

## **The Soluble (Pro)Renin Receptor in Health and Diseases: Foe or Friend?**

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**Abbreviations list**

ADAM19, a disintegrin and metalloproteinase 19

AGT, angiotensinogen

AngII, angiotensin II

AQP2, aquaporin 2

ATP6AP2, ATPase, H<sup>+</sup>-transporting, and lysosomal-accessory protein 2

ATP6IP2, ATPase, H<sup>+</sup>-transporting, and lysosomal-interacting protein 2

AVP, vasopressin

BP, blood pressure

CKD, chronic kidney disease

ELISA, enzyme-linked immunosorbent assay

fPRR, Full-length PRR

FZD8, frizzled-8

GDM, gestational diabetes mellitus

IMCD, inner medullary collecting duct

LDLR, low-density lipoprotein receptor

LRP6, low-density lipoprotein receptor-related protein 6

NDI, nephrogenic diabetes insipidus

OSAS, obstructive sleep apnea syndrome

PPAR $\gamma$ , peroxisome proliferator-activated receptor-gamma

PRR, (Pro)Renin receptor

RAS, Renin-angiotensin system

S1P, site-1-protease

SORT1, sortilin-1

sPRR, soluble PRR

V<sub>2</sub>R, AVP receptor 2

V-ATPase, vacuolar H<sup>+</sup>-ATPase

WD, water deprivation

## Abstract

The (pro)renin receptor (PRR) is a single-transmembrane protein that regulates the local renin-angiotensin system and participates in various intracellular signaling pathways, thus exhibiting a significant physio-pathological relevance in cellular homeostasis. A soluble form of PRR (sPRR) is generated through proteases-mediated cleavage of the full-length PRR and secreted into extracellular spaces. Accumulating evidence indicates pivotal biological functions of sPRR in various physiopathological processes. sPRR may be a novel biomarker for multiple diseases.

**Keywords:** Soluble (pro)renin receptor; renin-angiotensin system; cardiovascular disease; kidney disease; obesity

## Significance statement

Circulating sPRR concentrations are elevated in patients and animals under various physiopathological conditions. Here we highlight recent advances in sPRR functions in health and pathophysiological conditions. Results suggest that sPRR may be a novel biomarker for multiple diseases, but further studies are needed to determine the diagnostic value of sPRR.

## Introduction

(Pro)Renin receptor (PRR), a 39-kDa type-I transmembrane protein, also known as ATP6AP2 (ATPase, H<sup>+</sup>-transporting, and lysosomal-accessory protein 2) or ATP6IP2 (ATPase, H<sup>+</sup>-transporting, and lysosomal-interacting protein 2), was first discovered and assigned a renin-regulatory function in 2002 (Nguyen G et al., 2002). PRR is widely expressed in multiple tissues/organs throughout the body, including brain, heart, lung, liver, kidney, vascular, adipose tissue, etc., and plays key roles in various pathophysiological processes by its effects on biological systems and intracellular signaling pathways, including local renin-angiotensin system (RAS), wnt/ $\beta$ -catenin signaling, vacuolar H<sup>+</sup>-ATPase (V-ATPase), and mitogen-activated protein kinase signaling (Ichihara A and MS, 2019). Activation of PRR contributes to diseases such as cardiovascular diseases, kidney injury, hypertension, diabetes and its complications, and preeclampsia (Ichihara A and MS, 2019).

PRR consists of a large N-terminal extracellular domain, a single transmembrane domain, and a short cytoplasmic domain (**Figure 1**)(Nguyen G and DN, 2010). Full-length PRR (fPRR) is cleaved by proteases to generate a soluble form of PRR (sPRR) containing the N-terminal extracellular domain of PRR, to secrete into extracellular spaces such as plasma and urine (Cousin C et al., 2009; Fang H et al., 2017; Nakagawa T et al., 2017; Yoshikawa A et al., 2011), and a 8.9-kDa C-terminal intracellular domain contains the transmembrane and cytoplasmic domain of PRR, a truncated protein associated with the V-ATPase (Cruciat CM et al., 2010). Furin was the first reported enzyme for the intracellular cleavage of PRR in the *trans*-Golgi, by recognizing the conserved amino-acid sequence R<sup>275</sup>KTR<sup>278</sup>, a furin-like cleavage site (Cousin C et al., 2009). Subsequently, Yoshikawa *et al.* reported that transfection of a disintegrin and metalloproteinase 19 (ADAM19) increased, whereas transfection of dominant-negative ADAM19 inhibited the production of sPRR (Yoshikawa A et al., 2011). Neither the furin-deficient LoVo cells nor furin inhibitor-treated vascular smooth muscle cells lost sPRR in the media (Yoshikawa A et al., 2011). These results indicate that ADAM19 but not furin catalyzes the generation of sPRR in the Golgi.

Lately, two studies from two different groups using different approaches consistently stated the requirement of S1P for the generation of sPRR by recognizing the conserved amino-acid sequence R<sup>278</sup>TIL<sup>281</sup> of PRR (Fang H et al., 2017; Nakagawa T et al., 2017). They found the inhibitor of site-1-protease (S1P), not furin or ADAM19, suppressed brefeldin A (BFA) or bovine serum albumin (BSA) -induced sPRR generation (**Figure 2**) (Fang H et al., 2017; Nakagawa T et al., 2017). More importantly, they also pointed out that sPRR may be generated by sequential processing by S1P and furin (Nakagawa T et al., 2017). However, Morosin *et al.* has recently shown that a pro-protein convertase inhibitor DEC-RVKR-CMK, but not furin siRNA or S1P inhibitor PF429242, reduced the extracellular sPRR levels in the placental syncytiotrophoblast (Morosin SK et al., 2020). This finding is opposite to the previous observations from non-placental cells, suggesting that an unknown convertase but not S1P or furin is most probably responsible for the secretion of sPRR in the placental (Morosin SK et al., 2020). The reasons for these discrepancies are unknown but could be related to the differences in the intracellular environment determined by the specific cellular functions. The levels of sPRR in plasma and urine samples can be measured using a commercial sPRR enzyme-linked immunosorbent assay (ELISA) kit (Biswas KB et al., 2011; Maruyama N et al., 2013).

PRO20, the first 20 amino acid residues of the prorenin prosegment, worked as a decoy PRR inhibitor to block prorenin binding to the PRR, and exhibited anti-hypertensive (Li W et al., 2015; Wang F et al., 2015; Xu C et al., 2017a), reno-protective (Fang H et al., 2018; Luo R et al., 2020), diuretic (Wang F et al., 2016), natriuretic (Fu Z et al., 2019), and anti-kaliuretic (Xu C et al., 2016; Xu C et al., 2017b) actions by targeting the RAS. However, although Li *et al.* have demonstrated the binding affinity and specificity of PRO20 to the PRR in the mouse brain with dissociation constants ( $K_d$ ) of  $4.6 \pm 2.2$  nM and maximum binding ( $B_{max}$ ) of  $24.0 \pm 4.1$  RFU (relative fluorescence units) using FITC-labeled PRO20 peptide (Li W et al., 2015), the inhibition constant ( $K_i$ ) for the binding of prorenin by PRO20 and the *in vivo* half-life, bioavailability, clearance rate, and the apparent volume of distribution of PRO20, are unclear and needed to be further clarified. Furthermore, it also remains

to clarify whether PRO20 blocks prorenin binding to the sPRR or not.

Similar to the fPRR, accumulating evidence shows an essential role of sPRR in various physio-pathological processes (**Figure 3**), including the activation of tissue RAS (Gonzalez AA et al., 2011), the regulation of water balance (Lu X et al., 2016c), and the progress of diseases such as hypertension (Gatineau E et al., 2019b) and kidney injury (Xie S et al., 2020). The major objective of this article is to discuss the involvement of the sPRR in health and diseases, including the RAS, water and electrolyte homeostasis, hypertension, heart failure, kidney injury, obstructive sleep apnea syndrome, cancer, pregnancy, and diabetes.

### **Intracellular signals regulated by sPRR**

We used STRING (a search tool for the retrieval of interacting genes and proteins) to identify proteins that interact with sPRR searching by the sequences of multiple proteins (**Figure 4**). Among 17 candidate proteins, six are related to V-ATPase: ATP6V0D1 (V-type proton ATPase subunit d1), TCIRG1 (V-type proton ATPase 116 kDa subunit an isoform 3), ATP6AP1 (V-type proton ATPase subunit S1), ATP6V0D2 (V-type proton ATPase subunit d2), ATP6V1F (ATPase H<sup>+</sup> transporting V1 subunit F), and ATP6V0C (V-type proton ATPase subunit c); two are related to Wnt/ $\beta$ -catenin pathway: FZD8 (frizzled-8) and LRP6 (low-density lipoprotein receptor-related protein 6); and seven are related to RAS: ACE (angiotensin-converting enzyme 2), renin (REN), Mas1 (Proto-oncogene Mas, Receptor for angiotensin 1-7), AGTR1 (Type-1 angiotensin II receptor), ACE2 (Angiotensin-converting enzyme), AGTR2 (Type-2 angiotensin II receptor), and AGT. Thus, this data indicates the possible interaction between sPRR and the V-ATPase, Wnt/ $\beta$ -catenin pathway, and RAS.

Mice with most of the RAS components deficiency developed normally, while embryonic PRR ablation caused embryo lethality, and adult mice with PRR deletion caused multiple organ deficiencies including brain, heart, and kidney, resulting in rapid lethality (Wendling O et al., 2017). Consistently, cardiomyocyte-specific PRR

deletion resulted in heart failure and early death (Kinouchi K et al., 2010), and inducible nephron-specific deletion of PRR caused distal renal tubular acidosis (Trepiccione F et al., 2016). Most importantly, upon PRR deletion both the above phenotypes were a result of V-ATPase dysfunction and impaired autophagy independently of RAS (Kinouchi K et al., 2010; Trepiccione F et al., 2016). Although the extracellular and transmembrane domain of PRR but not the cleavage of PRR by proteases is indispensable for the V-ATPase activity (Cruciat CM et al., 2010; Kinouchi K et al., 2013); it is unclear whether endogenous sPRR deficiency affects the essential function of the V-ATPase. Thus, it is recommended to evaluate the V-ATPase activity in mice with endogenous sPRR deficiency. However, Endo *et al.* have reported that autophagy inhibition by bafilomycin A1 or chloroquine markedly elevated sPRR levels in cultured cancer cells, without affecting fPRR and S1P expression, suggesting that autophagy inhibition increased sPRR accumulation and subsequent secretion via reducing its degradation in the intracellular vesicles in cancer cells (Endo M et al., 2020). Therefore, sPRR may be a novel biomarker for the status of autophagy inhibition. Increased plasma sPRR concentrations may reflect the autophagy status and as a mechanism of compensation of PRR due to impaired autophagy in some non-neoplastic diseases, such as chronic kidney disease (CKD) (Hamada K et al., 2013), preeclampsia (Narita T et al., 2016), gestational diabetes mellitus (GDM) (Bonakdaran S et al., 2017), and obstructive sleep apnea syndrome (OSAS) (Wu JP et al., 2019), since the occurrence of autophagy disturbance has already been reported in these diseases (Guo X et al., 2019; Takabatake Y et al., 2014). However, it should be further clarified whether autophagy inhibition-induced sPRR accumulation presents in the non-neoplastic tissues and whether autophagy inhibition by PRR deficiency (Kinouchi K et al., 2010; Trepiccione F et al., 2016) reduces sPRR degradation in the intracellular vesicles and subsequent increase accumulated sPRR secretion by exocytosis.

sPRR from the medium of cultured human umbilical vein endothelial cells (HUVECs) (Biswas KB et al., 2011) or Chinese hamster ovary cells overexpressed human PRR (Yoshikawa A et al., 2011), increased the renin activity of the

recombinant prorenin. Exogenous sPRR (10 nM) incubation stimulated prorenin/renin secretion in cultured collecting duct-derived M1 cells (Xu C et al., 2020) and increased aldosterone release and CYP11B2 protein expression in primary cultured rat inner medullary collecting duct (IMCD) cells (Xu C et al., 2016). Recently, sPRR has been reported to directly bind AT1R to activate NOX<sub>4</sub>/H<sub>2</sub>O<sub>2</sub> signaling pathway that contributes to endothelial dysfunction (Fu Z et al., 2021). Thus, these *in vitro* results indicate the stimulation effect of sPRR on local RAS. However, whether sPRR can activate prorenin as effectively as fPRR is still unknown. A previous paper suggested that subcutaneous sPRR infusion (30  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , the concentration of exogenous sPRR in the blood is about 32 nM) in C57BL/6 female mice led to a rise of plasma renin concentrations and an elevation of renal and hepatic angiotensinogen (AGT) expression (Gatineau E et al., 2019a). However, there is still not enough *in vivo* evidence to support that prorenin in plasma can be bound and activated or stimulated by plasma sPRR. More importantly, several clinical studies indicated that plasma sPRR levels are not associated with the levels of plasma renin, prorenin, and aldosterone in humans of both sexes (Nguyen G et al., 2014; Watanabe D et al., 2020). The reasons for these discrepancies are unclear, but they may be related to the difference between the physiological concentrations of plasma sPRR in humans/animals and the used concentrations of exogenous sPRR in both *in vitro* and *in vivo* experiments. According to the published literature, the physiological plasma sPRR concentration in healthy humans was about 0.75-0.95 nM (Nguyen G et al., 2014). While the used concentrations of sPRR in both *in vitro* and *in vivo* experiments were consistently 12 to 60-fold above the physiological concentrations; this phenomenon may imply that the stimulation effect of sPRR requires high concentrations of sPRR. Another possibility is that the RAS-regulatory role of sPRR may be controlled by sex hormones. In support of this notion, increased plasma sPRR was positively correlated with the activation of systemic RAS in diabetic women, while decreased urinary sPRR excretion was correlated with intrarenal RAS stimulation in diabetic men, indicating a sex difference in sPRR concentrations and its contribution to RAS stimulation in plasma and urine of diabetic patients (Visniauskas

B et al., 2021).

In addition to the RAS-regulatory role, a high concentration of sPRR also triggers or regulates several intracellular signals independent of RAS, thus exhibiting cell-type-specific functions. For example, sPRR binds to FZD8 and LRP6 to activate Wnt/ $\beta$ -catenin signaling by binding assays (Cruciat CM et al., 2010; Lu X et al., 2016c), indicating that FZD8 and LRP6 may be the potential receptors of sPRR. Along this line, the stimulation of vasopressin (AVP) receptor 2 (V<sub>2</sub>R)-dependent cAMP formation and aquaporin 2 (AQP2) expression/trafficking in CD cells by recombinant sPRR protein (10 nM) was blocked by FZD8 inhibition (Lu X et al., 2016c). This finding may be a potential mechanism of the enhanced urine concentrating capability in sPRR-infused C57BL/6 mice (30  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) (Lu X et al., 2016c; Wang F et al., 2019b). Secondly, sPRR (10 nM) also interacts with peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) in differentiated 3T3L1 cells, resulting in increased insulin sensitivity that promotes glucose uptake (Wang F et al., 2019a). It may contribute to insulin resistance and ameliorated hyperglycemia in diet-induced obese mice with recombinant sPRR protein infusion (30  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , the concentration of exogenous sPRR in the blood is about 53 nM)(Wang F et al., 2019a). Lastly, recombinant sPRR (10 nM) treatment remarkably decreased *Apela* and *Apln* mRNA expression in cultured IMCD3 cells, indicating an inhibition effect of sPRR on the apelinergic system (Xu C et al., 2020). We recently reported that sPRR is a downstream target of cAMP/PKA signaling to mediate AVP-induced AQP2 expression and exogenous sPRR-His treatment partially reversed apelin-13-downregulated-AQP2 protein expression in AVP-treated IMCD cells (Chen Y et al., 2021). These results support the antagonistic interaction between ELA/apelin and sPRR. Moreover, sortilin-1 (SORT1) and low-density lipoprotein receptor (LDLR) may be other possible receptors of sPRR. PRR has been reported to bind SORT1 and LDLR to control their expression (Lu X et al., 2016a), but whether it requires the extracellular domain or the intracellular domain of PRR is unclear. However, we suspect that the extracellular domain of PRR is responsible for the binding of PRR to SORT1 and LDLR, similarly to the binding of PRR to FZD8 and LRP6 (Cruciat CM

et al., 2010). It needs to be further confirmed by binding assays using recombinant sPRR protein.

### **Impact of sPRR on urine concentrating capability**

It is well-established that PRR exhibits a significant role in maintaining urine concentration capability by regulating renal AQP2 and V<sub>2</sub>R expression (Ramkumar N et al., 2015; Wang F et al., 2016; Wang F et al., 2019b). Renal fPRR protein but not mRNA abundance is consistently upregulated in rats after water deprivation (WD) for 48-h (Wang F et al., 2016) or 72-h (Tamura Y et al., 2016). Tamura *et al.* reported that the decreased furin protein expression in the kidney contributes to increased fPRR protein levels in 72-h WD rats (Tamura Y et al., 2016). Thus they found a decreasing trend of the sPRR levels in the cytosolic fraction with no statistical significance and decreased plasma sPRR concentrations in these rats (Tamura Y et al., 2016). In comparison, another study showed that fPRR and sPRR protein abundance in the whole kidney and 24-h urinary sPRR excretion were significantly increased in rats with 48-h WD and regulated by EP<sub>4</sub> receptor (Wang F et al., 2016). The variation of renal sPRR protein levels in the above two studies may be related to the length of dehydration time and the different renal fractions (whole kidney *vs.* cytosolic fraction). Another possible explanation is that most of the sPRR protein in the cytoplasm has been secreted into extracellular space including urine since the sPRR protein abundance in the whole kidney and 24-h urinary sPRR excretion were markedly elevated in 48-h WD rats (Wang F et al., 2016). However, these results may indicate the different sources of plasma *vs.* urinary sPRR during WD.

The elevated renal fPRR protein in WD may not only contribute to the renal RAS activation and thus renal dysfunction (Wang F et al., 2016) but also be associated with the changes in the V-ATPase activity. Thus, it is worth exploring whether the renal V-ATPase activity is changed or not during WD. To our knowledge, most soluble receptors, including tumor necrosis factor (Tracey D et al., 2008), work as antagonists and compete with their membrane-associated counterparts for ligands,

but certain soluble receptors, including the soluble receptors of the interleukin-6 family of cytokines (Rose-John S et al., 2006), are agonists. Similarly, in addition to the stimulating role of sPRR on prorenin activity (Yoshikawa A et al., 2011), plasma sPRR may also work as an antagonist against prorenin and renin in WD. This notion may be supported by the observations that the plasma renin activity and plasma angiotensin II (AngII) concentrations were significantly elevated in 72-WD rats, with a decreased plasma sPRR concentrations in these rats (Tamura Y et al., 2016). However, further studies are necessary to elucidate whether observed lower circulating sPRR denotes a cause or consequence of increased tissue fPRR protein levels, or has some pathophysiological significance in 72-h WD. It has been reported that 48-h WD significantly inhibited, whereas 72-h WD markedly activated autophagy in the selfish brain (Ye Q et al., 2016). Thus, we suspect that the variations of autophagy activity in 48-h vs. 72-h WD may contribute to the inconsistent results on sPRR levels. The elevated renal sPRR levels and urinary sPRR excretion may be caused by autophagy inhibition during 48-h WD, which reduces sPRR degradation and enhances sPRR accumulation in the intracellular vesicles in the renal tubules, independently of increased fPRR protein levels. There have no relevant reports, however, which show the presence of autophagy inhibition in humans and animals during WD. Thus, it remains to be clarified whether autophagy inhibition presents in the kidney or not during WD.

Notably, sPRR can interact with FZD8 to activate the wnt/ $\beta$ -catenin signaling pathway, thereby stimulating AQP2 and V<sub>2</sub>R expression in primary cultured rat IMCD cells, predicting the antidiuretic action of sPRR (Lu X et al., 2016c; Wang F et al., 2019b). Along this line, chronic intravenous infusion of recombinant sPRR-His protein effectively blocked nephrogenic diabetes insipidus (NDI) phenotype in rats with the V<sub>2</sub>R antagonist OPC31260 or the liver X receptor agonist TO901317 infusion (Lu X et al., 2016c). However, intravenous infusion of exogenous sPRR-His did not influence lithium-induced NDI phenotype (Yang KT et al., 2017) but aggravated fat-induced NDI phenotype (Wang F et al., 2019a). The reasons for these variations are unclear, but they should be related to the different mechanisms involved in NDI.

Indeed, lithium not only blocks renal Gsk3 $\beta$  activity to activate renal COX-2/PGE<sub>2</sub> signaling but also inhibits wnt/ $\beta$ -catenin signaling, resulting in the decrease of cAMP production and AQP2 phosphorylation and thereby polyuria (Rao R et al., 2005). Diabetes insipidus in 36-wk-old diet-induced obese male mice (32 weeks of high-fat feeding) may be secondary to diabetic kidney disease caused by glomerular hyperfiltration in these mice.

Additionally, the urine concentrating ability of sPRR was also challenged by some conflicting reports (Gatineau E et al., 2019b; Wang F et al., 2019a). Firstly, chronic intravenous sPRR infusion for 2-wk did not change 24-h urine volume in the 36-wk-old C57BL/6 male mice (Wang F et al., 2019a), but reversed polyuria and the downregulation of AVP sensitivity (the magnitude of changes in urinary osmolality in response to acute AVP treatment) in mice (Lu X et al., 2016c; Wang F et al., 2019b). Secondly, although recombinant sPRR subcutaneously infusion for 4-wk increased urinary AVP excretion in 16-wk-old C57BL/6 female mice (Gatineau E et al., 2019a), it did not change the AVP/AQP2 pathway in 26-wk-old obese male mice (20 weeks of high-fat feeding) as reflected by the unchanged urine volume, urinary AVP and Na<sup>+</sup> excretion, and renal AQP2, V<sub>2</sub>R, FZD8, and LRP6 expression (Gatineau E et al., 2019b). The different routes of administration for recombinant sPRR protein and the setting of specific pathological conditions for inducing NDI may be the reasons for the above discrepancy. In particular, subcutaneous infusion may account for more significant degradation of sPRR protein compared with intravenous infusion. sPRR may only exhibit urine concentrating ability in models of idiopathic but not secondary diabetes insipidus. What's more, loss of endogenous sPRR in mice by mutating the cleavage site of the PRR did not cause polyuria (Ramkumar N et al., 2021), which may due to a compensatory response to the enhanced fPRR protein levels in these mice.

### **sPRR may promote Na<sup>+</sup> reabsorption and K<sup>+</sup> excretion**

Studies by employing both pharmacological and genetic approaches have well-established an essential role of PRR in the regulation of Na<sup>+</sup> and K<sup>+</sup> balance,

which involves RAS-dependent (Peng K et al., 2017; Prieto MC et al., 2017; Ramkumar N et al., 2018; Ramkumar N et al., 2016; Xu C et al., 2017b) and independent (Lu X et al., 2016b; Quadri S and HM, 2016; Quadri SS et al., 2018) mechanisms. Interestingly, a recent study showed that exogenous recombinant sPRR exhibited acute stimulation effect on ENaC activity via NOX<sub>4</sub> signaling and chronic promotion action on  $\alpha$ -ENaC dependent on  $\beta$ -catenin signaling (Wang F et al., 2020), implying the Na<sup>+</sup>-retaining action of sPRR. Another previous study from our group demonstrates that exogenous recombinant sPRR directly stimulated CYP11B2 expression and aldosterone release in primary rat IMCD cells (Xu C et al., 2016). Therefore, these results indicate that sPRR may control membrane Na<sup>+</sup>- and K<sup>+</sup>-transporting proteins via RAS-dependent and independent mechanisms, consequently maintaining electrolyte homeostasis.

## **Hypertensive actions of sPRR**

A series of pharmacological and transgenic studies have shown that PRR in the local tissue, including the kidneys and brain, contributes to the progression of hypertension via the activation of local RAS and other intracellular signaling independently of RAS (Nakagawa P et al., 2020; Yang T and C, 2017). Importantly, sPRR levels in the collecting duct and urine of AngII-infused rats (Gonzalez AA et al., 2011) were significantly increased, implying a positive correlation between renal sPRR and AngII-induced hypertension. Incubation of recombinant human prorenin with urine samples of AngII-infused rats increased AngI formation and thus intratubular AngII generation, which may be attributed to the non-proteolytic activation of prorenin triggered by the intraluminal sPRR or cell-surface located PRR (Gonzalez AA et al., 2011). These results suggest that enhanced sPRR may contribute to AngII-induced hypertension via the activation of the local tissue RAS. In support of this notion, S1P inhibition blocking sPRR generation significantly inhibited Ang II-induced hypertension in F1 B6129SF1/J mice, accompanied by decreased renal medullary and urinary renin levels and renal medulla  $\alpha$ -ENaC expression, both of

which were reversed by sPRR-His infusion (Feng Y et al., 2021). Consistently, loss of endogenous sPRR in mice by mutating the cleavage site of the PRR caused a decreased blood pressure at baseline and attenuated AngII-induced hypertension, which was partially reversed by exogenous recombinant sPRR infusion (Ramkumar N et al., 2021). Of note, endogenous sPRR deficiency induced by either S1P inhibition or the mutation of the cleavage site resulted in elevated fPRR protein levels, which was negatively correlated with blood pressure (BP) in AngII-infused mice (Feng Y et al., 2021; Ramkumar N et al., 2021), indicating that PRR via sPRR but not fPRR contributes to the hypertensive response to AngII infusion. However, these were confused by the observations that PRR inhibition by PRO20 without affecting sPRR generation attenuated AngII-induced hypertension (Wang F et al., 2015), thus we should clarify whether PRO20 blocks sPRR activity or not. Although plasma sPRR concentrations in patients with essential hypertension were not significantly different compared with those of normotensive subjects, they were positively correlated with urinary AGT excretion (Morimoto S et al., 2014), which may be attributed to the stimulatory role of sPRR on renal AGT expression (Gatineau E et al., 2019a). However, the levels of renal sPRR and urinary sPRR excretion in patients with essential hypertension and whether they are correlated with intrarenal RAS are unclear. Future studies are recommended to address these issues.

In response to either a regular diet or a high-fat diet, mice with adipose tissue-specific PRR deletion exhibited higher BP than wild-type mice, accompanied by increased plasma sPRR concentrations (Gatineau E et al., 2019a; Wu CH et al., 2016). The elevated plasma sPRR may increase BP in these mice since the supplement of exogenous recombinant sPRR elevated BP in diet-induced obese mice (Gatineau E et al., 2019b). Of note, Gatineau *et al.* has reported that losartan treatment blocked the elevation of BP in adipose-PRR deficient female mice but not in sPRR-infused C57BL/6 male mice during high-fat feeding (Gatineau E et al., 2019a; Gatineau E et al., 2019b), indicating a gender difference in sPRR-raised BP in obese mice. sPRR-induced activation of RAS may contribute to the BP elevation in female obese mice since sPRR infusion elevated plasma renin levels and renal and hepatic

AGT expression in C57BL/6 female mice (Gatineau E et al., 2019a). While the increase of BP in sPRR-infused male obese mice may be attributed to the impaired baroreflex sensitivity and the activation of the sympathetic nervous system, given by the observations that chlorisondamine (a ganglionic blocker) treatment downregulated BP in these mice (Gatineau E et al., 2019b). Of note, this is challenged by a recent study that concurrent treatment with losartan reversed sPRR-His-elevated blood pressure in obese C57/BL6 male mice (Fu Z et al., 2021). The reasons for this discrepancy are unclear. However, these results indicate a therapeutic potential of sPRR inhibition in the treatment of obesity-hypertension.

### **sPRR may be a promising diagnostic indicator for heart failure**

Both PRR expression in the heart (Hirose T et al., 2009; Mahmud H et al., 2012; Peng H et al., 2013) and plasma sPRR levels (Amari Y et al., 2020; Fukushima A et al., 2013; Gong L et al., 2019; Obradovic D et al., 2020) was observed to be strongly upregulated in patients with heart failure. The levels of plasma sPRR in these patients were independently and negatively correlated with the estimated glomerular filtration rate (eGFR) and left ventricular ejection fraction (LVEF), but positively correlated with left ventricular mass index (LVMI), left atrial diameter (LAD), left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic diameter (LVEDd), mitral valve flow velocity/myocardial wall velocity(at left ventricular early diastole), and plasma B-type natriuretic peptide (BNP) (Fukushima A et al., 2013; Gong L et al., 2019; Obradovic D et al., 2020), indicating an important correlation between the plasma sPRR level and cardiac function. By multivariate regression analysis, eGFR and LVMI were the independent determinants of the plasma sPRR levels (Fukushima A et al., 2013; Gong L et al., 2019). Thus, plasma sPRR may be a potential evaluative biomarker for heart failure. This notion also applies to heart failure (Amari Y et al., 2020) and atherosclerotic conditions (Amari Y et al., 2016) in hemodialysis (HD) patients. The changes in human atrial natriuretic peptide, BNP, and intraventricular septum thickness, were more significant in HD patients with plasma sPRR  $\geq 29.8$

ng/ml than in those with sPRR <29.8 ng/ml, indicating that high levels of plasma sPRR may be a diagnostic index for cardiac hypertrophy and heart failure (Amari Y et al., 2020). Similarly, the levels of plasma sPRR were considerably higher in HD patients with the ankle-brachial index (ABI) of < 0.9 than in those with ABI of  $\geq 0.9$  independently of other atherogenic factors, implying that plasma sPRR could also be a biomarker for atherosclerosis (Amari Y et al., 2016). However, a small clinical study that enrolled 11 patients with severe heart failure showed that plasma sPRR was persistently elevated and had no correlations with disease state in these patients, as evidenced by the low correlation coefficient between sPRR and brain natriuretic peptide (Ikeda Y et al., 2020). These variations may be related to the severity of heart failure. Thus, further extensive cohort studies are still encouraged to investigate the prognostic significance of plasma sPRR in cardiovascular diseases.

### **sPRR may be a novel diagnostic biomarker for renal damage**

Increasing evidence has suggested that renal PRR expression is significantly upregulated in mice with kidney diseases and contributes to kidney injury. The mechanisms may involve the activation of Wnt/ $\beta$ -catenin signaling (Li C and HM, 2014; Li Z et al., 2017), intrarenal RAS (Fang H et al., 2018), and mitochondria NOX<sub>4</sub>/SOD2/UCP2/NF- $\kappa$ B and Sirt1/FOXO3a signaling (Li C et al., 2019), and the inhibition of mitochondrial AMPK/SIRT-1/PGC-1 $\alpha$  signaling (Akhtar S and HM, 2019), respectively. Furthermore, PRR is crucial for normal podocyte function and survival attributed to its role in vacuolar H<sup>+</sup>-ATPase activity controlling autophagy and acidification, thereby activating the wnt/ $\beta$ -catenin signaling (Cruciat CM et al., 2010; Oshima Y et al., 2011; Riediger F et al., 2011). Therefore, PRR may be an expected therapeutic target for the therapy of kidney diseases.

In a nephropathy model induced by albumin-overloading, renal fPRR and sPRR protein expression and urinary sPRR excretion were significantly increased (Fang H et al., 2018). These results were consistent with the findings in cultured renal epithelial cells with albumin exposure (Fang H et al., 2017), indicating the

involvement of sPRR in this nephropathy model. Indeed, the levels of plasma sPRR are modulated in CKD (Hamada K et al., 2013) and may reflect PRR expression levels in infiltrated mononuclear cells and thus renal damage (Ohashi N et al., 2016). Along this line, plasma sPRR levels were positively correlated to the CKD stage and negatively associated with eGFR in CKD patients (Hamada K et al., 2013). Plasma sPRR levels were also significantly positively associated with tubulointerstitial fibrosis in patients with heminephrectomy (Ohashi N et al., 2016). Moreover, plasma sPRR levels were positively associated with serum blood urea nitrogen (BUN), indicating that increased plasma sPRR concentrations are correlated with renal dysfunction associated with heart failure (Fukushima A et al., 2013; Gong L et al., 2019). Therefore, plasma sPRR may be a useful biomarker for CKD.

Regarding the origin of plasma sPRR, Naro *et al.* reported that increased PRR protein expression was found in infiltrated mononuclear cells but not connecting tubules or collecting ducts or vessels in patients with heminephrectomy, excluding the possibility that increased plasma sPRR came from the kidneys (Ohashi N et al., 2016). However, the infiltrated cells positive for PRR are unlikely to come from other tissues/organs because no tissue is injured in other tissues/organs except for the kidneys. One possibility is that heminephrectomy directly triggers the immune response to increase monocytes/macrophages or T cells (Geisberger S et al., 2015). A functional PRR has already been found and plays an essential role in inflammation and cell development in these cells (Narumi K et al., 2015). However, the use of tissue-specific PRR KO mouse, especially renal tubule-, T cell-, and monocyte/macrophage cell-specific PRR KO mouse, is recommended to clarify the origin of sPRR during heminephrectomy. These results strongly indicate the involvement of sPRR in the progression of renal damage. This notion is further supported by the recent report that recombinant sPRR-His protein (60 nM) promoted the fibrotic response in cultured renal epithelial cells by simulating the Akt/ $\beta$ -catenin/Snail signaling pathway (Xie S et al., 2020). However, the used concentrations of sPRR here are over 70-fold above the physiological concentrations. Overall, sPRR may be a novel diagnostic biomarker for renal damage, and inhibition

of sPRR generation may serve as an expected therapeutic strategy for the therapy of kidney diseases.

### **sPRR may be a predictor of pregnancy syndrome**

Compared to the non-pregnant rats, PRR expression in the heart, aorta, and kidney tissues and 24-hour urinary sPRR excretion was significantly higher in the pregnant rats (Avila-Ramírez MA et al., 2019; Fu Z et al., 2019). A prospective cohort study showed that elevated plasma sPRR levels at early but not middle or late pregnancy were associated with the elevation of BP, and increased concentrations at delivery had a strongly increased incidence of preeclampsia (Watanabe N et al., 2012). Consistently, maternal serum sPRR levels were significantly higher in patients with hypertensive disorder of pregnancy or fetal growth restriction and positively associated with serum prorenin levels (Mikami Y et al., 2017). Thus, these results suggest probable participation of PRR during pregnancy, and increased sPRR might be correlated to the occurrence of preeclampsia. In support of this possibility, rats with preeclampsia pregnancy exhibited a significant elevation of PRR expression in the cardiac tissues and placental tissues and plasma sPRR concentrations, with a reduction of PRR expression in the aorta and kidneys (Avila-Ramírez MA et al., 2019; Thomason J et al., 2015). This phenomenon has been recapitulated by a cross-sectional study that the expression of placental PRR and the plasma sPRR levels were significantly increased in preeclamptic women compared with normal pregnant women (Narita T et al., 2016). However, future research is needed to figure out the relative contribution of cardiac tissues vs. placenta to circulating sPRR in preeclamptic women. Thus, it is recommended to generate preeclamptic models using inducible heart-specific and placenta-specific PRR deletion mice to analyze the status of plasma sPRR and the pathogenesis of preeclampsia.

Although systolic BP in normal pregnant women was positively associated with placental PRR levels and plasma sPRR levels, it was positively associated with placental PRR levels but not with plasma sPRR levels in preeclamptic women (Narita

T et al., 2016). eGFR in pregnant women was negatively correlated with placental PRR levels and plasma sPRR levels (Narita T et al., 2016). Still, it was negatively associated with plasma sPRR levels but not with placental PRR levels in preeclamptic women (Narita T et al., 2016). These results imply the involvement of placental PRR in the regulation of BP, whereas plasma sPRR may be involved in renal dysfunction in preeclamptic women (Narita T et al., 2016). Regarding the intracellular signaling mediated by PRR in preeclampsia placentas, Tamada *et al.* pointed out that increased PRR expression activated intracellular signaling via prorenin to increase the expression of plasminogen activator inhibitor-1 and transforming growth factor- $\beta$ , consequently increasing endothelin-1 (ET-1) production, and the pathogenesis of preeclampsia (Tamada S et al., 2019). However, the mechanisms for the involvement of plasma sPRR in the pathogenesis of decreased renal function in preeclampsia are unknown.

Several small cohort studies have suggested that sPRR is associated with GDM (Bonakdaran S et al., 2017; Gokulakrishnan K et al., 2015; Sugulle M et al., 2017; Watanabe N et al., 2013b), a risk factor for developing preeclampsia in pregnancy. Plasma sPRR levels are significantly higher in pregnant females with GDM than in healthy pregnancies or preeclampsia and positively associated with GDM (Bonakdaran S et al., 2017; Gokulakrishnan K et al., 2015; Sugulle M et al., 2017). These data indicate the pathophysiological relevance of sPRR in diabetic pregnancies, and the increased plasma sPRR may be a potential biomarker for predicting GDM. Extensive cohort studies of sPRR are needed to clarify the association between sPRR and GDM.

Compared to full-term neonates, the levels of umbilical serum prorenin and sPRR were significantly higher and negatively correlated with gestational age (Terada T et al., 2017). Similarly, Mikami *et al.* showed that umbilical serum sPRR levels in singleton pregnancies were significantly associated with gestational age at delivery and serum prorenin levels (Mikami Y et al., 2017). Indeed, high umbilical plasma sPRR levels are correlated with a lower small for gestational age birth likelihood (Watanabe N et al., 2013a). Therefore, these studies suggest that sPRR may be

associated with appropriate fetal growth, and umbilical plasma sPRR level may be a predictive index for fetal growth. It needs future investigations with extensive and long-term cohort studies to further clarify the association between sPRR and fetal growth.

## **A “double-edged sword” effect of sPRR in diet-induced obesity model**

Several studies suggest a correlation between PRR and insulin that exhibits some beneficial effects. It has been reported that PRR in the pancreatic  $\beta$  cells is essential for the release of insulin and thus diabetes prevention (Binger KJ et al., 2019). A series of pharmacological and transgenic studies have suggested a conceivable regulation of adipose tissue PRR in insulin sensitivity and adipose tissue structure (Shamansurova Z et al., 2016; Tan P et al., 2016; Tan P et al., 2014; Wu CH et al., 2016), indicating that adipose tissue PRR may be a potential therapeutic target for the therapy of obesity. However, although mice with adipocyte tissue-specific PRR deficiency were resistant to diet-induced obesity (Shamansurova Z et al., 2016; Wu CH et al., 2016), the mice exhibited lipodystrophy, hepatosteatosis, and hypertension in response to feeding high-fat diets (Gatineau E et al., 2019a; Wu CH et al., 2016). This finding may be explained by the increased levels of plasma sPRR and the activation of RAS in adipocyte tissue-specific PRR-deficient mice in response to high-fat diet feeding (Gatineau E et al., 2019a; Wu CH et al., 2016). Of note, both total hepatic sPRR contents and circulating sPRR levels in these mice were increased, but the liver may be the primary source of the increased plasma sPRR concentrations in these mice, the elevation of plasma sPRR levels in these mice may be secondary to lipodystrophy and hepatosteatosis and the increase of hepatic sPRR, independently of PRR levels in adipocytes, since the levels of plasma sPRR were significantly increased in  $Bscl2^{-/-}$  male mice [a mouse model of lipodystrophy and hepatosteatosis (Chen W et al., 2012)] (Gatineau E et al., 2019a). Thus, the increased hepatic sPRR contents in adipose-PRR KO mice may be involved in the progress of lipodystrophy and hepatosteatosis, subsequently elevating circulating sPRR levels and consequently

elevating BP and the resistance to diet-induced obesity. On the other hand, Gatineau et al. recently reported that hepatic-specific PRR deletion significantly elevated hepatic cholesterol and plasma sPRR concentration, accompanied by enhanced PRR, sPRR, furin, and S1P expression in the adipose tissue, indicating that adipose tissue could be the primary source of the increased plasma sPRR in these mice that contributes to hepatic cholesterol biosynthesis (Gatineau E et al., 2021). Therefore, these results indicate adipose tissue-liver cross-talk via sPRR controls lipid homeostasis.

However, the elevation of circulating sPRR may also trigger a compensatory protection mechanism for lipodystrophy and hepatosteatosis that may be beneficial in these mice. In support of this possibility, intravenous infusion of recombinant sPRR to increase circulating sPRR levels displayed beneficial actions on diet-induced obesity, lipodystrophy, and hepatosteatosis, and the mechanism may involve the interaction between sPRR and PPAR $\gamma$  in adipocytes that increases insulin sensitivity (Wang F et al., 2019a). These results may imply the dual roles of sPRR in the high-fat feeding models. Briefly, sPRR may work as an insulin sensitizer in adipocytes exhibiting beneficial actions on obesity, lipodystrophy, and hepatosteatosis. On the other hand, it may stimulate lipid synthesis and low-density lipoprotein clearance and inhibit fatty acid oxidation in hepatocytes contributing to the progress of lipodystrophy and hepatosteatosis. However, a supplement of sPRR may be an alternative strategy for treating the obesity and metabolic syndromes. Further studies are still recommended to clarify the source and exact role of elevated plasma sPRR in lipodystrophy and hepatosteatosis progression.

### **sPRR in cancers: a novel diagnostic biomarker?**

Accumulating evidence has already indicated a therapeutic potential of PRR for these cancers. PRR works as an upstream component and activator of wnt/ $\beta$ -catenin signaling to upgrade the development of various cancers (Kouchi M et al., 2017; Ohba K et al., 2020; Ohba K et al., 2014; Rahman A et al., 2020; Shibayama Y et al., 2015; Wang J et al., 2019; Zhao K et al., 2020). Plasma sPRR concentrations were

found significantly higher in patients with pancreatic ductal adenocarcinoma (Shibayama Y et al., 2015), prostate cancer (Mohammad AH et al., 2019), or breast cancer (Mohammad AH et al., 2020) compared to the healthy specimen. However, it did not change with respect to controls and was not correlated with primary epithelial ovarian cancer (Kreienbring K et al., 2016) or colorectal cancer (Beitia M et al., 2019) aggressiveness. The reasons for this variation are unclear, but several potential factors may contribute to the inconsistent results. Firstly, it may be related to the different pathogenesis of the cancers and conditions of the subjects. Secondly, given the limitation of ELISA, the aberrant testing methods and standards may also cause the above variation. Another possibility may be related to the distinct role of sPRR in these cancers. However, additional large-scale trials are needed to determine whether plasma sPRR has predictive, prognostic, and diagnostic value in various cancers.

### **sPRR may be a marker reflecting the severity of obstructive sleep apnea syndrome**

Plasma sPRR concentrations in patients with OSAS were significantly elevated compared with control subjects but markedly reduced after the nasal continuous positive airway pressure (nCPAP) treatment (Nishijima T et al., 2014; Nishijima T et al., 2016; Wu JP et al., 2019) or bariatric surgery (Nishijima T et al., 2018). The levels of plasma sPRR were raised in parallel with the severity of OSAS, as reflected by the significantly positive correlation between plasma sPRR levels and apnea-hypopnea index (AHI), arousal index, and oxygen desaturation index (Nishijima T et al., 2018; Nishijima T et al., 2014; Nishijima T et al., 2016; Wu JP et al., 2019). However, plasma sPRR was not related to the presence of hypertension, or plasma renin activity, or plasma aldosterone levels in OSAS (Nishijima T et al., 2014; Nishijima T et al., 2016). These results are consistent with the observations that plasma sPRR concentrations are independent of plasma prorenin/renin and aldosterone levels (Nguyen G et al., 2014). OSAS is characterized by intermittent hypoxia, resulting in oxidative stress in the multiple organs, contributing to the elevation of plasma sPRR

levels in patients with OSAS (Takahashi K et al., 2017). In support of this possibility, hypoxia has been reported to significantly increase intracellular sPRR levels in human placental trophoblast cells (Suda C et al., 2020). Additionally, female but not male OSAS patients with diabetic kidney disease had higher concentrations of plasma sPRR, indicating a more significant effect of diabetic kidney disease on plasma sPRR levels in female OSAS patients (Nishijima T et al., 2016). The reasons for this gender difference are unclear, but it may be related to sex hormones since the presence of sex differences in OSAS (Lin CM et al., 2008).

## **Conclusion and perspectives**

PRR is cleaved by proteases to generate sPRR and released into extracellular space, including plasma, urine, and interstitial fluid. Increasing evidence from clinical and animal studies has shown that plasma sPRR concentrations are elevated in patients and animals under various physiopathological conditions. sPRR may be a novel biomarker for diseases, including but not limited to, hypertension, heart failure, kidney diseases, pregnancy syndrome, obesity, and obstructive sleep apnea syndrome. Further studies are needed to determine the diagnostic value of sPRR in these diseases. To determine the exact functions and mechanisms of endogenous sPRR, mice with endogenous sPRR deficiency by generating a mutation of the cleavage site in the PRR gene may be a good option in future studies. Significantly, all the current clinical data on sPRR comes from the sPRR assay using a commercial sPRR ELISA kit. But given the limitation of ELISA assays, including the accuracy, specialty, and sensitivity of the kit, a uniform and reliable approach to measure the sPRR is still needed.

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## **Contributions**

Participated in research design: C.M. Xu.

Performed data analysis: C.M. Xu and M.M. Qin.

Contributed to the writing of the manuscript: C.M. Xu, M.M. Qin, and J.Yu.

## **Competing interests**

The authors have no conflict of interests to disclose.

## Figure Legends

**Figure 1.** Schematic illustration of the generation and functions of the soluble (pro)renin receptor (sPRR). The full-length PRR (fPRR) is cleaved by proteases at the indicated cleavage site to generate sPRR and M8.9. sPRR is involved in various physio-pathological processes via local renin-angiotensin system (RAS), wnt/ $\beta$ -catenin signaling, AKT-mediated signaling, and Elabela/Apelin. sPRR may be a biomarker for diseases. Vacuolar  $H^+$ -ATPase controls autophagy and acid-base homeostasis. SP, signal peptide; ECD, extracellular domain; TMD, transmembrane domain; CPD, cytoplasmic domain; ADAM19, a disintegrin and metalloproteinase 19; S1P, site-1-protease; ATP6AP1(Ac45), V-type proton ATPase subunit S1.

**Figure 2.** Overview showing the first important publication on the generation and relevance of the soluble (pro)renin receptor (sPRR) in various physio-pathological processes. The X-axis depicts years. PRR, (pro)renin receptor; ADAM19, a disintegrin and metalloproteinase 19; ELISA, enzyme-linked immunosorbent assay; S1P, site-1-protease.

**Figure 3.** Specific functions of the soluble (pro)renin receptor (sPRR) in various physio-pathological processes.

**Figure 4.** The predicted interaction partners of sPRR. We used STRING (a search tool for the retrieval of interacting genes and proteins) to identify proteins that interact with sPRR searching by the sequences of multiple proteins. (A) Networks of current interactions of sPRR. ACE2, Angiotensin-converting enzyme 2; LRP6, Low-density lipoprotein receptor-related protein 6; ATP6V0D1, V-type proton ATPase subunit d1; TCIRG1, V-type proton ATPase 116 kDa subunit an isoform 3; ATP6AP2, ATPase,  $H^+$ -transporting, and lysosomal accessory protein 2; REN, Renin; ATP6AP1, V-type proton ATPase subunit S1; ATP6V0D2, V-type proton ATPase subunit d2; ATP11A, Probable phospholipid-transporting ATPase IH; FZD8, Frizzled-8; Mas1,

Proto-oncogene Mas, receptor for angiotensin 1-7; AGTR1, Type-1 angiotensin II receptor; ACE, Angiotensin-converting enzyme; AGTR2, Type-2 angiotensin II receptor; ATP6V1F, ATPase H<sup>+</sup> transporting V1 subunit F; CDC5L, Cell division cycle 5-like protein; AGT, Angiotensinogen; ATP6V0C, V-type proton ATPase subunit c; V-ATPase, vacuolar H<sup>+</sup>-ATPase; RAS, renin-angiotensin system. (B) Summary of the score of predicted functional partners of sPRR.

**Figure 1**

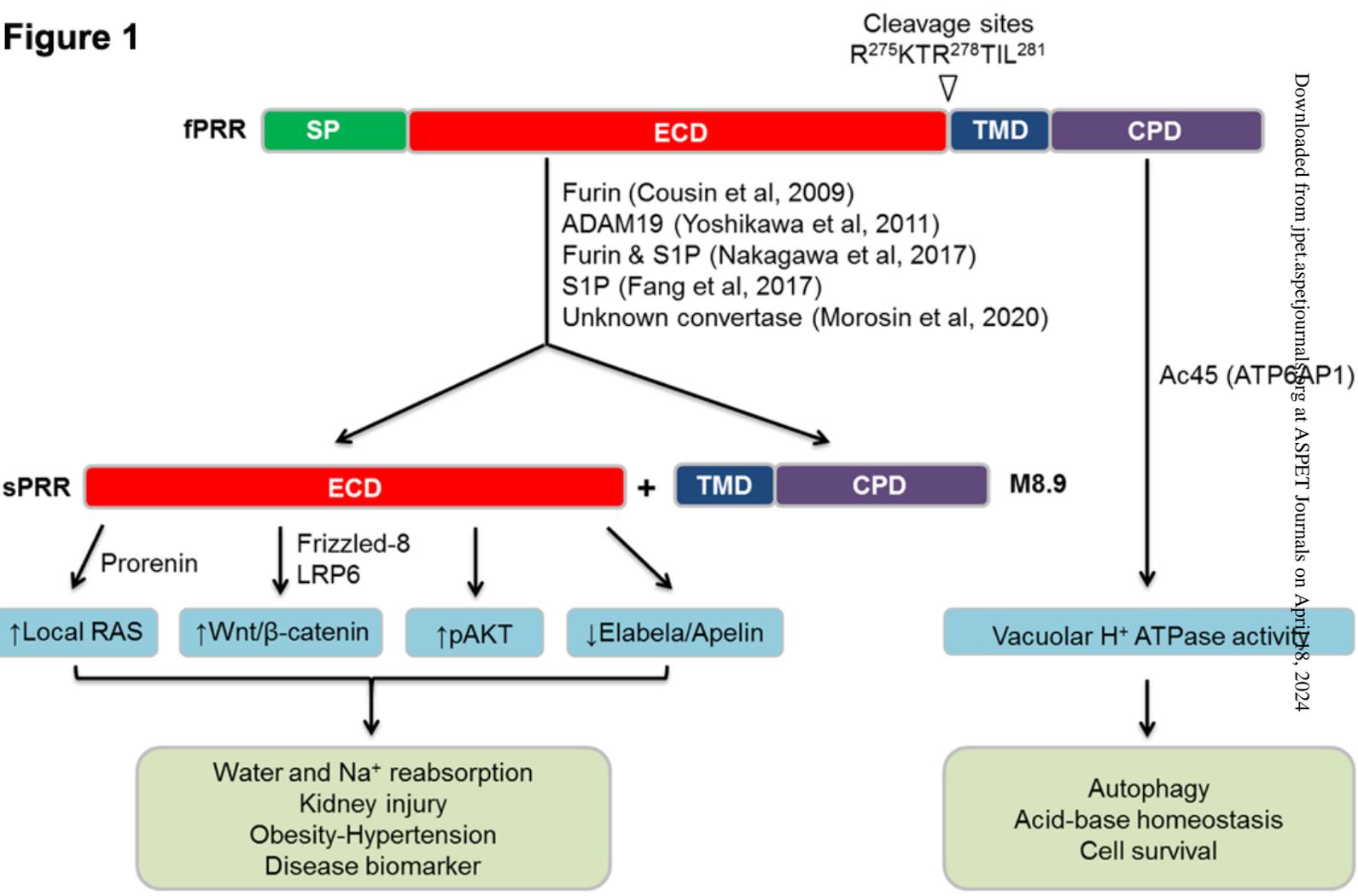
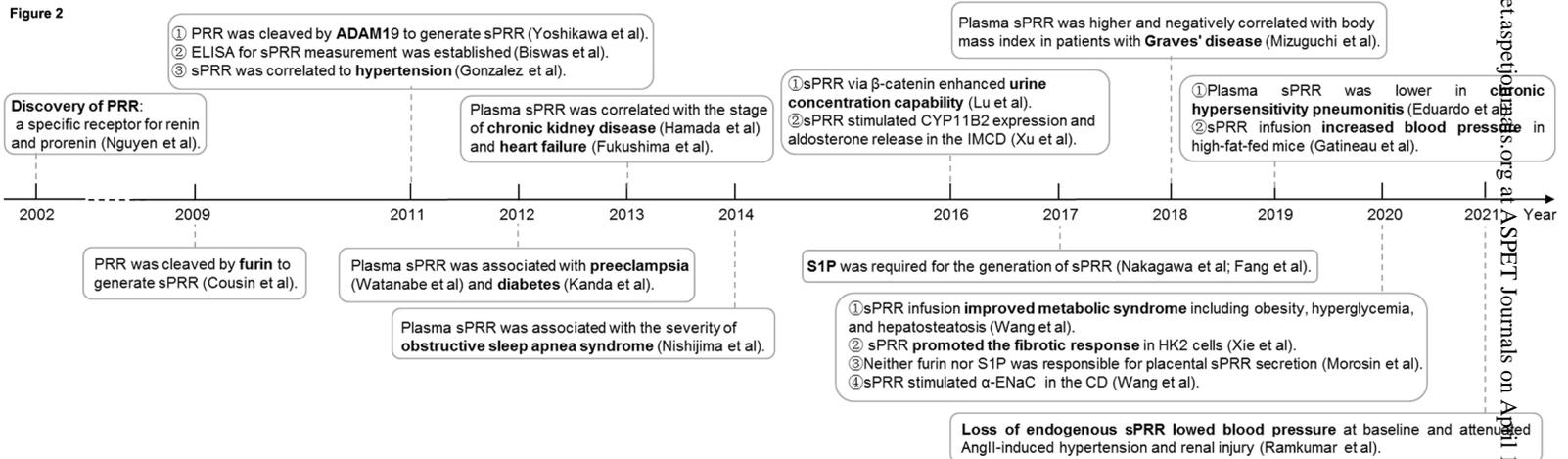
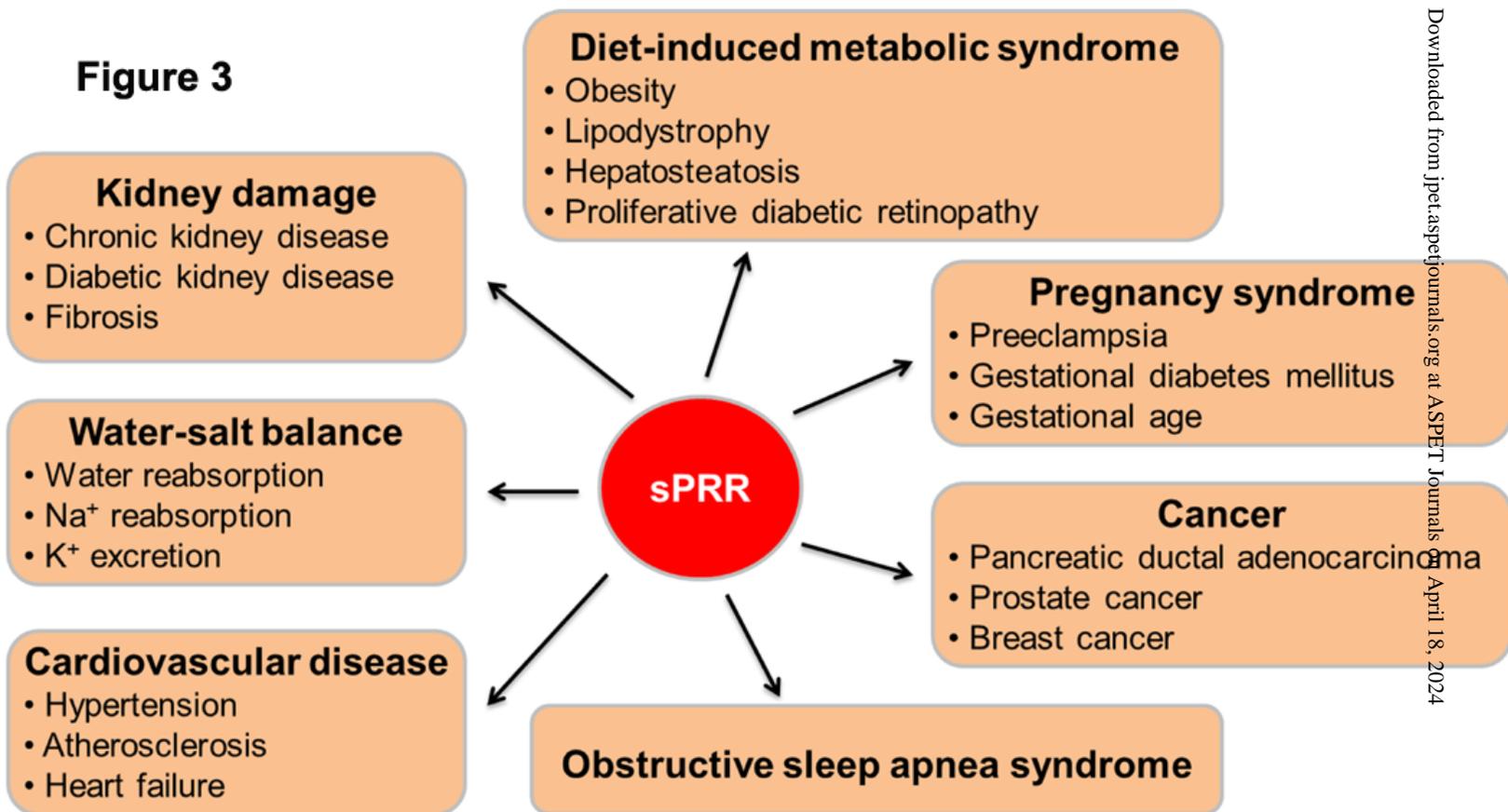


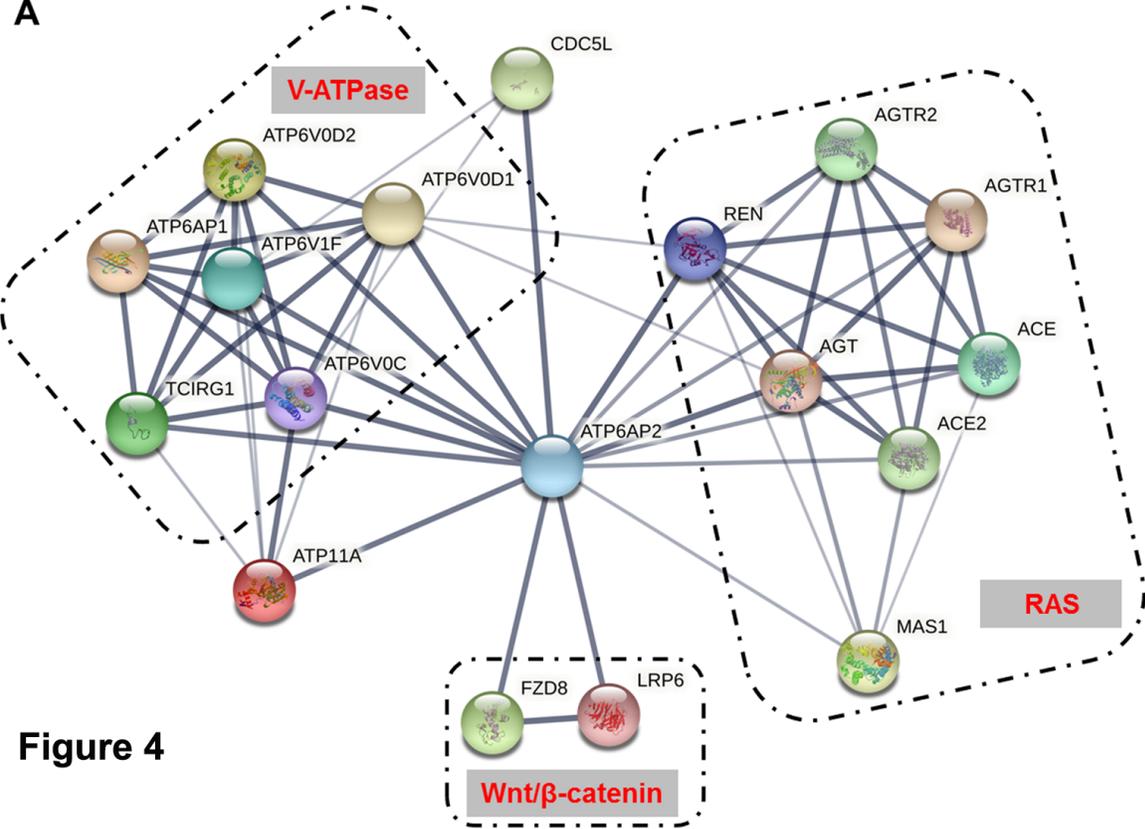
Figure 2



**Figure 3**



**A**



**Figure 4**

**B**

Interaction partners	Score
REN	0.998
ATP6V0C	0.993
ATP6AP1	0.992
AGT	0.982
CDC5L	0.980
ATP6V0D1	0.979
ATP6V0D2	0.967
ATP6V1F	0.944
ATP11A	0.933
TCIRG1	0.931
FZD8	0.925
LRP6	0.916
ACE	0.718
AGTR1	0.709
ACE2	0.700
AGTR2	0.675
MAS1	0.557

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