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SORLA/SORL1, a Neuronal Sorting Receptor Implicated in Alzheimer's Disease

Thomas E. Willnow, Anne-Sophie Carlo, Michael Rohe and Vanessa Schmidt

Max-Delbrueck-Center for Molecular Medicine, Robert-Roessle-Str. 10, D-13125 Berlin, Germany

SYNOPSIS

The proteolytic breakdown of the amyloid precursor protein (APP) to neurotoxic amyloid-β peptides in the brain has been recognized as a major pathological pathway in Alzheimer's disease (AD). Yet, the factors that control the processing of APP and their potential contribution to the common sporadic form of AD remain poorly understood. Here, we review recent findings from studies in patients and in animal models that led to the identification of a unique sorting receptor for APP in neurons, designated SORLA/SORL1, that emerges as a key player in amyloidogenic processing and as major genetic risk factor for AD.

KEY WORDS

APP, BDNF, neurodegeneration, protein trafficking, SORLA/LR11, secretases, VPS10P domain

INTRODUCTION

The amyloid hypothesis represents the major current concept to describe the cellular and pathological events underlying neurodegenerative processes in Alzheimer's disease (AD) /19/. Central to this hypothesis is the amyloid precursor protein (APP), a type-1 membrane protein expressed in many neuronal and non-neuronal cell types. In cells, including neurons in the brain, APP undergoes two alternative proteolytic processing pathways that generate multiple soluble as well as membrane-associated fragments from this polypeptide (Figure 1A, inset). The physiological relevance of APP processing is a focus of intense investigation and numerous functions have been assigned to the precursor and its processing products (Figure 1A). In terms of neurodegeneration, the conversion of APP to a 40 to 42 amino acid amyloid-β peptide (Aβ) through sequential cleavage by β- and γ-secretases is noteworthy. Aβ forms neurotoxic oligomers and senile plaques, pathological hallmarks of AD /9,37,79/.

Evidence that the extent of proteolytic breakdown of APP to Aβ is a determinant of onset and progression of AD comes from rare inheritable (familial) forms of the disease that are caused by defects in the genes encoding APP or presenilin-1 and -2, components of the γ-secretase complex /69/. Typically, these mutations are associated with an overall increase in Aβ peptide production or with a shift towards generation of the more amyloidogenic variant $A\beta_{42}$. Also, carrying an extra copy of the APP gene as in trisomy 21 is invariably associated with occurrence of AD at an early age.

Despite APP processing being critical to AD development, our understanding of the underlying regulatory mechanisms is rather incomplete. Thus, the goal has been to identify neuronal factors that control the metabolism of APP and to determine whether alterations in these pathways contribute to the common sporadic forms of the disease that afflict 90% of all patients.

Key to understanding APP processing is the complex trafficking behavior of the precursor

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Address for correspondence:
Thomas E. Willnow
Max-Delbrueck-Center for Molecular Medicine
Robert-Roessle-Str. 10, D-13125 Berlin, Germany
Phone: +49-30-9406-2569; Fax: +49-30-9406-3382
E-mail: willnow@mdc-berlin.de

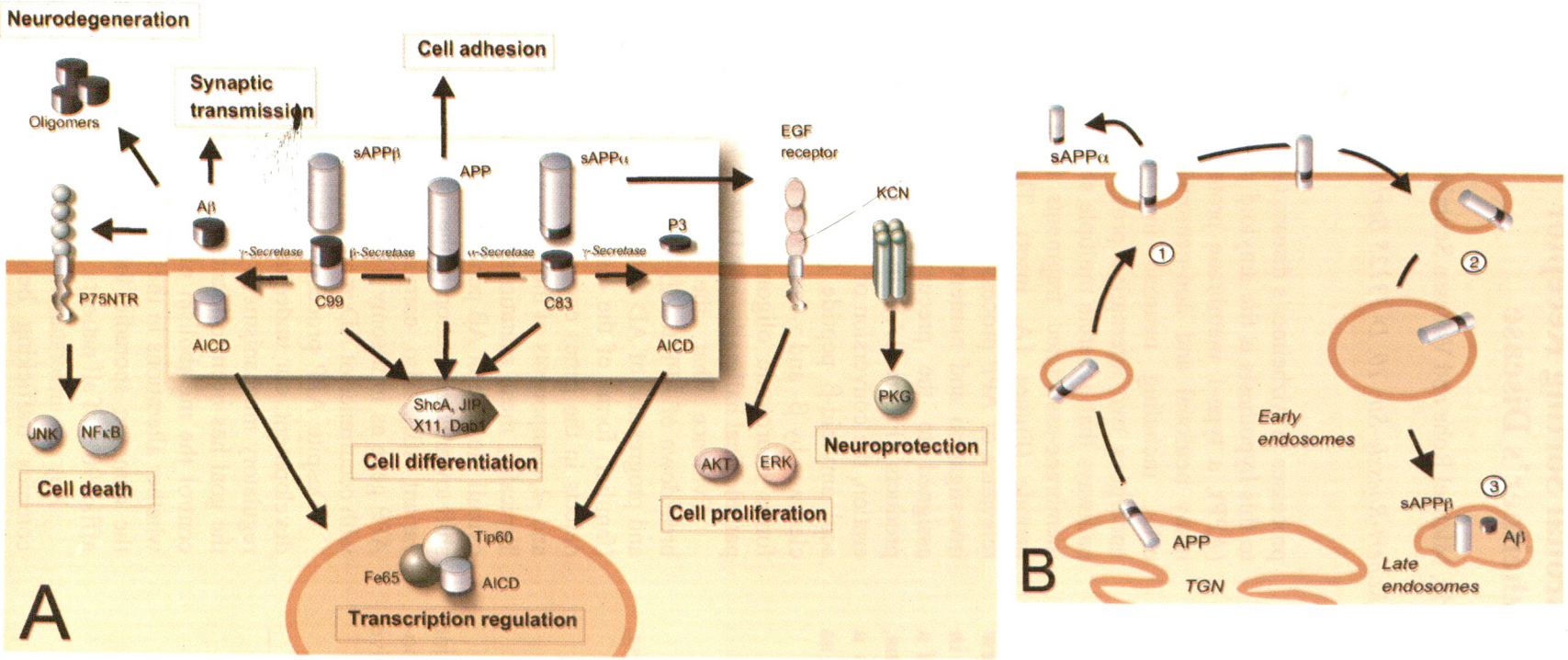

Fig. 1: Neuronal pathways in processing and signaling of amyloid precursor protein. (A) Alternative processing routes for the amyloid precursor protein (APP) through sequential cleavage by α- and γ-secretases (non-amyloidogenic pathway; to the right) or by β- and γ-secretases (amyloidogenic pathway; to the left). Functions proposed for APP and its various processing products—APP acts in cell adhesion, whereas soluble (s) APPα is believed to cooperate with the EGF receptor pathway to stimulate neuronal proliferation via extracellular regulated kinase (ERK) and protein kinase B (AKT). In addition, sAPPα directly/indirectly, activates high-conduction K^+ channels (KCN) and cGMP-dependent protein kinase (PKG) to protect neurons from excitotoxicity. The Aβ peptide modulates synaptic transmission, triggers cell death via binding to $p75^{NTR}$, and forms neurotoxic oligomers and plaques. The cytoplasmic tail of full-length APP as well as the membrane-associated carboxyl terminal fragments C99 and C83 interact with multiple adaptors and signaling molecules involved in cellular differentiation pathways (e.g., ShcA, JIP, X11, Dab1). The soluble intracellular domain of APP (AICD) acts as transcriptional regulator by association with the adaptor Fe65 and histone acetyltransferase Tip60 in the nucleus. (B) Intraneuronal trafficking and processing of APP. Newly synthesized APP molecules traverse the trans-Golgi network (TGN) en route to the plasma membrane where most are cleaved by α-secretase to sAPPα (step 1). Non-processed precursors internalize from the cell surface (step 2) and traffic from early to late endosomes for processing into sAPPβ, initiating the amyloidogenic pathway (step 3). For simplicity, Aβ formation is indicated in late endosomes (step 3). Apart from endosomes, generation of Aβ has been localized to the endoplasmic reticulum or the TGN /72/.

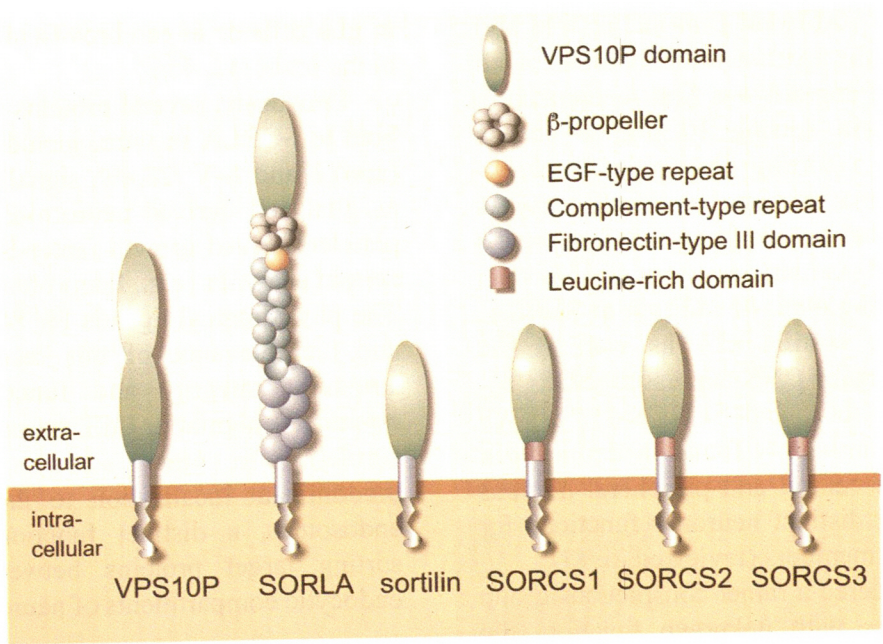

Fig. 2: Structural and evolutionary conservation of VPS10P domain receptors. Structural organization of vacuolar protein sorting 10 protein (VPS10P) domain receptors from yeast (VPS10P) and humans (SORLA, sortilin, SORCS-1, -2, -3). The extracellular domains of the receptors are either composed of one (sortilin, SORLA, SORCS-1, -2, and -3) or two VPS10P domains (VPS10P) which function as ligand binding sites. In addition, receptors may carry additional modules involved in protein-protein interaction (leucine-rich domains, complement-type repeats, EGF-type repeats and fibronectin-type III domains) or regulation of ligand binding (β-propeller). SORLA, sorting protein-related receptor with A-type repeats; SORCS, sortilin-related receptor CNS expressed.

protein through the intracellular compartments of neurons that determine its processing fate (Figure 1B). Most APP molecules are cleaved by α-secretase at or near the plasma membrane to produce soluble (s)APPα. Some precursor molecules, however, are re-internalized from the cell surface and delivered to late endosomes for β-secretase (and subsequent γ-secretase) processing to sAPPβ and Aβ (Figure 1B). The importance of regulated intracellular transport of APP for Aβ production is underscored by findings that faulty trafficking of APP through endocytic and secretory compartments of the cell contributes to AD-related processes /30,50,55,72/.

Recently, a breakthrough in solving the puzzle of APP transport and processing came with the identification of a neuronal sorting receptor for APP called *sorting protein-related receptor with A-type repeats* (SORLA). Independent lines of evidence from histopathological analyses of individuals with sporadic AD, to epidemiological studies in patient cohorts, to investigations in cell and animal models all converged on this novel receptor as a chief regulator of APP processing. In this review, we will summarize the latest findings on the sorting receptor SORLA, which is now considered one of the most important risk factors in sporadic AD.[1]

SORLA, AN INTRACELLULAR SORTING PROTEIN IN NEURONS

SORLA, also known as SORL1 or LR11, member of the VPS10P domain receptor family /24,83/ (Figure 2). The name derives fr structural motif common to all family mem the VPS10P domain. It is a 700 amino acid m

[1] Bertram L, Tram L, McQueen MB, Mullin K, Blacker RE. Systematic meta-analyses of Alzheimer disease ge ciation studies: the AlzGene database. Nat Genet 200 23. http://www.alzgene.org. Accessed [05.03.2010.

that forms a large 10-bladed β-propeller fold and composes part of the extra-cellular domain of all receptors /58/. The domain was first recognized in the vacuolar protein sorting 10 protein (hence VPS10P domain), a sorting protein in *Saccharomyces cerevisiae* that directs lysosomal enzymes from the Golgi to the vacuole (the yeast 'lysosome') /43/. Five VPS10P domain receptors are found in vertebrates, including man. In addition to SORLA, these proteins are sortilin /57/ as well as the sortilin-related receptor CNS expressed (SORCS)-1 /20/, SORCS-2 /60/, and SORCS-3 /18/. All receptors are predominantly found in defined cell populations of the central and peripheral nervous system, indicating distinct neuronal functions for the various family members (reviewed in /81/).

Initially considered a rather conspicuous group of sorting proteins with unknown function, the mammalian receptors of the gene family recently surfaced as potential neuronal disease genes in a number of association studies in patients. These diseases encompass Alzheimer disease (AD) and other types of age-related dementias (SORLA, SORCS1) /36,16/, bipolar disorders (SORCS2) /4/, and senescence of the nervous system (sortilin) /40/. The functional relevance of VPS10P domain receptors for the nervous system was confirmed by studies that uncovered sortilin as a receptor for neurotrophins in the control of neuronal cell death /26/.

SORLA is a 250-kDa protein widely expressed in neurons throughout the mammalian CNS (Figure 3A-D). In the mouse, expression starts at mid-gestation but increases significantly in the postnatal and adult brain /29/. In both rodent and human adult brain tissue, expression of the receptor is strongest in the cerebral and entorhinal cortex, hippocampus, cerebellum, and brain stem /11,45,53/. At the subcellular level, immunoreactivity for the receptor is restricted to the somatodendritic compartment (Figure 3E), where it mainly localizes to intracellular vesicles in the perinuclear region (Figure 3F) /1,11/. Co-immunostaining with markers of various intracellular compartments identified these subcellular structures as *trans*-Golgi network (TGN) and early endosomes in primary neurons and in established cells lines expressing the receptor /48,53,66,74/. In contrast to neurons, little if any expression is seen in glia cells or in cerebrovascular endothelial cells in the brain /41, 45/.

Previously, several proteins were identified that bind to SORLA in vitro, including apolipoproteins (apo) E and A-V /23,49/, signaling molecules such as glial cell derived neurotrophic factor /80/ and platelet derived growth factor-BB /14/, as well as certain enzymes (e.g., lipoprotein lipases) /23/.
The physiological ligands for SORLA in the brain and the relevance of this receptor pathway for structural integrity and function of the CNS remained enigmatic. Still, based on the structural similarity to other sorting proteins and its predominant localization to the TGN and early endosomes, a distinct function for SORLA in sorting target proteins between secretory and endocytic compartments of neurons seemed likely.

SORLA/SORL1, a risk gene in sporadic AD

The involvement of SORLA in AD was initially suggested by Lah and colleagues /65/, who used gene expression profiling to demonstrate low levels of *SORLA* transcript in lymphoblasts from patients with sporadic AD. The decreased mRNA levels coincided with a reduced expression of the receptor in the brain areas most vulnerable to neurodegeneration, including the frontal cortex and hippocampus, as shown by immunohistology. Expression of the receptor in other brain areas like the cerebellum was not affected /53/. Reduced amounts of SORLA in the brain were also found in individuals with mild cognitive impairment, a condition that may represent prodromal AD /64/. In contrast, normal expression of the receptor was documented in individuals with familial forms of AD /11/, suggesting that impaired receptor expression represents a primary event in sporadic AD rather than a secondary consequence of neurodegeneration. Loss of receptor expression also manifests itself in lower levels of SORLA degradation products in the cerebrospinal fluid of affected individuals /41/.

What could be the mechanism that determines SORLA levels in the brain and elsewhere in the organism? Evidence from association studies argues that the determination may lie in allelic receptor gene variants in the human population. As shown in a pioneering study by Rogaeva et al. /61/

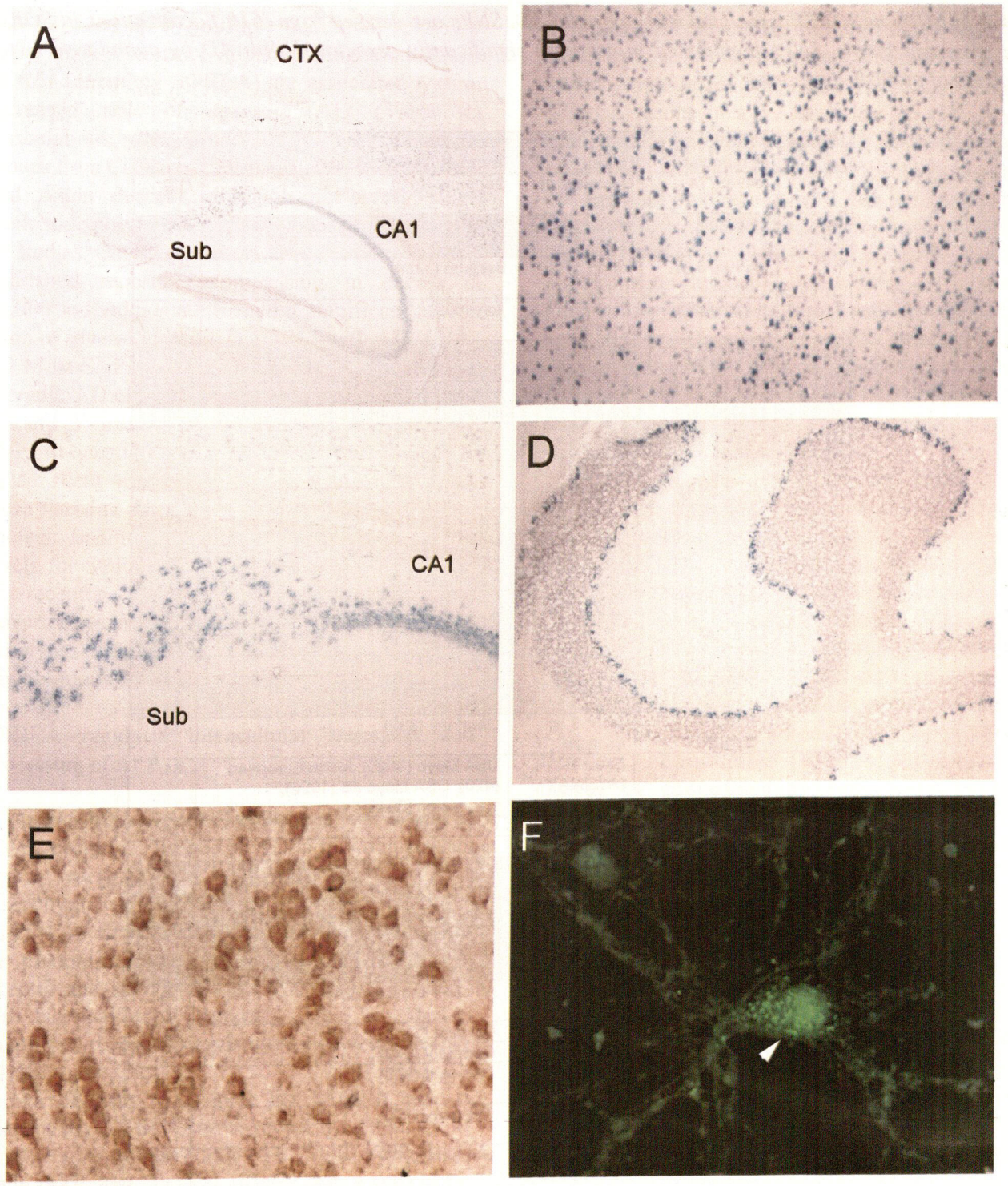

Fig. 3: Expression of SORLA in the adult mouse brain. (A-D) Detection of SORLA expression in subiculum (Sub) and CA1 region of the hippocampus and layer V of the cortex (CTX) based on activity of a □galactosidase reporter gene (lacZ) inserted into the *Sorl1* locus in mice /62/. Higher magnifications of lacZ positive layer V neurons in cerebral cortex (B), pyramidal neurons in subiculum and CA1 region of the hippocampus (C), and Purkinje cells in the cerebellum (D) are shown. (E) Immunohistological detection of SORLA in the soma of cortical neurons. (F) Immunofluorescence microscopy indicating SORLA localization to vesicles in the perinuclear (Golgi) region in primary mouse cortical neurons (arrowhead).

Table 1: *SNPs in SORLI associated with sporadic AD. SNPs are derived from /61/. Localizations in SORLI are presented below. SNPs highlighted in grey are significantly associated with AD by cumulative meta-analyses of published reports.*[2]

Marker	dbSNP rs number	SNP position (type)	Population (number of individuals)	Study
1	rs4935774	Upstream of 5'UTR	Germany (970)	/13/
4	**rs661057**	Intron 1	USA Mayo (3529), Caucasian (3949)	/61/
			Italy (609)	/8/
6	rs560573	Intron 5	Belgium (1184)	/5/
7	rs12364988	Exon 6 (H269H)	Italy (609)	/8/
8	**rs668387**	Intron 6	Israel (225), North European (420), Caucasian (3949)	/61/
			Belgium (1184)	/5/
9	**rs689021**	Intron 6	Israel (225), North European (420)	/61/
			Belgium (1184)	/5/
10	**rs641120**	Intron 6	Israel (225)	/61/
			Belgium (1184)	/5/
			Italy (609)	/8/
12	**rs12285364**	Intron 9	USA Mayo AUT (853), USA Mayo (3529)	/61/
			African-American (246), Caribbean Hispanics (372)	/36/
19	**rs2070045**	Exon 25 (S1184S)	North European (420), USA Mayo (3529), Caucasian (3949)	/61/
			UK1 (689)	/38/
			Japan (888)	/31/
20	**rs3824966**	Intron 25	Caucasian USA (106)	/36/
21	SORL1-18ex26	(–18) 5' of exon 26	Germany (832)	/33/
23	rs3824968	Exon 34 (A1584A)	USA Mayo (3529), North European (420), USA Mayo JS (1026), Caucasian (3949)	/61/
			China (486)	/75/
			Japan (888)	/31/
24	**rs2282649**	Intron 38	USA Mayo (3529), USA Mayo JS (1026), Caucasian (3949)	/61/
			Japan (888)	/31/
25	**rs1010159**	Intron 39	USA Mayo (3529), USA Mayo JS (1026), Caucasian (3949)	/61/
			Japan (888)	/31/
26	rs1784933	Intron 41	African-American (246)	/36/
27	rs1614735	Intron 45	Belgium (1184)	/5/
			Germany (970)	/13/
new	rs12576704	Upstream	Germany (970)	/13/
new	rs10502262	Intron 13	Germany (970)	/13/
new	rs3781835	Exon25/Intron 25 boundary	Germany (970)	/13/

[2] http://www.alzgene.org. Accessed 5 Mar 2010

and followed up by multiple additional epidemiologic studies, distinct allele variations in human *SORL1* (encoding SORLA) are associated with an increased risk of sporadic AD (Table 1). Associations were found across multiple ethnic groups from Caucasian, Hispanic, African-American, and Asian descent, although not every single nucleotide polymorphism (SNP) was reproduced in all studies. Cumulative meta-analyses on previously published reports encompassing in excess of 13,000 individuals confirmed a significant association of several markers in *SORL1* with AD /59/.[3]

Most SNPs in *SORL1* that are associated with sporadic AD cluster in two haplotype blocks in the 5'- and 3'- region of the gene (Table 1). As all SNPs in question are located in intronic regions or cause silent mutations, the mechanism whereby these variants predispose to sporadic AD remains unclear. In line with reduced mRNA and protein levels for SORLA in AD patients, genetic control of receptor expression seems a possibility. Nevertheless, a correlation between distinct *SORL1* genotypes and protein levels still awaits unambiguous documentation.

SORLA regulates intracellular transport and processing of APP

In the initial report implicating low levels of SORLA with occurrence of AD, a function for this orphan receptor in apoE clearance in brain parenchyma was proposed /65/. Although a role for SORLA in apoE catabolism cannot be ruled out, the predominant intracellular localization of the receptor and a poor endocytic capacity compared with classical apoE receptors (e.g., low-density lipoprotein receptor) argue against such an activity /21,48,66/.

An alternative function for SORLA that is relevant to AD was first reported by Andersen et al. /1/, who demonstrated that SORLA directly binds APP and thereby affects the intracellular transport and processing of the precursor protein. The interaction involves binding sites in the extracellular domains and in the cytoplasmic domains of both proteins /1,2,74/. In particular, fine mapping identified a binding epitope within the cluster of complement-type repeats in SORLA (see Figure 2) that forms a 1:1 stoichiometric complex with the carbohydrate-linked domain of APP /2/. Binding to SORLA results in a sequestration of APP in the TGN and an impaired transition to the cell surface, effectively reducing the extent of APP cleavage through amyloidogenic and non-amyloidogenic pathways /1,53,66/. Also, interaction with SORLA blocks access of β-secretase to APP, further impairing amyloidogenic processing /74/. These initial observations in cultured cells established a negative correlation between SORLA activity and conversion of APP to Aβ, providing a working hypothesis on why low levels of this receptor in some individuals may predispose to enhanced APP turnover and to sporadic AD /3/.

Given the proposed role for SORLA in directing APP transport through neuronal compartments harboring secretase activities, the signals that govern intracellular trafficking of the receptor warrant particular attention. Like other members of the VPS10P-domain receptor family, SORLA is produced as inactive precursor carrying a 53 amino acid pro-peptide at the amino terminus that is required to fold the receptor polypeptide properly /23/. Upon transport through the constitutive secretory pathway to the TGN, the pro-peptide is cleaved by convertases to produce the mature receptor /23/. From the TGN, newly synthesized SORLA moves to the cell surface where it exhibits rapid internalization that is mediated by an 'acidic cluster dileucine' motif in the cytoplasmic receptor domain /48/. Following internalization, SORLA molecules relocate from early endosomes back to the TGN, avoiding transit to late endosomal compartments. This step is unique and not seen with endocytic receptors that deliver their cargo to late endosomes before moving back to the plasma membrane. In contrast, internalized SORLA molecules do not return to the cell surface but rather appear to cycle between late secretory and early endocytic organelles /48,49/.

What evidence has been found that the peculiar trafficking behavior identified for SORLA in Chinese hamster ovary or human embryonic kidney cells bears any relevance for AD? Firstly, the central role of the Golgi in APP metabolism is well appreciated as the processing of APP requires an efficient transit of the precursor through this

[3] http://www.alzgene.org. Accessed 5 Mar 2010

organelle /17,84/. Experimentally disrupting Golgi transition blocks APP processing /30,55/ whereas treatment that enhances membrane shunt from TGN to plasma membrane increases it /82/. Also, tempering with sorting of APP between endocytic and Golgi compartments reduces APP cleavage /68/. All the above argues for the existence of factors (such as SORLA) in control of APP sorting at the TGN. Secondly, targeting SORLA to the wrong intracellular compartment results in an accumulation of APP in the very same location and an altered processing fate. For example, the co-expression of APP with SORLA mutants that are not retained in the TGN but sequester at the plasma membrane causes a shunt of APP to the cell surface and a massive increase in amyloidogenic processing. This effect is likely due to an increased number of APP molecules undergoing endocytosis, a pre-requisite for Aβ production /66/. Thirdly, several cytosolic adaptor proteins that regulate protein transport between early endosomes and TGN have been implicated in AD. Previously, their mode of action in APP metabolism remained unclear, but new findings that these adaptors control trafficking of SORLA provide the missing functional link. Two such adaptor complexes, GGAs and retromer, are discussed in the following.

CYTOSOLIC ADAPTOR PROTEINS IN CONTROL OF APP METABOLISM

The Golgi-localizing, γ-adaptin ear homology domain, ARF-interacting proteins (GGA1, GGA2, and GCA3) are three related adaptors that select cargo proteins at the TGN for transport to endosomes. The proteins bind a tetrapeptide motif *Asp-Val-Pro-Met* that is also present in the tail of SORLA /25/. A disruption of this binding motif impairs the proper recycling of SORLA and, consequently, alters APP processing /66/. Remarkably, previous studies have implicated GGA-1 in APP metabolism in as much as reduced expression of the adaptor enhances, whereas over-expression decreases Aβ formation /77/. These effects are independent of a direct interaction between APP and GGAs, suggesting that SORLA may be required to tether both components /78/. Also, decreased levels of GGA1 and GGA3 are seen in brain autopsy specimens from AD patients /76,78/.

As well as altered anterograde sorting, defects in reverse (or retrograde) sorting from endosomes to the TGN have also been linked to abnormal APP transport. Retromer is a tetrameric adaptor complex composed of VPS35, VPS29, VPS26, and sorting nexin 1/2 that mediates the retrograde sorting of cargo (reviewed in /67,71/). VPS35 and VPS26 are poorly expressed in AD brain autopsies /73/, and disruption of the *Vps35* gene in mice results in memory deficits and synaptic dysfunctions associated with elevated Aβ levels /46/. Given the interaction between mammalian retromer and SORLA /46/, defects in retromer-guided recycling of SORLA could be a cause of neurodegenerative processes /51/.

In conclusion, substantial experimental evidence from histopathological and cell biological studies suggest a model whereby SORLA acts as sorting receptor for APP at the TGN (Figure 4). SORLA seems to prevent transport into the intracellular pathways required for processing, thereby acting as negative regulator of Aβ production. Because it recognizes interaction motifs both in the extracellular /2/ and in the intracellular domain of APP /74/, it is tempting to speculate that SORLA may not only sort the mature precursor but also soluble (sAPP) or membrane-associated fragments (C99, C83) thereof (see Figure 1A).

SORLA DEFICIENCY PROMOTES AMYLOIDOGENIC PROCESSING AND PLAQUE DEPOSITION

Transgenic mouse models have been instrumental in exploring the relevance of novel risk genes for amyloidosis and plaque burden, and associated memory deficits in vivo. Models with genetically altered SORLA expression have been no exception to this rule.

As shown by Andersen and colleagues /1/ and by Rohe et al. /62/ in two different mouse models of targeted *Sorl1* gene disruption, a loss of receptor activity results in the enhanced turnover of murine APP and, consequently, in a significant increase in amyloidogenic (sAPPβ, Aβ) and non-amyloidogenic-

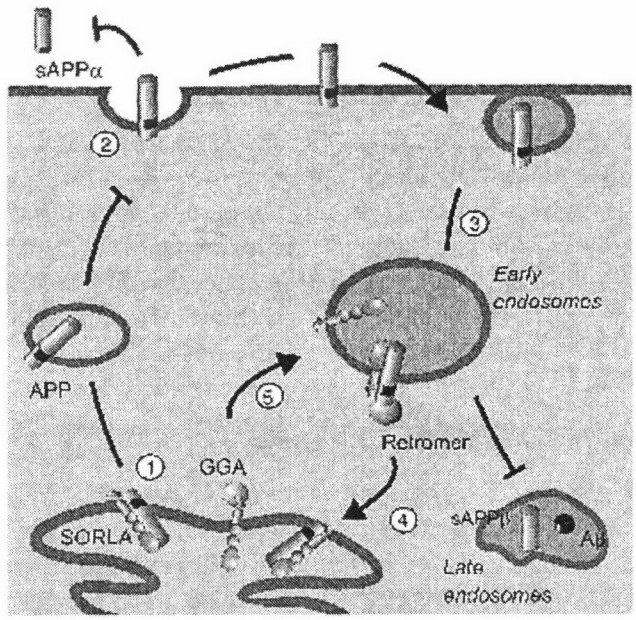

Fig. 4: SORLA guides trafficking and processing of APP. SORLA acts as sorting receptor that traps APP in the trans-Golgi network (TGN, step 1), reducing the number of precursor molecules that enter processing pathways at the cell surface (step 2, non-amyloidogenic) or in endocytic compartments (step 3, amyloidogenic). Potentially, SORLA may also shuttle APP from early endosomes back to the TGN (step 4), further reducing the extent of amyloidogenic processing in late endosomes. Retrograde endosome to TGN trafficking of SORLA/APP complexes may involve association with the retromer complex. Direct sorting of SORLA from TGN to early endosomes requires GGAs (step 5). Apart from retromer and GGAs, additional adaptors including PACS1 /66/, AP-1 /48/, X11/mint /21,32,70/, ubiquilin /22/, PAT1 /85/, and SNX17 /35/ may be involved in routing of APP/SORLA complexes.

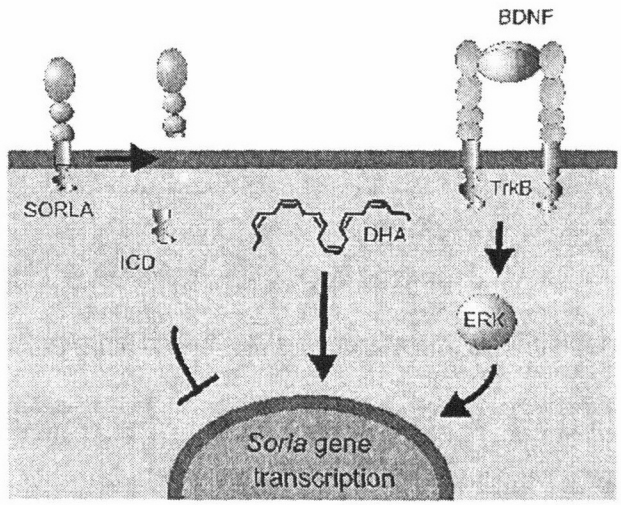

Fig. 5: Pathways that control expression of SORLA in the brain. (Left) Regulated intramembranous proteolysis releases the intracellular domain (ICD) from SORLA. It acts as negative regulator of SORLA gene transcription in the nucleus. (Middle) Docosahexaenoic acid (DHA) promotes SORLA gene transcription by yet unknown intracellular mechanisms. (Right) Brain derived neurotrophic factor (BDNF) induces SORLA gene transcription by binding to receptor tyrosine kinases (TrkB) and by subsequent stimulation of extracellular regulated kinase (ERK)-dependent signaling pathways.

products (sAPPα) in the brain. Introducing the murine *Sorl1* defect into mice expressing human APP transgene variants App^{V717F} (Ind) or $App^{K595M/N596L}$ (Swe) caused a two- to threefold increase in Aβ formation and plaque load /10,62/. Interestingly in both models, SORLA deficiency exacerbates early amyloid pathology, causing a forward shift in disease onset. This disease-promoting effect is dependent on the gene dose as seen comparing animals with two ($Sorl1^{+/+}$), one ($Sorl1^{+/-}$), or no functional *Sorl1* gene ($Sorl1^{-/-}$), providing further experimental evidence that SORLA levels in the human brain determine risk of AD /10/.

As well as studying the effects of enhanced amyloid β peptide formation, SORLA-deficient mouse models also enabled an analysis of the consequences of elevated levels of soluble APP products in the CNS. This question was particularly relevant given the proposed role for sAPPα as a stimulator of adult neurogenesis (Figure 1A) /7,34/. In line with this hypothesis, a significant increase in sAPPα levels in $Sorl1^{-/-}$ mice coincided with a profound stimulation of neuronal extracellular regulated kinase (ERK) signaling and with an enhanced adult neurogenesis in the subgranular zone of the hippocampus, providing in vivo support for the neurotrophic action of sAPPα /62/.

Taken together, studies on mouse models of human SORLA deficiency documented a role for the receptor not only in control of plaque burden but also in APP-dependent neuronal signaling and suggested a molecular explanation for the increased ERK activity and enhanced adult neurogenesis observed in some AD patients /12,27, 47,56,86,87/.

PATHWAYS IN CONTROL OF SORLA EXPRESSION IN THE BRAIN

So far, little is known about genetic or environmental factors in control of *SORL1* expression in the human brain. Although all available data suggest that allelic *SORL1* variants may determine transcription levels, convincing evidence to support this assumption is lacking. Tentative data from quantitative RT-PCR analyses indicate that carriers of the CTT haplotype at SNPs 22-24 may have less than half the levels of the *SORL1* transcript seen in carriers of the non-AD haplotype. Regression analysis, however, also shows that the *SORL1* haplotype status accounts for only 14% of the variance, indicating that additional factors modulate neuronal SORLA expression /61/.

Concerning the pathways modulating SORLA activity, the intracellular domain of the receptor has been shown to be released by γ-secretase cleavage /52/ and to act as a repressor of *SORL1* transcription /6/ (Figure 5). Another regulatory pathway was uncovered by investigations of docosahexaenoic acid (DHA), an essential dietary ω-3 polyunsaturated fatty acid that is implicated in AD. Higher blood levels of DHA are positively correlated with reduced risk of neurodegeneration in large epidemiological studies /28/. Dietary DHA significantly improves cognition, protects from synaptic protein loss, and lowers plaque deposition in mouse models, apparently by reducing Aβ production /15,39,54/. A recent report showed that DHA markedly up-regulates SORLA expression in primary neurons and in mouse models in vivo, suggesting that the protective effects of dietary fish oil supplementation may, at least in part, act through induction of *SORL1* /42/ (Figure 5).

Last but not least, screening approaches in primary neurons identified brain-derived neurotrophic factor (BDNF) as a major inducer of *Sorl1* that activates receptor gene transcription through ERK /63/ (Figure 5). In line with a physiological role as inducer of *Sorl1*, receptor expression was significantly impaired in mouse models with genetic ($Bdnf^{-/-}$) or disease-related loss of BDNF activity in the brain (e.g., Huntington's disease) /63/. Intriguingly, the exogenous application of BDNF reduced Aβ production in the brain of wild-type mice, but not in animals genetically deficient for *Sorl1*. The findings suggest that the beneficial effects ascribed to BDNF in APP metabolism /44/ work through the induction of *SORL1* encoding a negative regulator of neuronal APP processing /63/. Besides elucidating novel cellular pathways in control of *SORL1* expression in the brain, the studies described above provide proof that interventions, such as dietary DHA intake or BDNF application, designed to raise receptor

expression represent potential therapeutic approaches in the treatment of AD.

CONCLUSIONS

Recent years have witnessed the detailed clarification of the cellular pathways in control of APP processing and their potential contribution to neurodegenerative processes in patients. In particular, the functional characterization of SORLA/SORL1, a unique sorting receptor for APP, sheds light on a previously poorly understood process concerning the targeted transport of APP to distinct intraneuronal compartments harbouring the various secretase activities. The results from histopathological and epidemiologic studies in humans further substantiate the critical role of this receptor in sporadic AD. Although much still remains to be learned about this exciting pathway, SORLA/SORL1 certainly holds great promise as a novel biomarker and perhaps even as a new drug target in the treatment of this devastating disease.

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