Cell. Mol. Life Sci. (2009) 66:2677–2689
DOI 10.1007/s00018-009-0043-1

Cellular and Molecular Life Sciences

REVIEW

The Vps10p-domain receptor family

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Received: 23 March 2009 / Revised: 21 April 2009 / Accepted: 21 April 2009 / Published online: 12 May 2009

Abstract The family of mammalian type-I transmembrane receptors containing a Vps10p domain contains five members, Sortilin, SorCS1, SorCS2, SorCS3, and SorLA. The common characteristic of these receptors is an N-terminal Vps10p domain, which either represents the only module of the luminal/extracellular moiety or is combined with additional domains. Family members play roles in protein transport and signal transduction. The individual receptors bind and internalize a variety of ligands, such as neuropeptides and trophic factors, and Sortilin and SorLA mediate *trans*-Golgi network-to-endosome sorting. Their prominent neuronal expression, several of the identified ligands, and recent results support the notion that members of this receptor family have important functions in neurogenesis, plasticity-related processes, and functional maintenance of the nervous system. For instance, it has been demonstrated that Sortilin partakes in the transduction of proapoptotic effects, and there is converging biochemical and genetic evidence that implies that SorLA is an Alzheimer's disease risk factor.

Keywords Sortilin · SorLA · SorCS · Vps10p · Intracellular sorting

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Introduction

Vps10p-domain (Vps10p-D) receptors are type-I transmembrane proteins sharing as a common characteristic and hallmark an N-terminal Vps10p-D. This domain was named after the yeast-sorting protein Vps10p (Vps, for vacuolar protein sorting defective). Vps10p is a type-I transmembrane protein with a large N-terminal luminal moiety and a short cytoplasmic domain. The luminal part contains two homologous regions, each characterized by a C-terminal motif of 10 cysteine residues (10CC motif). The spacing of these cysteine residues is conserved [1].

This review focuses on the mammalian protein family of Vps10p-D receptors, which comprises the five members Sortilin, SorCS1, SorCS2, SorCS3, and SorLA [2–6]. All present a single Vps10p-D situated at the N-terminus of their luminal/extracellular moiety (Fig. 1). In Sortilin, also known as neurotensin receptor-3 [7], the Vps10p-D makes up the entire luminal/extracellular part of the receptor, but additional modules are found in the other four receptors. In SorLA, the Vps10p-D is followed by 5 low-density lipoprotein receptor (LDLR) class B repeats flanked by an EGF precursor-type repeat, a cluster of 11 LDLR class A repeats, and 6 fibronectin type-III repeats. Due to the presence of the 11 LDLR class A repeats, SorLA was also named LR11 [8]. The mutually highly homologous SorCS1, SorCS2, and SorCS3 contain a leucine-rich segment between the Vps10p-D and the transmembrane domain. Structure prediction of the leucine-rich segment suggests a beta-sandwich fold and relates the domain to the E-set superfamily [9]. Following the extracellular and transmembrane segment, each receptor carries a short (40–80 amino acids) cytoplasmic domain comprising typical motifs for interaction with cytosolic adaptor molecules.

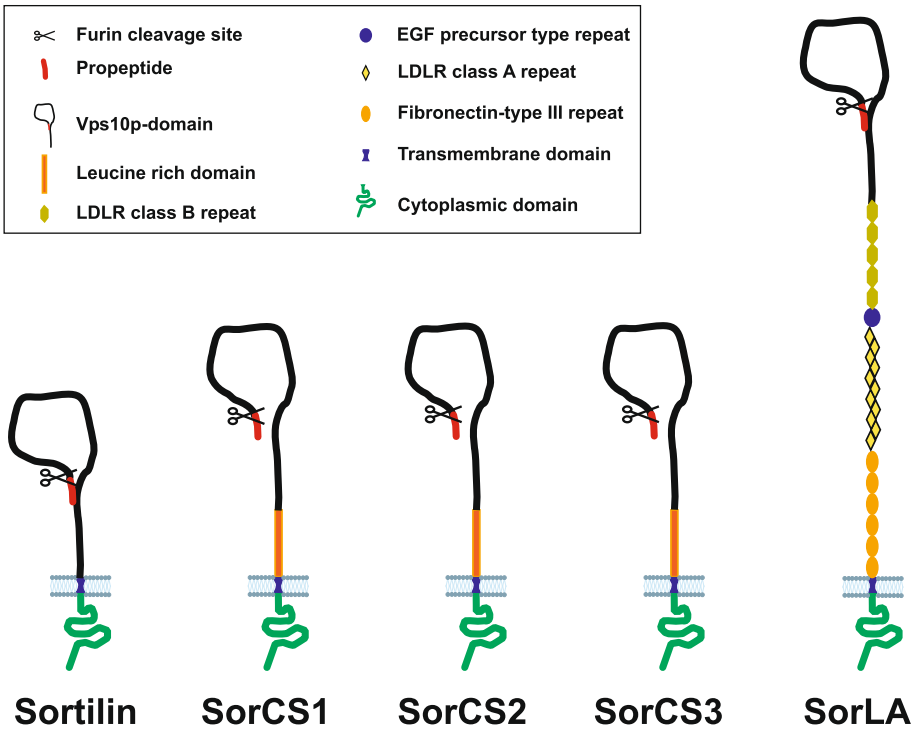

Fig. 1 Domain structure of the Vps10p-D receptors

Evolutionary history and gene organization

Receptors containing a Vps10p-D have been identified in several eukaryotes, but not all protein domain combinations are present in all phyla. The composition of two luminal Vps10p-Ds as presented in yeast is found only in fungi. A Sortilin-like domain composition with a Vps10p-D as an exclusive luminal/extracellular domain is conserved in fungi, Protozoa, Echinodermata and Vertebrata, but has so far not been identified in Protostomia. The modular organization of the SorLA luminal/extracellular part is conserved in all eumetazoans, although the number of LDLR-like or fibronectin type-III repeats is variable. Homologs are found in cnidarians, such as hydra [10], in several insects, and in deuterostomes, including echinoderms and vertebrates (Fig. 2). A SorCS-like composition of the luminal/extracellular part was identified only in vertebrates, and so far no Vps10p-D homologs have been described in plants.

Mammalian Vps10p-D receptor genes are large (up to 600 kb) and span multiple, usually small, exons [11]. Sequence similarity between the distinct mRNAs and proteins in an individual organism is very high for SorCS1 and SorCS3, e.g., 88% overall identity between the human mRNAs [12]. Whereas the other Vps10p-D receptor genes are dispersed throughout the genome, SorCS1 and SorCS3 are located adjacent to each other on one chromosome, e.g., human chromosome 10q23.3. This indicates that one gene originates from the other by gene duplication.

Within the receptor family, splice variants are known only for SorCS1. The alternative usage of composite internal/terminal and terminal exons results in different receptor isoforms with identical extracellular and transmembrane parts but different cytoplasmic domains [13–15]. Figure 3 illustrates the generation of human and murine SorCS1 isoforms. The 5′-end of exon 25 is encoding the SorCS1 transmembrane domain. All known splicing events

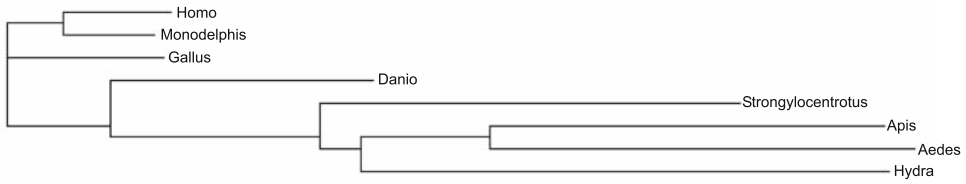

Fig. 2 A phylogenetic tree of SorLA proteins. Whole protein sequences of SorLA (accession numbers from Genbank are noted in *brackets*) from human (*Homo sapiens*) [NP_003096], gray short-tailed opossum (*Mondelphis domestica*) [XP_001370262], red jungle fowl (*Gallus gallus*) [XP_001232946], zebrafish (*Danio rerio*) [XP_696779], purple sea urchin (*Strongylocentrotus purpuratus*) [XP_001198637], honey bee (*Apis mellifera*) [XP_392519], yellow-fever mosquito (*Aedes aegypti*) [EAT42645], and freshwater polyp (*Hydra viridis*) [AF092920] were aligned. Multiple sequence alignment was performed using ClustalW [95]

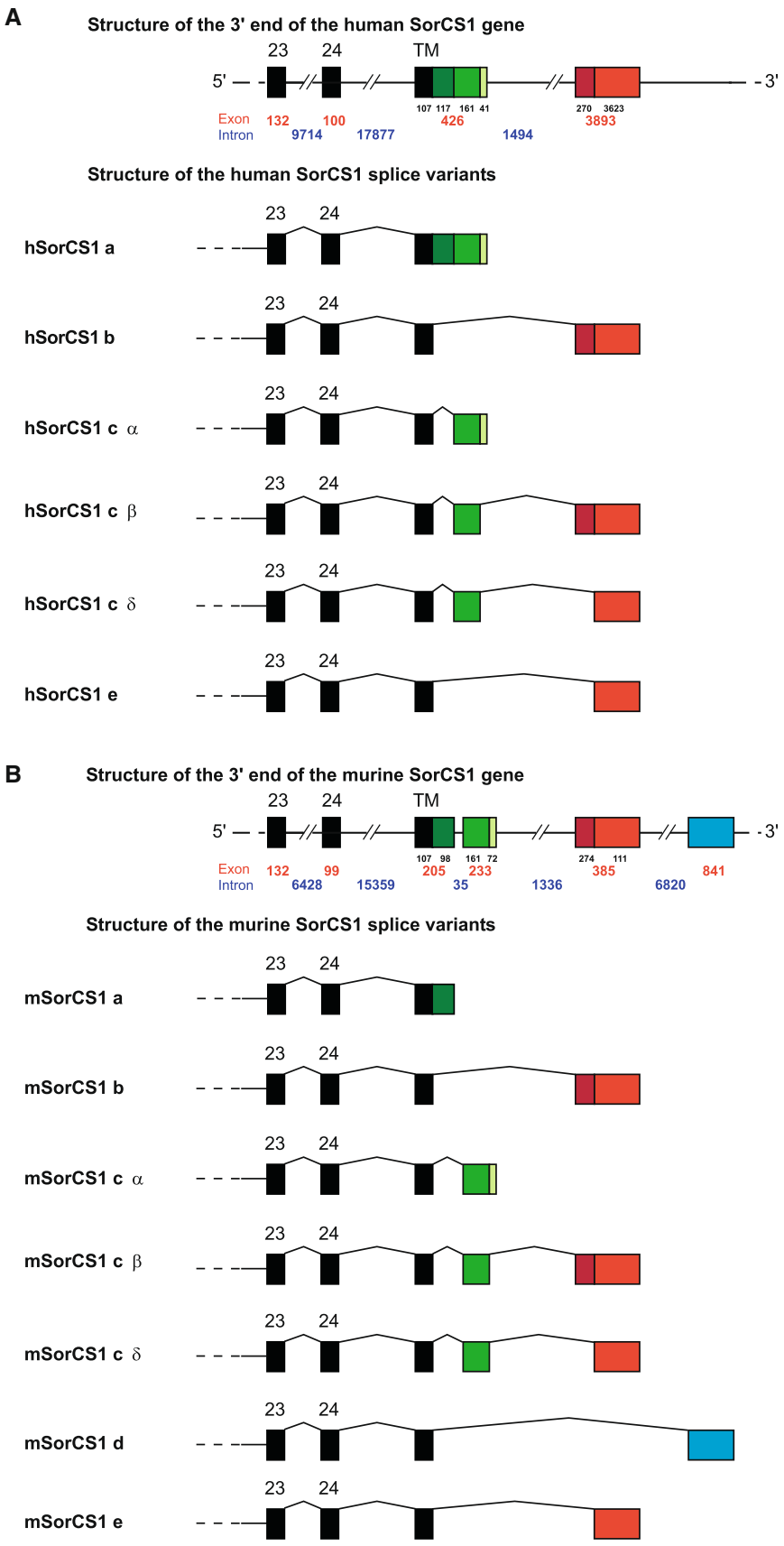

Fig. 3 Splice variants of human and murine SorCS1. The organization of the 3′ portion of the **a** human and of the **b** murine gene and of alternatively spliced transcripts is presented. Exons are shown as *boxes*, introns as *lines*. The sizes of exons and introns are indicated in base pairs. *Black boxes* represent exons 23 and 24 with typical 3′ and 5′ splice sites present in all splice variants. The part of exon 25 encoding the transmembrane domain, *TM*, is marked in *black* because it is found in all variants. Composite internal/terminal exons are shown in *green*, terminal exons are shown in *red* and *blue*

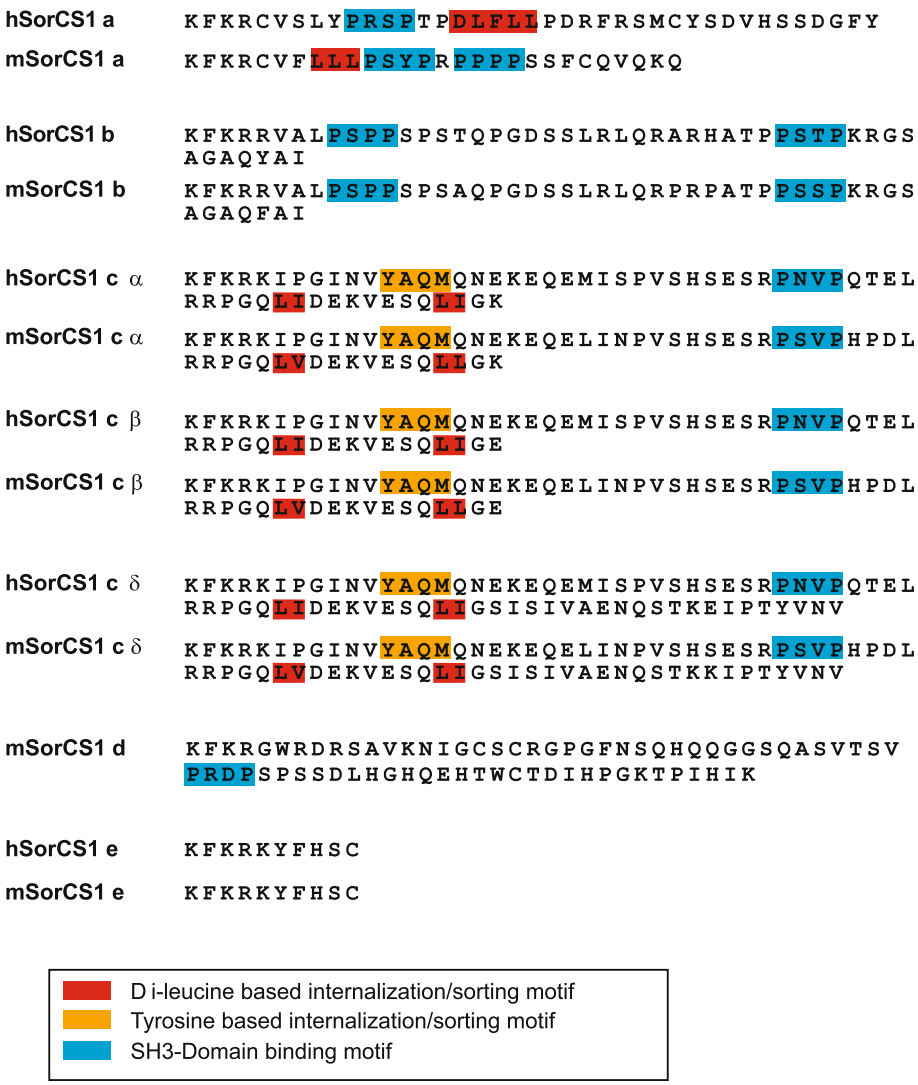

Fig. 4 Amino acid sequences of the human and murine cytoplasmic domains of SorCS1. Putative internalization and sorting signals and SH3-domain binding motifs are indicated. SorCS1c-α was initially designated hSorCS1c. Genbank accession numbers are hSorCS1a, AY099453; hSorCS1b, NM_052918; hSorCS1c-α, AY099452; hSorCS1c-*β*, EU281344; hSorCS1c-*δ*, AK123752; hSorCS1e, AK125464; mSorCS1a, AF137367; mSorCS1b, NM_021377; mSorCS1c-α, AF284755; mSorCS1c-*β*, BC007486; mSorCS1d, AK030440. mSorCS1c-*δ* and mSorCS1e were predicted from genomic sequence

are located 3′ to this part and result only in changes in the composition of the cytoplasmic domains. In humans, hSorCS1a is generated by using exon 25 as the terminal exon. When the 3′ part of exon 25 is skipped and the next exon is used as the terminal exon, hSorCS1b is generated. The 5′ part of this terminal exon is skipped in hSorCS1e. hSorCS1c-α is generated by omitting the middle part of exon 25. Leaving out the 3′-end of this transcript and adding the following exon generates hSorCS1c-*β*; skipping the 5′-end of this last exon generates hSorCS1c-*δ*. The organization of the murine genomic SorCS1 sequence is different for exon 25, which encodes only mSorCS1a-specific sequence. This sequence is not conserved and encodes a cytoplasmic domain completely different from the human protein (Fig. 4). In mouse, the part encoding the SorCS1c-specific sequence is separated by a short intron. The splicing events generating murine transcripts are identical to the events identified in humans. Murine cDNAs encoding mSorCS1a, mSorCS1b, mSorCS1c-α, and mSorCS1c-*β* were cloned [15], and mSorCS1c-*δ* and mSorCS1e were predicted from the genomic sequence. One additional exon was described in the mouse encoding a SorCS1d-specific sequence [15]. A homologous sequence has not been discovered in humans.

The alternative cytoplasmic domains differ in sequence and length and present different consensus motifs for interaction with cytosolic adaptor proteins (Fig. 4). SorCS1b, SorCS1d, and SorCS1e are unique within the Vps10p-D receptor family because their cytoplasmic domains contain no known internalization or sorting motifs. The three SorCS1c variants were grouped by designation because their cytoplasmic domains are identical in their first 58 amino acids. Although the alternative usage of composite internal/terminal exons as observed for SorCS1 appears to be complex and unique within the Vps10p-D receptor family, similar gene organization and alternative splicing have been described for other type-I transmembrane receptors [16].

Localization

Analysis of the expression of the Vps10p-D receptors was performed in mice and men. In the adult, all receptors are prominently expressed in the nervous system but are also found in other tissue and organs [2, 3, 5, 6, 8, 12, 17, 18]. During embryonic and postnatal development, all five genes are expressed in a dynamic and sometimes transient fashion [6, 12, 19–21]. Although the developmental expression of the receptors predominates in the nervous system, Sortilin is also highly expressed in the embryonic lung and SorLA is expressed in several developing glands, such as the thyroid gland, and presents strong expression in the embryonic lung and kidney. In addition to the nervous system in the adult, high expression was found for SorLA in liver, testis, and kidney, and Sortilin is highly expressed in testis and skeletal muscle. SorCS1 is expressed in adult liver, kidney, and heart, and SorCS2 expression was found in adult lung and testis. In developing and adult tissue other than the nervous system, SorCS3 presents only a low expression level. In the brain, SorCS1, SorCS2, and SorCS3 are predominantly expressed, and a complementary expression pattern is often observed. This is especially true for SorCS2 and SorCS3, whereas SorCS1 is sometimes coexpressed with one of the two other receptors. It has been demonstrated that the expression of SorCS1 and SorCS3 in the hippocampus is induced by neuronal activity. Whereas the induction of SorCS1 transcription requires protein synthesis, the induction of SorCS3 does not [12].

Characteristic structural features

The amino acid similarity among all Vps10p-Ds is only modest, but two structural features are conserved from yeast to mammals and characterize the domain: an N-terminus comprising a consensus motif for processing by proprotein convertases and a C-terminal segment containing 10 conserved cysteine residues (10CC motif).

All Vps10p-D receptors contain near the N-terminus a proprotein convertase consensus cleavage sequence (RXXR) [22] that defines the N-terminal propeptide (Fig. 1). It was demonstrated that Sortilin, SorLA, SorCS1, and SorCS3 are synthesized as precursors and converted in the *trans*-Golgi network to mature receptors by proprotein convertase-mediated cleavage and subsequent dissociation of their propeptides [7, 14, 23–25]. The Vps10p-Ds of Sortilin and SorLA need the propeptide cleavage to expose their ligand-binding region. Their propeptides bind the mature receptors with high affinity and inhibit binding of ligands, therefore propeptide cleavage conditions Sortilin and SorLA for ligand binding [23, 24]. The prevention of premature binding of ligands to the receptors was suggested as one function of the propeptides [24, 26]. In addition, the propeptides may have a chaperone-like function. It has been shown for Sortilin that its propeptide promotes the transport of the receptor through Golgi compartments but seems to be dispensable for receptor folding [26]. However, SorCS1 and SorCS3 do not bind their own propeptides and neither SorLA, SorCS1, nor SorCS3 depends on its propeptides for transport in the biosynthetic pathway [14, 25, 26], therefore it is likely that the propeptides have different functions or may be redundant in some of the Vps10p-D family members.

The C-terminal segment of the Vps10p-Ds is characterized by 10 cysteine residues. The spacing of these residues is conserved from yeast to humans (Fig. 5), and in Sortilin and SorLA, they form an identical pattern of five disulfide bridges [26]. Other cysteine residues more N-terminally located in the Vps10p-Ds are not involved in the formation of this structure, but also form disulfide bonds. The number of cysteine residues in the N-terminal half of the Vps10p-Ds is not conserved between the receptors and may determine structural differences within the N-terminal parts of the domains. Exchanging the 10CC module of Sortilin and SorLA leads to a corresponding change in affinity for receptor-specific ligands [26]. Therefore it was suggested that the 10CC module contributes to the binding of specific ligands [26].

A computational approach proposed that the N-terminal part of the Vps10p-D of Sortilin adopts a beta-propeller fold [27]. Recently, the crystal structure of the Sortilin Vps10p-D in complex with its ligand neurotensin revealed that the N-terminal part indeed has a 10-bladed beta-propeller structure and is followed by two small domains, designated 10CC-a and 10CC-b, which constitute the 10CC module. Both have a low content of secondary structure and interact extensively with the beta-propeller [28]. The C-terminal part of neurotensin binds in the tunnel of the N-terminal 10-bladed beta-propeller. Binding experiments and mutagenesis studies suggest that additional ligands, such as proNGF, target different binding sites in the tunnel. The ability of these ligands to compete with each other may rely more on steric hindrance than on identical binding sites or conformational changes of the domain [28]. The existence of different binding sites is further supported by the fact that the prodomain of the conotoxin TxVI binds to the N-terminal part of the Sortilin Vps10p-D, and this binding is not inhibited by the Sortilin propeptide [29]. Furthermore, two different binding sites were described in the second Vps10p-D of the yeast Vps10p receptor, of which one seems to be sequence-specific, while the other binds unfolded structures of misfolded proteins [30].

Additional ligand binding sites may exist outside the Vps10p-D in the composite receptors. At least SorLA has one other ligand binding site situated in the LDLR class A

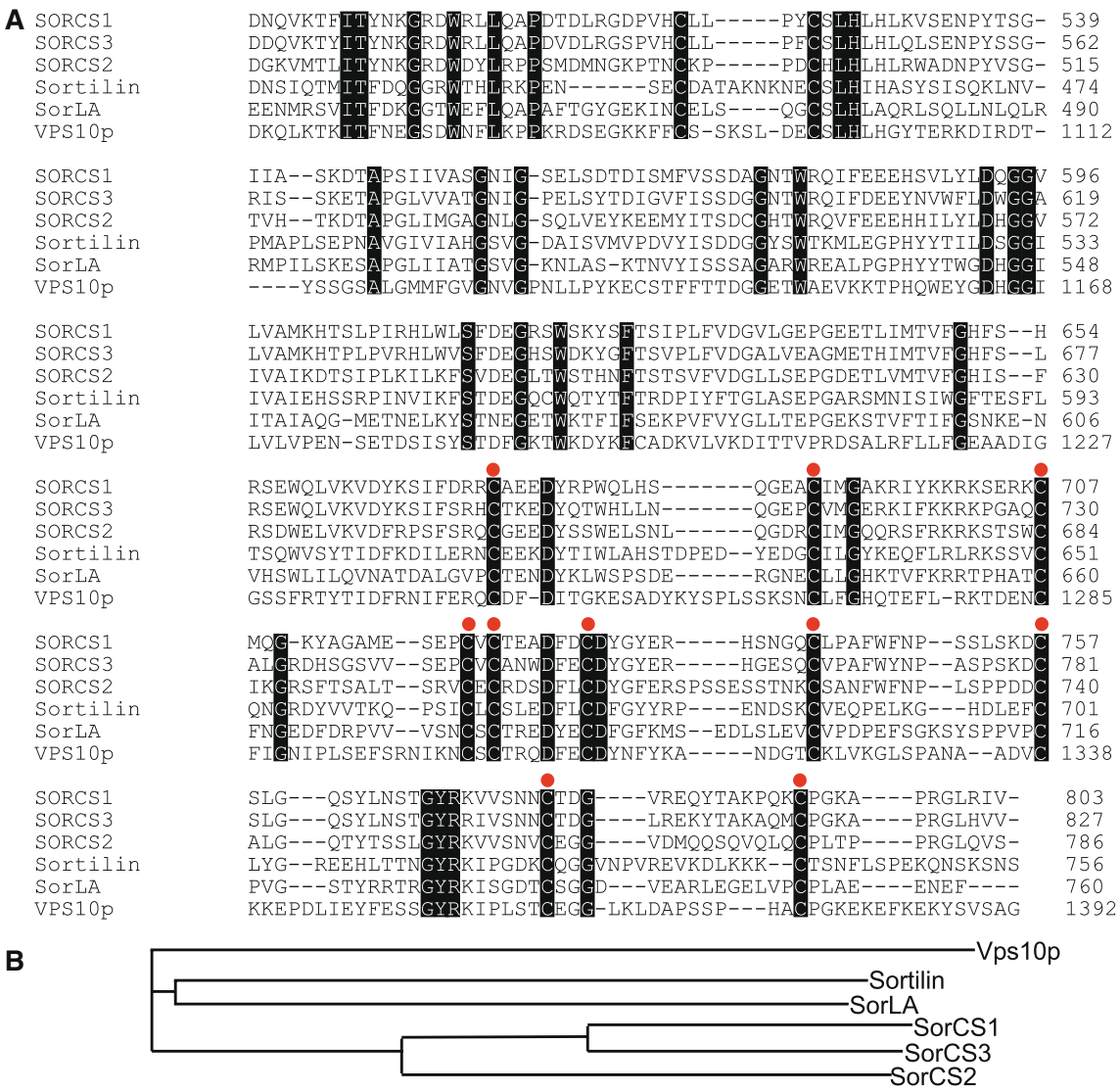

Fig. 5 Comparison of the C-terminal part of Vps10p domains. **a** Sequence alignment of the human Vps10p domains of Sortilin [NM_002959], SorLA [NP_003096], SorCS1 [NM_052918], SorCS2 [Q96PQ0], SorCS3 [NM_014978], and yeast Vps10p [EDN64600]. Multiple sequence alignment was performed using ClustalW [95]. Amino acids identical in all Vps10p-Ds are *highlighted*. *Red dots* mark the conserved cysteine residues of the 10CC motif. **b** A phylogenetic tree derived from **a**

repeats that interacts with several ligands shared with receptors of the LDLR family [23, 31]. SorLA is one of the few integral membrane glycoproteins modified with terminal, β1,4-linked GalNAc-4-SO_4 in vivo [32]. This modification may be cell type- or tissue-specific and may selectively modulate the binding of ligands to the Vps10p-D of SorLA.

Function

It is well established that in mammalian cells many newly synthesized hydrolytic enzymes are targeted to lysosomes by binding to mannose-6-phosphate receptors (MPRs). In addition, a mannose-6-phosphate-independent pathway has been suggested because in some cells from patients with I-cell disease, in which the phosphotransferase that adds the mannose-6-phosphate sorting signal is lacking, some soluble lysosomal proteins are targeted correctly [33]. The yeast vacuole is equivalent to the lysosomes of higher eukaryotes and vacuolar protein sorting in yeast, and lysosomal protein sorting in mammalian cells may share similar mechanisms, but no mannose-6-phosphate-mediated sorting has been found in yeast. The established pathway involves the yeast protein Vps10p as a sorting receptor. Vps10p binds the precursor of vacuolar hydrolases as carboxypeptidase Y in the late Golgi compartment, after which the receptor-ligand complex travels via

endosomes to prevacuolar compartments, releases its ligands, and is recycled back to the late Golgi compartment [1, 34, 35]. The identification of Vps10p-D receptors in mammals caused speculation that these receptors are also capable of mediating sorting of ligands from the *trans*-Golgi network (TGN) to late endosomes or lysosomes.

In their short cytoplasmic domains, the Vps10p-D receptors present typical consensus motifs for interaction with cytosolic adaptor proteins, internalization, and intracellular sorting. In accordance, Sortilin, SorLA, and SorCS1*a* and *c* present a prominent intracellular vesicular and perinuclear localization [5, 7, 14, 15, 23, 36–38]. Surprisingly SorCS3 predominates on the cellular surface and shows only minor intracellular expression [25]. Sortilin, SorLA, SorCS1a, SorCS1c, and SorCS3 mediate endocytosis [14, 15, 23, 37–39]. The SorCS1 splice variants that lack internalization or sorting signals are mainly localized to the cellular surface and do not convey internalization. It has been demonstrated that adaptor protein (AP)-2 complex mediates internalization of SorCS1 isoforms, and endocytosed receptors are capable of targeting cargo to lysosomes. SorCS1c is internalized through a canonical tyrosine-based motif, and internalization is very likely mediated by interaction with the $\mu 2$ subunit of the AP-2 complex. In contrast, hSorCS1a internalization depends on a DXXLL motif, and the hSorCS1a cytoplasmic domain interacts with the $\sigma 2$-αC subunits of the AP-2 complex [15]. Whereas SorCS1 isoforms and SorCS3 are not engaged in Golgi-endosomal transport, Sortilin and SorLA efficiently mediate this type of conveyance [15, 25, 37, 38].

Sortilin

Sortilin is internalized via clathrin-coated pits, and the identified internalization signals are known to facilitate binding to the AP-2 complex. Sortilin delivers internalized ligands to lysosomes and transports cargo from the TGN to endosomes, presumably mediated by Golgi-localized, γ-adaptin-ear-containing, ADP-ribosylation factor-binding proteins (GGAs) [37, 40]. Recent results demonstrate that trafficking of Sortilin is also facilitated by AP-1, and the endosome-to-TGN retrieval is mediated by the retromer complex [41–44]. The Sortilin cytoplasmic domain resembles that of MPRs, and Sortilin and MPRs colocalize in endosomes and endosome-to-TGN carrier vesicles [43]. Furthermore, Sortilin conveys lysosomal targeting of sphingolipid activator proteins (SAPs), acid sphingomyelinase, and cathepsin D and H to lysosomes [42, 45, 46]. Together, these data support a model of Sortilin being an endocytic and intracellular sorting receptor contributing to the targeting of ligands to lysosomes and the sorting between the Golgi apparatus and endosomes (Fig. 6). Therefore, the role in Golgi-endosomal trafficking is comparable to the function of MPRs.

Sortilin is expected to serve additional cell- and tissue-specific functions as it is expressed in several specialized cell types. For instance, Sortilin represents one of the major components of glucose transporter isoform 4 (Glut4)-containing vesicles of adipocytes and myocytes [47, 48]. In fat and skeletal muscle cells, Glut4 is translocated to the cell surface in response to insulin through a system of specialized vesicles. In adipocytes, Sortilin shows colocalization with Glut4. Moreover, Sortilin plays an essential role in the formation of Glut4-containing storage vesicles and may be involved in the regulation of the insulin-responsive glucose transport system [49, 50].

Initially, Sortilin was purified by LDL-receptor-associated protein (RAP) affinity chromatography [5]. The binding of RAP to the Sortilin Vps10p-D is remarkable as it appears to be the only RAP-binding receptor structurally not related to the LDL receptor family. In addition, binding and internalization of several other, unrelated ligands, such as lipoprotein lipase, apolipoprotein A–V, the unprocessed

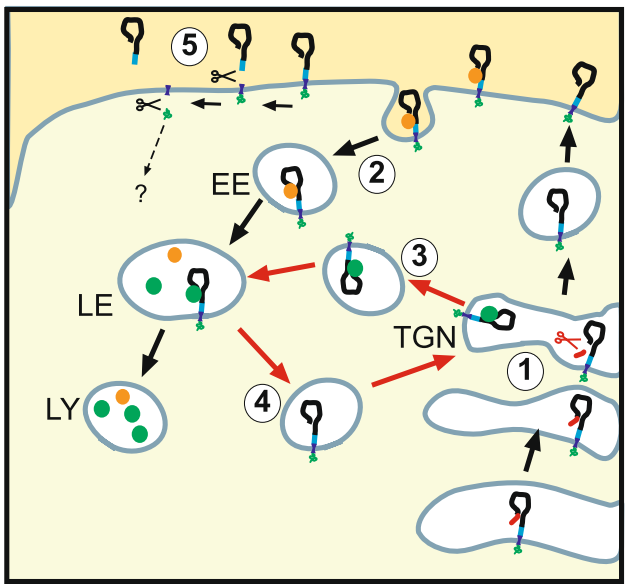

Fig. 6 Vps10p-D receptor processing and trafficking in cells. On their passage through the *trans*-Golgi network, all family members are processed by protein convertases (*1*). The N-terminal propeptides are cleaved off, and mature receptors traffic to the cellular surface via the constitutive secretory pathway and are capable of targeting internalized ligands (*orange circles*) to lysosomes (*2*). Only Sortilin and SorLA convey *trans*-Golgi network-to-endosome transport (*3*) (ligands indicated as *green circles*) and recycle to the *trans*-Golgi network (*4*) (*red arrows*). Surface-localized receptors can be subject to proteolytic cleavage (*5*). Cleavage of the ectodomain is catalyzed by the metalloprotease TACE/ADAM17, which generates a substrate for cleavage by the γ-secretase complex. This proteolytic processing mediates release of the intracellular domain. *EE* Early endosome, *LE* late endosome, *LY* lysosome, *TGN* *trans*-Golgi network

forms of the nerve growth factor (proNGF) and brain-derived nerve growth factor (proBDNF), and the neuropeptide neurotensin was demonstrated [7, 24, 39, 40, 51–53], and several findings suggest that Sortilin alone or in complex with the G-protein-coupled neurotensin receptor-1 may modulate neurotensin signalling (reviewed in [54]).

Thyroglobulin was identified as a ligand of Sortilin [55]. Thyroglobulin, the thyroid hormone precursor, is synthesized by thyroid epithelial cells (thyrocytes) and secreted into the lumen of thyroid follicles, where it undergoes hormone formation [56]. Hormone release is precisely regulated and requires uptake of thyroglobulin by thyrocytes, degradation in lysosomes, transcytosis, and recycling of the precursor. It is well established that Megalin, a member of the LDL receptor family, mediates thyroglobulin uptake and transcytosis [57]. A recent study demonstrates that Sortilin is expressed in thyrocytes in a thyroid-stimulating hormone (TSH)-dependent manner and that it interacts with thyroglobulin in postendocytic endosomes and partakes in thyroglobulin recycling [55]. Recycling of internalized ligands may be a general function of Sortilin in addition to internalization and Golgi-to-endosome sorting.

Sortilin binds the pro-neurotrophins proNGF and proBDNF in concert with the neurotrophin receptor $p75^{NTR}$ [51, 52]. The neurotrophins NGF and BDNF promote neuronal survival and growth, but by contrast the unprocessed forms induce cell death. Pro-neurotrophins are released by neurons and glia, particularly when cell death prevails, for instance, in the developing hypothyroid cerebral cortex, the prodromal and end-stages of Alzheimer's disease, or following brain trauma or seizure [58–63]. They form a death receptor complex in which Sortilin specifically binds the pro-domain of pro-neurotrophins with high affinity, whereas $p75^{NTR}$ simultaneously interacts with the mature domain. The formation of this ternary complex is crucial for the pro-apoptotic function, as Sortilin antagonists rescue cultured super cervical ganglion (SCG) neurons from proNGF- and proBDNF-induced cell death [51, 52]. Sortilin-deficient mice ($Sortilin^{-/-}$ mice) are born viable and show no gross abnormalities [60]. Neurons from $Sortilin^{-/-}$ mice are resistant to pro-neurotrophin-induced apoptosis. In the developing retina, these mice show reduced neuronal apoptosis indistinguishable from $p75^{NTR}$-deficient mice. Although Sortilin deficiency does not affect developmentally regulated apoptosis of sympathetic neurons, it prevents their age-dependent degeneration. Furthermore lesioned motor neurons from $Sortilin^{-/-}$ mice are protected from cell death [60]. In agreement, the release of recombinant Sortilin ectodomain at injury sites reduces death of axotomized sensory neurons to the same degree as neutralizing antibodies against the BDNF prodomain [64]. Thus, the formation of the ternary complex consisting of pro-neurotrophin, Sortilin, and $p75^{NTR}$ triggers apoptotic signalling under pathological conditions, as well as in specific stages of neuronal development and aging. In conclusion, Sortilin serves not only as a general intracellular sorting receptor, it also mediates specialized functions, for instance as a co-receptor determining a specific signalling pathway.

SorLA

SorLA is also an endocytic receptor and engaged in Golgi-endosomal trafficking. SorLA is internalized in an AP-2-dependent fashion and has been shown to facilitate internalization of several unrelated ligands [23, 31, 38, 53, 65]. Endocytosed receptors do not return to the plasma membrane, but mediate intracellular sorting events as Golgi-endosomal transport. Internalization depends on an acidic cluster presented in the cytoplasmic domain. Intracellular sorting depends, on one hand, on the acidic cluster combined with a di-leucine motif, and on the other hand, on the GGA-binding motif DXXM [38]. Interaction of SorLA with GGAs is well established [66]. In addition, the SorLA cytoplasmic domain interacts with AP-1, and the absence of the AP-1 complex results in an altered subcellular localization as compared with wild-type cells [38]. Acidic clusters are targets for interaction with the AP-1 complex, but also serve as binding sites for the adaptor protein PACS-1, which has been shown to mediate endocytosis and retrograde sorting [67]. Although an interaction of SorLA and PACS-1 has been demonstrated by immunoprecipitation [68] and pull-down experiments [38], cellular experiments demonstrated that internalization of SorLA was not effected by the reduction of PACS-1 levels, and PACS-1 knock down had no effect on SorLA-dependent sorting [38]. This indicates that PACS-1 plays a redundant or minor role in sorting of SorLA. Furthermore, two recent reports suggest that the retromer complex mediates the transport of SorLA from endosomes to the Golgi [38, 69]. Thus, identical cytosolic adaptor proteins facilitate the intracellular trafficking of SorLA and Sortilin, and although some functions may be shared, each receptor is expected to play unique physiological roles.

Trafficking of SorLA in neurons has been proposed to be of potential relevance to some forms of Alzheimer's disease because SorLA interacts with the amyloid precursor protein (APP) and affects its intracellular transport and processing [70–72]. Alzheimer's disease is a progressive neurodegenerative disorder characterized by amyloid plaques composed of the amyloid β peptide (Aβ). Aβ is derived from APP by sequential proteolytic cleavage [73]. Cleavage by β-secretase releases a large N-terminal APP ectodomain fragment (sAPPβ), and subsequent action of

γ-secretase on the remaining membrane-bound portion of APP produces Aβ. Alternatively, APP can be processed by α-secretase, which releases sAPPα and cleaves within the Aβ sequence, thus precluding Aβ formation by γ-secretase processing. APP follows a complex trafficking pathway through secretory and endocytic compartments that determines processing into amyloidogenic (Aβ) and non-amyloidogenic fragments. SorLA colocalizes with APP, and their interaction involves luminal and cytoplasmic domains of both proteins [74, 75]. Binding of APP to SorLA results in sequestration of APP in intracellular compartments and in reduced processing into Aβ [70]. In addition, SorLA directly interacts with the β-site APP-cleaving enzyme (BACE) and reduces BACE-APP interaction [75]. The significance of SorLA as a negative regulator of APP processing in vivo was supported by studying SorLA-deficient mice. These exhibit higher Aβ levels in the brain as compared with wild-type mice [70]. Furthermore, neuronal SorLA expression is reduced in patients with late-onset Alzheimer's disease (LOAD) but not in patients with early-onset familial Alzheimer's disease [76, 77], and recent studies show that SorLA is genetically associated with LOAD [69, 78]. In conclusion, there is converging biochemical and genetic evidence that implicates SorLA as a LOAD risk factor. As mentioned above, SorLA shares structural features with members of the LDL receptor family, and other receptors of this family have also been linked to Alzheimer's disease [79]. In addition to the structural features, SorLA shares several ligands with the LDL receptor family, such as apolipoprotein E (ApoE) [65], an established genetic risk factor for LOAD. However, a correlation among SorLA, ApoE, and Alzheimer's disease remains elusive. Other ligands of SorLA that interact with LDL receptors are apolipoprotein A–V, RAP, lipoprotein lipase, platelet-derived growth factor-BB (PDGF-BB), and components of the plasminogen-activating system, including urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) [23, 31, 80, 81]. These classical ligands of the LDL receptor family bind to the LDLR class A repeats of SorLA [23, 31]. The SorLA Vps10p-D binds RAP with a much lower affinity than the LDLR class A repeats and with a much lower affinity than the Sortilin Vps10p-D. The SorLA propeptide, neurotensin, and glial cell-derived neurotrophic factor (GDNF) bind specifically to the SorLA Vps10p-D [23, 26].

SorLA is subject to tumor necrosis factor alpha-converting enzyme (TACE)-mediated ectodomain shedding [82, 83]. In general, ectodomain shedding causes down-modulation of the full-length receptor and generation of a soluble ectodomain fragment. The function of soluble receptors, for instance as carrier proteins, is virtually undescribed. However, both the membrane-spanning and the soluble forms of SorLA bind to and co-localize with urokinase-type plasminogen activator receptor (uPAR) on the cell surface. This stabilizes the receptor-protease complex by inhibiting or delaying its degradation through other LDL receptors, such as LRP1 [31, 80]. These findings relate SorLA expression to the development of atherosclerosis. The migration of smooth muscle cells (SMCs) is one of the key events in the pathogenesis of atherosclerosis. It was demonstrated that SorLA is abundantly and specifically expressed in intimal SMCs during intimal thickening in different experimental models of atherogenesis and that SorLA expression is elevated in early stages of neointimal formation. Furthermore, treatment with PDGF-BB increases SorLA expression in SMCs, and overexpression of SorLA in SMCs enhances their migration. This is very likely due to increased cell-surface uPAR levels [80, 84, 85].

Ectodomain shedding has been observed for all five mammalian Vps10p-D receptors, although with different efficiencies [82, 83, 86, 87]. This cleavage event is carried out by TACE/ADAM17, a protease of the disintegrin and metalloprotease (ADAM) family, whose active site is located in the aqueous environment of the extracellular/luminal domain. The extracellular juxtamembrane cleavage can be stimulated by phorbol esters or by some ligands, e.g., PDGF-BB stimulates shedding of SorCS1, SorCS3, and SorLA, whereas other ligands have no effect [83]. The primary cleavage elicits subsequent γ-secretase-mediated proteolysis within the transmembrane segment. This cleavage releases the cytoplasmic domain, which is rapidly degraded [82, 83]. However, a nuclear localization of the SorLA cytoplasmic domain fused to green fluorescent protein was demonstrated and a transcriptional activity of the SorLA cytoplasmic domain suggested [82]. Further studies are necessary to resolve the role of the shed ectodomains and the released cytoplasmic domains and to confirm that shedding and subsequent intramembrane cleavage have other functions than receptor degradation.

SorCS

Information on the SorCS subgroup of Vps10p-D receptors is limited, and their functional properties remain elusive. Until now, SorCS2 function has been virtually not analyzed on a cellular or biochemical level; only a small number of ligands of SorCS1 and SorCS3 have been identified, and the functional relevance of these interactions is unclear. SorCS3 binds NGF as well as the NGF pro-domain. Whereas NGF binds equally well to Sortilin, the NGF pro-domain binds Sortilin with a much higher affinity [25]. It is undescribed whether SorCS3 can engage in a complex with $p75^{NTR}$, and the role of SorCS3 may be different from that

of Sortilin. Nevertheless, the binding of NGF to SorCS3 suggests neuronal functions. This is in agreement with the predominant neuronal expression of SorCS3 and the fact that SorCS3 expression in the hippocampus can be induced by neuronal activity [12]. In addition to SorCS3, SorCS1 expression is induced after kainic acid-provoked seizures. Therefore, both receptors may be involved in plasticity-related processes in the brain. It was demonstrated that SorCS1 and SorCS3 bind PDGF-BB with high affinity [83]. However, a prominent role of PDGF-BB in neuronal plasticity-related processes has not been established, but the receptors may bind other ligands that serve important functions in these processes.

Several reports relate SorCS1 to genetically complex disorders, such as type 2 diabetes and Alzheimer's disease. SorCS1 was identified as a type 2 diabetes quantitative trait locus in mice [88], and variations in the human gene are associated with diabetes-related traits [89]. This is further corroborated by the identification of a type 2 diabetes susceptibility locus containing the SorCS1 gene in congenic rat strains [90]. As SorCS1 binds PDGF-BB, which is crucial for pericyte recruitment to vascular endothelial cells, where they stabilize microvasculature, it was speculated that genetic changes in the SorCS1 gene promote β-cell failure and decreased insulin secretion by affecting the islet capillary network [88].

A potential association between SorCS1 and Alzheimer's disease has been assessed in different genetic studies and meta-analyses [69, 91–94]. A significant association was observed in some of these studies, and genetic variations in the SorCS1 gene may indeed alter the risk for Alzheimer's disease. However, we are far from drawing a mechanistic model involving SorCS1 function and the induction of neuronal disease processes. Therefore, more genetic and biochemical data will be needed to evaluate the relevance of this potential genetic association.

Perspectives

The ability to convey uptake and intracellular sorting has been studied for the Vps10p-D receptors, although several questions remain open in this context, the elucidation of downstream signaling pathways that these receptors may regulate will be the next challenging task. Sortilin mediates a pro-apoptotic signal in concert with $p75^{NTR}$, but signal-transduction pathways regulated by Sortilin are unknown. The mechanism of signal transduction may involve the translocation of the cytoplasmic domain. Shedding and γ-secretase-mediated cleavage of Vps10p-D receptors have been demonstrated, and it is conceivable that the intracellular domains act as regulatory components of transcriptional complexes.

The structure of the Sortilin Vps10p-D, the hallmark of this receptor family, has been characterized, but not the Vps10p-Ds of the other family members. Sortilin and SorLA share several ligands, but other ligands interact exclusively with one of the two receptors. In addition, most ligands of Sortilin and SorLA do not interact with the SorCS receptors. Crystal structures of all Vps10p-Ds will be important to define the structural determinants of the different interactions and to understand the function of the Vps10p-D receptors on a mechanistic level. Furthermore all receptors of this family may be multifunctional and bind several unrelated ligands. The identification of additional ligands of the SorCS receptors promises a better understanding of their functional roles. Moreover, the SorCS2 protein awaits a biochemical and cellular characterization.

Finally, the overall physiological roles of the receptors remain to be determined. This challenge requires the generation and analysis of mice or other model organisms deficient in one of the receptors. Several lines of evidence relate mutations in Vps10p-D receptor genes to genetically complex human diseases. Additional genetic studies, combined with the analysis of animal models and a greater knowledge of the molecular functions of Vps10p-D receptors will lead to a better understanding of their physiological roles and elucidate their implications in human diseases.

Acknowledgements I am grateful to Sady Keat for discussions and Claudia Mahlke, Jakob Gutzmann, and Nils Blüthgen for their helpful comments on the manuscript.

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