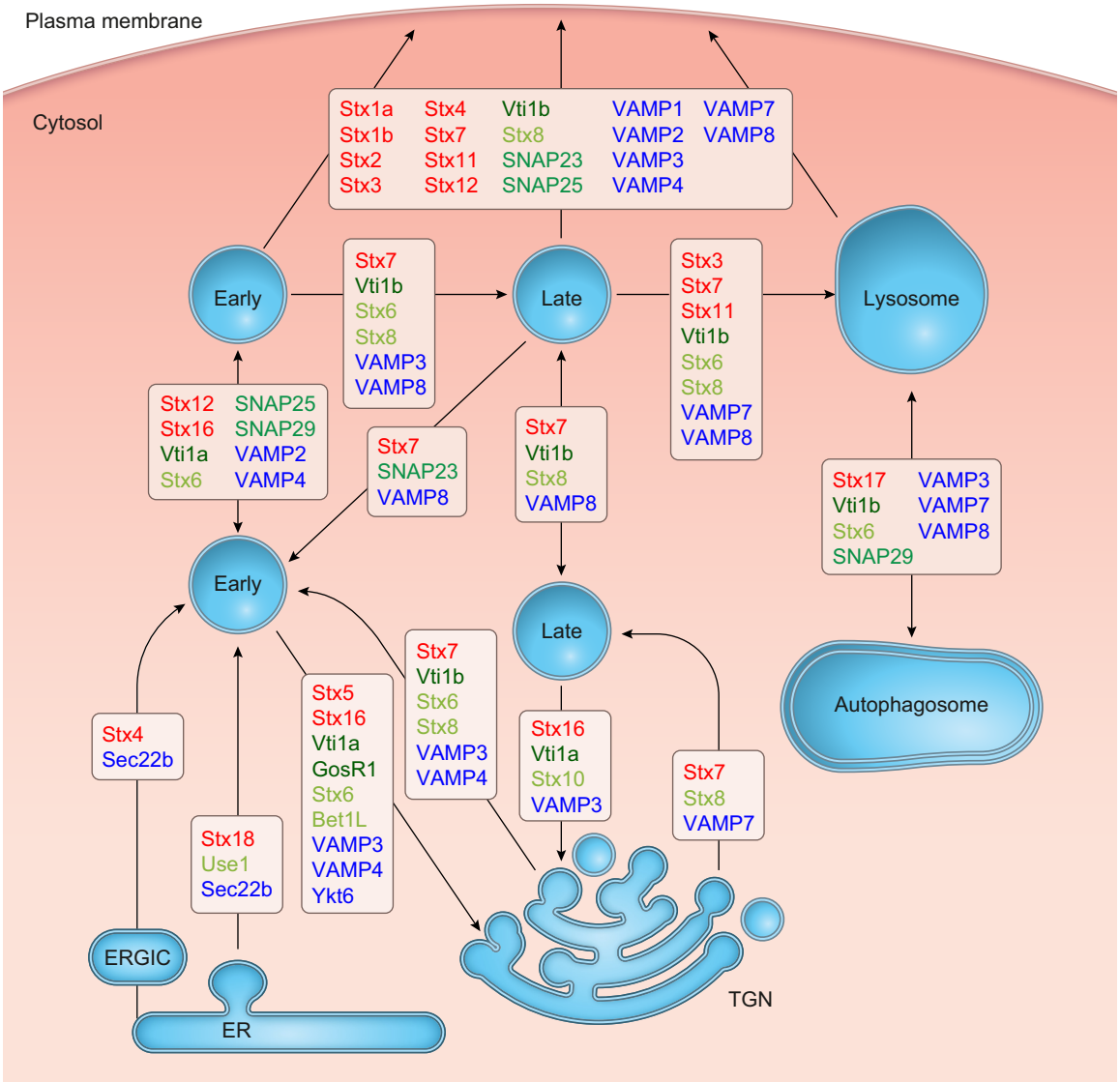

FIGURE 6. Schematic summary of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) with known functions in endosomal and phagosomal transport. Red, Qa-SNAREs; dark green, Qb-SNAREs; light green, Qc-SNAREs; medium green, Qbc-SNAREs; blue: R-SNAREs. Early, early and/or recycling endosome or phagosome; late, late endosome or phagosome; TGN, *trans*-Golgi network; ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment; Stx, syntaxin; SNAP, soluble *N*-ethylmaleimide-sensitive factor (NSF)-attachment protein; VAMP, vesicle-associated membrane protein. Note that, for clarity, the scheme is simplified, and early and recycling endosomes are not distinguished, many cell-specific routes are not included (e.g., for biogenesis of specialized secretory compartments), and endosomes and phagosomes are not distinguished.

Thus SNAREs can reach their target organelles both by being transported by other SNAREs and by actively engaging in their own trafficking. The first mechanism could offer a larger control over particulate trafficking pathways, but requires the recycling of the delivering SNAREs, which is not needed in the second mechanism **(FIGURE 7)**. Moreover, the second mechanism would explain not only the involvement of SNAREs in multiple consecutive trafficking routes, but also their large promiscuity. At least in vitro, most, if not all, combinations of Qa-Qb-Qc-R SNAREs can form fusogenic SNARE complexes (39), and, likely because of this promiscuity, SNARE knockout often results in no or relatively mild phenotypes (16, 28, 71, 98, 177, 338). Thus, a paradigm that emerges from this review is that the involvement of SNAREs in multiple trafficking routes is likely also important for transport of the SNAREs themselves.

The functional distribution of SNARE proteins over organellar membranes is still another open and important topic. In exocytosis, it is well-established that the secretory vesicles and granules carry the R-SNARE (e.g., VAMP2 in synaptic vesicles), which interacts with a Q-SNARE complex at

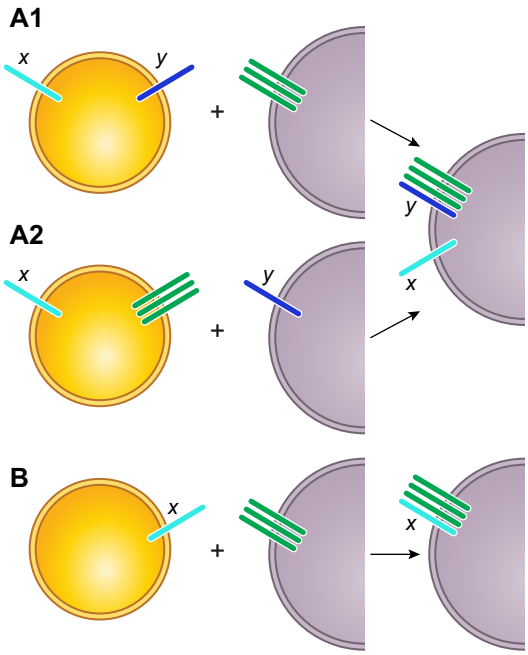

FIGURE 7. Two possibilities for delivering a soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein to its target organelle. *A*: *possibility 1*: R-SNARE protein *x* (cyan) is delivered to its target organelle by the complexing of R-SNARE protein *y* (blue) with acceptor Q-SNAREs (green). R-SNARE protein *y* can be either present in the vesicular (*A1*) or target (*A2*) membrane. Although this results in correct localization of cargo R-SNARE *x*, the delivering R-SNARE *y* is "mis-localized" during this process and needs to be recycled. *B*: *possibility 2*: R-SNARE *x* delivers itself at the target organelle by direct complexing with acceptor Q-SNAREs present on the target membrane. After *N*-ethylmaleimide-sensitive factor (NSF)/α-SNAP-mediated disassembly of the SNARE complex, R-SNARE *x* becomes available for subsequent trafficking functions on the target organelle.

the plasma membrane [e.g., Stx1 (Qa) and SNAP25 (Qbc)]. However, the functional SNARE distribution over the donor and target membranes for other intracellular transport routes is still unknown. Many (if not all) organellar membranes contain both R- and Q-SNAREs. This is especially apparent in homotypic fusion between the same types of organelles, such as endosomes, because, in this case, both membrane compositions are identical and contain the same sets of SNARE proteins. In vitro, Stx12 (Qa), Vti1a (Qb), Stx6 (Qc), and VAMP4 (R) can fuse liposomes with five out of seven possible combinations of distributions of these SNAREs over the donor and acceptor membranes (348), demonstrating that the functional topology of SNARE proteins does not necessarily have to be the R-SNARE on the donor membrane vs. the Q-SNAREs on the target membrane. One indication that the functional topology may be different comes from the finding that most Q-SNAREs contain NH_2-terminal regulatory domains, whereas these are absent in many R-SNAREs **(FIGURE 1)**. For instance, a late endosomal Q-SNARE acceptor complex of Stx7 (Qa), Vti1b (Qb), and Stx8 (Qc) would contain three Habc domains (12, 251), while the cognate R-SNARE VAMP8 does not have an NH_2-terminal regulatory domain. Because of these reasons, it seems reasonable to hypothesize that interorganellar transport routes might be mediated by different SNARE distributions than the canonical R- vs. Q-SNARE distribution (for instance R-Qa with Qb-Qc). This hypothesis could be tested by classical in vitro lipid dequenching experiments with artificial liposomes and purified organelles (24, 32), combined with the in vivo visualization of SNARE complexes in live cells by Förster resonance energy transfer coupled to fluorescence lifetime imaging microscopy (FRET-FLIM) (313).

Although the spatial control of membrane trafficking is increasingly well understood, it is still largely unknown how inter-organellar fusion events are regulated temporally. Cellular homeostasis requires not only the spatial regulation of membrane trafficking, but also the coordination of membrane fusion and fission rates for maintaining organellar integrity. In addition, many cell types actively need to respond to external stimuli, and this often requires a dynamic rerouting of intracellular trafficking. One still underinvestigated possibility is that intracellular membrane fusion events are regulated by calcium (132), similar to neuronal exocytosis (139, 148, 149, 294). Evidence supporting a role for calcium in endosome-endosome and endosome-lysosome trafficking comes from in vitro fusion experiments with purified endosomes (63, 252) and experiments with membrane-permeable calcium chelators (208). Moreover, ablation of the lysosomal calcium channel TRP protein mucolipin (TRPML1) results in enlarged endo/lysosomes and trafficking defects in the late endocytic pathway (80). Finally, several calcium-sensing proteins bind to endocytic SNAREs, for instance calmodulin [binds to Stx12 (Qa) and VAMP2 (R)] (126, 208), synaptotagmin-7 [binds to Stx4 (Qa) and SNAP23 (Qbc)] (256), and Hgs [calcium-dependent binding to SNAP25 (Qbc) and Stx12] (297, 337). The role of calcium in intracellular trafficking could be addressed by using intracellular calcium chelators, combined with FRET-FLIM to monitor the occurrence and conformations of SNARE complexes in live cells (262–264, 310, 313).

Overexpression of the SNAREs Vti1a (Qb), Vti1b (Qb) (44), Sec22b (R) (128), VAMP7 (R), or VAMP8 (R) (138) have been shown to result in a decreased phagocytosis efficiency, whereas gene ablation of Vti1a, Vti1b (44), Sec22b (128), Stx11 (Qa) (343), or VAMP8 (138) resulted in the opposite effect. Although nonphysiological effects cannot be excluded, these findings suggest that Stx11, Vti1a, Vti1b, Sec22b, VAMP7, and VAMP8 might act as negative regulators of phagocytosis (44, 128, 137, 138, 343). Such inhibition of phagocytosis could be caused by the complexing of the inhibitory SNARE with other SNAREs involved in phagocytosis. By such a competitive inhibition, the inhibitory SNARE reduces the availability of the other SNARE proteins, as has been shown for Sec22b, which blocks phagocytosis by sequestering Stx18 (Qa) (128). There are, in principle, two mechanisms by which an inhibitory

SNARE could sequester other SNAREs. First, it might form a nonfusogenic SNARE complex (that does not result in membrane fusion), and such complexes have been shown to negatively regulate membrane fusion for Stx6 (Qc) and Stx2 (Qa) (311, 345). Moreover, Sec22b and Vti1b have been shown to tether organelles by forming nonfusogenic *trans*-SNARE complexes (241, 254). In fact, nonfusogenic inhibitory SNAREs are exploited by various intracellular pathogens, such as *Legionella* and *Chlamydia*, which thereby reroute the membrane trafficking within the host cell to facilitate pathogen survival (236, 284). Nonfusogenic complexes are also the mechanism of SNARE regulation by amisyn, tomosyn-1, and tomosyn-2, which are soluble proteins that contain R-SNARE motifs and act as negative regulators of SNAREs (129, 277). Second, SNAREs may inhibit phagocytosis by sequestering other SNAREs to transport routes elsewhere in the cell (i.e., by forming a fusogenic complex). As described above, most SNAREs are engaged in multiple transport routes, and these could well interfere with each other. Such interfering transport is described for SNAP23 (Qbc) in adipocytes, whose exocytic function in insulin-stimulated translocation of GLUT-4 to the plasma membrane (162) competes with its intracellular function in lipid droplet formation (37), and this might contribute to the development of diabetes type 2 (288). Thus it seems a possibility that SNAREs can negatively affect phagocytosis (and other intracellular trafficking) by sequestering essential SNAREs to other transport routes within the cell. The presence of nonfusogenic SNARE complexes and postfusion *cis*-SNARE complexes could be distinguished by FRET-FLIM, as this allows resolving different SNARE conformations with simultaneous visualization of the subcellular localization of these SNARE complexes (262–264, 310, 313).

As summarized in this review, about two decades of research have led to the identification of many members of the SNARE protein family on endosomes and phagosomes **(FIGURE 6)**. For most of these SNAREs, binding factors that regulate membrane tethering, docking, and fusion have been characterized, and we now have a general mechanistic understanding of how many SNARE-mediated trafficking routes are regulated. As explained above, a key challenge for the near future will be to integrate this knowledge to answer one of the key questions in cell biology: how a relatively small family of SNARE proteins can have specific regulatory functions in so many distinct, and often cell-type-specific, trafficking functions. This question is important, given the central role of SNAREs in virtually all cellular processes, including cellular homeostasis, migration, growth, and nutrient uptake. Moreover, SNARE proteins are crucial for organism development and maintenance, as well as for immune function, because pathogens and apoptotic/necrotic cells are cleared by SNARE-dependent processes. Many intracellular pathogenic microorganisms and viruses subvert endo/phagosomal transport routes by targeting members of the SNARE protein family, and this has now been described for Stx3, Stx4, Stx6, Stx7, Stx8, Vti1a, Vti1b, VAMP3, VAMP4, and VAMP8. A better understanding of the molecular mechanisms underlying SNARE-mediated membrane trafficking in the endosomal and phagosomal pathways will aid in the development of new approaches to combat these pathogens. Interfering with such SNARE functions could well be a viable therapeutic strategy, as the *Botulinum* neurotoxins (Botox), which target the neuronal SNAREs, are now widely used in the clinic for treatment of muscle spasms.

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DISCLOSURES

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