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Review article

Protein sorting gone wrong – VPS10P domain receptors in cardiovascular and metabolic diseases

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ABSTRACT

VPS10P domain receptors are a unique class of sorting receptors that direct intracellular transport of target proteins in neurons and that play central roles in neurodegenerative processes. Surprisingly, genome-wide association studies now implicate the very same receptors in cardiovascular and metabolic disturbances. In this review, we discuss current findings that uncovered some of the molecular mechanisms whereby sorting receptors, such as SORLA, sortilin, and SORCS1 control homeostasis in cardiovascular and metabolic tissues, and how they promote hypercholesterolemia, atherosclerosis, obesity, and diabetes, when being altered.

1. Introduction

Genome-wide association studies (GWAS) have been widely used to identify loci associated with cardiovascular and metabolic diseases in humans and animal models. These studies have confirmed well-known culprits such as the low-density lipoprotein receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9), or the peroxisome proliferator-activated receptor-γ, just to name a few [1]. However, GWAS also uncovered unexpected perpetrators in cardiovascular and metabolic dysfunctions. One prominent example are VPS10P domain receptors, a group of intracellular sorting factors that direct target proteins between secretory and endocytic compartments in many cell types. The role of VPS10P domain receptors as causative agents in neurodegenerative diseases has long been appreciated (reviewed in [2,3]), yet their genetic implication in cardiovascular and metabolic disturbances came as a surprise. Here, we will discuss recent studies that have substantiated the involvement of VPS10P domain receptors in disturbances of the cardiovascular system and the metabolism, including hypercholesterolemia, atherosclerosis, obesity, and diabetes.

1.1. The complex cell biology of sorting receptors

VPS10P domain receptors were initially identified in a quest for new lipoprotein receptors that may share structural resemblance with the LDLR. These studies led to the cloning of two type-1 transmembrane proteins termed sortilin [4] and sortilin-related receptor with A-type repeats (SORLA, also known as LR11) [5,6]. Although SORLA and sortilin bound apolipoproteins, they did not share much structural similarity to prototypical lipoprotein receptors of the LDLR gene family (Fig. 1A). 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 [7,8]. Cloning of SORCS1, SORCS2, and SORCS3 (sortilin-related receptor CNS expressed) added three more mammalian members to the VPS10P domain receptor gene family (Fig. 1A) [9,10].

VPS10P serves as a sorting factor that moves newly synthesized hydrolases from the Golgi compartment to their place of action in the vacuole (the yeast lysosome) [11]. An even 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 (Fig. 1B). Sorting of

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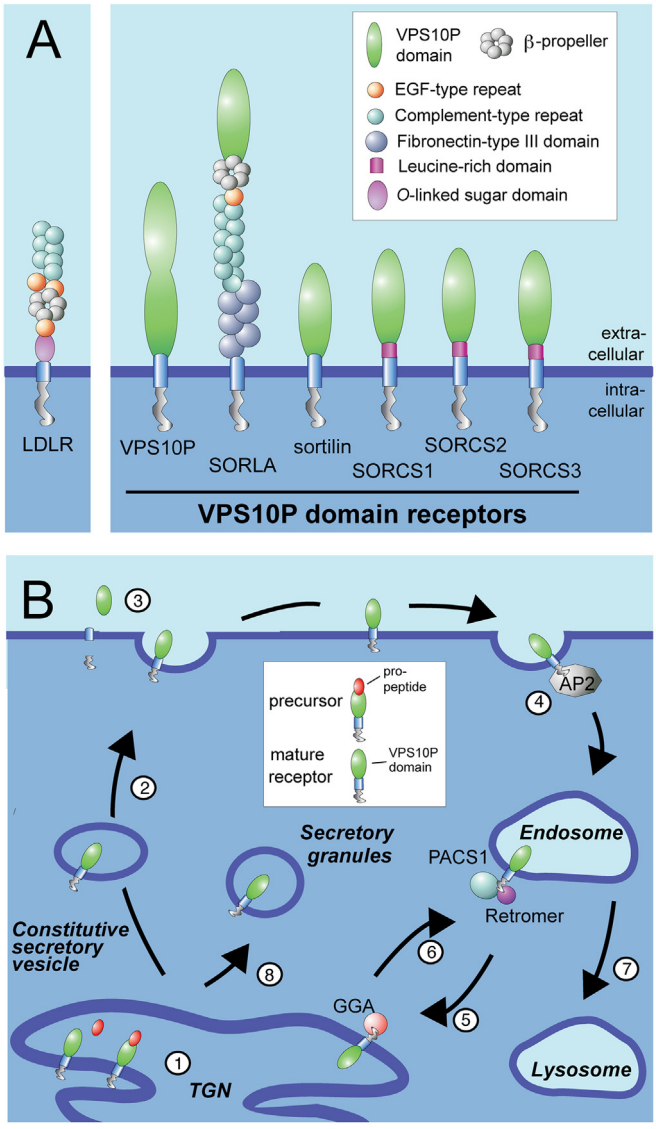

Fig. 1. Structure and cell biology of VPS10P domain receptors. (A) Structural organization of VPS10P domain receptors from yeast (VPS10P) and mammals (sortilin, SORLA, SORCS1, SORCS2 and SORCS3). The extracellular domains of the receptors are composed of one or two VPS10P domains, and may carry additional modules for protein–protein interaction (leucine-rich domains, complement-type repeats, EGF-type repeats and fibronectin-type III domains) or regulation of ligand binding (β-propeller). The structure of the low-density lipoprotein receptor (LDLR) is shown for comparison. (B) 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. Removal of the pro-peptide by pro-protein convertases in the trans-Golgi network (TGN) activates nascent receptor molecules (step 1). 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 2). Some receptor molecules at cell surface are subject to shedding, releasing the soluble ectodomain to act as diffusible regulator by sequestering ligands [33,68]. 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 4) [69,70]. From endosomes, internalized receptors (and some of their cargo) return to the TGN (step 5) [71,72]. This retrograde sorting path requires the interaction with the adaptor complex retromer [71–75] and with PACS1 [76]. A second route for exiting the TGN involves anterograde movement of VPS10P domain receptors to endosomes (step 6), employing the monomeric clathrin adaptor GGA1, GGA2, and GGA3 (Golgi-localizing, g-adaptin ear homology domain, ARF-interacting proteins) [70,77,78]. From endosomes, ligands, and in some instances even the receptor, may be targeted for lysosomal degradation (step 7) [78]. A third pathway for TGN export exists in cells capable of regulated secretion whereby receptors move endogenous ligands from the TGN to secretory granules (step 8). The scheme summarizes trafficking paths identified for various VPS10P domain receptors, but not every route has been confirmed for each receptor.
Fig. 1B adopted from [2].

VPS10P domain receptors is 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, pivotal to activate ligand binding and to shed soluble receptor domains (see Fig. 1B for details). For more detailed discussions, the reader is referred to recent reviews on the molecular concepts of VPS10P domain receptor trafficking [2,12].

All mammalian VPS10P domain receptors are expressed in neurons of the central and peripheral nervous system. Thus, earlier work mainly focused on the neurobiology of these receptors uncovering their ability to sort a number of target proteins in control of neuronal cell death and survival. 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 (reviewed in [2,3]). However, VPS10P domain receptors are also expressed in peripheral tissues with relevance to cardiovascular and metabolic processes. For example, SORLA is produced in adipose tissue and in smooth muscle cells [6,13]. Sortilin is found in hepatocytes [14], while SORCS1 is expressed in pancreatic islets [15]. 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 type 2 diabetes (Table 1). 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. In the following, we will focus on three main aspects of such receptor functions, on SORLA in triacylglyceride metabolism and progression of atherosclerosis, on sortilin in control of systemic cholesterol levels, and on SORCS1 in glucose homeostasis and insulin secretion.

1.2. SORLA impacts vascular integrity and promotes atherosclerosis

SORLA is a 250 kDa receptor that harbors a VPS10P domain but also displays structural elements found in the LDLR and other members of the LDLR gene family (such as a β-propeller and complement-type repeats). The encoding gene had been mapped as a pro-atherogenic locus in inbred strains of mice [16]. The relevance of SORLA for atherosclerotic processes was further

Table 1
Genetic association of VPS10P domain receptors with cardiovascular and metabolic traits in humans and animal models.

Receptor	Association	Cohort	Reference
SORLA	Cerebral small-vessel disease	Human	[20]
	Obesity	Human	[64]
		Mouse	[65]
	Atherosclerosis	Mouse	[16]
sortilin	Hypercholesterolemia	Human	[34–37]
SORCS1	Type 1 diabetes	Human	[57]
	Type 2 diabetes	Mouse	[15]
		Rat	[55]
		Human	[56]
	Obesity	Human	[66]
SORCS2	Biomarkers of cardiovascular disease	Human	[67]
SORCS3	Type 2 diabetes	Rat	[55]