

Review Article

The emerging role of sorting nexins in cardiovascular diseases

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The sorting nexin (SNX) family consists of a diverse group of cytoplasmic- and membrane-associated phosphoinositide-binding proteins that play pivotal roles in the regulation of protein trafficking. This includes the entire endocytic pathway, such as endocytosis, endosomal sorting, and endosomal signaling. Dysfunctions of SNX pathway are involved in several forms of cardiovascular disease (CVD). Moreover, SNX gene variants are associated with CVDs. In this review, we discuss the current knowledge on SNX-mediated regulatory mechanisms and their roles in the pathogenesis and treatment of CVDs.

Introduction

Cardiovascular diseases (CVDs), including hypertension, coronary heart disease, heart failure, and stroke, are the leading causes of morbidity and mortality, worldwide, accounting for substantial suffering and healthcare-related expenditures [1]. According to the American Heart Association, the duration of informal caregiving hours increases from 0.10 h/wk for patients with coronary heart disease to 6.12 h/wk for patients with stroke. This informal caregiving for patients with CVD is projected to increase total CVD costs by 11%, from \$616 billion in 2015 to \$1.2 trillion in 2035, in the United States [2]. Thus, increasing the efficacy in preventing and controlling CVDs worldwide is expected to have a huge potential in decreasing health costs and improving global health [2,3].

Genetic and environmental factors and their interaction determine an individual's risk for CVDs. Recent studies have shown that diet and environmental factors, such as air pollution, influence the development of CVDs [4–7]. There is also strong evidence for the roles of genetics and epigenetics in the prediction, prevention, and treatment (pharmacogenomics) of CVDs [7–10]. Although few single-gene-associated CVDs can now be precisely diagnosed and treated [11], the underlying mechanisms of most CVDs are still unclear.

The sorting nexin (SNX) family consists of a diverse group of cytoplasmic and membrane-associated proteins orchestrating the process of cargo sorting, through the membranous maze that is the endosomal network [12,13]. SNXs play pivotal roles in the whole pathway of endocytic trafficking, including endocytosis, endosomal sorting, and endosomal signaling [12,13]. The perturbation of this process and/or deficiency of SNXs may lead to receptor dysfunction, impaired homeostatic responses, and possibly disease states, including CVDs [14–17]. To our knowledge, there is no review on the association between SNXs and CVDs. In this review, we discussed the evolving understanding of the role of SNXs in CVDs and summarized the current knowledge on SNX-mediated regulatory mechanisms and their role in the pathophysiology and treatment of CVDs.

Received: 14 January 2019
Revised: 19 February 2019
Accepted: 28 February 2019

Version of Record published:
15 March 2019

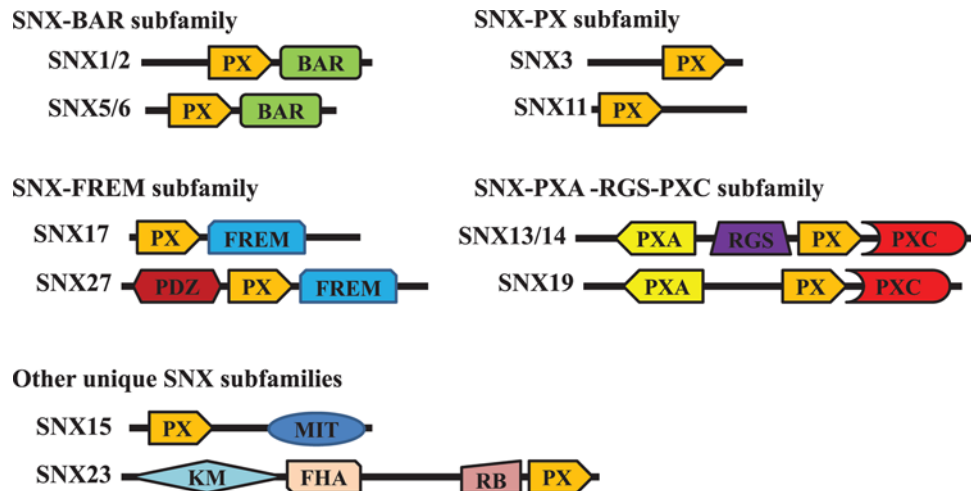


Figure 1. Domain architecture of representative SNXs in different subfamilies

All SNXs share a conserved PX domain. Other domain structures of SNXs in different subfamilies are also indicated. BAR, Bin/Amphiphysin/Rvs domain; FERM, protein 4.1/ezrin/radixin/moesin domain; FHA, forkhead associated domain; KM, kinesin motor domain; MIT, microtubule interacting and trafficking domain; PDZ, postsynaptic density 95/discs large/zonula occludens domain; PX, phagocyte oxidase (phox) homology domain; PXA, PX-associated domain A; PXC, PX-associated domain C; RB, Rab5-binding domain; RGS, regulator of G-protein signaling domain; SNX, sorting nexin.

The basic characteristics of sorting nexins

The SNX family consists of a diverse group of cytoplasmic and membrane-associated proteins involved in various aspects of cargo endocytosis and trafficking through the endosomes [12,13]. SNXs have been identified across phyla, from yeast to mammals. Currently 10 yeast, 8 fruit, and 33 mammalian SNXs have been identified [12–14]. All SNX family members contain the evolutionarily canonical 100–130-amino acid phagocyte oxidase (phox) homology (PX) domain, which facilitates the interaction of SNXs with phosphatidylinositols, most commonly phosphatidylinositol 3-phosphate (PI3P) [15,16]. Thus, most SNXs are associated with PI3P-enriched early endosomes. Based on their domain organization, the SNX family is categorized into five subfamilies: SNX-BAR (Bin/Amphiphysin/Rvs), SNX-PX, SNX-FERM (protein 4.1/ezrin/radixin/moesin), SNX-PXA-RGS-PXC, and other unique SNX subfamilies (Table 1 and Figure 1) [14–18]. In addition to these domains, certain SNXs also contain special structures. For example, SNX27 is unique within the SNX family for having a PDZ domain, a type of protein–protein interaction domain of roughly 90 amino acid residues [19].

Physiological functions of SNXs

Typical functions of SNXs

The balance of protein recycling and degradation is crucial for cellular homeostasis; inappropriate sorting of proteins to either fate leads to cellular dysfunction. The involvement of SNXs in endocytic trafficking, includes several components [20–26] (Figure 2). First of all, the most important physiological function of SNXs is being a component of the retromer, a multi-subunit protein complex, which mediates the recycling or retrograde trafficking of trans-membrane proteins, termed as cargoes, from endosomes to either the trans-Golgi network (TGN) or the plasma membrane [20–23]. These cargoes include G protein-coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), transport carriers for enzymes and the Wnt sorting receptor, glucose and metal ion transporters, polarity proteins, among others [20–23]. The mammalian retromer complex is composed of two distinct subunits: a vacuolar protein sorting associated protein 26 (VPS26)-VPS29-VPS35 trimeric subcomplex, which engages and concentrates cargo to be transported, and a membrane-associated SNX dimer that binds to endosomal membranes and organizes the formation of tubulovesicular carriers that transport cargoes to their final destination. There are three distinct forms of the mammalian retromer complex: SNX-BAR-retromer, SNX3-retromer, and SNX27-retromer. Some SNXs have been the focus of several studies, SNX1/2/5/6 of the SNX-BAR subfamily, SNX3 of the SNX-PX subfamily, and SNX27 of the SNX-FERM subfamily [24–26]. The SNX-BAR-retromer, containing the core retromer trimer and the SNX-BAR subunits, mediates the retrograde trafficking of cargoes. For example, heterodimers of the SNX-BAR proteins, SNX1,

Table 1 Summary of SNX family

Subfamilies	Members	Characteristics of structure	Typical examples involving intracellular physiological functions
SNX-BAR	SNX1, SNX2, SNX4, SNX5, SNX6, SNX7, SNX8, SNX9, SNX18, SNX30, SNX32, SNX33	In addition to the SNX-PX domain, these proteins have a C-terminal BAR domain comprising three α -helices capable of dimerizing with another BAR domain to form a rigid banana-shaped structure. Their BAR domains allow SNX-BARs to form specific homo- and hetero-dimers (e.g. SNX1 and SNX2; SNX5 and SNX6).	SNX1, SNX2, SNX5, and SNX6 are involved in the endosomal membrane sorting processes [25,27]. SNX4 prevents BACE1 trafficking to the lysosomal degradation system [40]. SNX6, a member of the IGF1–IGF1 receptor pathway, regulates the signaling of IGF-1 stimulation [41]. SNX9 and SNX18 are associated with clathrin-mediated and independent endocytosis [30–32]. SNX9, SNX18, and SNX33 are required for mitosis through both endocytosis- dependent and -independent processes [103].
SNX-PX	SNX3, SNX10, SNX11, SNX12, SNX16, SNX20, SNX21, SNX22, SNX24, SNX29	The subfamily of proteins is a relatively poorly characterized group of molecules, which have not any conserved domains outside the defining PX domain. These proteins are of various lengths and typically contain long extended sequences with no predicted secondary structure.	SNX3-retromer is indentified as a distinct form of the mammalian retromer complex [24]. SNX11 promotes the trafficking of TRPV3 from the plasma membrane to lysosomes for degradation [35]. SNX10 controls mTOR activation in colorectal cancer [42]. SNX16 functions in the trafficking of proteins between the early and late endosomal compartments, and plays a role in the regulation of late endosome membrane dynamics [104,105].
SNX-FERM	SNX17, SNX27, SNX31	The three proteins contain a typical C-terminal FERM domain, which is comprised of approximately 300 amino acids. In addition, SNX27 possesses an N-terminal PDZ domain. The sequence homology of the PX-associated FERM domains with the canonical FERM domain is low.	SNX27-retromer is an important form of the mammalian retromer complex [26]. SNX17 prevents lysosomal degradation of β_1 integrins by binding to the β_1 -integrin tail [38]; SNX17 also inhibits the movement of P-selectin into lysosomes [39]; SNX31 mediates the endocytic degradation of proteins such as uroplakins [106].
SNX-PXA -RGS-PXC	SNX13, SNX14, SNX19, SNX25	Each member possesses two putative N-terminal transmembrane helices. SNX13, SNX14, and SNX25 have a long C-terminal structure containing four modular domains (PXA-RGS-PX-PXC); however, SNX19 has only three (PXA-PX-PXC).	SNx13 is involved in the degradative sorting of apoptosis repressor with caspase recruitment domain [93]. SNX14 is a dual endogenous negative regulator in 5-HT6R-mediated signaling pathway [107]. SNX25 negatively regulates TGF- β signaling via enhancing the receptor degradation [108].
Other unique SNX subfamilies (SNX15-MIT and SNX23)	SNX15 SNX23 (also known as kinesin-family protein 16B, KIF16B)	SNX15, first identified via database searches for SNX1 homologs, includes a C-terminal MIT domain. SNX23, a member of the kinesin family, contains kinesin motor, a putative FHA domain, and coiled coil dimerization domains.	SNX15 is associated with the endocytic and endosomal sorting [109,110]. SNX23 regulates receptor recycling and degradation [111].

Abbreviations: BACE1, β -site amyloid precursor protein-cleaving enzyme 1; BAR, Bin/Amphiphysin/Rvs domain; FERM, protein 4.1/ezrin/radixin/moesin domain; FHA, forkhead associated domain; IGF1, insulin-like growth factor 1; MIT, microtubule interacting and trafficking domain; mTOR, mammalian target of rapamycin; PDZ, postsynaptic density 95/discs large/zonula occludens domain; PX, phagocyte oxidase (phox) homology domain; PXA, PX-associated domain A; PXC, PX-associated domain C; RGS, regulator of G-protein signalling domain; SNX, sorting nexin; TGF- β , transforming growth factor- β ; TRPV3, transient receptor potential vanilloid channel 3.

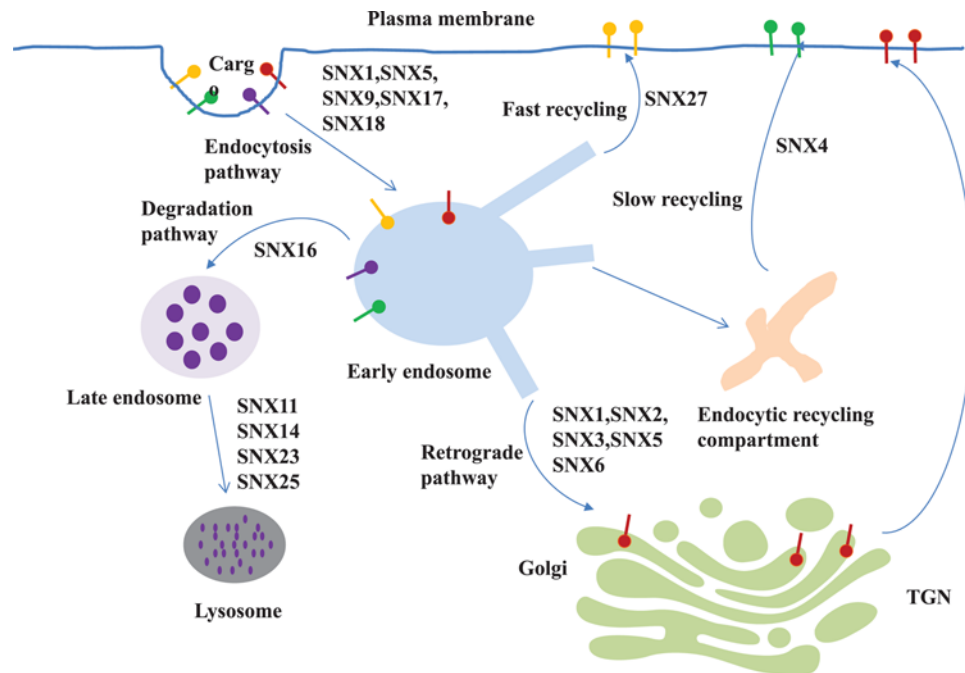


Figure 2. Schematic diagram of representative SNXs involved in the trafficking pathways of cargoes

Different transmembrane proteins, termed as cargoes, are internalized into early endosomes from the plasma membrane via the endocytosis process. Then, retromer mediates some cargo recycling to the trans-Golgi network or back to the plasma membrane. On the other side, maturation of early endosomes into late endosomes leads to cargo degradation via lysosome. Representative SNXs are shown in the different trafficking routes of cargoes. SNX, sorting nexin; trans-Golgi network, TGN.

SNX2, SNX5, and SNX6, independent of the core retromer trimer, are the cargo-selective elements required for the retrograde transport of the cation-independent mannose 6-phosphate receptor from the endosomes to the TGN [27]. The SNX3-retromer, composed of the core retromer trimer and SNX3, traffics the Wnt-binding protein, Wntless, from the endosomes to the TGN [28]. By contrast, the SNX27-retromer mediates the direct endosome-to-plasma membrane trafficking, without passing through the TGN, e.g. recycling of glucose transporter type 1 [29]. These SNXs associate with the retromer or retriever complex, which mediates endosomal trafficking pathways for the delivery of various cargo proteins to the right location for fundamental cellular processes.

Second, SNXs are involved in endocytosis. For example, SNX9 partially localizes to clathrin-coated pits and binds directly to both dynamin-1 and dynamin-2, which are central players in clathrin-mediated endocytosis [30]. SNX9 is required for efficient clathrin-mediated endocytosis by regulating dynamin assembly and also functions in several clathrin-independent endocytosis pathways that are driven by actin polymerization [30,31]. SNX18 heterodimerizes and colocalizes with SNX9 in tubular membrane structures. SNX18 and SNX9 can compensate for each other deficiency during clathrin-mediated transferrin endocytosis [32]. Our previous studies also found that in human renal proximal tubule (RPT) cells, SNX1 is required for the endocytosis of D₅R following agonist stimulation but not for basal receptor trafficking. By contrast, SNX5 is necessary not just for the endocytosis of the agonist-activated D₁R but also for its recycling and reinsertion back to the plasma membrane [33,34].

Third, SNXs are involved in protein degradation. Some SNXs are involved in the lysosomal degradation of proteins. For example, SNX11 promotes the trafficking of TRPV3 from the plasma membrane to lysosomes for degradation via protein–protein interactions [35]. SNX1 facilitates the sorting and degradation of the epidermal growth factor receptor (EGFR) to lysosomes [36]. SNX6 participates in the endolysosomal degradation of tumor suppression p27^{Kip1} [37]. However, other SNXs inhibit the protein degradation. SNX17 prevents the lysosomal degradation of β_1 integrins by binding to the β_1 -integrin tail [38]. SNX17 also inhibits the movement of P-selectin into lysosomes, reducing its degradation while increasing its endocytosis from the plasma membrane [39]. SNX4 interacts with β -site amyloid precursor protein-cleaving enzyme 1 (BACE1) and prevents BACE1 trafficking to the lysosomes, increasing the half-life of BACE1 and production of β -amyloid [40].

Table 2 Summary of SNX family and CVDs

SNX isoform	SNX modification	Effects of SNX modification on CVDs and related functions	Expression and function of SNX and SNX SNP in CVDs
SNX1	SNX1 knockout	Elevates systolic and diastolic blood pressure, blunts natriuretic response to stimulation of D ₅ R, increases the level of oxidative stress, and the expression of sodium transport including Na ⁺ ,K ⁺ -ATPase, NHE3, and NCC [56]; increases levels of triglycerides and cholesterol (unpublished data).	Reduced SNX1 expression in human RPT cells of hypertensive Caucasian males compared with normotensive subjects [56].
	SNX1 knockdown	Increases the systolic and diastolic blood pressures in SNX1-depleted C57BL/6J mice and SNX1-depleted BALB/cJ mice; abrogates D ₅ R-mediated cAMP production, GTP binding, and sodium transport inhibition [34].	
SNX3	SNX3 overexpression	Increases ENaC levels in the total lysate and at the cell surface in mouse cortical collecting duct cells [67].	None
SNX5	SNX5 knockdown	Results in a further increase in systolic blood pressure and a decrease in sodium excretion in SHR, and also increases blood insulin and glucose levels, decreases urinary insulin excretion, and causes insulin resistance in C57Bl/6J mice [33,55]; increases non-fasting serum insulin and glucose levels in WKY rats [55]; results in higher phosphorylation of D ₁ R, impairment of D ₁ R endocytosis, marked delay in receptor recycling, and failure of agonist-induced cAMP production [33]; decreases phosphorylations of insulin receptor and its substrate, protein kinase B phosphorylation [44].	Reduced renal SNX5 expression in SHR; decreased SNX5 expression in RPT cells of SHR and hypertensive humans compared with WKY rats and normotensive subjects [55].
SNX8	SNX8 overexpression	Exacerbates aberrant handling of neuronal cholesterol [46].	Reduced SNX8 expression after extreme changes in cholesterol such as treatment with mevinolin, a cholesterol-lowering statin [46].
SNX9	None	None	SNP rs2364349 in SNX9 is associated with changes in heart rate in response to β-blockers [99].
SNX13	SNX13 knockdown	Results in a markedly decrease in cardiac systolic function with striking cardiomyocyte apoptosis, facilitates the degradative sorting of apoptosis repressor with caspase recruitment domain [93].	Reduced SNX13 expression in the failing hearts of humans and mouse model of heart failure [93].
SNX17	SNX17 overexpression	Promotes the endocytosis of P-selectin from the plasma membrane and inhibits the movement of P-selectin into lysosomes, thereby reducing its degradation in human umbilical vein endothelial cells [39].	Decreased SNX17 expression in ischemic myocardium, accompanied with cardiac electrical disturbances [92].
SNX19	SNX19 knockdown	Increases blood pressure in C57Bl/6J mice; decreases D ₁ R expression and its mediated-cAMP response, abrogates the D ₁ R mediated-increased intracellular sodium in human RPT cells [57]; decreases insulin secretion and the number/size of dense core vesicles in mouse pancreatic β-cells [70].	The SNP of SNX19 is associated with the incident of coronary artery disease in white participants of United States [79]; white participants with a high genetic risk score derived from combined multiple variants including SNX19 had a 57% increased risk of incident coronary artery disease [80].
SNX24	SNX24 knockdown	Decreases expressions of proinflammatory cytokines including IL-1β, IL-6, and IL-8 [89].	Lesser coronary artery aneurysm complications in patients with CC + CT genotypes (rs28891) in SNX24 in Taiwanese children of Han Chinese ethnic background with Kawasaki disease [89].
SNX25	SNX25 overexpression	Enhances D ₁ R and D ₂ R expression and receptors-mediated signaling, perturbs both endocytosis and recycling of D ₂ R [63].	None
	SNX25 knockdown	Decreases the D ₁ R and D ₂ R expression [64].	
SNX27	SNX27 knockdown	Decreases GLUT4 expression [51]; inhibits recycling of β2AR [98]; decreases GLP-1R plasma membrane recycling, fails to sustain endosomal cAMP increases and reduces basal GLP-1R levels and increases exendin-4-induced receptor degradation in murine insulinoma MIN6B1 cells [78]; reduces exocytic insertion of NHE3 to the plasma membrane [66].	None

Abbreviations: β₂AR, β₂ adrenergic receptor; cAMP, cyclic adenosine monophosphate; CVD, cardiovascular disease; D₁R, dopamine D₁ receptor; D₂R, dopamine D₂ receptor; D₅R, dopamine D₅ receptor; ENaC, epithelial sodium channel; GLP-1R, glucagon-like peptide-1 receptor; GLUT4, glucose transporter isoform 4; GTP, guanosine triphosphate; HCTZ, hydrochlorothiazide; IL, interleukin; NCC, thiazide-sensitive sodium-chloride cotransporter; NHE3, sodium-hydrogen exchanger 3; RPT, renal proximal tubule; SHR, spontaneously hypertensive rat; SNP, single-nucleotide polymorphism; SNX, sorting nexin; WKY, Wistar-Kyoto.

Fourth, SNXs play important roles in intracellular signaling. SNXs can directly participate in the intracellular signaling cascade, as a member of the pathway. For example, the knockdown of SNX6, a member of the insulin-like growth factor 1 (IGF1)–IGF1 receptor pathway, decreases IGF1-mediated ERK1/2 phosphorylation, but does not affect IGF1 receptor internalization [41]. SNX10 inhibits mTOR activation by regulating chaperone-mediated autophagy-dependent amino-acid metabolism in colorectal cancer [42]. SNX9 preferentially binds to phosphorylated Smad3, independent of Smad2 and Smad4, the primary mediators of TGF- β responses, and promotes its more rapid nuclear delivery [43].

SNXs can also indirectly regulate downstream signaling by impairing the expression or function of transmembrane proteins such as GPCRs and RTKs. For example, our studies found that SNX5 regulates insulin receptor expression, distribution, dynamics and function in human RPT cells; SNX5 knockdown leads to a decrease in insulin receptor expression, causing the decrease in downstream signaling cascade, including the abundance of phosphorylated insulin receptor substrate and phosphorylated protein kinase B [44].

Regulation of SNXs

So far, there are only a few studies on the regulation of SNXs. The expression of SNXs *per se* is regulated by some hormones, enzymes, and other SNX family members. Estradiol (E_2) decreases SNX5 expression in the mammary gland of E_2 receptor α ($ER\alpha$) wild-type mice. However, in the mammary gland of $ER\alpha$ knockout mice, E_2 increases SNX5 expression, presumably via $ER\beta$ [45]. Neuronal SNX8 expression was decreased by extreme changes in cholesterol such as treatment with mevinolin, a cholesterol-lowering statin, but unchanged in the presence of moderately high cholesterol [46]. Itch (atrophin-1 interacting protein 4), a member of the NEDD4 family of E3 ubiquitin ligases, expressed in HEK cells, increases the ubiquitination and degradation of SNX9 [47]. In HeLa cells undergoing apoptosis, both SNX1 and SNX2 are cleaved by initiator caspases and executioner caspase-6, in the case of SNX2. Moreover, SNX1 but not SNX2 is cleaved at multiple sites, including sites that follow glutamate residues [48]. The interaction among SNXs can regulate specific SNX expression. For example, suppression of SNX5 and/or SNX6 results in the loss of SNX1 in HeLa cells, an effect that seems to result from post-translational regulation of the SNX1 level [49].

SNX function, independent of expression, can be regulated, as well. In 3T3L1 adipocytes, insulin stimulates the movement of SNX9 out of the cytosol and into the plasma membrane [50]. Another study also found in mature adipocytes that insulin stimulates the redistribution of a proportion of retromer and its associated proteins, including SNX27 but not SNX1, from intracellular compartments to the plasma membrane along with glucose transporter 4 storage vesicles [51]. Our studies found that insulin treatment increases SNX5 levels and the colocalization of SNX5 and insulin receptor in the perinuclear area of human RPT cells [44]. Stimulation with the D_1 -like receptor agonist, fenoldopam, promotes the internalization of SNX5 and enhances its colocalization with D_1R at the brush border and cytoplasm of RPTs, demonstrating an essential role for SNX5 in regulating D_1R function [33]. Treatment with fenoldopam can also markedly enhance the interaction between SNX1 and D_5R and promote their internalization in HEK293 cells expressing V5-tagged D_5R , showing a crucial role for SNX1 in D_5R trafficking [34].

Role of SNXs in cardiovascular diseases

SNXs and hypertension

Hypertension is one of the most common and important health problems worldwide. The kidney plays an important role in the long-term control of blood pressure and is the major organ involved in sodium homeostasis. Humans with polygenic essential hypertension have increased renal sodium transport, which is not properly regulated by natriuretic and anti-natriuretic hormones and humoral factors, including dopamine [52,53]. Studies have shown that SNXs exert their physiological effects by regulating the expression and function of GPCRs, such as dopamine receptors, and RTKs, activated by hormones such as insulin, which lead to either natriuresis or anti-natriuresis to maintain a normal blood pressure [33,34,44,54].

Evidence of a role of SNXs in the regulation of blood pressure

There are a few studies showing impaired expression and function of SNXs in hypertension. The protein expression of SNX5 is decreased in the kidney of spontaneously hypertensive rats (SHRs), as well as immortalized RPT cells from hypertensive humans compared with WKY rats and normotensive subjects, respectively [55]. The pathophysiological significance of decreased SNX5 expression has been proved by down-regulating its expression, selectively in the kidney, using siRNA infusion. Depletion of renal SNX5 expression by the infusion of *Snx5*-specific siRNA into the kidney of SHRs caused a further increase in systolic blood pressure, a decrease in sodium excretion [33]. Moreover,

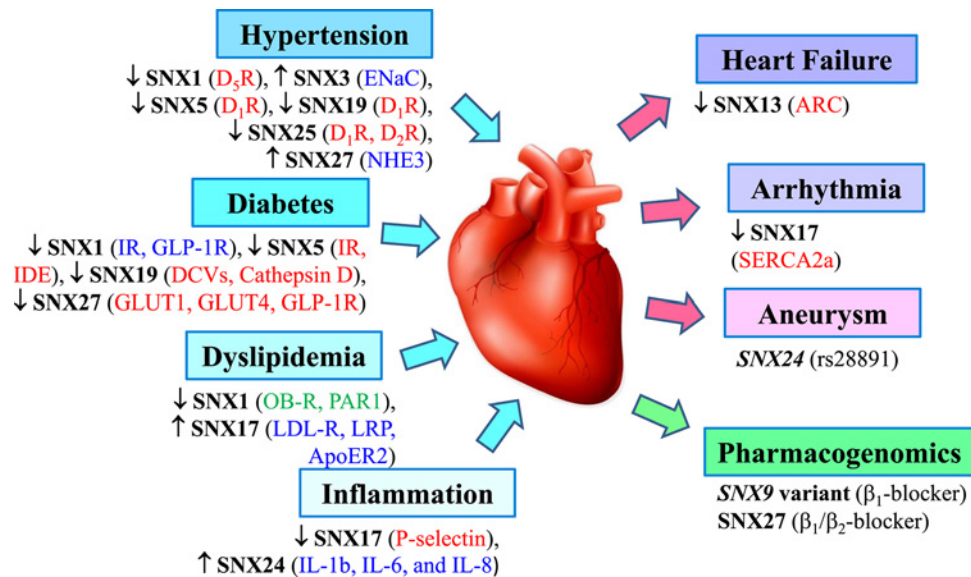


Figure 3. Impact of various sorting nexins (SNXs) on the etiology and sequelae of cardiovascular disease

Several SNXs have been identified to impinge on some of the well-known underlying mechanisms, complications, and utility for pharmacogenomics for cardiovascular disease. Arrows (↑ or ↓) indicate the pathological change in the expression or activity of SNXs in the respective disease, and the corresponding change of their targets (receptor/enzyme/transporter/inflammatory cytokines) is also in brackets, either activation (in blue), inactivation (in red), or unknown (in green). rs28891 is a SNP of SNX24 that predispose to the development of coronary artery aneurysm. The PDZ domain of SNX27 is essential for PDZ-directed recycling of the β₂AR, apolipoprotein E receptor 2 (ApoER2), apoptosis repressor with caspase recruitment domain (ARC), β₁-adrenergic receptor blocker (β₁-blocker), β₂-adrenergic receptor blocker (β₂-blocker), dense core vesicles (DCVs), dopamine D₁ receptor (D₁R); dopamine D₂ receptor (D₂R); dopamine D₅ receptor (D₅R), epithelial sodium channel (ENaC), glucagon-like peptide-1 receptor (GLP-1R), glucose transporter 1 (GLUT1) or 4 (GLUT4), insulin degrading enzyme (IDE), insulin receptor (IR), interleukin (IL), leptin receptor (OB-R), low density lipoprotein receptor (LDL-R), LDL-R-related protein (LRP), protease-activated receptor (PAR1), sarcoplasmic reticulum Ca²⁺-ATPase2a (SERCA2a), sodium hydrogen exchanger type 3 (NHE3), sorting nexin (SNX).

renal-selective silencing of SNX5 in C57Bl/6J mice also increases blood insulin and glucose levels, decreases urinary insulin excretion, and causes insulin resistance [55].

The blood pressure can be regulated by other SNXs. Our previous study showed that *Snx1*^{-/-} mice had elevated systolic and diastolic blood pressure measured under pentobarbital anesthesia, compared with wild-type littermates [56]. Further studies showed that *Snx1*^{-/-} mice had elevated night time blood pressure, the level of which was not affected by dietary salt intake, indicating that the blood pressure of *Snx1*^{-/-} mice is not salt-sensitive [56]. Although SNX1 is not involved in the salt-sensitive hypertension, there are evidence showing its role in hypertension, for example, SNX1 expression is decreased in RPT cells from hypertensive compared with normotensive Caucasian males [56]. Further studies also showed that both the systolic and diastolic blood pressures (under pentobarbital anesthesia) were higher by 13 and 15 mm Hg, respectively, in renal SNX1-depleted C57Bl/6J mice and by 26 and 23 mm Hg in renal SNX1-depleted BALB/cJ mice compared with mock-treated controls [34]. Those evidence indicate that decreased SNX1 expression and dysfunction of SNX1 may be a potential common mechanism in several hypertensive models, including salt-sensitive- and salt-resistant hypertensive models. Our preliminary data also showed that SNX19, an SNX subtype containing a central PX domain and non-BAR domains at the C-terminal region, regulates blood pressure; depletion of renal SNX19 increases blood pressure in C57Bl/6J mice [57].

The decreased expression of SNX and increased blood pressure in SNX knockout or knockdown animal models indicate that SNX may have clinical significance as potential therapeutic targets for hypertension. Our preliminary studies also showed that the expression of endogenous SNX1 is reduced in human RPT cells from hypertensive compared with normotensive Caucasian males [56]. However, three SNX1 variants (rs34910981, rs1130604, and s1802376), and one SNX5 variant (rs6045116) are not associated with salt-sensitive hypertension in Euro-Americans [58]. It is conceivable that other gene variants could affect the expression, localization, and activity of SNX5, because SNX5 is replete with SNPs, such as rs754299876, rs758576026 and rs746381456, and structural variations, such as changes in

copy number and indels (insertions and deletions) [58], which may be associated with or link to hypertension, salt sensitivity, and insulin resistance. The overexpression of SNX subtypes in the kidney may decrease blood pressure and may be another approach for the treatment of hypertension.

The mechanisms by which SNXs regulate blood pressure

Regulation of dopamine receptors by SNX

Dopamine, via 5 subtypes of receptors (D₁-like receptors [D₁R and D₅R] and D₂-like receptors [D₂R, D₃R, and D₄R]), plays an important role in the control of blood pressure. Disruption of any of the dopamine receptor genes in mice results in hypertension [52,53]. During conditions of moderate sodium balance, more than 50% of renal sodium excretion is regulated by the D₁-like receptors (D₁R and D₅R).

SNX1 and D₅R

SNX1, the first mammalian SNX, is essential for the trafficking and function of D₅R. The elevated blood pressure in *Snx1*^{-/-} mice or renal SNX1-depleted mice is associated with blunted natriuretic response to fenoldopam, an agonist of the two D₁-like receptors [34,52,53,56]. SNX1 is required for D₅R trafficking following agonist stimulation; loss of SNX1 abrogates D₅R-mediated cAMP production and inhibition of renal sodium transport [34]. This is associated with increased expression of genes that increase renal sodium reabsorption, including Na⁺-K⁺-ATPase, sodium-hydrogen exchanger 3 (NHE3), and the thiazide-sensitive sodium-chloride cotransporter (NCC) [56]. The dysfunction of D₅R caused by SNX1 silencing also increases oxidative stress [56]. The SNX1-mediated regulation of D₅R may be related to their ability to interact directly and physically [34]. SNX1 distinguishes between D₁R and D₅R by binding strongly to the D₅R but not to the D₁R C-terminal tail [59].

SNX5 and D₁R

D₁R, the other D₁-like receptor, is regulated by SNX5 and not SNX1 that regulates D₅R as discussed above. The impaired regulation of blood pressure and renal sodium excretion caused by renal-selective depletion of SNX5, discussed above is due to impairment of D₁R function [33]. Renal-selective silencing of SNX5 increases agonist-activated D₁R phosphorylation, prevents D₁R internalization, delays D₁R recycling, and impairs of agonist-induced cAMP production [33]. The efficient recycling of the D₁R and its targeting to the plasma membrane involves the C-terminus of the human and rat D₁R [54,60–62]. SNX5 colocalizes with the D₁R at the brush border of proximal tubules and the distal convoluted tubule in the human renal cortex [33]. Stimulation with fenoldopam, an agonist of D₁-like receptors, promotes the internalization of D₁R and SNX5 and enhances their colocalization at the brush border and the cytoplasm [33]. The essential role for SNX5 in the regulation of D₁R function may have important implications in the diagnosis, prognosis, and treatment of essential hypertension.

SNX25, SNX19, SNX13, and D₁R

Besides SNX5, other SNXs are involved in the regulation of renal D₁R. The full-length SNX25 contains a typical PX domain, a PX-associated (PXA) domain, and a regulator of G protein signaling (RGS) domain. SNX25 overexpression enhances the expression levels of both D₁R and D₂R, causes an increase in receptor-mediated signaling, and perturbs both endocytosis and recycling of D₂R, but does not affect D₁R desensitization [63,64]. Depletion of endogenous SNX25 causes a decrease in D₁R and D₂R expression. The interaction between SNX25 and D₁R *in vivo* remains to be determined. SNX19 also colocalizes with D₁R in the human and mouse kidney. Silencing of SNX19 in human RPT cells decreases D₁R, but not D₅R, expression, impairs D₁R mediated-cAMP response, abrogates the D₁R mediated-decrease in sodium transport. Renal-selective silencing of SNX19 decreases renal D₁R expression and increases blood pressure in C57Bl/6J mice (unpublished data) [57]. SNX13 may also interact with D₁R in the regulation of albumin excretion [65].

Regulation of cellular sodium handling by SNXs

SNXs such as SNX27 and SNX3 can directly regulate the expression and function of genes that regulate sodium movement. SNX27 interacts with the C-terminus of NHE3 through its PDZ domain, which maintains basal NHE3 activity and surface expression in HEK-293 and polarized epithelial Caco-2BB cells [66]. It is required not only for the exocytosis of NHE3 from early endosome to plasma membrane, but also for the retention of NHE3 at the plasma membrane [66]. SNX3 increases total and plasma membrane α and γ ENaC in HEK-293 cells expressing these tagged proteins. Vasopressin increases the expression of ubiquitin-specific protease 10, which de-ubiquitinylates and stabilizes SNX3 to increase the cell surface expression of these ENaC subunits in HEK-293 and mouse renal cortical collecting duct

cells [67]. SNX3 also physically interacts with α ENaC [67]. However, the role of SNX27 and SNX3 in the regulation of blood pressure remains to be determined.

SNXs and insulin resistance

Insulin resistance, with or without hyperinsulinemia, participates in the pathogenesis of hypertension [68,69]. SNXs are associated with insulin resistance and hyperinsulinemia. SNXs can regulate insulin action by at least three mechanisms: insulin secretion, degradation, and signaling. SNX can regulate insulin secretion. The knockdown of SNX19 in mouse pancreatic β -cells decreases insulin secretion and the number/size of dense core vesicles (DCV) [70]. Further studies showed that the half-life of DCVs is decreased, but the number of lysosomes and the activity of lysosome enzyme cathepsin D are increased in SNX19 knockdown cells. The rescue of SNX19 in these SNX19 knockdown cells reverses the decrease in DCVs, number of lysosomes, and activity of cathepsin D [70].

Insulin degradation can be regulated by SNX5. The kidney, especially the RPT, is the major site of the clearance of insulin from the systemic circulation, removing 50% of circulating insulin [71,72]. Insulin-degrading enzyme (IDE) is the major enzyme responsible for degrading insulin in kidney [73]. We have reported that IDE and SNX5 dynamically interact in the kidney. SNX5 and IDE colocalized with IDE in the brush border membrane of proximal tubules of human, rat, and mouse kidneys. The renal-selective silencing of *Snx5* in mice decreases IDE expression and activity, increases blood insulin and glucose levels, decreases urinary insulin excretion, and causes insulin resistance. The renal-selective silencing of *Snx5* in normotensive Wistar-Kyoto rats also increased blood insulin and glucose levels [55]. RPT cells from hypertensive rats and humans have decreased expression of IDE and SNX5 [55].

SNX5 can also regulate insulin signaling. Our previous data have shown that SNX5 is necessary for normal insulin receptor expression and activity. SNX5 and insulin receptor colocalize in the brush border of RPTs, both of which are increased after insulin stimulation. SNX5 silencing decreases the phosphorylation of insulin receptor and its substrate, protein kinase B [44].

SNX1, SNX2, SNX4, and SNX27 can also interact with the insulin receptor [74,75]; the activation of insulin signaling increases the interaction between SNX27 and insulin receptor [74]. SNX27 has also been reported to regulate the expression of the glucose transporter isoform 1 (GLUT1) by preventing its lysosomal degradation, maintaining its cell surface levels [76]. Moreover, GLUT4, another insulin-responsive glucose transporter that mediates glucose uptake in adipose and skeletal muscle cells, is also regulated by SNX27 because SNX27 knockdown leads to decreased expression of GLUT4 [51].

SNXs can also promote insulin secretion and function by regulating other hormones, such as the glucagon-like peptide 1 (GLP-1), a 30-amino acid long peptide hormone derived from proglucagon and secreted by L-cells in small intestines [77]. For example, SNX27 and SNX1 increase insulin secretion from murine insulinoma cells mouse and human β -cell lines and human islets in response to the GLP-1 analog exendin-4. Moreover, both SNX27 and SNX1 control overall β -cell incretin responses by regulating the balance between GLP-1 receptor plasma membrane recycling and lysosomal degradation [78]. Thus, SNXs are important in the regulation of insulin function and prevention of insulin resistance.

SNXs and coronary artery disease

Population studies have shown the association between coronary artery disease and SNXs, such as SNX19. An SNX19 SNP, rs2298566, is associated with the incidence of coronary artery disease in the Atherosclerosis Risk in Communities (ARIC) study among Euro-Americans [79]. Further studies in the ARIC study showed that genetic variants of kinesin family member 6 (rs2045), myosin heavy chain 15 (rs3900940), paladin cytoskeletal-associated protein (rs7439293), vesicle-associated membrane protein 8 (rs1010), and SNX19 (rs2298566) had a 57% increased risk of coronary artery disease [80]. However, there still a lack of direct evidence to show the causal relationship between SNXs and coronary artery disease in human and animal models.

The mechanisms by which SNXs cause coronary artery disease are still unclear. However, indirect evidence suggest that SNXs may affect the pathogenesis of coronary artery disease via the regulation of lipid metabolism. First, SNX can directly regulate the serum lipid level. In animal studies, we have found that *Snx1*^{-/-} mice have increased levels of triglycerides and cholesterol (Villar VA et al., unpublished data). The effects of SNXs on lipid level may be through the interaction of SNX1, SNX1A (splice variant of SNX1), SNX2, and SNX4 with the leptin receptor [75]. Another study also showed that overexpression of SNX8 exacerbates aberrant handling of neuronal cholesterol, causing redistribution of cholesterol within neurons creating a phenotype similar to the treatment of U18666a, which causes cholesterol to accumulate within the lysosome [46]. The low density lipoprotein (LDL) receptor (LDL-R) is a transmembrane protein that participates in lipid homeostasis [81]. SNX17, via its FERM-like and carboxyl-terminal

domains, regulates the cellular trafficking of the LDL-R by the interaction of the NPVY motif in its (LDL-R) cytoplasmic domain and the SNX17 PX domain with subcellular membrane compartments [82]. The LDL-R-related protein (LRP), an endocytic recycling receptor with two cytoplasmic tyrosine-based basolateral sorting signals, is also regulated by SNX17. SNX17 binds to the proximal NPXY motif of the LRP tail distinct from its endocytosis signals, interacts preferentially with PtdIns(3)P through its PX domain, and promotes LRP sorting to the recycling pathway in the early endosomes [83,84]. The NPXY motif recognized by SNX17 is required for the exit of LRP1 from basolateral sorting endosome, indicating that polarized traffic of LRP1 involves SNX17 operating on Y-dependent sorting motifs [84]. Further study showed that a sorting nexin 17-binding domain, a cluster of 32 amino acid residues within the LRP1 cytoplasmic tail, mediates receptor recycling through the basolateral sorting endosome [85]. By interacting with the NPxY domain of ApoER2, another member of the LDL-R family, SNX17 facilitates its trafficking from early endosomes to recycling endosomes and to the plasma membrane, participates in the reelin-induced receptor degradation pathway, and regulates the processing of the carboxy-terminal fragment of ApoER2 [86]. Another study also suggests an essential role for endogenous SNX1 in sorting activated PAR1, a G-protein-coupled receptor activated by thrombin and contributing to the pathogenesis of atherosclerosis by impairing cholesterol efflux from cells and by recruiting leukocytes to arteries [87,88]. However, until now, the potential mechanism for the hypertriglyceridemia in the *Snx1*^{-/-} mice is still unknown. Further study will be needed in the future.

Another mechanism by which SNXs can affect the development of coronary artery disease may be via the SNX-mediated regulation of inflammation. SNXs directly regulate some inflammatory factors. For example, endothelial cell injury and inflammation are known to be the main mechanisms in the development of vascular diseases. In lipopolysaccharide-treated human umbilical vein endothelial cells, SNX24 knockdown decreases the expression of some proinflammatory cytokines including IL-1 β , IL-6, and IL-8, indicating its role on the regulation of endothelial inflammation [89]. Another member of SNX family, SNX17, was also identified as a P-selectin-interacting protein. P-selectin, a cell adhesion molecule found in platelet and endothelial cells, mediates the binding of leukocytes. SNX17, identified as a putative intracellular P-selectin binding protein, interacts with the C-terminus of P-selectin and promotes its endocytosis from the plasma membrane, and decreases the degradation of P-selectin in lysosomes by restricting its transport into the late endosomes, thereby affecting leucocyte recruitment [90,91].

Besides of the role of SNX in the pathogenesis of coronary artery disease, there is also evidence showing a role of SNX in the complications of coronary artery disease, especially in the ischemia-induced arrhythmia. In the ischemic myocardium, SNX17 is decreased, accompanied by cardiac electrical disturbances [92]. This is related to the finding that loss of SNX17 causes intracellular Ca²⁺ overload as revealed by the abnormal rise of resting [Ca²⁺]_i and deceleration of decay of Ca²⁺ transient indicative of sarcoplasmic reticulum Ca²⁺-ATPase2a (SERCA2a) dysfunction, whereas SNX17 overexpression produced the opposite effects [92]. SNX17, via its PX domain, also facilitates the lysosomal degradation of SERCA2a. These indicate that SNX17 exerts its anti-arrhythmic effects by preserving functional SERCA2a protein in myocardial infarction.

SNXs and other cardiovascular diseases

Heart failure is also associated with abnormal SNX expression. Endogenous SNX13 is reduced in the failing hearts of humans and mice, the latter induced by transverse aortic constriction [93]. SNX13-deficient zebrafish have a marked decrease in cardiac systolic function associated with cardiomyocyte apoptosis, the inhibition of which largely rescues the cardiac dysfunction associated with SNX13 deficiency [93]. SNX13, via its N-terminal PXA domain, mediates endosomal trafficking of apoptosis repressor with caspase recruitment domain (ARC), a multifunctional inhibitor of apoptosis; loss of SNX13 facilitates the lysosomal degradation of ARC, promoting cardiomyocyte apoptosis and heart failure [93].

SNXs are also associated with some vascular diseases including coronary artery aneurysm. The SNX24 SNP rs28891 correlates with the development of coronary artery aneurysm formation in Taiwanese children of Han Chinese ethnic background with Kawasaki disease. Patients with CC + CT genotypes in *SNX24* have lesser coronary artery aneurysm complications, indicating that polymorphisms in *SNX24* gene may be used as genetic markers for the diagnosis and prognosis of coronary artery aneurysm formation in Kawasaki disease [89].

Potential role of SNXs in pharmacogenomics of diseases

SNXs have been shown to be valuable in the treatment for some diseases such as several types of cancer. Decreased expression of SNX1 in colorectal cancer cells is associated with overall survival. SNX1 may be a tumor suppressor; increased expression of SNX1 inhibits proliferation of colorectal cancer cells and increases their sensitivity to most commonly used chemotherapeutic drugs (oxaliplatin and 5-fluorouracil) for colorectal cancer [94]. The down-regulation

of SNX2 leads to the overcoming of drug resistance to EGFR-targeted drugs in lung cancer cells harboring c-Met gene amplification [95]. The incidence of hypertension is increased in patients with cancer, including those treated with antibodies against vascular endothelial growth factor receptor [96,97].

β_1 -Adrenergic receptor (β_1 -AR) agonists and antagonists are widely used in the treatment of cardiovascular diseases, including heart failure and hypertension. SNX27 mediates the efficient recycling of the β_1 -AR from plasma membrane into the recycling endosome; SNX27 down-regulation increases the degradation of β_1 -AR in lysosomes [98]. SNXs are also associated with heart rate response to some drugs such as β -adrenergic receptor blockers (β -blockers). Shahin et al. performed a genome-wide association analyses for the decrease in heart rate in response to β_1 -AR blocker, as monotherapy or add-on therapy in whites and blacks separately from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study [99]. The results showed that SNP rs2364349 in SNX9 is associated with the β_1 -AR-mediated decrease in heart rate [99]. SNX27 mediates the recycling of PDZ-domain binding motif-containing cargo, of β_1 -AR and β_2 -AR. The SNX27 PDZ-domain binds to the β_1 -AR and β_2 -AR tails, which is essential for PDZ-directed recycling of the β_2 -AR [100,102]. Indeed, knockdown of SNX27 inhibits the recycling of β_2 -AR [101].

Conclusions and perspectives

In summary, increasing evidence show that SNXs play a crucial role in various aspects of cargo endocytosis and trafficking through the endosomes, including endocytosis, endosomal sorting, and endosomal signaling. Recent studies have begun to highlight the pivotal roles of SNXs in the pathogenesis of CVDs (Figure 3), showing that dysfunction of SNXs may be involved in the pathogenesis of CVDs (Table 2). Further research using innovative silencing techniques and appropriate animal models, such as conditional and global knockout mice and renal-specific silencing, as well as gene rescue will lead to advances in our understanding of the functions of SNXs. Such studies may demonstrate not only the crucial role of SNXs in the pathogenesis of CVDs, but also their utility in the treatment of CVDs.

Funding

These studies were supported in part by grants from the National Natural Science Foundation of China [81570379, 81770425]; National Key R&D Program of China [2018YFC1312700]; Program of Innovative Research Team by National Natural Science Foundation [81721001]; the Natural Science Foundation Project of Chongqing [cstc2015jcyjA10060]; and the National Institutes of Health [5R01DK039308-31, 5R01HL092196-10, and 5P01HL074940-11].

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Author Contribution

All authors contributed to the writing of this manuscript.

Abbreviations

ARIC, atherosclerosis risk in communities; BACE1, β -site amyloid precursor protein-cleaving enzyme 1; β_1 -AR, β_1 -adrenergic receptor; β -blockers, β -adrenergic receptor blockers; BAR, Bin/Amphiphysin/Rvs; CVD, cardiovascular disease; D₁R, dopamine D₁ receptor; D₂R, dopamine D₂ receptor; D₅R, dopamine D₅ receptor; DCV, dense core vesicles; EGFR, epidermal growth factor receptor; ENaC, epithelial sodium channel; ER α , E₂ receptor alpha; GLP-1, glucagon-like peptide 1; GLUT1, glucose transporter isoform 1; GPCR, G protein-coupled receptor; IDE, insulin-degrading enzyme; IGF1, insulin-like growth factor 1; LDL-R, low density lipoprotein receptor; NCC, thiazide-sensitive sodium-chloride cotransporter; NHE3, sodium-hydrogen exchanger 3; PEAR, pharmacogenomic evaluation of antihypertensive responses; PI3P, phosphatidylinositol 3-phosphate; RPT, renal proximal tubule; SERCA2a, sarcoplasmic reticulum Ca²⁺-ATPase2a; SHR, spontaneously hypertensive rat; SNX, sorting nexin; TGN, trans-Golgi network.

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