ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Sorting Receptor SORLA: New Strategy for Various Diseases- A Review

Nisha V T*, Chippy S Kumar
Ezhuthachan College of Pharmaceutical Sciences
Marayamuttom, Neyyattinkara,Thiruvananthapuram-695124

Abstract:

SORLA (Sorting-related receptor with A – type repeats) is a 250 – kDa type 1 membrane glycoprotein that directs cargo proteins such as kinases, phosphatases, and signalling receptors to their correct location within the cell. The dysfunction of SORLA (VPS10P domain receptor) is the underlying cause of common human malignancies including Alzheimer's disease, Atherosclerosis and obesity. Excessive proteolytic breakdown of the amyloid precursor protein (APP) to neurotoxic β peptides by secretases in the brain is a molecular cause of Alzheimer's disease. SORLA stimulates proliferation and migration of smooth muscle cells and monocytes, processes that accelerated the atherosclerotic plaque formation. Over expression of human SORLA in murine adipose tissue blocked hydrolysis of triacylglycerides and caused excessive adiposity. The objective of this review is to highlight the molecular mechanisms that govern sorting of SORLA and its cargo in multiple cell types and why genetic defects in this receptor results in devastating diseases.

Keywords: SORLA, APP, VPS10P domain receptors, 250-kDa type 1 membrane glycoprotein, Signaling receptors.

INTRODUCTION

Protein targeting or protein sorting is the biological mechanism by which proteins are transported to the appropriate destinations in the cell or outside it. Proteins can be targeted to the inner space of an organelle, different intracellular membranes and plasma membrane or to exterior of the cell via secretion. Sorting of proteins to their destined location in sub cellular components is essential for proper cell function and faulty protein sorting will result in cellular dysfunction and disease. Protein sorting is essential for all cell types, but particularly challenging in neurons in which cell compartments of axons and dendrites may be as far away as 1m from the soma of motor neurons. Within cells the Golgi is the central hub that sorts the bulk of proteins. Protein sorting proceeds in the trans most cisterna of this organelle called the trans Golgi network (TGN) that consists of branching tubular membrane domains. From the TGN proteins may be targeted to the apical or basolateral plasma membranes, to the endosomal or lysosomal system or to the specialised secretory granules for activity dependent release. Directed protein trafficking is mediated by sorting receptors, transmembrane proteins that interact with cytosolic adaptors at the Golgi membranes to guide their protein cargo to and from the TGN.

One type of sorting receptors called the VPS10P (Vacuolar Protein Sorting 10 Protein) domain receptors received a special attention because of their casual involvement in human diseases, such as Alzheimer's disease, Huntington's disease, psychiatric disorders, atherosclerosis, dyslipidemia and diabetes. VPS10P now emerge as a key regulator of intracellular protein sorting not only in nervous system but also in many other tissues as well. [1]

Sorting related receptor with A type repeats (SORLA or SORL1 or LR11) is a 250 kDa type 1 membrane glycoprotein which comes under the of VPS10P domain receptors. SORLA shows structural similarity with the family of low density lipoprotein receptors (LDLRs). It was identified and characterised independently using biochemical purification of proteins from human brain binding to the receptor associated protein and subsequently confirmed by genetic screening of novel LDLR family members in other species. SORL1 gene is located on the human chromosome 11q23/24. [3]

SORLA is located widely in the mammalian central nervous system (CNS) notably the cerebral and entorhinal cortex, hippocampus, cerebellum and brain stem as well as in non neuronal tissues like ovary, testis, liver, adrenal gland and lymph nodes. This highly putative receptor is located mainly in Golgi bodies, trans Golgi network (TGN), early endosomes and plasma membrane of the cell. SORLA is transported between TGN and endosomal compartments by cargo molecules like Adaptor Protein 1 (AP1), Adaptor Protein 2 (AP2), Golgi-localised Gamma ear containing ADP ribosylation factor binding (GGA), Phosphofurin Acidic Cluster Sorting protein 1(PACS 1) and the retromer complex. Interactions with these adaptors are important for the implication of SORLA in AD. Because of deletion of the binding motifs in the cytoplasmic domain for these adaptors led to defective routing and altered APP processing. [9]

Protein cargo sorted by SORLA in neurons is not restricted to APP (Amyloid Precursor Protein). SORLA acts as a sorting factor for the Tropomyosin receptor Kinase B (TrkB), the receptor for Brain Derived Neurotrophic factor (BDNF). Another trophic pathway modulated by SORLA acts through Glial cell line Derived Neurotrophic Factor (GDNF) that promotes the survival of distinct populations of central and peripheral neurons. SORLA also impacts signaling through a heterodimeric neurotrophic cytokine called cardiotrophin like cytokine: cytokine like factor 1 (CLC: CLF1). SORLA dependent endocytosis is required for neurotrophic signaling through CLC: CLF1, but it also downregulates signal reception by directing ligand and receptor to lysosomal degradation.

Besides the protein sorting in neurons, SORLA have some other important roles in non neuronal cell types. SORLA is abundantly expressed in the thick ascending limb of the Henle's loop, a distal segment of the renal nephron

responsible for water ion homeostasis. Lack of SORLA expression in epithelial cells of the thick ascending limb results in failure to properly reabsorb sodium and chloride. Also SORLA controls the phosphoregulation of Na-K-Cl cotransporter 2 (NKCC2) by interacting with both the Ste 20 related proline alanine rich kinase (SPAK) and the calcineurin phosphatases. [1]

VPS10P DOMAIN RECEPTORS

VPS10P domain receptors are a unique class of sorting receptors that direct intracellular transport of target proteins in neurons. They play central role in neurodegenerative processes and also in cardiovascular and metabolic disturbances. SORLA is unique among the members of the VPS10P domain receptor gene family as it contains additional functional modules not shared by other receptors including domains for protein protein interaction (fibrinectin type III domains, complement type repeats) or for PHdependent release of ligands in endosomes (6 bladed β propeller).

Structural organization of VPS10P domain receptors from yeast and mammals (sortilin, SORLA, SORCS1, SORCS2 and SORCS3). The extracellular domains of the receptors are composed of one or two VPS10P domains and carries additional module for protein protein interaction or regulation of ligand binding. The structure of low density lipoprotein (LDL) is shown for comparison.VPS10P domain receptors share structural resemblance with the LDLR. There are two type 1transmembrane proteins termed as sortilin and sortilin related Receptor with A type repeats (SORLA, also known as LR11). Although SORLA and sortilin bound apolipoproteins, they did not share much structural similarity to prototypical lipoprotein receptors of the LDLR gene family (Fig.1).

Rather, both receptors exhibited a structural motif in their extracellular domain that had been identified in a sorting receptor in yeast, the vacuolar protein sorting 10 protein (VPS10P). This VPS10P domain represents a 700 amino acid module that folds into a ten bladed β propeller and that serves as a binding site for ligands. Cloning of SORCS1, SORCS2and SORCS3 (sortilin related receptor CNS expressed) added three more mammalian members to the VPS10P domain receptor family. VPS10P serves as a sorting factor that moves newly synthesized hydrolases from the Golgi compartment to their place of action in the vacuole. A more complex trafficking path has been identified for mammalian VPS10P domain receptors that are able to shuttle between the cell surface and endocytic and secretory compartments of cells.

VPS10P domain receptors are guided by cytosolic adaptors that bind to distinct motifs in the intracellular domains of these receptors and determine their trafficking path. Sorting also determines proteolytic processing of the receptors to activate ligand binding and to shed soluble domains.

VPS10P domain receptors are synthesized as precursor proteins harboring a 40-55 amino acid pro peptide that act as intrinsic chaperones for proper folding and prevent premature ligand binding.VPS10P serves as a sorting factor that moves newly synthesized hydrolases from the Golgi compartment to their place of action in the vacuole. An even more complex trafficking path has been identified for VPS10P receptors that are shuttle between the cell surface and endocytic and secretory compartments of cells.

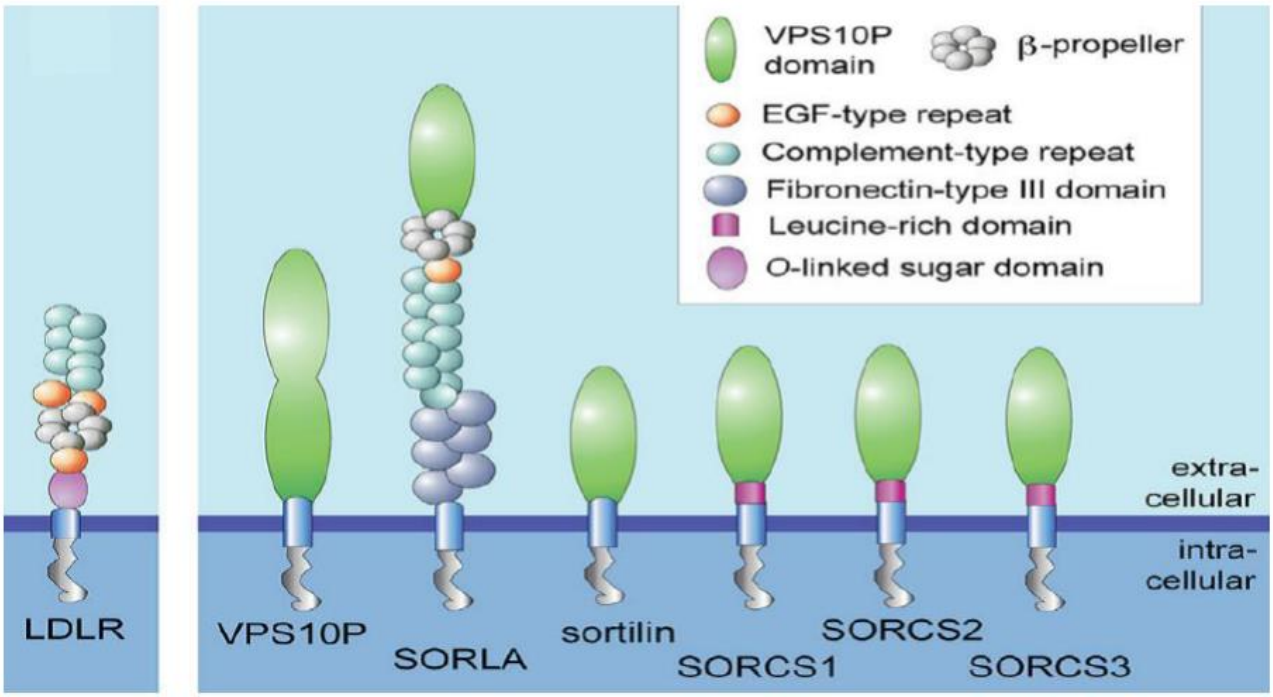

Fig. 1 VPS10P domain receptors

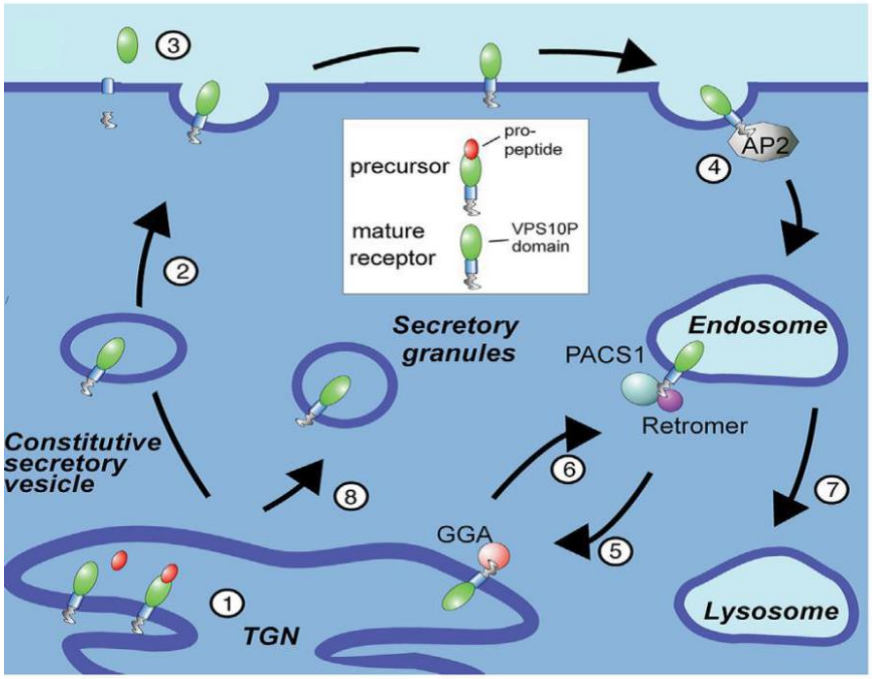

Fig. 2 Trafficking path for VPS10P domain receptors

Step 1- Removal of the pro peptide by proprotein convertases in the trans Golgi network (TGN) activates nascent receptor molecules.

Step 2- From the TGN, mature VPS10P domain receptors follow at least three alternative trafficking routes. Firstly, they may be directed to the cell surface via constitutive secretory vesicles.

Step 3- Some receptor molecules at cell surface are subject to shedding, releasing the soluble ectodomain to act as diffusible regulator by sequestering ligands.

Step 4- Intact receptor molecules at the cell surface may perform clathrin dependent endocytosis of ligands, a process facilitated by binding of the adaptor protein, AP 2.

Step 5- From endosomes, internalized receptors (and some of their cargo) return to the TGN. This retrograde sorting path requires the interaction with the adaptor complex retromer and with PACS1.

Step 6- A second route for exiting the TGN involves anterograde movement of VPS10P domain receptors to endosomes, employing the monomeric clathrin adaptor GGA1, GGA2, and GGA3 (Golgi localizing g adaptin ear homology domain ARF interacting proteins).

Step 7- From endosomes, ligands, and in some instances even the receptor may be targeted for lysosomal degradation.

Step 8- A third pathway for TGN export exists in cells capable of regulated secretion whereby receptors move endogenous ligands from the TGN to secretory granules.

All mammalian VPS10P domain receptors are expressed in neurons of the central and peripheral nervous system. Neuronal ligands for VPS10P domain receptors include neurotrophins and their receptors or the amyloid precursor protein and progranulin, etiologic agents in Alzheimer's disease and in frontotemporal lobar degeneration respectively. VPS10P domain receptors are also expressed in peripheral tissues with relevance to cardiovascular and metabolic processes. Eg: SORLA is produced in adipose tissue and in smooth muscle cells. Sortilin is found in hepatocytes, while SORCS1 is expressed in pancreatic islets. In contrast to the situation in the nervous system, the expression patterns for VPS10P domain receptors in peripheral tissues are largely non overlapping suggesting unique functions for each receptor in cardiovascular and metabolic processes.This hypothesis received recent support from genetic studies documenting association of loci close to SORL1 (encoding SORLA) with hypertriglyceridemia, obesity and vessel disease, SORT1 (encoding sortilin) with hypercholesterolemia and risk of myocardial infarction and SORCS1 and SORCS3 with type 1 and type2 diabetes. Although all SNPs were non coding variants and the disease gene in question remained unclear at times, functional studies in cell and animal models have now confirmed the importance of VPS10P domain receptors for systemic metabolism. [3]

CELL BIOLOGY OF SORLA

SORLA (also known as LR11 or SORL1) was initially uncovered in the search for receptors that share structural similarity to the low density lipoprotein (LDL) receptor, the main endocytic receptor for uptake of lipid loaded lipoproteins into vertebrate cells. These studies identified a 250 kDa type 1 transmembrane protein in brain and liver that contained complement type repeats and a β propeller, structural elements in the LDL receptor required for binding and for PH dependent release of ligands, respectively (Fig. 3).

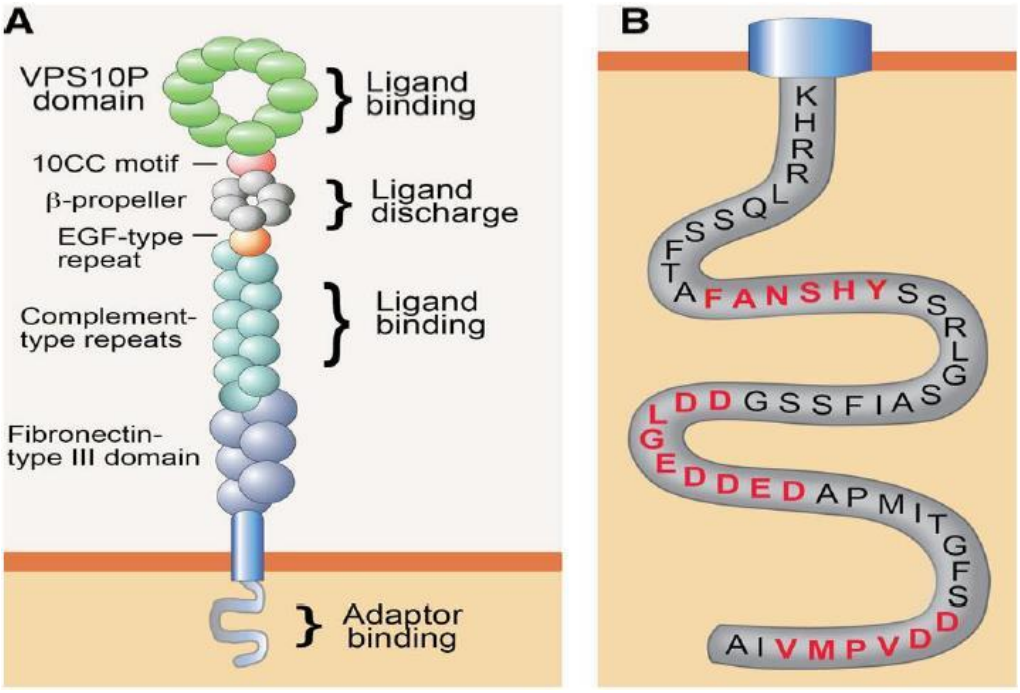

Fig. 3 Structural organization of SORLA

A. Organization of the SORLA polypeptide is shown, indicating the main structural elements and their documented functions. The VPS10P domain and the cluster of complement type repeats serve as major ligand binding sites in the luminal receptor domain. The β propeller interacts with the molecular chaperone MESD (mesodermal development deletion) interval to facilitate folding of the receptor polypeptide and it may be involved in PH dependent release of bound ligands in acidic endosomal compartments.
B. Amino acid sequence of the cytoplasmic receptor tail highlighting three main binding motifs for cytosolic adaptors, termed FANSHY, the acidic motif (DDLGEDDED) and the GGA binding site (DDVPMV).
The ability of SORLA to internalize lipoproteins seemingly supported the notion of a novel species of lipoprotein receptor. But SORLA have additional structural elements not found in the LDL receptor, namely a VPS10P domain and six fibronectin type III domains. The VPS10P domain was identified earlier in an intracellular sorting protein in yeast called the VPS10P.

VPS10P directs newly synthesized peptidases from the TGN to the vacuole (the yeast lysosome) where they act in proteolytic breakdown of internalized proteins. A similar function for SORLA in intracellular protein sorting in mammalian cell types was supported by the fact that the bulk of the receptor molecules were present in the Golgi rather than at the cell surface.
SORLA is synthesized as a pro receptor containing a 53 amino acid pro peptide at the ultimate amino terminus. This pro peptide is believed to block the binding site for ligands in the VPS10P domain, a major site for interaction with peptide ligands. Removal of the pro peptide by convertases in the TGN activates the ligand binding capability of the receptor. This activation step may be required to prevent premature binding of ligands to nascent receptor molecules in the biosynthetic pathway of the cell. Apart from the VPS10P domain, the cluster of complement type repeats in SORLA constitutes another site for ligand recognition. Binding of ligands to the VPS10P domain or the complement type repeats is lost at low PH(<5.5). The significance of additional structural elements in the extracellular domain for receptor functions is less clear. Based on analogy to other proteins, the fibronectin type III domain may be involved in protein protein interactions while the β propeller may facilitate PH dependent release of ligands in endocytic compartments.
Newly synthesized SORLA molecules follow the constitute secretory pathway from the endoplasmic reticulum through the Golgi to the cell surface, a default route for transmembrane proteins that does not require distinct sorting motifs (Fig. 4).

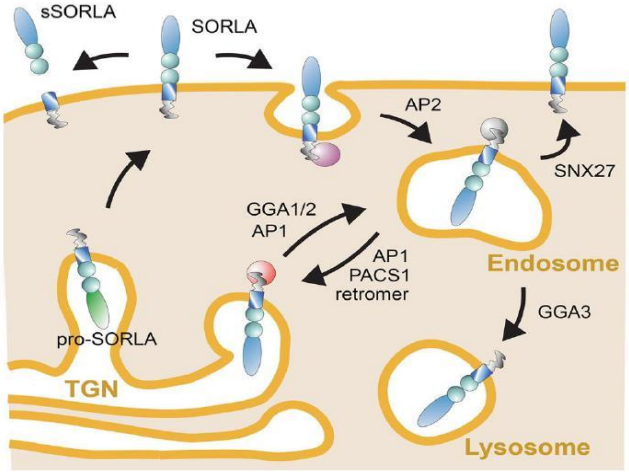

Fig. 4 Intracellular trafficking path for SORLA

Nascent SORLA is an inactive pro receptor (pro SORLA) that is activated by proteolytic removal of an amino terminal pro peptide in the TGN, resulting in transfer of the active receptor (SORLA) through the constitutive secretory pathway to the cell surface. Some receptor molecules at the cell surface are subjected to ectodomain shedding, resulting in release of the extracellular receptor domain. Ectodomain shedding disrupts the ability of SORLA to act as a sorting receptor, but may serve to produce a soluble receptor fragment termed soluble (s) SORLA that acts as a signaling molecule. Still, most SORLA molecules at the cell surface remain intact and undergo clathrin dependent endocytosis facilitated by the clathrin adaptor protein 2 (AP2). The bulk of internalized receptors move from endosomes back to the TGN to continuously shuttle between TGN and endosomal compartments thereafter. Adaptors GGA1 and GGA2 guide anterograde movement of SORLA from the TGN to endosomes, whereas PACS1 and the retromer complex facilitate retrograde sorting from endosomes back to the Golgi. AP1 may be involved in bi directional sorting.

Retrograde movement of SORLA from endosomes to the TGN is guided by PACS 1 that also binds to the acidic cluster and by the multimeric adaptor complex retromer that binds to the F2172ANSHY tail motif. Anterograde sorting of SORLA from the TGN to endosomes is mediated by the monomeric clathrin adaptors GGA1 and GGA2. Finally, binding of the adaptor protein AP1 to the acidic tail motif may aid in anterograde as well as retrograde sorting of SORLA. The shuttling of protein cargo between TGN and endosomes likely constitutes the major trafficking route taken by SORLA in neurons. Also SORLA have the ability to move ligands from endosomes to the cell surface guided by the sorting nexin family member (SNX) or from endosomes to lysosomes, potentially sorted by GGA3. The complex trafficking path for SORLA has mainly been elucidated in established cell lines. However, recent studies in mouse models expressing mutant SORLA variants lacking individual adaptor binding sites have substantiated this model in the brain by documenting impaired anterograde sorting in receptor mutants lacking the GGA binding site and impaired retrograde sorting in mutants unable to interact with PACS1 or retromer. [1]

SORLA REGULATION

There are various regulatory pathways for controlling SORLA expression. Shedding of SORLA leading to loss of neuron associated receptor activity is regulated by ROCK2 dependent phosphorylation of the cytoplasmic tail, as well as an endocytosis dependent glycosylation of the ectodomain (Fig. 5).

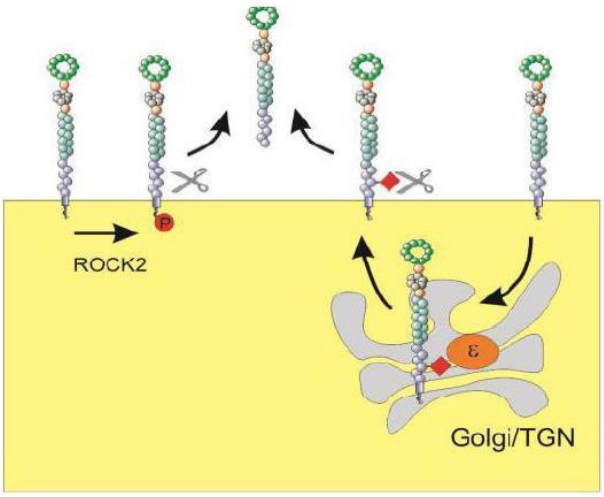

Fig. 5 Shedding of SORLA

Interactions of extracellular stimuli like BDNF and serotonin with their cognate receptors at the plasma membrane (ie. TrkB and the serotonin receptor) lead to activation of signaling pathways that enhance SORL1 expression. Fatty acids like DHA and CLA are also speculated to activate SORLA gene expression by yet unknown mechanisms. Besides the direct role in regulation of SORL1 transcription, regulation can also occur indirectly by induction of other genes encoding RNA molecules that indirectly leads to changes in SORL1 mRNA levels, e.g. mi RNA (micro RNA) or non coding RNA that initiates degradation of mRNA or leads to alternative splicing of the mRNA (Fig. 6).

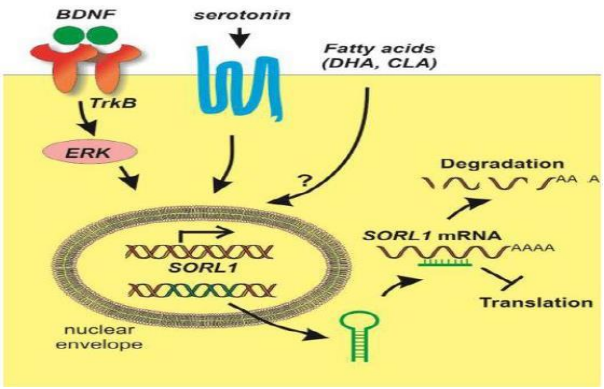

Fig. 6 Activation of signaling pathways

Regulation at the level of the SORL1 gene is dependent on binding of transcription factors (TF) that either activates (act) or represses (rep) transcription. Transcription from different promoters (I and II) where the activity is modulated by the methylation state of its CpG islands presents yet another way to control correct timely and spatial SORLA expression (Fig. 7). [6]

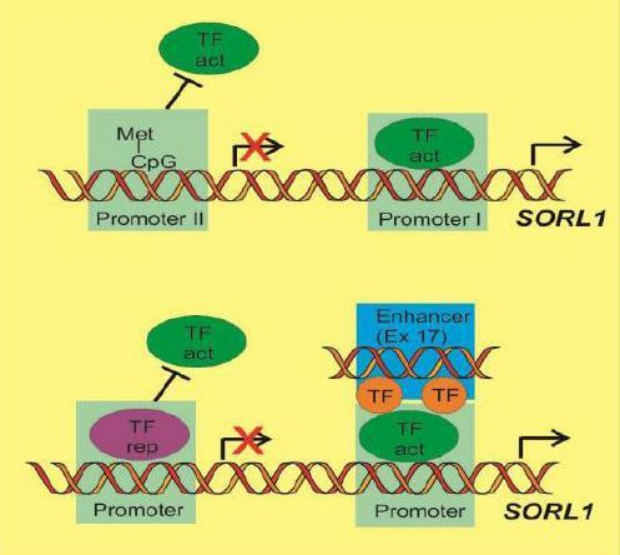

Fig. 7 Binding of transcription factors

SORLA is documented to interact with the Rho associated coiled coil containing protein kinase 2 (ROCK2), which in turn has been implicated in controlling the metabolism of APP and Aβ. The binding of ROCK2 to SORLA leads to phosphorylation of the receptor at serine 2206 within the cytoplasmic domain and enhances the shedding of the SORLA ectodomain. It describes SORLA as a phosphoprotein, where shedding and consequently the intraneuronal level are regulated through a phosphostate sensitive mechanism.

Glycosylation is another post translational modification known to regulate the shedding of many transmembrane proteins. The homology of SORLA with LDL receptors, which is a group of proteins known to undergo glycosylation dependent shedding, suggests that cleavage and secretion of this receptor may also be regulated by specific glycan structures. Even though the exact physiological significance of the resulting soluble ectodomain is unclear, it may control functions relevant to AD pathogenesis. Besides the obvious effect of leaving less functional receptor inside the cell available for sorting activities when SORLA is released from the cell surface, the cleavage of SORLA also generates a C-terminal fragment that can be processed by γ secretase. This cleavage generates a soluble intracellular domain with a potential function in regulation of gene expression, which may represent a way to also control SORLA transcription itself. The genetic factors that may contribute to the regulation of SORLA can only be assigned a minor fraction of 14% indicating involvement of extragenous molecules in the process. One such molecule is the brain derived neurotrophic factor (BDNF) found to increase SORLA expression in cultured neurons and *in vivo*.

Fatty acids also influence SORLA regulation. Eg: Docosahexaenoic acid (DHA), an essential dietary omega 3 polyunsaturated fatty acid (PUFA) has effects on synaptic membrane properties, learning and memory along with reducing the Aβ induced oxidative stress. The link between a lipid regulated diet in form of DHA and an increase in SORLA levels was demonstrated in a variety of *in vitro* and *in vivo* systems like primary rat neurons, aged non transgenic mice and an aged DHA depleted AD mouse model. However, conflicting data have also been reported, suggesting the opposite function that DHA enriched diets either do not modulate the levels of SORLA in transgenic mouse models of AD or even reduces SORLA expression in AD patients. Conjugated linoleic acid (CLA) is another example of a PUFA suggested to influence SORLA expression. Another dietary supplement, citrus pectin increases the endogenous levels of methanol which in turn was shown to upregulate SORL1 transcription by approximately 1.5 fold in white blood cells of healthy human volunteers after citrus pectin intake. Endothelial SORLA is modulated by shear stress and modified low density lipoproteins by a p38 MAPK dependent mechanism which accelerates atherogenesis. These molecules are all examples of extracellular factors that stimulate SORLA expression. Besides a direct role in the induction of SORL1 transcription, they also work by a more indirect pathway, Eg: activation of other genes that are able to regulate SORLA in classical signaling pathways or genes that contain precursors at the level of nucleic acid regulator. Micro RNAs have been in focus for their role in neurodegenerative diseases. These small non coding RNAs that function in complex networks can fine tune protein expression. [10]

Another class of RNA molecules that could target expression of SORLA is the non coding RNA family that regulates the expression of other protein coding genes at the level of transcriptional and post transcriptional processing. Recently, the synthesis of a non coding RNA termed 51A was demonstrated to decrease synthesis of SORLA with subsequent impairment of APP processing and increased amyloid secretion. DNA methylation is one of the important epigenetic markers, which can modify gene regulation pathways. Besides these, other mechanisms of gene regulation include alternative splice variants not containing all the 48 exons present in the SORL1 gene. The first example of a splice variant of SORLA was identified recently, suggested the existence of a receptor variant lacking exon 2. Besides its function of encoding the amino acid sequence of a protein, exons may also act as transcriptional enhancers that regulate gene expression. Recently, this was suggested as an important regulatory mechanism for SORLA expression as it was found that SORL1 exon 17 shows enhancer activity. [6]

SORLA IN VARIOUS DISEASES WITH CELLULAR MECHANISMS

SORLA is an intracellular sorting receptor that directs cargo proteins such as kinases, phosphatases and signaling receptors to their correct location within the cell. The activity of SORLA assures proper function of cells and tissues and receptor dysfunction is the underlying cause of common human malignancies including Alzheimer's disease, atherosclerosis, obesity etc.

1. SORLA controls amyloidogenic processes in the brain

Central to the pathology of AD is the amyloid precursor protein (APP), a type 1 transmembrane protein expressed

in many cell types including neurons. In a naturally occurring process, APP is broken down into various proteolytic fragments including the amyloid β peptides (Aβ), peptides of 37–43 amino acid length that encompass part of the transmembrane and extracellular domains of APP. Amyloid β peptides, notably Aβ42 are considered main culprits in neurodegenerative processes as they exhibit a tendency to aggregate to neurotoxic oligomers and senile plaques, pathological features causative of neuronal dysfunction and cell loss in AD patients. Amyloidogenic processing requires endocytosis of APP molecules from the cell surface and delivery to endosomes whereby proteolytic breakdown to Aβ occurs. As it turns out, SORLA acts as a sorting receptor for APP that shuttles internalized precursor molecules from endosomes back to the TGN to decrease production of Aβ. Binding of APP proceeds through the cluster of complement type repeats in SORLA that forms a 1:1 stoichiometric complex with the luminal domain of APP. Overexpression of SORLA in cells reduces Aβ formation while loss of expression accelerates Aβ production and senile plaque deposition documenting a protective function for SORLA in AD progression. The interaction of SORLA and APP is blocked by signaling through β adrenergic receptors via yet unknown mechanism, resulting in impaired Golgi retrieval and in increased endosomal accumulation of APP. Nascent SORLA is an inactive pro receptor (pro SORLA) that is activated by proteolytic removal of an amino terminal pro peptide in the TGN, resulting intransfer of the active receptor (SORLA) through the constitutive secretory pathway to the cell surface. Some receptor molecules at the cell surface are subjected to ectodomain shedding, resulting in release of the extracellular receptor domain.

Ectodomain shedding disrupts the ability of SORLA to act as a sorting receptor, but may serve to produce a soluble receptor fragment termed soluble (s) SORLA that acts as a signaling molecule. Still, most SORLA molecules at the cell surface remain intact and undergo clathrin dependent endocytosis facilitated by the clathrin adaptor protein 2 (AP 2). The bulk of internalized receptors move from endosomes back to the TGN to continuously shuttle between TGN and endosomal compartments thereafter. Adaptors GGA1 and GGA2 guide anterograde movement of SORLA from the TGN to endosomes, whereas PACS1 and the retromer complex facilitate retrograde sorting from endosomes back to the Golgi. AP1 may be involved in bi directional sorting. As alternative routes, SORLA may sort from endosomes to the cell surface (aided by adaptor SNX27) or to lysosomes (aided by GGA3). Taken together, the ability of SORLA to sort APP and Aβ likely represents major mechanisms, whereby this receptor reduces the amyloidogenic burden and delays progression of neurodegeneration. This hypothesis received strong support from genetic studies in AD patients that identified gene variants in SORL1, the gene encoding SORLA, as being associated with the risk of the sporadic form of AD. Some of these sequence variants have been shown to impair efficiency of SORL1 transcription or translation in line with low levels of SORLA being disease promoting in patients and mouse models. Furthermore, a mutation in SORL1 that disrupts its ability to bind Aβ has been identified in a family with autosomal dominant form of AD.

2. SORLA in neurotrophin signaling

Protein cargo sorted by SORLA in neurons is not restricted to APP and its processing products, but also encompasses a number of neurotrophin receptors, cell surface proteins that transmit trophic signals to support growth and survival of neurons. Specifically, SORLA acts as a sorting factor for TrkB and BDNF. SORLA facilitates trafficking of TrkB between synaptic membranes and the cell soma, a step critical for BDNF signal transduction into cells. Loss of SORLA results in impaired neuritic transport of TrkB and in a blunted response to BDNF. SORLA is also a downstream target of BDNF with receptor gene transcription being induced almost 10 fold by BDNF signaling in neurons. BDNF enhances trophic signaling through induction of SORL1, the gene encoding the sorting receptor for TrkB. Another trophic pathway modulated by SORLA acts through glial cell line derived neurotrophic factor (GDNF) that promotes survival of distinct populations of central and peripheral neurons such as midbrain dopaminergic neurons and spinal motor neurons. SORLA interacts with GDNF to increase its regulated secretion from cells. In addition, SORLA interacts with GFRα1, the co-receptor for GDNF. SORLA facilitates internalization of GFRα1/GDNF complexes from the plasma membrane, resulting in lysosomal catabolism of GDNF but cell surface recycling of GFRα1. This sorting route provides an efficient pathway for clearance of GDNF from the extracellular space and counteracts consequences of excessive GDNF signaling such as hyperactivity and reduced anxiety. Finally, SORLA also impacts signaling through a heterodimeric neurotrophic cytokine called cardiotrophin like cytokine: cytokine like factor 1 (CLC:CLF1). Specifically, SORLA interacts with the CLF-1 moiety to facilitate internalization of the cytokine in complex with the ciliary neurotrophic factor receptor α (CNTFRα). SORLA dependent endocytosis is required for neurotrophic signaling through CLC:CLF1, but it also downregulates signal reception by directing ligand and receptor to lysosomal degradation. The ability of this receptor to impact pathways both for trophic support but also of amyloidogenic insult to neurons makes this sorting pathway an important target in control of neurodegenerative processes in patients.

3. SORLA in renal ion homeostasis

Besides the role of SORLA in protein sorting, other important roles of this protein in non neuronal cell types are also known. SORLA is abundantly expressed in the thick ascending limb of Henle's loop, a distal segment of the renal nephron responsible for water and ion homeostasis. Lack of SORLA expression in epithelial cells of the thick ascending limb results in failure to properly reabsorb sodium and chloride, a defect attributed to the inability of these cells to activate the major sodium transporter in the distal nephron NKCC2. SORLA controls

the phosphoregulation of NKCC2 by interacting with both the SPAK and the calcineurin phosphatase that carry out phosphorylation and dephosphorylation of NKCC2 respectively.These findings suggest SORLA mediated sorting of kinases and phosphatases as a regulatory process in modulation of renal ion balance. [1]

4. SORLA in vascular cell migration and atherosclerosis

Atherosclerosis or thickening of the artery wall is a major risk factor for cardiovascular morbidity and mortality, including myocardial infarction and stroke. Atherosclerosis is caused by excessive accumulation of lipids in macrophages in the vessel wall (foam cells) and by the proliferation of intimal smooth muscle cells. These processes contribute to the formation of fibrous plaques that may obstruct the vessel lumen. SORL1 has been mapped as a pro atherogenic locus in mice. The relevance of SORLA for atherosclerotic processes was further supported by correlating circulating levels of the shedded ectodomain sSORLA with intima media thickness in subjects with coronary artery disease or acute coronary syndrome. There are two main hypotheses for how SORLA impacts atherosclerotic plaque formation. One model suggests a role for SORLA in control of plasma triacylglyceride levels through regulation of lipolysis. Triacylglyceride rich lipoproteins are highly proatherogenic particles. Their turnover is determined by hydrolysis of triacylglycerides to free fatty acids through lipoprotein lipase (LPL) in the circulation. SORLA traffics newly synthesized LPL molecules from the TGN to lysosomes, reducing the amount of the enzyme being secreted by cultured cells. In addition, SORLA mediates the endocytosis of apoAV, an activator of LPL. Modulation of LPL activity through clearance of apoAV is supported by the loss of SORLA binding in an apoAV variant found in individuals with severe hypertriglyceridemia. Potentially, either through control of LPL or apoAV levels, SORLA may inhibit lipolysis and raise the levels of proatherogenic lipoprotein particles in the circulation.

An alternative model suggests a more direct role for SORLA in atherosclerotic processes in the vessel wall. It is based on the ability of SORLA to stimulate proliferation and migration of intimal smooth muscle cells and monocytes, processes that accelerated intimal thickening and atherosclerotic plaque formation. Potentially, the stimulation of smooth muscle cells (SMC) migration by SORLA works through modulation of cell surface expression of the urokinase receptor (uPAR). The uPAR is a glycosyl phosphatidyl inositol anchored receptor for urokinase, a protease that activates plasminogen to plasmin, which in turn breaks down the extracellular matrix. Binding of urokinase to uPAR on the surface of cells increases their proteolytic potential and facilitates migration. The ability to regulate surface exposure of uPAR is seen for full length SORLA but also for sSORLA, suggesting both cell autonomous and non autonomous modes of action. [3]

5. SORLA is a risk factor for obesity

Genome wide association studies not only confirmed the relevance of SORL1 as a genetic risk factor for sporadic AD, but also revealed a surprising association of this locus with metabolic traits (Eg: obesity and waist circumference) in humans and mouse models. In addition, loss of SORLA expression in mice with targeted SORL1 disruption is protected from diet-induced obesity, suggesting a so far unknown function for this receptor in metabolic regulation. Recent studies in transgenic mouse models shed light on potential modes of receptor action, proposing distinct roles for SORLA and sSORLA in this context. sSORLA impair thermogenesis in mice by binding to bone morphogenetic protein (BMP) receptors and inhibiting BMP/TGF β signaling in adipocytes. Thermogenesis is the process of heat production from metabolic fuel and a driving force for consumption of body lipid stores by brown adipose tissue. Mice genetically deficient for SORLA are protected from diet induced obesity because of enhanced thermogenesis in adipose tissue, providing an explanatory model for the association of SORL1 with obesity in the human population.

An alternative model to explain the role of SORLA in energy homeostasis entails intracellular sorting of the insulin receptor (IR). One of the actions of insulin signaling in adipocytes is the downregulation of lipolysis. This mechanism reduces energy production from breakdown of lipid stores in a state of sufficient energy supply from carbohydrates. Cellular signal transduction proceeds through binding of insulin to the IR on the surface of target cells and subsequent endocytosis of receptor and hormone complexes. Internalization serves two purposes. First, it delivers receptor ligand complexes to endosomes, a pre requisite for signal transduction. Second, it moves receptor ligand complexes to lysosomal compartments for catabolism, a mean to downregulate signal reception. In a process reminiscent of APP sorting in neurons, SORLA interacts with internalized IR (Insulin Receptor) molecules in endosomes and shuttles them back to the TGN. Retrograde trafficking reduces lysosomal catabolism and increases the fraction of IR molecules recycled back to the cell surface. SORLA dependent recycling sensitizes adipocytes for insulin signal reception and enhances the impact of insulin on blockade of lipolysis. Consequently, overexpression of SORLA in adipose tissue of mice inhibits lipolysis and promotes the fat mass gain, while loss of the receptor expression increases lipolysis rate and protects animals from obesity and secondary metabolic complications.

In obese human subjects the levels of SORLA in adipose tissue and those of sSORLA in the circulation positively correlate with the body mass index. Although the exact mode of action in adipose tissues as humoral factor or as sorting receptor still await further clarification. All current data support the significance of SORL1 as genetic risk factor of obesity in the human population.

Future trends of SORLA

Besides these, SORLA also act as a risk factor for diabetes, mainly SORCS1 by which it acts as a major causative for sporadic AD. Type II diabetes is a disease characterized by lack of responsiveness of cells to insulin is one of the major risk factor for sporadic AD. As well as in peripheral tissues such as muscle, liver and fat insulin signaling is also widespread in the neurons in brain. In AD patients brain signaling is impaired, partially due to reduced levels of the hormone and abnormal intracellular sequestration of IR in neurons caused by Aβ. Altered levels of insulin signaling in a diabetic state may impact Aβ metabolism by changing rates of production and metabolism. The mechanistic link between brain insulin resistance and amyloidogenic processes is not yet cleared. [1]

CONCLUSION

SORLA, a sorting receptor for multiple ligands in organs such as brain, kidney, adipose tissue etc. SORLA dysfunction may explain some of the comorbidities commonly seen in the human population as exemplified for AD, atherosclerosis and obesity. Besides these, SORLA also act as a risk factor for diabetes, mainly SORCS1. Although quite speculative at present, low levels of receptor expression in carriers of SORL1 may cause insulin resistance and increased amyloidogenic burden. This will be an explanatory model for the link between neurodegenerative and metabolic diseases that warrant further exploration. As a type 1 transmembrane protein, SORLA holds great promise as a genetic risk factor and new biomarker for diagnosis and perhaps it might even constitute a druggable target for the treatment of AD.

BIBLIOGRAPHY

1. Vanessa Schmidt, Aygul Subkhangulove, Thomas E Willnow. Sorting receptor SORLA: cellular mechanisms and implications for disease. Cell. Mol. Life Sci. 2017; 74(8): 1475-1483.
2. Olav M Andersen, Ina Maria Rudolph, Thomas E Willnow. Risk factor SORL1: from genetic association to functional validation in Alzheimer's disease. Acta Neuropathol. 2016; 132(5): 653-665.
3. Vanessa Schmidt, Thomas E Willnow. Protein sorting gone wrong-VPS10 P domain receptors in cardiovascular and metabolic diseases. ELSEVIER. 2016; 245: 194-199.
4. Stine C Klinger, Anne Hojland, Shweta Jain, MadsKjolby, Peder Madsen, Anna Dorst Svendsen, Gunilla Olivecrona, Juan S Bonifacino, Morten S Neilsen. Polarized trafficking of the sorting receptor SORLA in neurons and MDCK cells. FEBS Journal. 2016; 283(13): 2476-2493.
5. Timothy Y Huang, Yingjun Zhao, Xiaoguang Li, Xin Wang, I Chu Tseng, Robert Thompson, Shichum Tu, Thomas E Willnow, Yun wu Zhang, Huaxi Xu. SNX27 and SORLA interact to reduce amyloidogenic subcellular distribution and processing of amyloid precursor protein. The Journal of Neuroscience. 2016; 36(30): 7996-8011.
6. Ishita Guha Thakurta, Olav M Andersen. Associations of sorLA/SORL1 with Alzheimer's disease. Receptors and Clinical investigation. 2015; 2(3): 1-15.
7. Sonya B Dumanis, Tilman Burgert, Safak, Caglayan Annette Fuchtbauer, Ernst Martin Fuchtbauer, Vanessa Schmidt, Thomas E Willnow. Distinct functions for anterograde and retrograde sorting of SORLA in amyloidogenic processes in the brain. The journal of Neuroscience. 2015; 37(35): 12703-12713.
8. Thomas E Willnow, Olav M Andersen. Sorting receptor SORLA- a trafficking path to avoid Alzheimer's disease. Journal of cell science. 2013; 126: 2751-2760.
9. Vanessa Schmidt, Anje Sporbert, Michael Rohe, Tatjana Reimer, Armin Rehm. SORLA/LR11 Regulates processing of Amyloid precursor protein via interaction with adaptors GGA and PACS 1. The Journal of Biological Chemistry. 2007; 282(45): 32956-32964.
10. Qiu Lan Ma, Bruce Teter, Oliver J Ubeda, Takashi Morihara, Dilsher Dhoot, Michael D Nyby, Micheal L Tuck, Greg M Cole. Omega 3 fatty acid docosahexaenoic acid increases sorLA/SORL1, a sorting protein with reduced expression in sporadic Alzheimer's disease (AD): relevance to AD prevention. The Journal of Neuroscience. 2007; 52(27): 14299-14307.