
Sortilins in Neurotrophic Factor Signaling

S. Glerup, A. Nykjaer, and C.B. Vaegter

Abstract

The sortilin family of Vps10p-domain receptors includes sortilin, SorLA, and SorCS1–3. These type-I transmembrane receptors predominate in distinct neuronal tissues, but expression is also present in certain specialized non-neuronal cell populations including hepatocytes and cells of the immune system. The biology of sortilins is complex as they participate in both cell signaling and in intracellular protein sorting. Sortilins function physiologically in signaling by pro- and mature neurotrophins in neuronal viability and functionality. Recent genome-wide association studies have linked members to neurological disorders such as Alzheimer's disease and bipolar disorder and outside the nervous system to development of coronary artery disease and type-2 diabetes. Particularly well described are the receptor functions in neuronal signaling by pro- (proNT) and mature (NT) neurotrophins and in the processing/metabolism of amyloid precursor protein (APP).

Keywords

Vps10p-domain receptors • Proneurotrophins • p75NTR • SorCS1 • SorCS2 • SorCS3 • Alzheimer's disease • Bipolar disorder • Cell death • Amyloid precursor protein • Protein sorting • Apoptosis

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1 The Vps10p Domain Receptor Family: Sortilins

Sortilins, also denoted Vps10p domain receptors, are emerging as critical regulators of neuronal survival and function (Fig. 1). They partake in a multitude of functions from anterograde and retrograde protein sorting to signal transduction induced by neurotrophic factors (Willnow et al. 2008). The mammalian sortilin family includes sortilin, SorLA, and SorCS1–3 and appears to have evolved with increasing demand for cellular complexity. The unifying structural Vps10p domain, short for vacuolar protein sorting 10 protein, was first identified in the yeast (Marcusson et al. 1994). Vps10p is a type I receptor with two copies of the domain in its extracellular part that participates in a mannose-6-phosphate receptor-independent pathway for sorting of proteins targeted for the yeast vacuole. Human sortilin and SorLA were first isolated from brain homogenates by receptor-associated protein (RAP) affinity chromatography in an attempt to discover novel low density lipoprotein receptor-related proteins (Jacobsen et al. 1996; Petersen et al. 1997). Sortilin is the prototype family member as its entire extracellular domain consists of a single copy of the ~700 amino acids Vps10p domain followed by a transmembrane domain and a short cytoplasmic tail. In contrast, SorLA is a mosaic receptor with a large extracellular part. In SorLA, the Vps10p domain is followed by an EGF precursor-type repeat, a cluster of 11 complement repeats, and six fibronectin type-III repeats (Fig. 1). Interestingly, SorLA appears to have originated in the first organism with a nervous system, the hydra, where it acts as a receptor for the neuropeptide head activator (Hampe et al. 2000).

The homologues SorCS1, SorCS2, and SorCS3 were identified by database mining (Hampe et al. 2000; Hermey 2009; Rezgaoui et al. 2001), and contain in their extracellular domains in addition to the Vps10p domain, a polycystic kidney disease (PKD) module, and a juxtamembrane leucine-rich region (Fig. 1). The global sequence identity between SorCS1 and SorCS3 proteins is 70 %, whereas their identity with SorCS2 is much lower ranging from 45 to 47 % with highest conservation found in the Vps10p domain and lowest identity in their propeptides and cytoplasmic tails.

The composition of the yeast Vps10p with two luminal copies of the domain is only found in fungi whereas a sortilin-like composition is conserved in protozoans, echinoderms, and vertebrates. Highly conserved orthologues of all the mammalian family members are found in birds and fish, but no Vps10p orthologues have been identified in species such as flies, nematodes, and plants (Hermey 2009).

In mammals, sortilins prevail in most regions of the developing and adult nervous system. However, receptors are also expressed in a dynamic manner in a number of non-neuronal cell types. Sortilin and SorLA, for example, are abundant in tissues such as embryonic lung, kidney, liver, and several developing glands. In the adult organism expression persists in most tissues and now also appears in cells of the immune system (Hermans-Borgmeyer et al. 1999; Sarret et al. 2003; Fauchais et al. 2008; Wahe et al. 2010; Kjolby et al. 2010). While expression of sortilin and SorLA mostly overlap, SorCS1, -2, and -3 show a much more restricted and complementary pattern of expression. For instance, SorCS1 and SorCS3 are highly expressed in CA1 of the hippocampus, whereas SorCS2 displays the highest

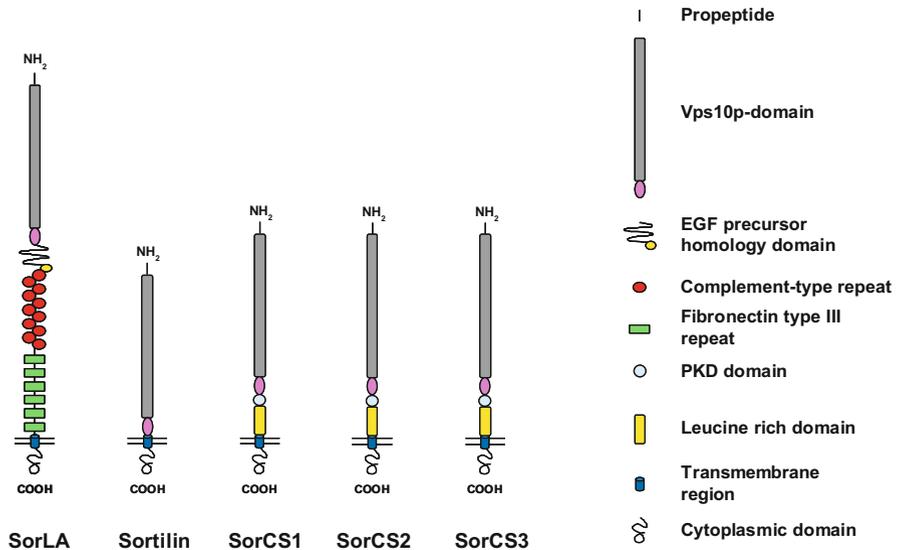


Fig. 1 The Vps10p domain receptor family. Sortilin represents the prototype family member containing an N-terminal propeptide followed by the Vps10p domain that constitutes the entire extracellular part of the mature receptor. The receptor also contains a transmembrane region and a short cytoplasmic domain containing several functional sorting motifs. The propeptide is cleaved off by furin during processing of the receptor in the Golgi. In the extracellular part of SorLA, the Vps10p domain is followed by an EGF precursor homology domain, a series of complement repeats originally known from the low-density lipoprotein receptor and a series of fibronectin type III repeats. SorCS1-3 are global homologues and contain in addition to the Vps10p domain, a polycystic kidney disease (PKD) domain and a leucine-rich domain

expression in the CA2 and dentate gyrus. Of note, the hippocampal expression of SorCS1 and SorCS3 is dynamically regulated as both can be induced by neuronal activity, suggesting their potential participation in activity-dependent synaptic modifications (Hermey et al. 2004).

2 The Vps10p Domain Structure

Sortilins bind a wide variety of ligands through the Vps10p domain, ranging from transmembrane receptors to soluble proteins involved in processes as diverse as lipid metabolism and signaling by neurotrophic factors. Mammalian sortilin and yeast Vps10p show low amino acid sequence identity, yet they are both predicted to adopt a beta-propeller fold. The crystal structure of sortilin in complex with the small neuropeptide ligand neurotensin (Table 1) was recently solved and revealed a completely novel fold (Quistgaard et al. 2009) (Fig. 2). The domain forms an unusually large ten-bladed beta-propeller structure creating a large tunnel with multiple ligand-binding sites formed by loops protruding from the beta-strand ends into the tunnel cavity. The beta-propeller is followed C-terminally by a

Table 1 Known binding partners of sortilins

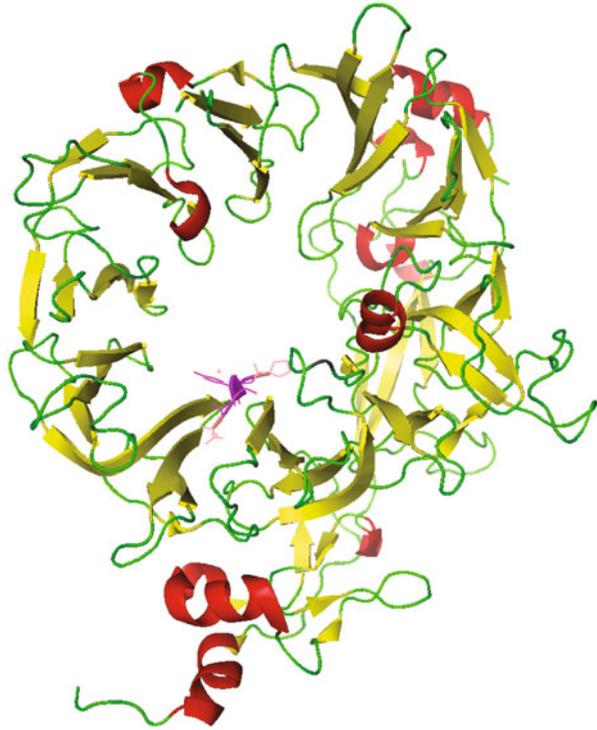
Ligands	Sortilin	SorLA	SorCS1	SorCS2	SorCS3	Function
APP		+				Golgi retention (Andersen et al. 2005)
ApoB100	+					VLDL particle assembly (Kjolby et al. 2010)
CLC/CLF-1	+					Signaling (Larsen et al. 2010)
CNTF	+					Signaling (Larsen et al. 2010)
LPL	+	+				Lysosomal sorting (Nielsen et al. 1999)
Neurotensin	+	+				Unknown (Mazella et al. 1998)
P75 ^{NTR}	+					Apoptosis (Nykjaer et al. 2004)
PDGF β		+	+		+	Unknown (Hermey et al. 2006)
ProBDNF	+					Apoptosis (Teng et al. 2005)
Progranulin	+					Lysosomal sorting (Hu et al. 2010)
ProNGF	+				+	Apoptosis (Nykjaer et al. 2004)
ProNT3	+					Apoptosis (Yano et al. 2009; Tauris et al. 2011)
Prosaposin	+					Lysosomal sorting (Lefrancois et al. 2003)
RAP	+	+				Unknown (Petersen et al. 1997; Jacobsen et al. 1996)
SorLA propeptide	+	+				Inhibition of premature ligand binding (Jacobsen et al. 2001)
Sortilin propeptide	+	+				Inhibition of premature ligand binding (Munck Petersen et al. 1999)
TGF β	+					Lysosomal sorting (Kwon and Christian 2011)
Thyroglobulin	+					Recycling (Botta et al. 2009)
TrkA, -B, -C	+					Sorting (Vaegter et al. 2011)

APP amyloid precursor protein, *CLC/CLF-1* cardiotrophin-like cytokine/receptor cytokine-like factor-1, *CNTF* ciliary neurotrophic factor, *LPL* lipoprotein lipase, *PDGF β* platelet-derived growth factor- β , *proBDNF* pro-brain-derived neurotrophic factor, *proNGF* pro-nerve growth factor, *proNT3* pro-neurotrophin-3, *RAP* receptor-associated protein, *Trk* tropomyosin-related kinase

small domain designated 10CC. This domain has no secondary structure but comprises ten cysteine residues forming five disulfide bonds. 10CC interacts extensively with one side of the propeller and is believed to stabilize the tunnel while restricting the access of ligands to this side of the tunnel.

Neurotensin inhibits the binding of most sortilin ligands in a competitive manner, and the co-crystal structure showed that the neurotensin binding site resides inside the tunnel cavity. This suggests that different binding sites for soluble ligands are formed within the tunnel likely by differential combinations of the protruding loops. Most Vps10p domain ligands compete with each other for binding, but this ability most likely relies on steric hindrance rather than on identical binding sites. The ten blades of the Vps10p domain propeller results in a fourfold increase in the tunnel

Fig. 2 Crystal structure of the sortilin Vps10p domain in complex with neurotensin. The structure is visualized using PyMOL



volume as compared to, for example, the eight-bladed propeller peptidase IV. Thus, unlike smaller beta propellers, the sortilin tunnel can accommodate large protein ligands and provide specific binding sites for an extended set of ligands. Also, confining binding sites to the tunnel, rather than being scattered on an exposed outer surface, ensures that sortilin accommodates only one ligand at a time.

Another interesting structural feature of the Vps10p domain is two protruding hydrophobic loops (Quistgaard et al. 2009). These loops have been proposed to interact directly with the cell membrane or with transmembrane receptor partners such as the p75 neurotrophin receptor (p75NTR) or the tropomyosin-related kinase (Trk) family of receptors (see below). Apart from the sortilin Vps10p domain, the solution structures of the second SorLA fibronectin type III domain (PDB code: 2DM4) in addition to SorCS2 PKD (PDB code: 1WGO) have been solved by NMR. The PKD structure related it to the immunoglobulin superfamily.

3 Ligands of Sortilins

A number of both soluble and transmembrane ligands binding to the extracellular domains of sortilin family members have been described, and those shown to bind in a direct manner are listed in Table 1. Sortilin has the highest number of ligands

followed by SorLA with many overlaps. Only two ligands have been identified for SorCS1 and -3, whereas SorCS2 is so far an orphan receptor. The majority of sortilin ligands are related to lipid metabolism such as lipoprotein lipase (LPL) (Nielsen et al. 1999) and ApoB100 (Kjolby et al. 2010), or to neurotrophic factor signaling, notably, the neurotrophin system and their receptors (Nykjaer et al. 2004; Teng et al. 2005; Yano et al. 2009; Tauris et al. 2011; Vaegter et al. 2011) in addition to a subset of helical type I cytokines (Larsen et al. 2010). SorLA is unique in binding amyloid precursor protein (APP), and this interaction is considered important to avoid pathological amyloid plaque formation (Andersen et al. 2005) (see below).

4 Processing Conditions Sortilin and SorLA for Ligand Binding

An additional unifying feature of Vps10p domain receptors throughout species is an N-terminal propeptide containing an RXXR motif that defines the consensus cleavage site for furin and other proprotein convertases. Sortilin, SorLA, and SorCS1–3 are all synthesized as proproteins, and their ~50 amino acids propeptides are removed late in the trans-Golgi network (TGN), possibly following internalization and recycling of the newly synthesized receptor, as processing of mutated sortilin lacking the cytoplasmic tail is slowed dramatically (Munck Petersen et al. 1999; Nielsen et al. 2001). Furin cleavage results in dissociation of propeptide from the mature receptor and in the case of sortilin and SorLA, this conditions the receptors for ligand binding (Munck Petersen et al. 1999; Jacobsen et al. 2001). Accordingly, mutation of the furin cleavage sites results in receptor variants that are unable to bind Vps10p domain ligands (Munck Petersen et al. 1999; Jacobsen et al. 2001). Also, recombinant soluble propeptides are potent antagonists of sortilin and SorLA ligand binding, e.g., proneurotrophin binding by sortilin (Munck Petersen et al. 1999; Jacobsen et al. 2001; Nykjaer et al. 2004; Teng et al. 2005; Tauris et al. 2011). Neurotensin also completely inhibits this binding, implicating that the tunnel cavity is critically involved in the interaction with proneurotrophins (Nykjaer et al. 2004; Quistgaard et al. 2009). The above has important functional implications as it indicates that prosortilin cannot interact with Vps10p domain ligands prior to propeptide processing, whereas the SorCS3 propeptide appears to have no effect on its ability to bind pro-nerve growth factor (proNGF) (Westergaard et al. 2005). In the case of sortilin, SorLA, SorCS1, and SorCS3, it has been further demonstrated that the propeptide acts as a chaperone in the endoplasmic reticulum (ER) required for efficient folding of the newly synthesized receptors (Munck Petersen et al. 1999; Jacobsen et al. 2001; Westergaard et al. 2005; Hermey et al. 2003).

5 Cellular Trafficking of Sortilins

Sortilin and SorLA are mainly found intracellularly in perinuclear vesicles and in the TGN with less than 10 % of the receptor pool present on the cell surface (Petersen et al. 1997; Jacobsen et al. 1996; Nielsen et al. 2001). In neurons, sortilin and SorLA also show a vesicle-like staining in the soma, but receptors can also be found in axons and dendrites and at the nerve terminals (Sarret et al. 2003; Hermey et al. 2001). In contrast, SorCS3 is predominantly surface exposed (Westergaard et al. 2005). Notably, SorCS1 is unique among the sortilins as it exists in several distinct splice variants, denoted SorCS1-a, -b, and -c, that encode cytoplasmic domains differing in length and sequence. While the SorCS1-a variant is almost exclusively intracellular, the -b and -c isoforms mainly localize to the cell surface (Hermey et al. 2003; Nielsen et al. 2008).

As mentioned above, sortilins are matured in the TGN (Munck Petersen et al. 1999). This organelle is a sorting station important for distributing proteins between various cellular compartments. From here, proteins are directed to the constitutive or regulated secretory pathway, and to endosomes or lysosomes. Neuronal TGN is also involved in axonal transport and in the formation of signaling endosomes (Bonifacino and Rojas 2006). Trafficking between the TGN and the different cellular compartments is assisted by specific adaptor proteins that directly or indirectly connect the cytoplasmic tail of sortilins to the clathrin coat of transport vesicles, to lipid membranes, or to the cytoskeleton (Nielsen et al. 2001, 2008) (Fig. 3).

At the cell surface sortilin and SorLA are rapidly internalized into endosomes through clathrin coated pits. For SorLA, this is mediated by adaptor protein 2 (AP-2) by binding to an acidic cluster dileucine-like site in the cytoplasmic tail (Nielsen et al. 2007). In the case of sortilin, internalization is mediated by a tyrosine-based internalization motif (Nielsen et al. 2001). SorCS1-c, SorCS2, and SorCS3 also contain tyrosine-based internalization motifs, but their activity and adaptor proteins remain to be determined. Internalized receptors exit endosomes and are returned to the TGN through retrograde sorting pathways, thus escaping lysosomal degradation (Nielsen et al. 2001, 2007). Four distinct complexes of cargo adaptor proteins have been implicated in this transport pathway including the AP-1 complex that links cargo to the clathrin coat of endosomal and TGN vesicles, the clathrin adaptors Golgi-localizing, γ -adaptin ear homology domain, ARF-interacting proteins (GGA-1, -2, -3), the retromer complex, and the phosphofurin acidic cluster sorting protein (PACS1). The existing data suggest a model in which AP-1 and the GGAs transport sortilin and SorLA from the Golgi to endosomes whereas the retromer and possibly AP-1 mediate their return from the tubular endosomal network of early endosomes to the TGN (Nielsen et al. 2001, 2007). In the case of SorLA, PACS1 also appears to be implicated in TGN transport (Schmidt et al. 2007). At present, no data are available for SorCS1–3.

At the cell surface, sortilins are subject to events other than endocytosis as they can also be cleaved by ADAM10 or -17 and released from the cell surface (Hermey et al. 2006). Whether the soluble receptor product, which is capable of ligand

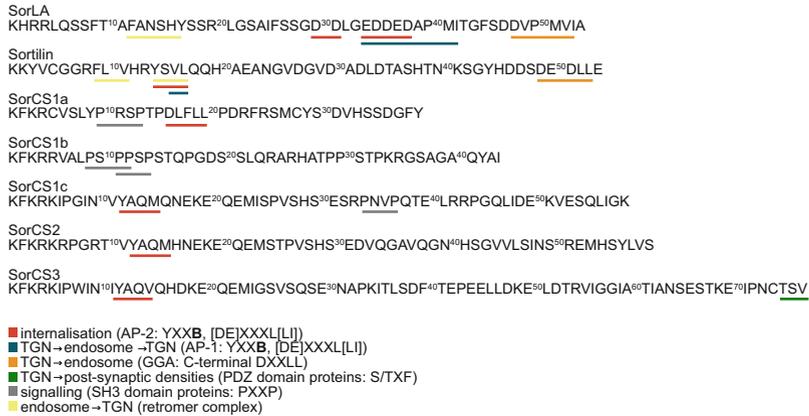


Fig. 3 Cytosolic adaptor sites in sortilins. Both putative and experimentally confirmed sites are indicated together with the type of trafficking they conduct. The responsible adaptor proteins and their consensus recognition motifs are listed in parenthesis (Nielsen et al. 2001, 2007, 2008; Schmidt et al. 2007; Hermey et al. 2003)

binding, serves as a decoy receptor is currently unclear. However, the remaining transmembrane fragment can undergo regulated intramembrane proteolysis (RIP) by the gamma-secretase complex. The fate of the resulting intracellular fragment is unclear, but in the case of the SorLA cytoplasmic tail, it is targeted to the nucleus where it possibly can induce gene expression as proposed by use of a reporter gene assay (Bohm et al. 2006). Whether RIP of sortilin is implicated signaling by neurotrophic factors remains to be determined, but the role of p75^{NTR} RIP is well described in neuronal survival and death (see below).

6 Sortilin in Proneurotrophin-Induced Apoptosis

Contrasting their inherent name “neurotrophins,” literally meaning “nerve nourishments,” these molecules not only elicit neuronal survival, growth, and differentiation but are also capable of apoptotic signaling. The trophic signals are governed by binding of the neurotrophins (NT) to their respective Trk receptor. Nerve growth factor (NGF) binds to TrkA, brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4) to TrkB, and neurotrophin-3 (NT-3) to TrkC, respectively. Co-expression with p75^{NTR} fortifies the trophic activities as it strengthens both affinity and specificity of the NTs towards their cognate Trk receptor. Intriguingly, p75^{NTR} is also required for NTs to stimulate apoptosis, suggesting that this receptor is able to switch between survival and death signaling depending on the cellular context. For some time this was a puzzling observation, but an indication of the underlying mechanism came with the recognition that while trophic activities are mediated by mature NTs, their proform, denoted proneurotrophins (proNT), can provoke apoptosis in a Trk-independent manner

(Lee et al. 2001). Earlier studies had reported that NT binding to p75^{NTR} can induce apoptosis in cultured neurons and oligodendrocytes lacking the corresponding Trk receptor. However, the non-physiologically high ligand concentrations required suggests that proNTs most likely are accountable for the pro-apoptotic activity in vivo (Bamji et al. 1998; Casaccia-Bonnel et al. 1996; Kenchappa et al. 2006; Yoon et al. 1998).

It has been intensively debated whether proNTs are merely intracellular precursors that require processing by pro-convertases in the TGN to mature before their secretion, or whether they can indeed be secreted in their unprocessed form. Recent reports have now settled this dispute by the demonstration of proNGF release from cultured sympathetic (Hasan et al. 2003) and cortical (Bruno and Cuello 2006; Hasan et al. 2003) neurons, microglia (Srinivasan et al. 2004), and astrocytes (Domeniconi et al. 2007). Likewise, release of proBDNF has been demonstrated in prenatal (Mowla et al. 1999; Teng et al. 2005) and postnatal (P0) (Yang et al. 2009) derived hippocampus cultures. Perhaps more convincing, in pathological conditions characterized by neurodegeneration such as Alzheimer's disease (AD), spongiform encephalomyelopathy, spinal cord injury, and seizures, proNT levels are increased (Fahnestock et al. 2001; Stoica et al. 2008; Harrington et al. 2004; Beattie et al. 2002; Volosin et al. 2006), and inhibitory antibodies against the proNTs significantly attenuate neuronal cell death associated with the latter two conditions (Harrington et al. 2004; Volosin et al. 2008).

Initially believed that p75^{NTR} by itself was sufficient to bind and transmit the apoptotic signal, subsequent studies revealed a critical role of sortilin in this process. When analyzed separately, p75^{NTR} and sortilin both bind proNGF with estimated affinities (Kd) of ~5–15 nM, but upon their co-expression in cells the affinity increases to ~160 pM (Nykjaer et al. 2004). This binding cooperativity is accomplished in part by a direct interaction between the two receptors, and in part by formation of a ternary receptor complex enabled by the simultaneous binding of the proNT pro-domain with sortilin and the mature part of the molecule with p75^{NTR}. In accordance with the dimeric confirmation of neurotrophins, a recent structural study revealed that proNGF shapes a 2:2 complex with p75^{NTR} and that the binding of proNGF to sortilin is enhanced when proNGF is in a preformed complex with p75^{NTR} (Feng et al. 2010). Although most ligands have been demonstrated to occupy sortilin in the tunnel (see above), p75^{NTR} is unlikely to do so as its interaction with sortilin is not inhibited by the tunnel-specific inhibitor neurotensin. In contrast, the binding of proNGF is abolished by neurotensin, suggesting that sortilin potentially may bind proNT and p75^{NTR} simultaneously by engaging different binding epitopes.

The important role of sortilin in neuronal cell death has been substantiated by in vivo studies demonstrating increased expression of sortilin as well as increased co-expression of sortilin with p75^{NTR} following seizure (Volosin et al. 2006), facial nerve and spinal cord injury (Harrington et al. 2004; Provenzano et al. 2008; Jansen et al. 2007), retinal ischemia (Wei et al. 2007), spongiform encephalomyelopathy (Stoica et al. 2008), or aging (Al-Shawi et al. 2008), conditions where proNGF is also upregulated (see above). However, studies in mice deficient in sortilin

expression have provided the most compelling evidence. Cultured knockout neurons that lack sortilin (*Sort1*^{-/-}) but still express p75^{NTR} are resistant specifically to proNT-induced cell death. In vivo, *Sort1*^{-/-} mice are characterized by reduced apoptosis in the developing retina that is indistinguishable from that observed in p75^{NTR} knockout mice, and upon aging deficiency for sortilin protects sympathetic neurons against degeneration. Finally, in a neuronal injury protocol, lesioned corticospinal neurons were fully rescued from death in the *Sort1*^{-/-} mice, a phenotype shared with mice treated with inhibitory antibodies to proNGF (Jansen et al. 2007; Harrington et al. 2004).

7 Sortilins and Proneurotrophin Signaling

What might be the molecular mechanisms by which sortilin affects proNT signaling in neurons? As described above, modulation of proNT affinity towards p75^{NTR} would be a qualified suggestion as sortilin is required for high-affinity proNT binding to p75^{NTR}. Whereas this obviously appears to be the simplest mechanistic explanation, additional mechanisms could indeed be involved such as regulation of adaptors to p75^{NTR} or modulation of p75^{NTR} cleavage-dependent signaling. Finally, direct signaling by sortilin can also be envisioned.

While some p75^{NTR} signaling pathways are initiated from the cell surface upon ligand binding (e.g., JNK activation (Reichardt 2006)), other signaling pathways require p75^{NTR} internalization and subsequent receptor sorting from early to recycling endosomes, forming p75^{NTR}-signaling endosomes (Bronfman et al. 2003). The molecular mechanisms involved in p75^{NTR} internalization and intracellular sorting are poorly characterized, and as previous studies have described the function of sortilin in internalization and intracellular sorting events, it is not unreasonable to speculate that sortilin could be involved. Thus, proNGF is rapidly internalized in cells expressing p75^{NTR} and sortilin, whereas endocytosis of proNGF is absent in sortilin-deficient cells (Nykjaer et al. 2004). Interestingly, the expression of sortilin on the neuronal cell surface also appears to be positively regulated, thereby increasing responsiveness to proNT during specific developmental stages correlating with cell apoptosis (Nakamura et al. 2007). Thus, a mammalian p75^{NTR} homologue NRH2 was reported to interact with sortilin and function as a trafficking switch, redistributing sortilin from the predominant TGN/perinuclear localization to the cell surface and promoting p75^{NTR}-sortilin receptor complex formation. Accordingly, knock down of NRH2 in sympathetic neurons significantly reduced proNT-induced apoptosis in these cells (Kim and Hempstead 2009).

The intracellular signaling cascades initiated by the sortilin-p75^{NTR} complex upon proNT binding remain largely elusive. However, several signaling pathways activated following NT binding to p75^{NTR} are mediated through the binding of adaptor proteins to the cytoplasmic domain of p75^{NTR}, including Traf6, neurotrophin receptor-interacting factor (NRIF), melanoma-associated antigen (MAGE), and neurotrophin receptor p75 interacting MAGE homologue (NRAGE) (Yamashita et al. 2005; Reichardt 2006). As the mechanisms that govern

ligand-induced adaptor docking to p75^{NTR} are still largely unknown, it can be speculated whether the formation of a complex between p75^{NTR} and sortilin is able to modulate/enhance adaptor binding to p75^{NTR}. Interestingly, Teng et al. (2005) investigated whether complexes of proBDNF and the soluble extracellular domain of sortilin was capable of initiating apoptosis of sympathetic neurons that express endogenous p75^{NTR} and sortilin. Although a ternary complex likely forms between sortilin, p75^{NTR}, and proNT with only the extracellular domains of the receptors present (Feng et al. 2010), Teng and colleagues found no induction of apoptosis using a preformed, soluble sortilin–proBDNF complex (Teng et al. 2005). This argues that the transmembrane or intracellular part of sortilin is critical in p75^{NTR}- and proNT-mediated apoptosis, perhaps by contributing to the correct stoichiometry of the receptor–ligand complex to allow signaling. So far there has been no description of whether sortilin has any signaling property in its own right. However, it has been described how SorLA under certain circumstances can be processed by TNF- α converting enzyme (TACE) and subsequently by the γ -secretase, releasing both intra- and extracellular fragments. The cytoplasmic tail is subsequently translocated to the nucleus where it acts as a transcriptional activator and enhances proliferation of neuronal precursor cells (Bohm et al. 2006). Another indication that members of the Sortilins may directly signal came from the finding that SorLA interacts with the kinase Ste20-related proline–alanine-rich kinase (SPAK) in the distal nephron of the kidney. Intracellular trafficking of SPAK by SorLA is crucial in the regulation of Na⁺-K⁺-Cl⁻ cotransporter 2 (NKCC2) and hence in the maintenance of renal ion balance (Reiche et al. 2010).

Finally, a potential regulatory function of sortilin is upon p75^{NTR} cleavage. On the cell surface and/or in the endosomal compartments, p75^{NTR} is subject to cleavage by gamma-secretase (Bronfman 2007), and proNGF and proBDNF are reported to induce such cleavage in several neuronal systems, including sympathetic neurons, Schwann cells, and photoreceptors. The intracellular domain (ICD) of p75^{NTR} is consequently released, and the p75^{NTR} adaptor neurotrophin receptor interacting factor (NRIF) translocates to the nucleus to induce apoptosis (Kenchappa et al. 2006; Volosin et al. 2008; Srinivasan et al. 2007; Podlesniy et al. 2006). The binding of sortilin (and proNT) to p75^{NTR} could potentially affect p75^{NTR} cleavage as conformational changes upon complex formation might increase the affinity of p75^{NTR} for the gamma-secretase (Fig. 4).

8 Potentiation of Neurotrophic Factor Signaling by Sortilins

As mentioned, the first evidence for a role of sortilin in proNT-mediated apoptosis was described in 2004 (Nykjaer et al. 2004), and this concept has subsequently been confirmed in numerous other studies. Surprisingly, recent data suggest that sortilin, like p75^{NTR}, may also engage in trophic signaling by mature neurotrophins. Thus, endogenous sortilin and Trks were found not only to be co-expressed in subgroups of sensory neurons as well as hippocampal and cortical neurons but also to be physically associated as determined by coimmunoprecipitation analysis and

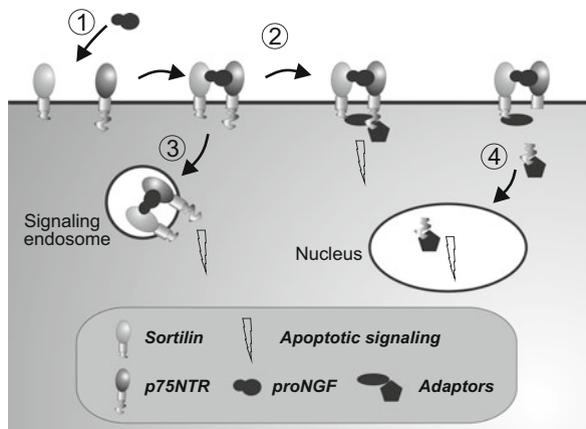


Fig. 4 Potential mechanisms of sortilin in $p75^{\text{NTR}}$ -dependent proNT apoptotic signaling. (1) Sortilin and $p75^{\text{NTR}}$ constitute a high-affinity binding site for proNT, strongly increasing proNT binding to the cell surface. (2) Signaling of $p75^{\text{NTR}}$ depends on the binding of adaptor molecules to the cytoplasmic tail of $p75^{\text{NTR}}$, and the formation of a complex between $p75^{\text{NTR}}$ and sortilin might modulate/enhance adaptor binding to $p75^{\text{NTR}}$. (3) Some signaling pathways are reported to require $p75^{\text{NTR}}$ internalization with the formation of $p75^{\text{NTR}}$ -signaling endosomes, perhaps assisted by sortilin. (4) $p75^{\text{NTR}}$ can be cleaved upon proNT binding, with the C-terminal fragment and adaptors translocating to the nucleus to induce apoptosis

fluorescence resonance energy transfer (FRET) microscopy. Studies in neuron cultures and in knockout mice revealed that sortilin facilitates efficient anterograde axonal transport and synaptic targeting of the Trks. However, the mechanism by which sortilin links to the microtubule motor is currently unknown. Somewhat surprisingly, the sortilin-deficient mice do not appear to be seriously affected by the reduction in peripheral Trk levels, at least when assessing sensory nerve morphology and functionality (Vaegter et al. 2011). These observations are, however, in accordance with previous work on Trk heterozygote mice which display reductions in Trk levels and activity of approximately 50 % (comparable to observations in the sortilin-deficient mouse) but are phenotypically normal (Ernfors et al. 1994; Klein et al. 1993; Minichiello et al. 1995) (Fig. 5).

The combined observations suggest the tripartite model for neurotrophin signaling illustrated in Fig. 6 (“the neurotrophin triangle”): Sortilin is essential to form a death complex with $p75^{\text{NTR}}$ activated by proNT. Signaling by Trk receptors, conversely, requires $p75^{\text{NTR}}$ on the plasma membrane to facilitate binding of NT and to strengthen trophic signals. To complete this triangular interaction, sortilin supports and fine-tunes trophic signaling by facilitating anterograde Trk transport along the axonal path.

Yet another function of sortilin in NT signaling was put forward by Chen and colleagues, who showed that sortilin is involved in sorting of BDNF from the TGN into the pathway for regulated secretion (Chen et al. 2005). In untreated primary hippocampal neurons and the neuroblastoma cell line PC12, (pro)BDNF

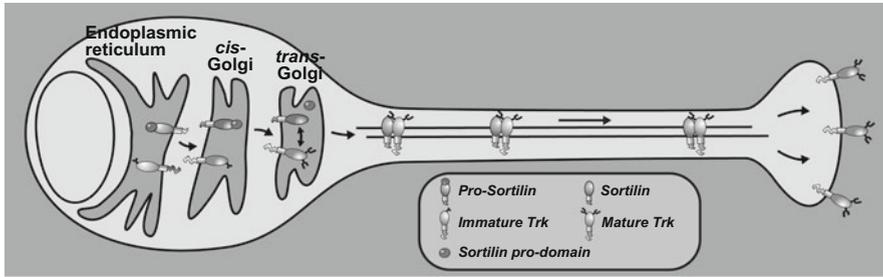


Fig. 5 Schematic model of sortilin involvement in Trk receptor trafficking. Prior to the trans-Golgi network (TGN), the pro-domain of sortilin inhibits binding of ligands to sortilin. However, following furin-mediated pro-convertase cleavage in the TGN, mature sortilin is now able to bind fully glycosylated Trk and facilitate anterograde transport of this receptor, assuring sufficient peripheral Trk levels to sustain efficient neurotrophin signaling by neurotrophins released from target tissues

colocalized with secretogranin II that labels vesicles destined for regulated secretion. Inhibiting sortilin activity by siRNA knockdown or overexpression of dominant-negative receptor mutants redistributed proBDNF from the regulated to the constitutive secretory pathway and reduced depolarization-induced (pro)BDNF secretion with a concomitant increase in constitutive release (Chen et al. 2005). Biochemical mapping subsequently identified a conserved binding motif in the pro-domain of BDNF that is capable of binding the luminal domain of sortilin. A recent study further supports the role of sortilin in vesicular transport and stabilization of proBDNF. Yang and colleagues found that proBDNF forms complex with sortilin and Huntingtin-associated protein-1 (HAP1) and that this complex is important for the transport of proBDNF/BDNF-containing vesicles to facilitate synaptic targeting of proBDNF in neurites of cortical neurons. Furthermore, the association of sortilin to the proBDNF/HAP1 complex prevents proBDNF degradation and facilitates the furin cleavage to release mature BDNF (Yang et al. 2011). How sortilin affects vesicular transport is unclear, but it is noteworthy that KIF1A, a subunit of kinesin-3 that transports synaptic vesicles, has been identified as a sortilin interaction partner (Vaegter et al. 2011) (Peder Madsen, personal communication).

Signaling by neurotrophic factors other than neurotrophins have also been reported to be positively regulated by sortilin. Ciliary neurotrophic factor (CNTF) belongs to the family of helical type 1 cytokines, which also includes interleukin-6 (IL-6), IL-11, leukemia inhibitory factor (LIF), and others. CNTF was initially identified (and named) for its ability to maintain survival of parasympathetic neurons of chicken ciliary ganglia (Adler et al. 1979). Since then it has been reported to support the survival of a variety of neuronal cell types, including sensory (Simon et al. 1995) and motor (Oppenheim et al. 1991) neurons. Furthermore, it is believed to act as a lesion factor released from tissues subjected to trauma as several studies have reported a marked change in the localization and expression of CNTF (Rudge et al. 1995; Sendtner et al. 1992; Friedman et al. 1992). CNTF signaling is elicited by the formation of a trimeric receptor complex composed of

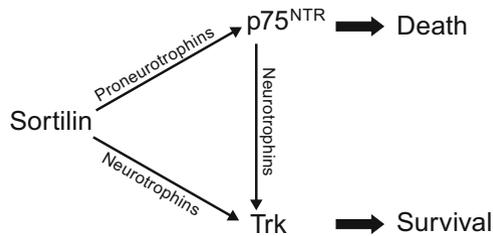


Fig. 6 Schematic illustration of “the neurotrophin triangle” concept, linking sortilin and key receptors in survival and death signaling by mature/pro-neurotrophins

the GPI-anchored CNTF receptor α (CNTFR α), the signaling subunit 130-kDa glycoprotein (gp130), and the LIF receptor β (LIFR β) (Davis et al. 1993). However, CNTFR α is not an absolute requirement for signaling because CNTF at relatively high concentrations is able to activate the gp130/LIFR β heterodimer (Gearing et al. 1994). Interestingly, Larsen and colleagues demonstrated that sortilin interacts with LIFR β , thereby facilitating CNTF signaling and mediating CNTF-dependent proliferation through the gp130/LIFR β heterodimeric complex (Larsen et al. 2010). It will be interesting for future studies to investigate the effect of sortilin upon CNTF signaling in relation to, e.g., motor neuron regeneration following nerve injury in vivo.

9 Sortilins and Neuronal Disease

The first member of the family to be associated with a neurodegenerative disease was SorLA, with the finding of low levels of SorLA gene expression (*SORL1*) in patients with sporadic AD (Scherzer et al. 2004). Whereas several subsequent association studies confirmed this connection, some failed to do so. However, a recent comprehensive and unbiased meta-analysis of all published and unpublished data from studies on *SORL1* SNPs, including approximately 12,000 cases of AD and 17,000 controls, significantly substantiated the involvement of *SORL1* gene variants in AD and further suggested multiple causative gene variants in distinct regions of *SORL1* (Reitz et al. 2011a). Neuronal processing of amyloid-precursor protein (APP) by the β -secretase, with formation of the cleavage product A β and subsequently development of neurotoxic A β oligomers and senile plaques, are pathological hallmarks of AD. The involvement of SorLA in APP processing was described by Andersen and colleagues in 2005, demonstrating that the proteins colocalize in Golgi compartments and early endosomes. Further studies demonstrated that the neuronal production of A β inversely correlated with the level of SorLA, as APP is retained in the TGN by SorLA and thereby impairs transit to the plasma membrane or late endosomes for β -secretase cleavage (Andersen et al. 2005; Schmidt et al. 2007).

Intriguingly, another member of the sortilins has been associated with AD. Association of SorCS1 with AD was suggested approximately concurrently with the genetic association between SorLA and AD (Rogaeva et al. 2007; Grupe et al. 2006). A later study substantiated the association and found significantly lower SorCS1 expression in AD brains, suggesting an inverse correlation between SorCS1 levels and A β production, and this correlation was further supported by biochemical studies in cell lines (Reitz et al. 2011b). However, while genetic and biochemical data support a relationship between SorCS1 and AD, the mechanisms by which SorCS1 modulates A β is currently not clear.

Although AD is characterized by A β plaque formation, neurotrophins are likely involved in the subsequent process with loss of neurons. The cortex of AD brain is characterized by an increase in proNGF levels during disease progression and stable levels of p75^{NTR} and sortilin but reduced levels of TrkA (Mufson et al. 2010; Counts et al. 2004; Al-Shawi et al. 2008; Peng et al. 2004; Fahnestock et al. 2001). As the balance of pro-survival versus pro-apoptotic signaling may depend on the stoichiometry of these proteins (Masoudi et al. 2009; Capsoni et al. 2010), the shift in ratio may very well change the functional outcome of proNGF on neurons in the brain. Because TrkA is necessary for NGF pro-survival signaling, this shift in NGF receptor stoichiometry paralleled with increased proNGF may favor the trimeric interactions of proNGF with p75^{NTR} and sortilin, activating pro-apoptotic pathways during the early stages of AD. Further, although some studies indicate that proNGF can bind to TrkA (albeit with less with less affinity than NGF) to induce neurotrophic response (Fahnestock et al. 2004), the lower levels of TrkA may not be sufficient to initiate proNGF-induced cell survival signaling in the AD brain.

Sortilin has recently been functionally linked to frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U), a form of frontotemporal dementia (FTD) characterized by neuronal loss within, and atrophy of, the frontal and temporal lobes of the brain. FTLD-U cases are caused by haplo-insufficiency due to mutations in the GRN gene encoding progranulin (PGRN), a common feature in FTD with about 50 identified mutations in GRN linked to these disorders (Mackenzie et al. 2010). Despite intense investigation, the normal and pathological roles of PGRN within the CNS are still largely unknown. Apparently, PGRN can function as a nerve growth, protective, or survival factor (Bateman and Bennett 2009), and the reduction of PGRN levels observed in, e.g., FTLD-U would indeed be consistent with the observed neurodegeneration. Hu and colleagues identified sortilin as a major neuronal receptor for the PGRN, providing an important mechanistic link to understand normal CNS functions of PGRN and how partial loss of PGRN function may lead to neurodegenerative disease. Importantly, they showed that sortilin regulates PGRN levels as mice lacking sortilin had elevated brain and serum PGRN levels and further that PGRN binds sortilin and colocalizes with sortilin in endocytic vesicles and eventually with Lamp1, a marker for lysosomes (Hu et al. 2010). Together with the finding that mice lacking PGRN develop lysosomal dysfunction, this might implicate a normal role of PGRN in the lysosome (Ahmed et al. 2010).

A further hallmark of FTL-D-U is the loss of nuclear localization of TAR DNA binding protein (TDP-43) but the presence of cytosolic accumulation of ubiquitinated inclusions of TDP-43. Two studies show that TDP-43 binds many target RNAs, approximately 30 % of the mouse transcriptome and preferably within the intron, suggesting a function in splicing regulation. Intriguingly, knock-down of TDP-43 affected in particular splicing of sortilin, suggesting another possible regulatory link between sortilin and key molecules in FTL-D-U (Tollervey et al. 2011; Baum et al. 2008).

A single nucleotide polymorphism in the *bdnf* gene resulting in a valine (Val) to methionine (Met) mutation at amino acid 66 in the BDNF prodomain has been linked to neuropsychiatric disorders including depression, bipolar disorders, and memory impairment (Sen et al. 2003; Neves-Pereira et al. 2002; Sklar et al. 2002; Egan et al. 2003; Hariri et al. 2003; Rybakowski et al. 2003). The molecular mechanisms underlying the altered-variant function is not understood, but the Met-variant has been reported to have reduced activity-dependent (or regulated) secretion (Egan et al. 2003; Chen et al. 2004). Interestingly, Chen and colleagues reported in 2005 that the binding site of sortilin within the prodomain of BDNF is overlapping the region containing the Val–Met substitution and that the Met-variant has decreased interaction with sortilin (Chen et al. 2005). Thus, identification of the sortilin–BDNF interaction in regulated secretion of BDNF provides a possible molecular model in the attempt to understand the effect of the BDNF polymorphism in the selective impairment of CNS function.

Lastly, it should be noted that recent genome-wide association studies (GWAS) implicated *SorCS2* in the etiology of bipolar disorder. Generally, the diagnosis and lack of quantitative physiological parameters in this disorder makes genomic studies challenging. However, a number of independent studies have now described association of the same three SNPs in the *SORCS2* gene to the risk of bipolar disorder, and *SORCS2* is in fact one of the top candidate genes to emerge from these GWAS (Baum et al. 2008; Christoforou et al. 2011; Ollila et al. 2009).

10 The Role of Sortilins in Metabolic Disorders

Although expression of sortilin family members predominates in neuronal tissues, they are also present in specific cell types in tissues outside the nervous system (skeletal muscle, pancreas, thyroid, liver, lung, heart) (Petersen et al. 1997; Hermey 2009; Jansen et al. 2007; Vaegter et al. 2011). The functions of the receptors outside the nervous system are still only beginning to be unraveled but appear to embrace involvement in many apparently unrelated molecular pathways. In particular, sortilin and *SorCS1* have recently attracted attention due to their proposed roles in metabolic disorders such as regulation of plasma cholesterol levels/coronary heart disease (sortilin) and insulin metabolism/type 2 diabetes (sortilin and *SorCS1*).

Genome-wide association studies of large human cohorts showed a strong correlation between single-nucleotide polymorphisms (SNPs) in the chromosome

1p13.3 locus (that harbors the sortilin gene) and hypercholesterolemia as well as coronary heart disease (Kathiresan et al. 2008; Willer et al. 2008; Sandhu et al. 2008; Dube et al. 2011; Willnow et al. 2011). Effort has subsequently been mobilized to identify the mechanistic basis of this association, and independent groups have recently described their findings after focusing on the sortilin gene (*SORT1*), located at this locus. However, these studies find opposite effects of how sortilin might affect plasma cholesterol level. A study by Kjolby and colleagues found that loss of sortilin in a transgenic mouse model results in a reduction of plasma cholesterol. Furthermore, sortilin bound apoB100 containing lipoproteins in the secretory pathway, suggesting a stimulatory involvement in very-low-density lipoproteins (VLDL) secretion (Kjolby et al. 2010). In opposition to these findings, Musunuru and colleagues used a very different mouse model and reported that sortilin levels inversely correlate with plasma cholesterol, as sortilin impaired VLDL secretion from hepatocytes (Musunuru et al. 2010). While these contradictory findings may appear incompatible, they perhaps rather demonstrate that the specific function of regulatory proteins might significantly differ depending on the genetic background and chow and hence molecular conditions in which they are studied. Therefore, sortilin may partake in a broader range of functions in lipoprotein sorting/secretion depending on the overall metabolic milieu in vivo.

Other studies have linked sortilin and SorCS1 to insulin/glucose metabolism and the risk of type 2 diabetes development. Thus, SorCS1 was identified as a diabetes susceptibility gene, affecting fasting insulin and glucose plasma levels in mice (Clee et al. 2006; Stoehr et al. 2000). Genetic variants of the *SORCS1* gene were subsequently associated with diabetes risk and age of onset of diabetes in a human genetic association study (Goodarzi et al. 2007), reducing in vivo insulin secretion and hence interfering with compensatory mechanism when type 2 diabetic patients become severely insulin resistant. Insulin resistance in fat and skeletal muscle tissues may be caused not only by defective insulin signaling but also by abnormal glucose transporter Glut4 regulation. Under basal conditions, Glut4 is present in multiple subcellular compartments but majorly in a distinct population of vesicles named insulin-responsive vesicles (IRV) or alternatively Glut4 storage vesicles (GSV). Upon insulin stimulation, glucose uptake in fat and skeletal muscle tissues is achieved by translocating Glut4 from the intracellular storage pool to the plasma membrane. In this context it is therefore interesting that sortilin shows a high degree of colocalization with Glut4 and represents one of the major component proteins of Glut4 vesicles (Lin et al. 1997; Morris et al. 1998). Furthermore, sortilin has been demonstrated to be essential for biogenesis of IRVs and for the acquisition of insulin responsiveness in adipose cells (Shi and Kandror 2005).

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