REVIEW

20 Years Anniversary for SORLA/SORL1 (1996-2016)

Giulia Monti, Olav M. Andersen

Danish Research Institute of Translational Neuroscience (DANDRITE) Nordic-EMBL Partnership, Department of Biomedicine, Aarhus University, Ole Worms Allé 3, DK-8000 Aarhus C, Denmark

Correspondence: Olav M. Andersen
E-mail: o.andersen@biomed.au.dk
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SORLA is a sorting receptor known to control the intracellular trafficking of the amyloid precursor protein, which impaired pathway has a central role in the development of Alzheimer's disease (AD). Recently, genetic analyses confirmed the casual role for SORLA in AD, as coding variants and single nucleotide polymorphisms of *SORL1* (gene encoding SORLA) were identified in individuals affected by early-onset AD and late-onset AD, respectively. However, many other different types of ligands were found to target the receptor, thus strongly indicating that SORLA can exert multifunctional activities. In the current review, we provide an overview of the multi-ligand properties of SORLA, showing how this complex receptor is involved in a variety of biological functions.

Keywords: SORL1; SORLA; receptor

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SORLA is a multifunctional and hybrid receptor

In 1996, Petersen and colleagues at Aarhus University, Denmark described the identification of the 250 kDa intracellular sorting-related receptor with A-type repeats (SORLA, also known as SORL1 and LR11) in quest for novel lipoprotein receptors in human brain capable of binding to the 39 kDa receptor-associated protein (RAP) [1]. Almost simultaneously, its expression was also described for rabbit by Saito's group [2] and later SORLA was identified as a novel homolog for many other species [3-5]. Currently, orthologs of the *SORL1* gene encoding SORLA have been identified from more than 200 species, showing strong cross-species conservation that suggests important physiological functions for this protein. However, an interesting variation in the number of domains included in the translated polypeptide has been noticed by comparing the protein structure of different species. For instance, differences in the numeric composition of extracellular modules were found in the homologous head-activator (HA) binding protein from hydra, a receptor able to bind to the neuropeptide HA which controls hydra head regeneration by promoting cell proliferation [6].

Jacobsen and colleagues proposed the first structural description of this novel protein, revealing that SORLA is a unique hybrid receptor that shares structural similarity with both low-density lipoprotein receptors (LDLRs) and the vacuolar protein sorting 10 protein (VPS10p), a Golgi transmembrane receptor that acts in sorting carboxypeptidase Y in yeast [1]. In addition to the cluster of 11 complement-type repeats (CR) found in other LDLRs family

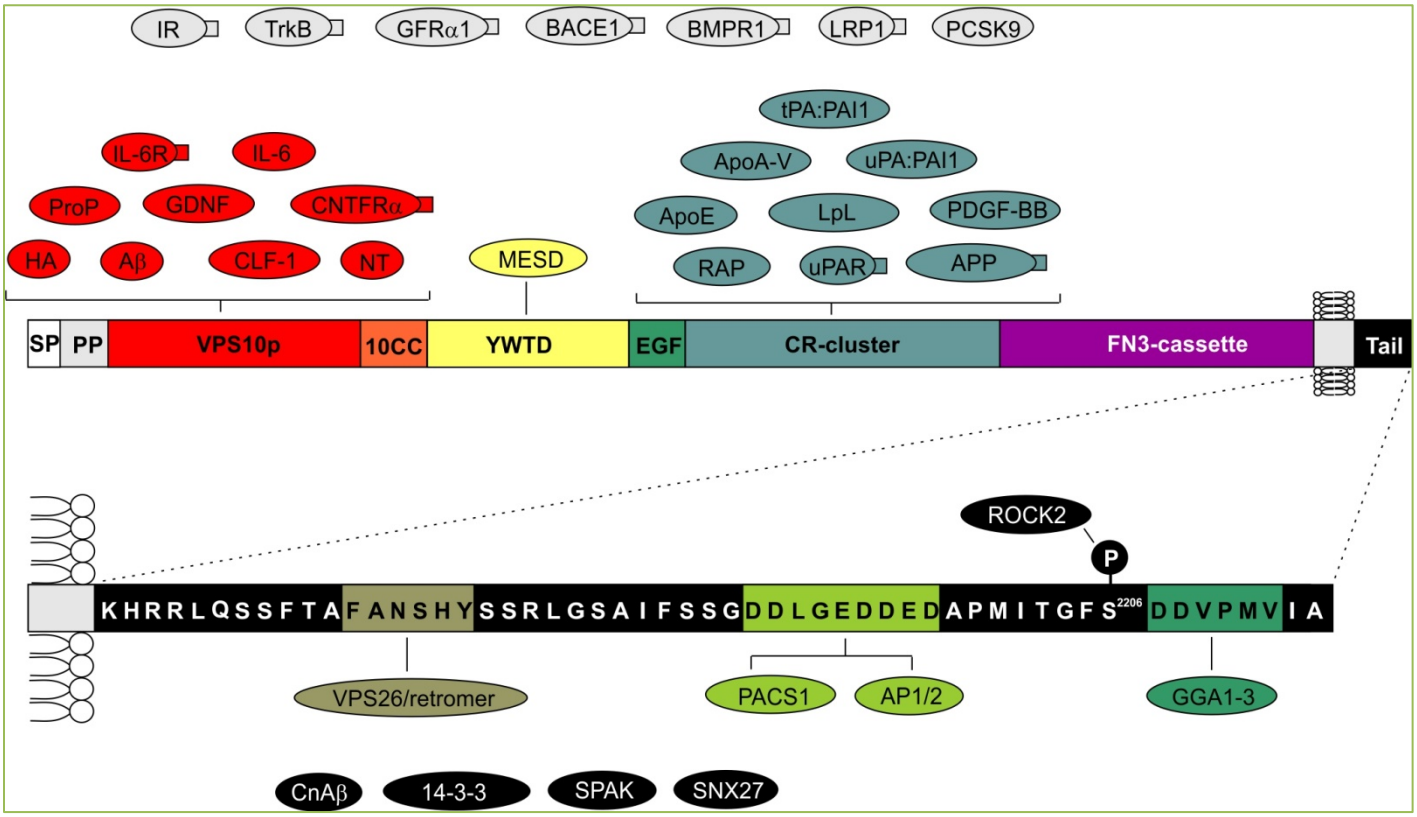

Figure 1. Schematic representation of interaction partners of SORLA. SORLA interacts with a broad panel of proteins via its extracellular (top) and its intracellular (bottom) domains. Identified binding regions in the receptor are indicated using the *same color code* as for ligands. Membrane-anchored interactors are presented in a circle with a small rectangle, whereas secreted and soluble protein ligands are only encircled. All abbreviations are explained in Table 1 that also includes a link to a reference that reported on the identifed interaction.

member and the 700 amino acids VPS10p domain, SORLA also contains a YWTD β-propeller domain, six fibronectin type III repeats (FnIII) prior to the transmembrane domain and a 56-amino acids cytoplasmic tail presenting a putative internalization signal that suggested a possible function also as endocytic receptor.

Besides the binding of RAP to the luminal part of the receptor, many different ligands have been found to interact with SORLA, including proteinases, lipoproteins, co-receptors, and signaling factors. Binding studies revealed that these compounds bind to different domains on the receptor, addressing SORLA to a variety of cellular physiological roles (Figure 1). All this evidence validated SORLA as a multifunctional hybrid receptor and major efforts have been devoted to elucidate the role played by this receptor in a variety of malignancies, such as Alzheimer's Disease (AD), atherosclerosis, obesity and impaired renal ion homeostasis.

At first glance on the mapped binding pattern shown in Figure 1, it is evident that most of the identified interaction partners of SORLA are able to associate with either the VPS10p domain or the CR-cluster. On the contrary, no specific ligands have been found to interact with the YWTD-repeated region, although this region in related receptors (LRP5, LRP6) is involved in binding of many different types of ligands (reviewed in [7]). Furthermore, no interaction partners have yet been identified for binding to the cassette with the six FnIII domains of SORLA, although FnIII domains are known to be engaged in direct ligand binding for a variety of other proteins [8]. A possible explanation for the latter could be that the function of the FnIII domains is merely linked to the regulation of the overall conformation of the SORLA ectodomain instead of ligand binding. However, the importance of this region is underscored by the identification of several mutations in the sequence of the FnIII region found to be associated with diseases [9-11], strongly suggesting an important function for this receptor fragment.

The aim of the current review is to provide a comprehensive overview of the different ligands that interact with SORLA (as presented in Table 1), showing how the challenge of elucidating the multi-ligand properties of this receptor has significantly attracted increasing interest of researchers over the last two decades.

Table 1. Reported ligand interactions of SORLA

Extracellular Interaction partner	Abbreviation	Primary citation
Amyloid precursor protein	APP	[41]
Amyloid β-peptide	Aβ	[47]
Apolipoprotein A-V	ApoA-V	[26]
Apolipoprotein E	ApoE	[34]
β-site APP-cleaving enzyme 1	BACE1	[46]
Bone morphogenic protein receptor, type 1	BMPR1A, BMPR1B	[28]
Ciliary neurotrophic factor receptor α	CNTFRα	[58]
Cytokine-like factor-1	CLF-1	[58]
GDNF family receptor α-1	GFRα1	[60]
Glia-derived neurotrophic factor	GDNF	[59]
Head activator	HA	[61]
Insulin receptor	IR	[29]
Interleukin-6	IL-6	[62]
Interleukin-6 receptor	IL-6R	[62]
Lipoprotein lipase	LpL	[27]
Low-density lipoprotein receptor related protein	LRP1	[63]
Mesoderm development	MESD	[43]
Neurotensin	NT	[34]
Platelet-derived growth factor-BB	PDGF-BB	[21]
Pro-peptides	ProP	[34]
Proprotein convertase subtilisin/kexin type 9	PCSK9	[64]
Receptor-associated protein	RAP	[1]
Tissue-type plasminogen activator	tPA	[21]
Tropomyosin-related kinase receptor B	TrkB	[65]
Type-1 plasminogen activator inhibitor	PAI-1	[21]
Urokinase-type plasminogen activator	uPA	[21]
Urokinase-type plasminogen activator receptor	uPAR	[19]
Intracellular Interaction partner	**Abbreviation**	**Primary citation**
14-3-3	14-3-3	[66]
Adaptor protein-1 complex	AP1	[67]
Adaptor protein-2 complex	AP2	[68]
Calcineurin Aβ	CnAβ	[69]
Golgi-localizing γ-adaptin ear homology ADP-ribosylation factor-binding protein	GGA	[70]
Phosphofurin acidic cluster sorting protein-1	PACS1	[71]
Rho-associated coiled-coil containing protein kinase 2	ROCK2	[72]
Sorting nexin 27	SNX27	[73]
Ste-20-related proline-alanine-rich kinase	SPAK	[74]
Vacuolar protein sorting-associated protein 26	VPS26	[75]

Examples of SORLA functions

First investigations on SORLA demonstrated that the receptor is broadly expressed in the central nervous system (CNS), with highest levels observed in neurons of the cerebellum, cortex, hippocampus and spinal cord [4, 12, 13]. The abundant distribution in the brain suggested that SORLA might play important and specific brain functions. In addition, since SORLA is also an apolipoprotein E (ApoE) receptor, this represented a yet further strengthening of its cerebral role in view of the known strong association of ApoE receptors with neurodegenerative diseases [14, 15]. Further studies showed that this receptor is also expressed in some non-neuronal tissues as ovary, prostrate, testis, and pancreas with less detectable levels in kidney, placenta, lung and heart [1]. Accordingly, the wide distribution of SORLA throughout the body suggested the involvement of the receptor in different cellular events and pathways. SORLA has emerged as a receptor with important physiological functions and several significant findings have greatly contributed to progress the research in this field, of which selected results are presented in Figure 2.

Cardiovascular disease

Smooth muscle cells migration

Besides the hypothesis about the significance of SORLA in the CNS, researchers started to focus on the role played by this receptor in different tissues, including the arterial wall. In fact, it was known that dysregulation of LDLR pathway is critical for the formation of atherosclerotic lesions [16, 17]. In 1998, a first study described a direct role for SORLA during atherogenesis using two different models for experimental atherosclerosis constituted by cholesterol-fed rabbits and balloon-injured rats [18]. Kanaki and colleagues demonstrated that the expression of SORLA is significantly induced in the atherosclerotic lesions of these two models, with a predominant localization of the receptor in intimal smooth muscle cells (SMCs). These findings suggested an

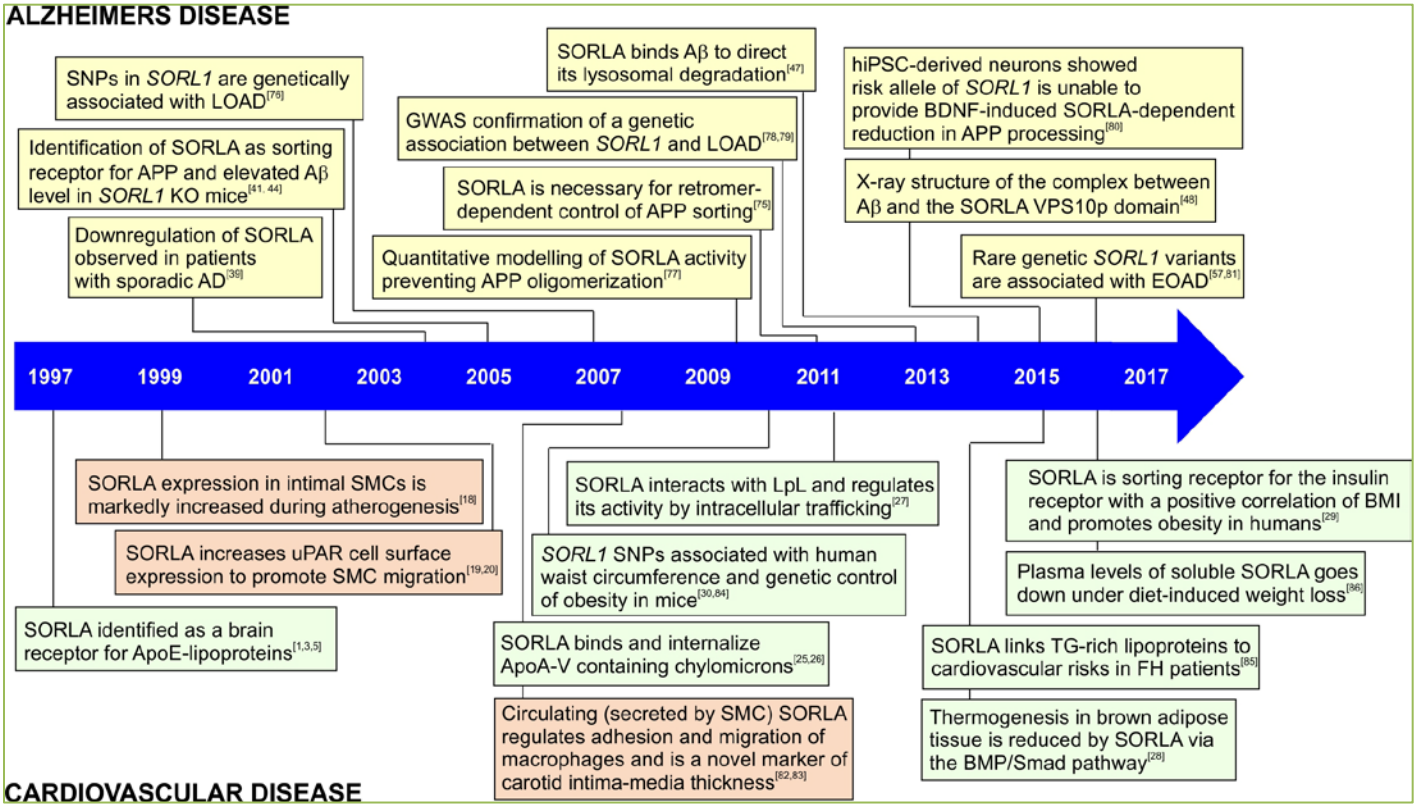

Figure 2. Timeline of key findings in *SORL1*/SORLA related research. The identification of key research results related to the structural and functional biology of SORLA is listed here in chronological order. The research leading to support an important function in the pathology of Alzheimer's disease are shown above the timeline in yellow boxes. The findings that related to its established role in cardiovascular diseases are indicated below the timeline, where findings associated with a role in the smooth muscle cells migration are shown in red boxes and research towards understanding the involvement of SORLA in metabolic disorders is outlined in green. Abbreviations are indicated in the text.

involvement of SORLA in the processes of proliferation and migration of SMCs into the intimal layer, paving the way to further studies about the role played by the receptor during atherosclerotic plaque formation and vascular remodeling.

In 2004, Zhu and colleagues described the urokinase-type plasminogen activator receptor (uPAR) as a novel binding partner of SORLA, which interaction represents a valid explanation for the previously observed ability of the receptor of inducing SMCs migration *in vitro*. The uPAR is a glycosyl-phosphatidyl-inositol anchored membrane protein that activates uPA-mediated cleavage of plasminogen into plasmin resulting in the degradation of the extracellular matrix and promoting the invasion of SMCs. It was found that SORLA is able to bind to and colocalize with uPAR on the cell surface increasing its expression and reducing its internalization within the cell. Accordingly, the enhanced availability of uPAR at the plasma membrane results in promoting matrix degradation [19, 20].

On the other hand, another ligand of SORLA is constituted by the complex between uPA and its type-1 inhibitor PAI-1 [21]. By interacting with the CR-cluster of SORLA, the uPA-PAI-1 complex is less efficiently internalized into cells reducing the induced downregulation of uPAR and thus increasing the migratory potential of the cells. Taken together, these results show how the interaction of SORLA with different components of the plasminogen activating system leads to induce the migration of intimal SMCs and accelerate plaque formation.

In the same work, the authors demonstrated that also the platelet-derived growth factor-BB (PDGF-BB) directly binds to SORLA [21]. Exposure to PDGF-BB is known to be fundamental for promoting SMC migration in the intima mediated by the specific membrane PDGF β-receptor (PDGFR-β) [22, 23]. The alternative binding between PDGF-BB and SORLA may inhibit the clearance of the growth factor and promote overexpression of its specific receptor PDGFR-β with subsequent stimulation of the migratory activity of SMCs.

Based on these crucial bindings, it was suggested that the modulation of the uPAR/PDGFR-β system has possible significance for preventing atherosclerosis. In particular, the pharmacological efficiency of statins in being protective for

plaque formation has been found to suppress the endogenous SORLA production, thus modulating the SORLA/uPAR system and reducing the migration of intimal SMCs [24].

Metabolic disorders

Among the multiple activities of SORLA, the receptor appears to be involved in lipoprotein metabolism and metabolic disorders via binding of different components required for the maintenance of both lipid and glucose homeostasis.

Recently, binding studies have described Apolipoprotein A-V (ApoA-V) as a novel ligand for the CR-cluster of SORLA which association is implied in controlling the plasma levels of tryglicerides (TGs) [25, 26]. ApoA-V is known to act as positive modulator of the lipoprotein lipase (LpL), a key factor for the hydrolysis of tryacilglycerols of very-low density lipopoproteins and chylomicrons in the blood stream that stimulates the plasma clearance of TGs. The binding of ApoA-V to SORLA has been proposed to enhance the interaction of CMs to the receptor and to cause the internalization of ApoA-V into cells, thus resulting in reduced LpL activity and lipolysis [25, 26].

Interestingly, another ligand of SORLA is constituted by the same LpL, which binding occurs between the C-terminal domain of LpL and the CR-cluster of the receptor under neutral and acidic conditions [27]. This interaction promotes the direct transport of newly synthesized molecules of LpL from the trans Golgi network (TGN) to the endosomes, from which the ligand is routed to the lysosomes for degradation.

In addition to the role in controlling plasma lipid levels, very recent studies have highlighted novel functions for SORLA in brown adipose tissue (BAT) [28, 29]. Previously, genome-wide association studies have identified *SORL1* as a gene with significant association with obesity and body mass index in humans [30]. In 2015, Whittle and colleagues demonstrated that SORLA is able to bind to bone morphogenetic protein (BMP) receptors and to suppress thermogenic signalling in adipose tissue, confirming the involvement of the receptor in metabolic processes [28]. The physiological activation of BMPRs leads to increased phosphorylation of intracellular Smad proteins, representing an essential signalling cascade for the regulation of BAT formation [31, 32]. By interacting with BMPR, SORLA inhibits the BMP/Smad pathway resulting in the suppression of the transcription of key thermogenic genes. Accordingly, this finding suggests that SORLA may play an important role in mediating energy conservation in adipose tissue and that loss of the receptor can represent a protective factor against obesity.

Moreover, Schmidt and colleagues have described the insulin receptor (IR) as a novel ligand for SORLA, providing further evidence about the function of SORLA in glucose metabolism and its association with human obesity [29]. From these studies, SORLA emerged as an intracellular sorting factor that traffics IR molecules to the plasma membrane, enhancing surface expression and thus promoting insulin-induced suppression of lipolysis in adipocytes.

Neurodegeneration – Alzheimer's disease

The prominent expression of SORLA in the brain directed major efforts to elucidate its physiological relevance in the CNS. As other members of the LDLR family, SORLA is an ApoE-receptor able to bind and internalize ApoE-containing lipoproteins [33, 34]. In the past years, several investigations have determined that ApoE is abundantly produced by glial cells in the brain where it is believed to have a central role in cholesterol and lipid delivery to neurons, transport required for maintenance of synaptic connections and support synaptogenesis [35, 36]. Strong evidence has showed that ApoE genotype is firmly associated with neurodegeneration and to date the ε4 allele of the gene is the strongest genetic risk factor of AD [37, 38]. Accordingly, the emergent importance of lipid biology in neurodegeneration and the direct interaction with ApoE-rich lipoproteins have led to stress the hypothesis that SORLA exerts fundamental functions in the human brain.

In 2004, Scherzer and colleagues were the first to establish the connection between SORLA and AD by demonstrating that the expression of this receptor is significantly decreased in the brain of patients with sporadic late-occurring AD (LOAD) [39]. In addition, parallel studies revealed that mouse models deficient of SORLA show increased level of β-amyloid peptide (Aβ) production and deposition, suggesting that lack of receptor activity can be a primary cause of AD by modulating the amyloidogenic process [40, 41]. The accumulation of neurotoxic Aβ in senile plaques is known to have a central role in the pathogenesis of AD, leading to cell death and neuronal dysfunctions [42]. Over the past decades, the formulation of the "Amyloid hypothesis" have led to the identification of the molecules that control amyloidogenic metabolism, focusing on the mechanisms underlying the processing of the Amyloid precursor protein (APP) into Aβ peptides.

Interestingly, several studies revealed the ability of SORLA to bind to some of the major players involved in the amyloid cascade and formation of Aβ plaques, demonstrating once more the wide range of molecular partners of the receptor and its complex involvement in the onset of AD.

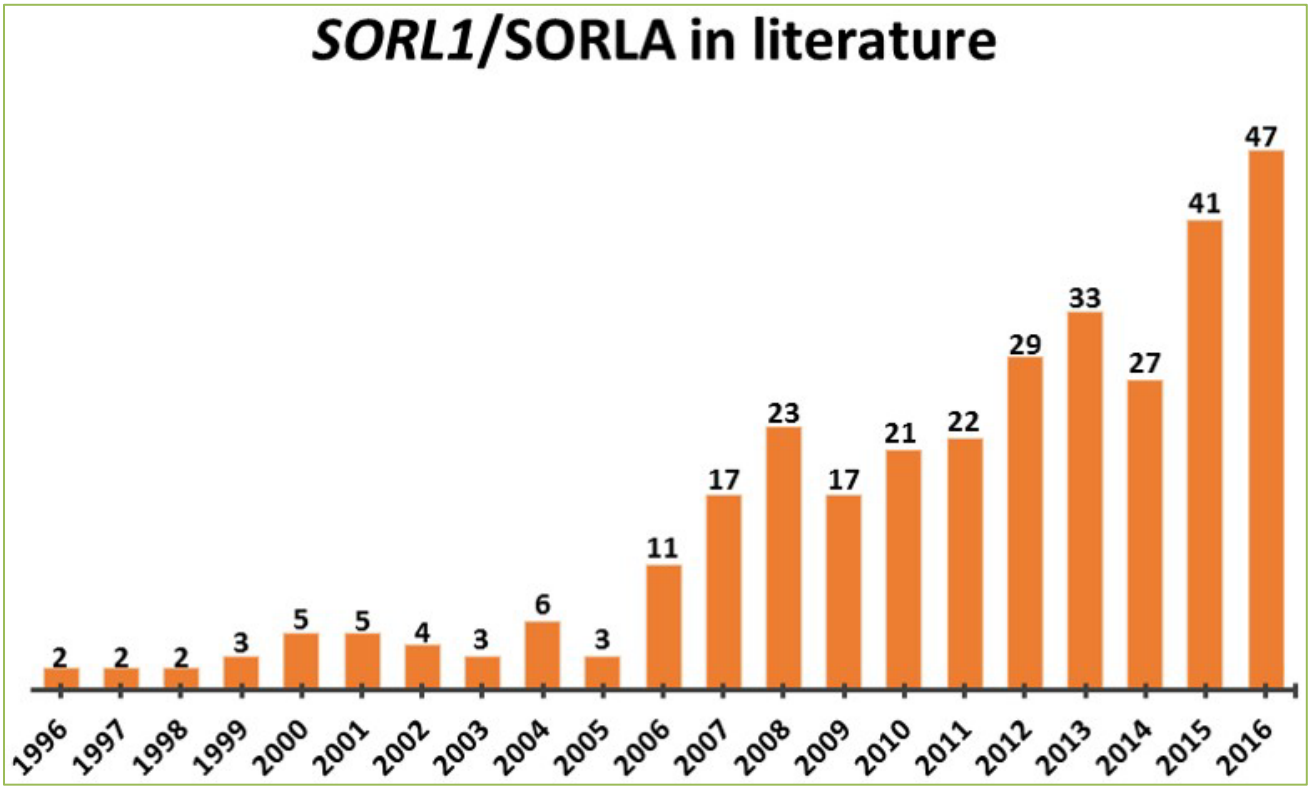

Figure 3. Bibliometric analysis of *SORL1*/SORLA in the published literature. A total of 323 entries in PubMed is revealed when using the search terms "SORL1", "SORLA", or "LR11". Bar graph showing the number of entries for each year from the first report describing the discovery of *SORL1*/SORLA in 1996 until 2016, showing a steadily increasing number of publications from 2004/2005.

To date, APP represents one of the most investigated ligands of SORLA and their interaction results in the protection from processing of the precursor into Aβ peptide [41, 43]. In 2005, SORLA was first described as a neuronal sorting determinant of APP trafficking between the TGN and the early endosomal compartments, significantly slowing down the export rate of APP from the TGN and thus resulting in decreased Aβ secretion from neurons [41, 44]. Later, binding studies revealed that APP directly interacts with the CR 5-8 cluster domain in SORLA, forming a 1:1 stoichiometric complex that is essential for the protective activity of the sorting receptor in amyloidogenesis [45].

Besides the binding of APP, co-immunoprecipitation analysis revealed direct interaction between SORLA and the β-site APP-cleaving enzyme 1 (BACE-1), an aspartic-acid proteinase involved in the amyloidogenic cleavage of APP [46]. In light of this finding, the authors hypothesized that SORLA could affect APP metabolism and Aβ production also by affecting BACE–APP complex formation in the Golgi apparatus and thus preventing secretase cleavage. Accordingly, reduced SORLA expression may enhance the interaction between APP and the secretase, resulting in increased Aβ processing.

More recently, further studies provided evidence for an additional binding of Aβ peptides directly to SORLA [47]. In particular, the amino-terminal VPS10p domain of the receptor is responsible for the interaction with Aβ and trafficking of newly produced peptides to lysosomes for final degradation [48]. This finding validated that SORLA plays several roles also in Aβ catabolism and clearance, showing how the versatile activity of this multi-ligand receptor can have a central function in different steps of APP proteolytic pathway.

Cancers - cell cycle

Interestingly, several studies have reported a possible involvement of SORLA in proliferation and differentiation of neuroblastoma cells, shedding new light on receptor functions in neuronal and vascular cells [49]. However, the nature of protein interactions that underlies this relation still remains mostly unidentified. Hirayama and colleagues studied the proliferation-dependent expression of SORLA using two different cell lines as models of neurodifferentiation, such as human neuroblastoma and pheochromocytoma cells. They could demonstrate that the transcription of the *SORL1* gene is regulated in different ways during proliferation and differentiation, speculating a possible contribution of SORLA in the rapid growth of

malignant cells as described for other LDLR family members [50-52].

More recently, a linear correlation between *SORL1* expression levels and the prognosis of different cancers was demonstrated, including diffuse large B-cell lymphoma, non-Hodgkin lymphoma and follicular lymphoma as well as biliary tract and pancreatic cancers [53-56]. However, to date it remains unclear how serum *SORL1* concentrations are significantly changed in oncologic patients and further investigations are necessary to elucidate the mechanisms underlying cancer pathways.

Scene is set for novel research and interest findings

Over the last two decades, much has been learnt about the *SORL1* gene and its corresponding translational product, and the progress made in this field has provided relevant information for our understanding of human physiology. Moreover, the discovery of SORLA allowed to gain new insights into sorting receptor functionality, leading to the formulation of new hypothesis about the mechanisms underlying the development of several human pathologies. Multiple methodological and theoretical approaches started to address this challenging issue by identifying new receptor molecular partners and providing more information about the complex structure of SORLA using biochemical and molecular biology techniques. Based on these findings, clinical research greatly contributed to the advancement of receptor investigation, validating the exciting data from laboratories. In addition, the decoding of the human genome sequence and the revolution in genetic research contributed to outline the significance of *SORL1* as new genetic risk factor of different common conditions in the human population [57]. Given the physiological importance, major efforts have been devoted to elucidate the role played by SORLA in human biology and an emerging interest from the scientific community has been recorded over the recent years.

To document this, we conducted a PubMed literature search using “SORL1”, ”SORLA”, ”LR11” as keywords and found 323 published materials from 1996 to 2016 (Figure 3). Based on this results, we noticed an exponential increasing interest and the number of publications per year reveals strong ongoing efforts to understand the biological significance of *SORL1* and its translational product. In particular, the upward trend in publications seems to spark around 2004/2005, when the scientific world learnt about the identification of a role for SORLA in AD and in cardiovascular disorders.

Accordingly, we expect that future studies will certainly help strengthening our knowledge in this field, thus leading to the development of more specific possibilities of interventions that could hopefully pave the way to medical successes.

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References

1 Jacobsen L, Madsen P, Moestrup SK, Lund AH, Tommerup N, Nykjær A, *et al*. Molecular characterization of a novel human hybrid-type receptor that binds the alpha2-macroglobulin receptor-associated protein. J Biol Chem 1996; 271:31379-31383.

2 Yamazaki H, Bujo H, Saito. A novel member of the LDL receptor gene family with eleven binding repeats is structurally related to neural adhesion molecules and a yeast vacuolar protein sorting receptor. J Atheroscler Thromb 1997; 4:20-26.

3 Yamazaki H, Bujo H, Kusunoki J, Seimiya K, Kanaki T, Morisaki N, *et al*. Elements of neural adhesion molecules and a yeast vacuolar protein sorting receptor are present in a novel mammalian low density lipoprotein receptor family member. J Biol Chem 1996; 271:24761-24768.

4 Kanaki T, Bujo H, Hirayama S, Tanaka K, Yamazaki H, Seimiya K, *et al*. Developmental regulation of LR11 expression in murine brain. DNA Cell Biol 1998; 17:647-657.

5 Mörwald S, Yamazaki H, Bujo H, Kusunoki J, Kanaki T, Seimiya K, *et al*. A novel mosaic protein containing LDL receptor elements is highly conserved in humans and chickens. Arterioscler Thromb Vasc Biol 1997; 17:996-1002.

6 Hampe W, Urny J, Franke I, Hoffmeister-Ullerich SA, Herrmann D, Petersen CM, *et al*. A head-activator binding protein is present in hydra in a soluble and a membrane-anchored form. Development 1999; 126:4077-4086.

7 Andersen OM, Dagil R, Kragelund BB. New horizons for lipoprotein receptors: communication by beta-propellers. J Lipid Res 2013; 54:2763-2774.

8 Bencharit S, Cui CB, Siddiqui A, Howard-Williams EL, Sondek J, Zuobi-Hasona K, *et al*. Structural insights into fibronectin type III domain-mediated signaling. J Mol Biol 2007; 367:303-309.

9 Zhuang S, Linhananta A, Li H. Phenotypic effects of Ehlers-Danlos syndrome-associated mutation on the FnIII domain of tenascin-X. Protein Sci 2010; 19:2231-2239.

10 Zhang P, Becka S, Craig SE, Lodowski DT, Brady-Kalnay SM, Wang Z. Cancer-derived mutations in the fibronectin III repeats of PTPRT/PTPrho inhibit cell-cell aggregation. Cell Commun Adhes 2009; 16:146-153.

11 Robertson A, MacColl GS, Nash JA, Boehm MK, Perkins SJ, Bouloux PM. Molecular modelling and experimental studies of mutation and cell-adhesion sites in the fibronectin type III and

whey acidic protein domains of human anosmin-1. Biochem J 2001; 357:647-659.

12 Motoi Y, Aizawa T, Haga S, Nakamura S, Namba Y, Ikeda K. Neuronal localization of a novel mosaic apolipoprotein E receptor, LR11, in rat and human brain. Brain Res 1999; 833:209-215.

13 Hermans-Borgmeyer I, Hampe W, Schinke B, Methner A, Nykjær A, Süsens U, *et al*. Unique expression pattern of a novel mosaic receptor in the developing cerebral cortex. Mech Dev 1998; 70:65-76.

14 Giau VV, Bagyinszky E, An SS, Kim SY. Role of apolipoprotein E in neurodegenerative diseases. Neuropsychiatr Dis Treat 2015; 11:1723-1737.

15 Tudorache IF, Trusca VG, Gafencu AV. Apolipoprotein E - A Multifunctional Protein with Implications in Various Pathologies as a Result of Its Structural Features. Comput Struct Biotechnol J 2017; 15:359-365.

16 Hiltunen TP, Ylä-Herttuala S. Expression of lipoprotein receptors in atherosclerotic lesions. Atherosclerosis 1998; 137:S81-88.

17 Mani A, Radhakrishnan J, Wang H, Mani A, Mani MA, Nelson-Williams C, *et al*. LRP6 mutation in a family with early coronary disease and metabolic risk factors. Science 2007; 315:1278-1282.

18 Kanaki T, Bujo H, Hirayama S, Ishii I, Morisaki N, Schneider WJ, *et al*. Expression of LR11, a mosaic LDL receptor family member, is markedly increased in atherosclerotic lesions. Arterioscler Thromb Vasc Biol 1999; 19:2687-2695.

19 Zhu Y, Bujo H, Yamazaki H, Ohwaki K, Jiang M, Hirayama S, *et al*. LR11, an LDL Receptor Gene Family Member, Is a Novel Regulator of Smooth Muscle Cell Migration. Circ Res 2004; 94:752-758.

20 Zhu Y, Bujo H, Yamazaki H, Hirayama S, Kanaki T, Takahashi K, *et al*. Enhanced expression of the LDL receptor family member LR11 increases migration of smooth muscle cells in vitro. Circulation 2002; 105:1830-1836.

21 Gliemann J, Hermey G, Nykjær A, Petersen CM, Jacobsen C, Andreasen PA. The mosaic receptor sorLA/LR11 binds components of the plasminogen activating system and PDGF-BB similarly to low density lipoprotein receptor-related protein (LRP1) but mediates slow internalization of bound ligand. Biochem J 2004; 381:203-212.

22 Yu J, Moon A, Kim HR. Both platelet-derived growth factor receptor (PDGFR)-alpha and PDGFR-beta promote murine fibroblast cell migration. Biochem Biophys Res Commun 2001; 282:697-700.

23 Rönnstrand L, Heldin CH. Mechanisms of platelet-derived growth factor-induced chemotaxis. Int J Cancer 2001; 91:757-762.

24 Jiang M, Bujo H, Zhu Y, Yamazaki H, Hirayama S, Kanaki T, *et al*. Pitavastatin attenuates the PDGF-induced LR11/uPA receptor-mediated migration of smooth muscle cells. Biochem Biophys Res Commun 2006; 348:1367-1377.

25 Nilsson SK, Lookene A, Beckstead JA, Gliemann J, Ryan RO, Olivecrona G. Apolipoprotein A-V interaction with members of the low density lipoprotein receptor gene family. Biochemistry 2007; 46:3896-3904.

26 Nilsson SK, Christensen S, Raarup MK, Ryan RO, Nielsen MS, Olivecrona G. Endocytosis of apolipoprotein A-V by members of the low density lipoprotein receptor and the VPS10p domain receptor families. J Biol Chem 2008; 283:25920-25927.

27 Klinger SC, Glerup S, Raarup MK, Mari MC, Nyegaard M, Koster G, *et al*. SorLA regulates the activity of lipoprotein lipase by intracellular trafficking. J Cell Sci 2011; 124:1095-1105.

28 Whittle AJ, Jiang M, Peirce V, Relat J, Virtue S, Ebinuma H, *et al*. Soluble LR11/SorLA represses thermogenesis in adipose tissue and correlates with BMI in humans. Nat Commun 2015; 6:8951.

29 Schmidt V, Schulz N, Yan X, Schürmann A, Kempa S, Kern M, *et al*. SORLA facilitates insulin receptor signaling in adipocytes and exacerbates obesity. J Clin Invest 2016; 126:2706-2720.

30 Parks BW, Nam E, Org E, Kostem E, Norheim F, Hui ST, *et al*. Genetic control of obesity and gut microbiota composition in response to high-fat, high-sucrose diet in mice. Cell Metab 2013; 17:141-152.

31 Boon MR, van den Berg SA, Wang Y, van den Bossche J, Karkampouna S, Bauwens M, *et al*. BMP7 activates brown adipose tissue and reduces diet-induced obesity only at subthermoneutrality. PLoS One 2013; 8:e74083.

32 Canalis E, Economides AN, Gazzerro E. Bone morphogenetic proteins, their antagonists, and the skeleton. Endocr Rev 2003; 24:218-235.

33 Taira K, Bujo H, Hirayama S, Yamazaki H, Kanaki T, Takahashi K, *et al*. LR11, a mosaic LDL receptor family member, mediates the uptake of ApoE- rich lipoproteins in vitro. Arterioscler Thromb Vasc Biol 2001; 21:1501-1506.

34 Jacobsen L, Madsen P, Jacobsen C, Nielsen MS, Gliemann J, Petersen CM. Activation and functional characterization of the mosaic receptor SorLA/LR11. J Biol Chem 2001; 276:22788-22796.

35 Pfrieger FW. Role of cholesterol in synapse formation and function. Biochim Biophys Acta 2003; 1610:271-80.

36 Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A, *et al*. CNS synaptogenesis promoted by glia-derived cholesterol. Science 2001; 294:1354-1357.

37 Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, *et al*. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 1993; 261:921-923.

38 Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, *et al*. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997; 278:1349-1356.

39 Scherzer CR, Offe K, Gearing M, Rees HD, Fang G, Heilman CJ, *et al*. Loss of apolipoprotein E receptor LR11 in Alzheimer disease. Arch Neurol 2004; 61:1200-1205.

40 Dodson SE, Andersen OM, Karmali V, Fritz JJ, Cheng D, Peng J, *et al*. Loss of LR11/SORLA enhances early pathology in a mouse model of amyloidosis: evidence for a proximal role in Alzheimer's disease. J Neurosci 2008; 28:12877-12886.

41 Andersen OM, Reiche J, Schmidt V, Gotthardt M, Spoelgen R, Behlke J, *et al*. SorLA/LR11, a neuronal sorting receptor that regulates processing of the amyloid precursor protein. Proc Natl Acad Sci U S A 2005; 102:13461-13466.

42 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's

disease: progress and problems on the road to therapeutics. Science 2002; 297:353-356.

43 Andersen OM, Schmidt V, Spoelgen R, Gliemann J, Behlke J, Galatis D, *et al*. Molecular dissection of the interaction between APP and its neuronal trafficking receptor SorLA/LR11. Biochemistry 2006; 45:2618-2628.

44 Offe K, Dodson SE, Shoemaker JT, Fritz JJ, Gearing M, Levey AI, *et al*. The lipoprotein receptor LR11 regulates amyloid beta production and amyloid precursor protein traffic in endosomal compartments. J Neurosci 2006; 26:1596-1603.

45 Mehmedbasic A, Christensen SK, Nilsson J, Rüetschi U, Gustafsen C, Poulsen ASA, *et al*. SorLA Complement-type Repeat Domains Protect the Amyloid Precursor Protein against Processing. J Biol Chem 2015; 290:3359-3376.

46 Spoelgen R, von Arnim CA, Thomas AV, Peltan ID, Koker M, Deng A, *et al*. Interaction of the cytosolic domains of sorLA/LR11 with the amyloid precursor protein (APP) and beta-secretase beta-site APP-cleaving enzyme. J Neurosci 2006; 26:418-428.

47 Caglayan S, Takagi-Niidome S, Liao F, Carlo AS, Schmidt V, Burgert T, *et al*. Lysosomal sorting of amyloid-beta by the SORLA receptor is impaired by a familial Alzheimer's disease mutation. Sci Transl Med 2014; 6:223ra20.

48 Kitago Y, Nagae M, Nakata Z, Yagi-Utsumi M, Takagi-Niidome S, Mihara E, *et al*. Structural basis for amyloidogenic peptide recognition by sorLA. Nat Struct Mol Biol 2015; 22:199-206.

49 Hirayama S, Bujo H, Yamazaki H, Kanaki T, Takahashi K, Kobayashi J, *et al*. Differential expression of LR11 during proliferation and differentiation of cultured neuroblastoma cells. Biochem Biophys Res Commun 2000; 275:365-373.

50 Kancha RK, Stearns ME, Hussain MM. Decreased expression of the low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor in invasive cell clones derived from human prostate and breast tumor cells. Oncol Res 1994; 6:365-372.

51 Lopes MBS, Bogaev CA, Gonias SL, VandenBerg SR. Expression of α2-macroglobulin receptor/low density lipoprotein receptor-related protein is increased in reactive and neoplastic glial cells. FEBS Letters 1994; 338:301-305.

52 Yamamoto M, Ikeda K, Ohshima K, Tsugu H, Kimura H, Tomonaga M. Increased expression of low density lipoprotein receptor-related protein/alpha2-macroglobulin receptor in human malignant astrocytomas. Cancer Res 1997; 57:2799-2805.

53 Sugita Y, Ohwada C, Kawaguchi T, Muto T, Tsukamoto S, Takeda Y, *et al*. Prognostic impact of serum soluble LR11 in newly diagnosed diffuse large B-cell lymphoma: A multicenter prospective analysis. Clin Chim Acta 2016; 463:47-52.

54 Fujimura K, Ebinuma H, Fukamachi I, Ohwada C, Kawaguchi T, Shimizu N, *et al*. Circulating LR11 is a novel soluble-receptor marker for early-stage clinical conditions in patients with non-Hodgkin's lymphoma. Clin Chim Acta 2014; 430:48-54.

55 Kawaguchi T, Ohwada C, Takeuchi M, Shimizu N, Sakaida E, Takeda Y, *et al*. LR11: a novel biomarker identified in follicular lymphoma. Br J Haematol 2013; 163:277-280.

56 Terai K, Jiang M, Tokuyama W, Murano T, Takada N, Fujimura K, *et al*. Levels of soluble LR11/SorLA are highly increased in the bile of patients with biliary tract and pancreatic cancers. Clin Chim Acta 2016; 457:130-136.

57 Verheijen J, Van den Bossche T, van der Zee J, Engelborghs S, Sanchez-Valle R, Lladó A, *et al*. A comprehensive study of the genetic impact of rare variants in SORL1 in European early-ons*et Al*zheimer's disease. Acta Neuropathol 2016; 132:213-224.

58 Larsen JV, Kristensen AM, Pallesen LT, Bauer J, Vægter CB, Nielsen MS, *et al*. Cytokine-Like Factor 1, an Essential Facilitator of Cardiotrophin-Like Cytokine:Ciliary Neurotrophic Factor Receptor alpha Signaling and sorLA-Mediated Turnover. Mol Cell Biol 2016; 36:1272-1286.

59 Westergaard UB, Sørensen ES, Hermey G, Nielsen MS, Nykjær A, Kirkegaard K, *et al*. Functional organization of the sortilin Vps10p domain. J Biol Chem 2004; 279:50221-50229.

60 Glerup S, Lume M, Olsen D, Nyengaard JR, Vaegter CB, Gustafsen C, *et al*. SorLA controls neurotrophic activity by sorting of GDNF and its receptors GFRalpha1 and RET. Cell Rep 2013; 3:186-199.

61 Lintzel J, Franke I, Riedel IB, Schaller HC, Hampe W. Characterization of the VPS10 domain of SorLA/LR11 as binding site for the neuropeptide HA. Biol Chem 2002; 383:1727-1733.

62 Larsen JV, Petersen CM. SorLA in Interleukin-6 Signaling and Turnover. Mol Cell Biol 2017; 37: e00641-16.

63 Spoelgen R, Adams KW, Koker M, Thomas AV, Andersen OM, Hallet PJ, *et al*. Interaction of the apolipoprotein E receptors low density lipoprotein receptor-related protein and sorLA/LR11. Neuroscience 2009; 158:1460-1468.

64 Gustafsen C, Skelda S, Jensen SL, Andersen OM, Petersen CM, Madsen P, *et al*. SorLA is a novel high affinity PCSK9 receptor that inhibits its activation by furin. Atherosclerosis 2016; 252:e264.

65 Rohe M, Hartl D, Fjorback AN, Klose J, Willnow TE. SORLA-mediated trafficking of TrkB enhances the response of neurons to BDNF. PLoS One 2013; 8:e72164.

66 Hartl D, Nebrich G, Klein O, Stephanowitz H, Krause E, Rohe M. SORLA regulates calpain-dependent degradation of synapsin. Alzheimers Dement 2016; 12:952-963.

67 Klinger SC, Højland A, Jain S, Kjolby M, Madsen P, Svendsen AD, *et al*. Polarized trafficking of the sorting receptor SorLA in neurons and MDCK cells. FEBS J 2016; 283:2476-2493.

68 Nielsen MS, Gustafsen C, Madsen P, Nyengaard JR, Hermey G, Bakke O, *et al*. Sorting by the cytoplasmic domain of the amyloid precursor protein binding receptor SorLA. Mol Cell Biol 2007; 27:6842-6851.

69 Borschewski A, Himmerkus N, Boldt C, Blankenstein KI, McCormick JA, Lazelle R, *et al*. Calcineurin and Sorting-Related Receptor with A-Type Repeats Interact to Regulate the Renal Na(+)-K(+)-2Cl(-) Cotransporter. J Am Soc Nephrol 2016; 27:107-119.

70 Jacobsen L, Madsen P, Nielsen MS, Geraerts WP, Gliemann J, Smit AB, *et al*. The sorLA cytoplasmic domain interacts with GGA1 and -2 and defines minimum requirements for GGA binding. FEBS Lett 2002; 511:155-158.

71 Schmidt V, Sporbert A, Rohe M, Reimer T, Rehm A, Andersen OM, *et al*. SorLA/LR11 regulates processing of amyloid precursor protein via interaction with adaptors GGA and PACS-1. J Biol Chem 2007; 282:32956-32964.

72 Herskowitz JH, Seyfried NT, Gearing M, Kahn RA, Peng J, Levey

AI, *et al*. Rho kinase II phosphorylation of the lipoprotein receptor LR11/SORLA alters amyloid-beta production. J Biol Chem 2011; 286:6117-6127.

73 Huang TY, Zhao Y, Li X, Wang X, Tseng IC, Thompson R, *et al*. SNX27 and SORLA Interact to Reduce Amyloidogenic Subcellular Distribution and Processing of Amyloid Precursor Protein. J Neurosci 2016; 36:7996-8011.

74 Reiche J, Theilig F, Rafigi FH, Carlo AS, Militz D, Mutig K, *et al*. SORLA/SORL1 functionally interacts with SPAK to control renal activation of Na+-K+-Cl- cotransporter 2. Mol Cell Biol 2010; 30:3027-3037.

75 Fjorback AW, Seaman M, Gustafsen C, Mehmedbasic A, Gokool S, Wu C, *et al*. Retromer binds the FANSHY sorting motif in sorLA to regulate amyloid precursor protein sorting and processing. J Neurosci 2012; 32:1467-1480.

76 Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, *et al*. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 2007; 39:168-177.

77 Schmidt V, Baum K, Lao A, Rateitschak K, Schmitz Y, Teichmann A, *et al*. Quantitative modelling of amyloidogenic processing and its influence by SORLA in Alzheimer's disease. EMBO J 2011; 31:187-200.

78 Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, *et al*. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013; 45:1452-1458.

79 Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, *et al*. SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. PLoS One 2013; 8:e58618.

80 Young JE, Boulanger-Weill J, Williams DA, Woodruff G, Buen F, Revilla AC, *et al*. Elucidating molecular phenotypes caused by the SORL1 Alzheimer's disease genetic risk factor using human induced pluripotent stem cells. Cell Stem Cell 2015; 16:373-385.

81 Holstege H, van der Lee SJ, Hulsman M, Wong TH, van Rooij JG, Weiss M, *et al*. Characterization of pathogenic SORL1 genetic variants for association with Alzheimer's disease: a clinical interpretation strategy. Eur J Hum Genet 2017; 25:973-981.

82 Ohwaki K, Bujo H, Jiang M, Yamazaki H, Schneider WJ, Saito Y. A secreted soluble form of LR11, specifically expressed in intimal smooth muscle cells, accelerates formation of lipid-laden macrophages. Arterioscler Thromb Vasc Biol 2007; 27:1050-1056.

83 Jiang M, Bujo H, Ohwaki K, Unoki H, Yamazaki H, Kanaki T, *et al*. Ang II-stimulated migration of vascular smooth muscle cells is dependent on LR11 in mice. J Clin Invest 2008; 118:2733-2746.

84 Smith EN, Chen W, Kähönen M, Kettunen J, Lehtimäki T; Peltonen L, *et al*. Longitudinal genome-wide association of cardiovascular disease risk factors in the Bogalusa heart study. PLoS Genet 2010; 6:e1001094.

85 Vongpromek R, Bujo H, Hoekstra M, Schneider WJ, van der Zee L, Schinkel AF, *et al*. LR11/SorLA links triglyceride-rich lipoproteins to risk of developing cardiovascular disease in FH patients. Atherosclerosis 2015; 243:429-437.

86 Berk KA, Vongpromek R, Jianh M, Schneider WJ, Timman R, Verhoeven AJ, *et al*. Levels of the soluble LDL receptor-relative LR11 decrease in overweight individuals with type 2 diabetes upon diet-induced weight loss. Atherosclerosis 2016; 254:67-72.