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Minireview

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

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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 physiopathologic relevance in cellular homeostasis. A soluble form of PRR (sPRR) is generated through protease-mediated cleavage of the full-length PRR and secreted into extracellular spaces. Accumulating evidence indicates pivotal biologic functions of sPRR in various physiopathological processes. sPRR may be a novel biomarker for multiple diseases.

SIGNIFICANCE STATEMENT

Circulating sPRR concentrations are elevated in patients and animals under various physiopathological conditions. This minireview highlights 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 1 transmembrane protein (also known as ATPase, H^+-transporting, and lysosomal accessory protein 2 or ATPase, H^+-transporting, and lysosomal-interacting protein 2), was first discovered and assigned a renin-regulatory function in 2002 (Nguyen 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 biologic systems and intracellular signaling pathways, including local renin-angiotensin system (RAS), wnt (wingless-type MMTV integration site)/β-catenin signaling, vacuolar H^+-ATPase (V-ATPase), and mitogen-activated protein kinase signaling (Ichihara and Yatabe, 2019). Activation of PRR contributes to diseases such as cardiovascular diseases, kidney injury, hypertension, diabetes and its complications, and pre-eclampsia (Ichihara and Yatabe, 2019).

PRR consists of a large N-terminal extracellular domain, a single transmembrane domain, and a short cytoplasmic domain (Fig. 1) (Nguyen and Muller, 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 et al., 2009; Yoshikawa et al., 2011; Fang et al., 2017; Nakagawa et al., 2017), 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 et al., 2010). Furin was the first reported enzyme for the intracellular cleavage of PRR in the *trans-*

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ABBREVIATIONS: ACE, angiotensin-converting enzyme; ADAM19, a disintegrin and metalloproteinase 19; AGT, angiotensinogen; AngII, angiotensin II; AQP2, aquaporin 2; ATP6AP1, V-type proton ATPase subunit S1; AVP, vasopressin; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ENaC, epithelial sodium channel; fPRR, full-length PRR; FZD8, frizzled-8; GDM, gestational diabetes mellitus; HD, hemodialysis; IMCD, inner medullary collecting duct; KO, knockout; LDLR, low-density lipoprotein receptor; LRP6, low-density lipoprotein receptor–related protein 6; NDI, nephrogenic diabetes insipidus; NOX_4, NADPH oxidase 4; OSAS, obstructive sleep apnea syndrome; PRO20, the first 20 amino acid residues of the prorenin prosegment; PRR, (pro)renin receptor; RAS, renin-angiotensin system; SORT1, sortilin-1; S1P, site-1-protease; sPRR, soluble PRR; V-ATPase, vacuolar H^+-ATPase; V_2R, AVP receptor 2; WD, water deprivation; Wnt, Wingless-type MMTV integration site .

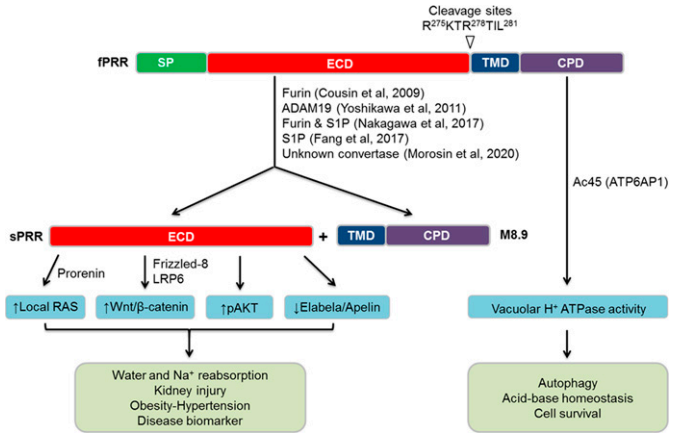


Fig. 1. Schematic illustration of the generation and functions of sPRR. fPRR is cleaved by proteases at the indicated cleavage site to generate sPRR and M8.9. sPRR is involved in various physiopathologic processes via local RAS, wnt/β-catenin signaling, AKT-mediated signaling, and Elabela/Apelin. sPRR may be a biomarker for diseases. Vacuolar H^+-ATPase controls autophagy and acid-base homeostasis. CPD, cytoplasmic domain; ECD, extracellular domain; SP, signal peptide; TMD, transmembrane domain; AKT, protein kinase B.

Golgi, by recognizing the conserved amino acid sequence $R^{275}KTR^{278}$, a furin-like cleavage site (Cousin et al., 2009). Subsequently, Yoshikawa et al. (2011) reported that transfection of a disintegrin and metalloproteinase 19 (ADAM19) increased, whereas transfection of dominant-negative ADAM19 inhibited the production of sPRR. Neither the furin-deficient LoVo cells nor furin inhibitor-treated vascular smooth muscle cells lost sPRR in the media (Yoshikawa 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 site-1-protease (S1P) for the generation of sPRR by recognizing the conserved amino acid sequence $R^{278}TIL^{281}$ of PRR (Fang et al., 2017; Nakagawa et al., 2017). They found that the inhibitor of S1P, not furin or ADAM19, suppressed brefeldin A or bovine serum albumin–induced sPRR generation (Fig. 2) (Fang et al., 2017; Nakagawa et al., 2017). More importantly, they also pointed out that sPRR may be generated by sequential processing by S1P and furin (Nakagawa et al., 2017). However, Morosin et al. (2020) has recently shown that a proprotein convertase inhibitor DEC-RVKR-CMK (Decanoyl-Arg-Val-Lys-Arg-chloromethylketone), but not furin siRNA or S1P inhibitor PF429242, reduced the extracellular sPRR levels in the placental syncytiotrophoblast. This finding is opposite to the previous observations from nonplacental cells suggesting that an unknown convertase, but not S1P or furin, is most probably responsible for the secretion of sPRR in the placenta (Morosin 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 ELISA kit (Biswas et al., 2011; Maruyama 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 antihypertensive (Li et al., 2015; Wang et al., 2015; Xu et al., 2017a), renoprotective (Fang et al., 2018; Luo et al., 2020), diuretic (Wang et al., 2016), natriuretic (Fu et al., 2019), and antikaliuretic (Xu et al., 2016; Xu et al., 2017b) actions by targeting the RAS. However, although Li et al. (2015) have demonstrated the binding affinity and specificity of PRO20 to the PRR in the mouse brain with dissociation constants of 4.6 ± 2.2 nM and maximum binding of 24.0 ± 4.1 relative fluorescence units using fluorescein isothiocyanate–labeled PRO20 peptide, the inhibition constant 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 physiopathologic processes (Fig. 3), including the activation of tissue RAS (Gonzalez et al., 2011), the regulation of water balance (Lu et al., 2016c), and the progress of diseases such as hypertension (Gatineau et al., 2019b) and kidney injury (Xie 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.

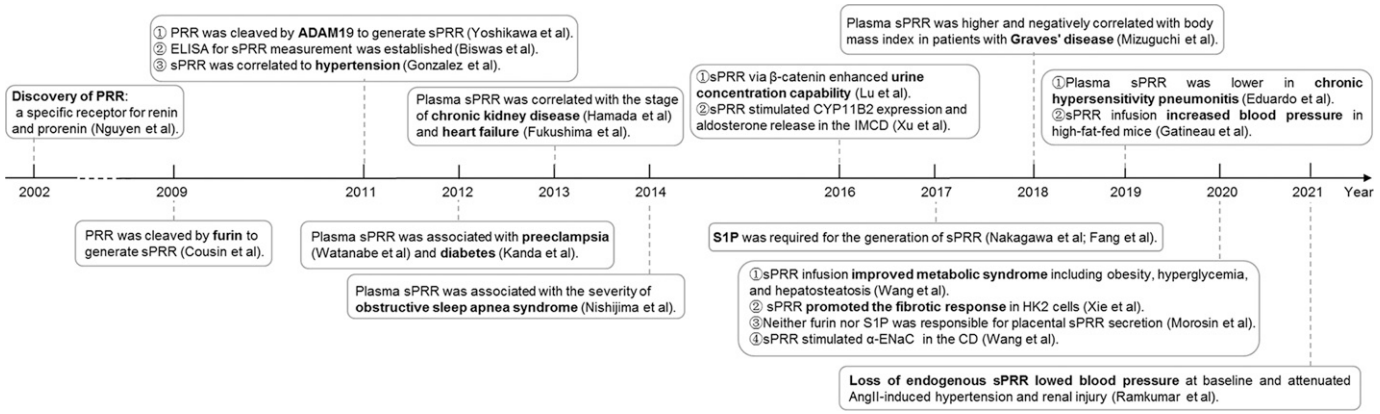


Fig. 2. Overview showing the first important publication on the generation and relevance of sPRR in various physiopathologic processes. The x-axis depicts years. CD, collecting duct.

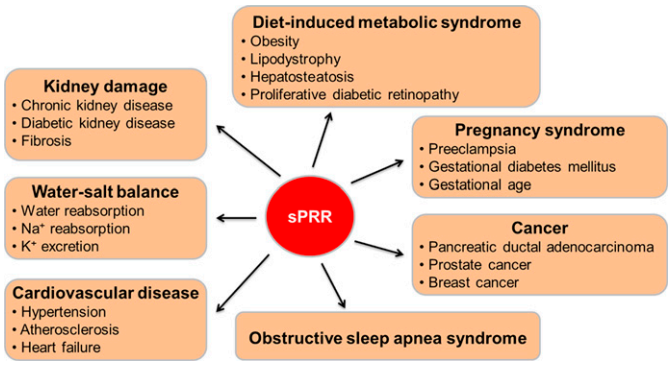
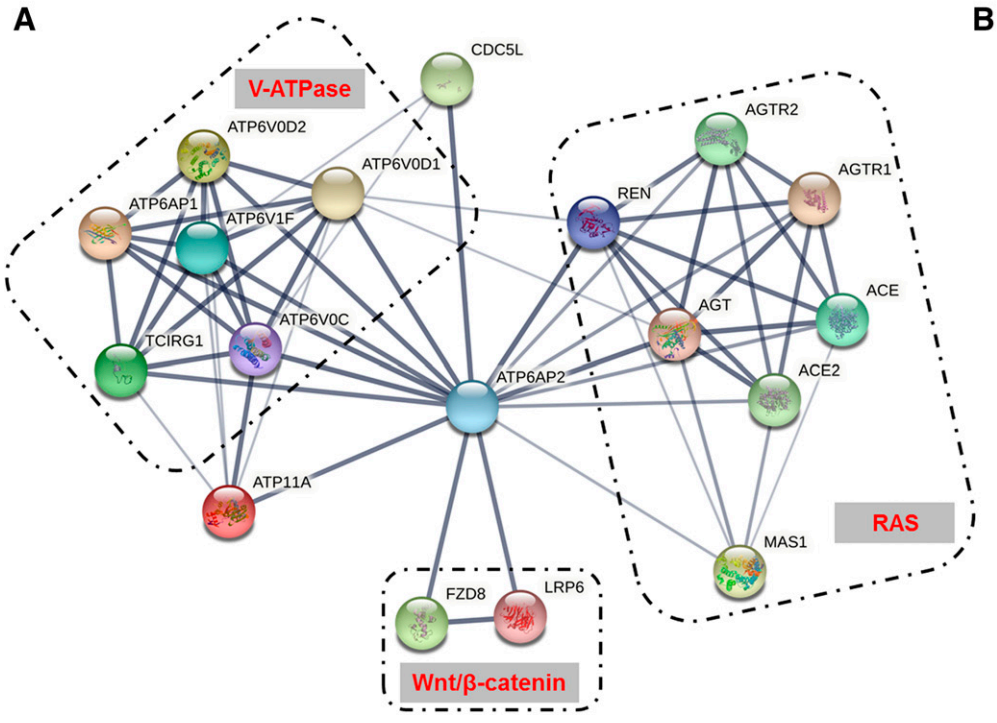


Fig. 3. Specific functions of sPRR in various physiopathologic processes.

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 by searching with the sequences of multiple proteins (Fig. 4). Among 17 candidate proteins, six are related to V-ATPase [V-type proton ATPase subunit d1, V-type proton ATPase 116-kDa subunit a isoform 3, V-type proton ATPase subunit S1 (ATP6AP1), V-type proton ATPase subunit d2, ATPase H^+-transporting V1 subunit F, and V-type proton ATPase subunit c], two are related to Wnt/β-catenin pathway [frizzled-8 (FZD8) and low-density lipoprotein receptor–related protein 6 (LRP6)], and seven are related to RAS [angiotensin-converting enzyme (ACE); renin; proto-oncogene Mas, receptor for angiotensin 1–7; type 1 angiotensin II receptor; ACE2; type 2 angiotensin II receptor; and angiotensin (AGT)]. Thus, these data indicate the possible interaction between sPRR and the V-ATPase, Wnt/β-catenin pathway, and RAS.

Mice with most of the RAS component deficiencies developed normally, whereas 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 et al., 2017). Consistently, cardiomyocyte-specific PRR deletion resulted in heart failure and early death (Kinouchi et al., 2010), and inducible nephron-specific deletion of PRR caused distal renal tubular acidosis (Trepiccione et al., 2016). Most importantly, upon PRR deletion, both of the above phenotypes were a result of V-ATPase dysfunction and impaired autophagy independent of RAS (Kinouchi et al., 2010; Trepiccione 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 et al., 2010; Kinouchi 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. (2020) 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. Therefore, sPRR may be a novel



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

Fig. 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. (B) Summary of the score of predicted functional partners of sPRR. AGTR1, type 1 angiotensin II receptor; AGTR2, type 2 angiotensin II receptor; ATP11A, probable phospholipid-transporting ATPase IH; ATP6AP2, ATPase, H^+-transporting, and lysosomal accessory protein 2; ATP6V0D1, V-type proton ATPase subunit d1; ATP6V0D2, V-type proton ATPase subunit d2; ATP6V0C, V-type proton ATPase subunit c; ATP6V1F, ATPase H^+-transporting V1 subunit F; CDC5L, cell division cycle 5-like protein; REN, Renin; Mas1, proto-oncogene Mas, receptor for angiotensin 1–7; TCIRG1, V-type proton ATPase 116 kDa subunit an isoform 3.

biomarker for the status of autophagy inhibition. Increased plasma sPRR concentrations may reflect the autophagy status and act as a mechanism of compensation of PRR and as a result of the impaired autophagy in some non-neoplastic diseases, such as chronic kidney disease (CKD) (Hamada et al., 2013), pre-eclampsia (Narita et al., 2016), gestational diabetes mellitus (GDM) (Bonakdaran et al., 2017), and obstructive sleep apnea syndrome (OSAS) (Wu et al., 2019), since the occurrence of autophagy disturbance has already been reported in these diseases (Takabatake et al., 2014; Guo et al., 2019). 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 et al., 2010; Trepiccione et al., 2016) reduces sPRR degradation in the intracellular vesicles and subsequent increased accumulated sPRR secretion by exocytosis.

sPRR from the medium of cultured human umbilical vein endothelial cells (Biswas et al., 2011) or Chinese hamster ovary cells overexpressed human PRR (Yoshikawa 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 et al., 2020) and increased aldosterone release and CYP11B2 protein expression in primary cultured rat inner medullary collecting duct (IMCD) cells (Xu et al., 2016). Recently, sPRR has been reported to directly bind AT1R to activate NOX_4 (NADPH oxidase 4)/H_2O_2 signaling pathway that contributes to endothelial dysfunction (Fu 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 $\mu g \cdot kg^{-1} \cdot day^{-1}$, 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 AGT expression (Gatineau 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 et al., 2014; Watanabe et al., 2020). The reasons for these discrepancies are unclear, but they may be related to the difference between the physiologic 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 physiologic plasma sPRR concentration in healthy humans was about 0.75–0.95 nM (Nguyen et al., 2014). Although the used concentrations of sPRR in both in vitro and in vivo experiments were consistently 12- to 60-fold above the physiologic 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 women with diabetes, whereas decreased urinary sPRR excretion was correlated with intrarenal RAS stimulation in men with diabetes, indicating a sex difference in sPRR concentrations and its contribution to RAS stimulation in plasma and urine of patients with diabetes (Visniauskas 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/β-catenin signaling by binding assays (Cruciat et al., 2010; Lu 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_2R)-dependent cAMP formation and aquaporin 2 (AQP2) expression/trafficking in collecting duct cells by recombinant sPRR protein (10 nM) was blocked by FZD8 inhibition (Lu et al., 2016c). This finding may be a potential mechanism of the enhanced urine concentrating capability in sPRR-infused C57BL/6 mice (30 $\mu g \bullet kg^{-1} \bullet day^{-1}$) (Lu et al., 2016c; Wang et al., 2019b). Secondly, sPRR (10 nM) also interacts with peroxisome proliferator–activated receptor-γ in differentiated 3T3L1 cells, resulting in increased insulin sensitivity that promotes glucose uptake (Wang et al., 2019a). It may contribute to insulin resistance and ameliorated hyperglycemia in diet-induced obese mice with recombinant sPRR protein infusion (30 $\mu g \bullet kg^{-1} \bullet day^{-1}$, the concentration of exogenous sPRR in the blood is about 53 nM) (Wang et al., 2019a). Lastly, recombinant sPRR (10 nM) treatment remarkably decreased *Apela (apelin receptor early endogenous ligand)* and apelin mRNA expression in cultured IMCD3 cells, indicating an inhibition effect of sPRR on the apelinergic system (Xu et al., 2020). We recently reported that sPRR is a downstream target of cAMP/PKA (protein kinase A) 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 et al., 2021). These results support the antagonistic interaction between ELABELA (**E**piboly **LA**te **B**ecause of **E**ndoderm **LA**te)/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 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, similar to the binding of PRR to FZD8 and LRP6 (Cruciat 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_2R expression (Ramkumar et al., 2015; Wang et al., 2016, 2019b). Renal fPRR protein but not mRNA abundance is consistently upregulated in rats after water deprivation (WD) for 48 (Wang et al., 2016) or 72 hours (Tamura et al., 2016). Tamura et al. (2016) reported that the decreased furin protein expression in the kidney contributes to increased fPRR protein levels in 72-hour WD rats. 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 et al., 2016). In

comparison, another study showed that fPRR and sPRR protein abundance in the whole kidney and 24-hour urinary sPRR excretion were significantly increased in rats with 48-hour WD and regulated by EP_4 (prostaglandin E_2 type 4) receptor (Wang 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-hour urinary sPRR excretion were markedly elevated in 48-hour WD rats (Wang et al., 2016). However, these results may indicate the different sources of plasma versus 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 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 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 et al., 2006), are agonists. Similarly, in addition to the stimulating role of sPRR on prorenin activity (Yoshikawa 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-hour WD rats, with a decreased plasma sPRR concentrations in these rats (Tamura 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-hour WD. It has been reported that 48-hour WD significantly inhibited autophagy in the selfish brain, whereas 72-hour WD markedly activated autophagy (Ye et al., 2016). Thus, we suspect that the variations of autophagy activity in 48-hour versus 72-hour 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-hour 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 been no relevant reports, however, that 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/β-catenin signaling pathway, thereby stimulating AQP2 and V_2R expression in primary cultured rat IMCD cells, predicting the antidiuretic action of sPRR (Lu et al., 2016c; Wang 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_2R antagonist OPC31260 or the liver X receptor agonist TO901317 infusion (Lu et al., 2016c). However, intravenous infusion of exogenous sPRR-His did not influence lithium-induced NDI phenotype (Yang et al., 2017) but aggravated fat-induced NDI phenotype (Wang 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 Gsk 3β (Glycogen synthase kinase-3β) activity to activate renal COX-2 (cyclooxygenase-2)/PGE_2 (prostaglandin E_2) signaling but also inhibits wnt/β-catenin signaling, resulting in the decrease of cAMP production and AQP2 phosphorylation and, thereby, polyuria (Rao et al., 2005). Diabetes insipidus in 36-week-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 et al., 2019b; Wang et al., 2019a). Firstly, chronic intravenous sPRR infusion for 2 weeks did not change 24-hour urine volume in the 36-week-old C57BL/6 male mice (Wang 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 et al., 2016c; Wang et al., 2019b). Secondly, although recombinant sPRR subcutaneous infusion for 4 weeks increased urinary AVP excretion in 16-week-old C57BL/6 female mice (Gatineau et al., 2019a), it did not change the AVP/AQP2 pathway in 26-week-old obese male mice (20 weeks of high-fat feeding), as reflected by the unchanged urine volume; urinary AVP and Na^+ excretion; and renal AQP2, V_2R, FZD8, and LRP6 expression (Gatineau et al., 2019b). The different routes of administration for recombinant sPRR protein and the setting of specific pathologic 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 is more, loss of endogenous sPRR in mice by mutating the cleavage site of the PRR did not cause polyuria (Ramkumar et al., 2021), which may due to a compensatory response to the enhanced fPRR protein levels in these mice.

sPRR May Promote Na^+ Reabsorption and K^+ Excretion

Studies employing both pharmacological and genetic approaches have established an essential role of PRR in the regulation of Na^+ and K^+ balance, which involves RAS-dependent (Ramkumar et al., 2016, 2018; Peng et al., 2017; Prieto et al., 2017; Xu et al., 2017b) and -independent (Lu et al., 2016b; Quadri and Siragy, 2016; Quadri et al., 2018) mechanisms. Interestingly, a recent study showed that exogenous recombinant sPRR exhibited an acute stimulation effect on epithelial sodium channel (ENaC) activity via NOX_4 signaling and chronic promotion action on α-ENaC–dependent β-catenin signaling (Wang et al., 2020), implying the Na^+-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 et al., 2016). Therefore, these results indicate that sPRR may control membrane Na^+- and K^+-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 (Yang and Xu, 2017; Nakagawa et al., 2020). Importantly, sPRR levels in the collecting duct and urine of AngII-infused rats (Gonzalez 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 nonproteolytic activation of prorenin triggered by the intraluminal sPRR or cell surface–located PRR (Gonzalez 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 AngII-induced hypertension in F1 B6129SF1/J mice, accompanied by decreased renal medullary and urinary renin levels and renal medulla α-ENaC expression, both of which were reversed by sPRR-His infusion (Feng 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 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 et al., 2021; Ramkumar 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 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 et al., 2014), which may be attributed to the stimulatory role of sPRR on renal AGT expression (Gatineau 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 (Wu et al., 2016; Gatineau et al., 2019a). 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 et al., 2019b). Of note, Gatineau et al. (2019a,b) 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, indicating a sex 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 et al., 2019a). However, 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 the observations that chlorisondamine (a ganglionic blocker) treatment downregulated BP in these mice (Gatineau 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 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-related hypertension.

sPRR May Be a Promising Diagnostic Indicator for Heart Failure

Both PRR expression in the heart (Hirose et al., 2009; Mahmud et al., 2012; Peng et al., 2013) and plasma sPRR levels (Fukushima et al., 2013; Gong et al., 2019; Amari et al., 2020; Obradovic et al., 2020) were 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 but positively correlated with left ventricular mass index, left atrial diameter, left ventricular posterior wall thickness, left ventricular end-diastolic diameter, mitral valve flow velocity/myocardial wall velocity (at left ventricular early diastole), and plasma B-type natriuretic peptide (Fukushima et al., 2013; Gong et al., 2019; Obradovic et al., 2020), indicating an important correlation between the plasma sPRR level and cardiac function. By multivariate regression analysis, eGFR and left ventricular mass index were the independent determinants of the plasma sPRR levels (Fukushima et al., 2013; Gong et al., 2019). Thus, plasma sPRR may be a potential evaluative biomarker for heart failure. This notion also applies to heart failure (Amari et al., 2020) and atherosclerotic conditions (Amari et al., 2016) in patients undergoing hemodialysis (HD). The changes in human atrial natriuretic peptide, B-type natriuretic peptide, and intraventricular septum thickness were more significant in patients undergoing HD 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 et al., 2020). Similarly, the levels of plasma sPRR were considerably higher in patients undergoing HD with the ankle-brachial index of $<$0.9 than in those with ankle-brachial index of $\geq$0.9 independent of other atherogenic factors, implying that plasma sPRR could also be a biomarker for atherosclerosis (Amari 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 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/β-catenin signaling (Li and Siragy, 2014; Li et al., 2017), intrarenal RAS (Fang et al., 2018), and mitochondria NOX_4/SOD2 (superoxide dismutase 2)/UCP2 (uncoupling protein 2) /NF-κB (nuclear factor kappa-B) and Sirt1 (sirtuin-1)/FOXO3a (forkhead box O3a) signaling (Li et al., 2019), and the inhibition of mitochondrial AMPK [Adenosine 5'-monophosphate (AMP)-activated protein kinase]/Sirt1/PGC-1α (peroxisome proliferator-activated receptor γ coactivator-1α) signaling (Akhtar and Siragy, 2019), respectively. Furthermore, PRR is crucial for normal podocyte function and survival attributed to its role in vacuolar H^+-ATPase activity controlling autophagy and acidification, thereby activating the wnt/β-catenin signaling (Cruciat et al., 2010; Oshima et al., 2011; Riediger 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 et al., 2018). These results were consistent with the findings in cultured renal epithelial cells with albumin exposure (Fang et al., 2017), indicating the involvement of sPRR in this nephropathy model. Indeed, the levels of plasma sPRR are modulated in CKD (Hamada et al., 2013) and may reflect PRR expression levels in infiltrated mononuclear cells and thus renal damage (Ohashi et al., 2016). Along this line, plasma sPRR levels were positively correlated to the CKD stage and negatively associated with eGFR in patients with CKD (Hamada et al., 2013). Plasma sPRR levels were also significantly positively associated with tubulointerstitial fibrosis in patients with heminephrectomy (Ohashi et al., 2016). Moreover, plasma sPRR levels were positively associated with serum blood urea nitrogen, indicating that increased plasma sPRR concentrations are correlated with renal dysfunction associated with heart failure (Fukushima et al., 2013; Gong et al., 2019). Therefore, plasma sPRR may be a useful biomarker for CKD.

Regarding the origin of plasma sPRR, Ohashi 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 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 et al., 2015). A functional PRR has already been found and plays an essential role in inflammation and cell development in these cells (Narumi et al., 2015). However, the use of tissue-specific PRR knockout (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 (PKB, protein kinase B)/β-catenin/Snail signaling pathway (Xie et al., 2020). However, the used concentrations of sPRR here are over 70-fold above the physiologic 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 with the nonpregnant rats, PRR expression in the heart, aorta, and kidney tissues and 24-hour urinary sPRR excretion were significantly higher in the pregnant rats (Avila-Ramírez et al., 2019; Fu 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 pre-eclampsia (Watanabe 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 et al., 2017). Thus, these results suggest probable participation of PRR during pregnancy, and increased sPRR might be correlated with the occurrence of pre-eclampsia. In support of this possibility, rats with pre-eclampsia 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 (Thomason et al., 2015; Avila-Ramírez et al., 2019). 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 women with pre-eclampsia compared with normal pregnant women (Narita T et al., 2016). However, future research is needed to figure out the relative contribution of cardiac tissues versus placenta to circulating sPRR in women with pre-eclampsia. Thus, it is recommended to generate pre-eclamptic models using inducible heart-specific and placenta-specific PRR deletion mice to analyze the status of plasma sPRR and the pathogenesis of pre-eclampsia.

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 women with pre-eclampsia (Narita et al., 2016). eGFR in pregnant women was negatively correlated with placental PRR levels and plasma sPRR levels (Narita et al., 2016). Still, it was negatively associated with plasma sPRR levels but not with placental PRR levels in women with pre-eclampsia (Narita 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 women with pre-eclampsia (Narita et al., 2016). Regarding the intracellular signaling mediated by PRR in pre-eclampsia placentas, Tamada et al. (2019) pointed out that increased PRR expression activated intracellular signaling via prorenin to increase the expression of plasminogen activator inhibitor-1 and transforming growth factor-β, consequently increasing endothelin-1 production and the pathogenesis of pre-eclampsia. However, the mechanisms for the involvement

of plasma sPRR in the pathogenesis of decreased renal function in pre-eclampsia are unknown.

Several small cohort studies have suggested that sPRR is associated with GDM (Watanabe et al., 2013b; Gokulakrishnan et al., 2015; Bonakdaran et al., 2017; Sugulle et al., 2017), a risk factor for developing pre-eclampsia in pregnancy. Plasma sPRR levels are significantly higher in pregnant females with GDM than in healthy pregnancies or pre-eclampsia and positively associated with GDM (Bonakdaran et al., 2017; Gokulakrishnan et al., 2015; Sugulle 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 with full-term neonates, the levels of umbilical serum prorenin and sPRR were significantly higher and negatively correlated with gestational age (Terada et al., 2017). Similarly, Mikami et al. (2017) showed that umbilical serum sPRR levels in singleton pregnancies were significantly associated with gestational age at delivery and serum prorenin levels. Indeed, high umbilical plasma sPRR levels are correlated with a lower likelihood of small-for-gestational-age birth (Watanabe 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. Future investigations with extensive and long-term cohort studies are needed 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 β cells is essential for the release of insulin and thus diabetes prevention (Binger 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 (Tan et al., 2014, 2016; Shamansurova et al., 2016; Wu 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 et al., 2016; Wu et al., 2016), the mice exhibited lipodystrophy, hepatosteatosis, and hypertension in response to feeding high-fat diets (Wu et al., 2016; Gatineau et al., 2019a). 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 (Wu et al., 2016; Gatineau et al., 2019a). 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, and 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 (Bernardinelli Seip congenital lipodystrophy 2)$^{-/-}$ male mice (a mouse model of lipodystrophy and hepatosteatosis) (Chen et al., 2012; Gatineau 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. (2021) 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. Therefore, these results indicate that adipose tissue-liver crosstalk 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 proliferator-activated receptor-γ in adipocytes that increases insulin sensitivity (Wang 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 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/β-catenin signaling to upgrade the development of various cancers (Ohba et al., 2014, 2020; Shibayama et al., 2015; Kouchi et al., 2017; Wang et al., 2019; Rahman et al., 2020; Zhao et al., 2020). Plasma sPRR concentrations were found significantly higher in patients with pancreatic ductal adenocarcinoma (Shibayama et al., 2015), prostate cancer (Mohammad et al., 2019), or breast cancer (Mohammad et al., 2020) compared with the healthy specimen. However, it did not change with respect to controls and was not correlated with primary epithelial ovarian cancer (Kreienbring et al., 2016) or colorectal cancer (Beitia 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 treatment (Nishijima et al., 2014, 2016; Wu et al., 2019) or bariatric surgery (Nishijima 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, arousal index, and oxygen desaturation index (Nishijima et al., 2014, 2016, 2018; Wu 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 et al., 2014, 2016). These results are consistent with the observations that plasma sPRR concentrations are independent of plasma prorenin/renin and aldosterone levels (Nguyen et al., 2014). OSAS is characterized by intermittent hypoxia, resulting in oxidative stress in multiple organs, which contributes to the elevation of plasma sPRR levels in patients with OSAS (Takahashi et al., 2017). In support of this possibility, hypoxia has been reported to significantly increase intracellular sPRR levels in human placental trophoblast cells (Suda et al., 2020). Additionally, female but not male patients with OSAS and diabetic kidney disease had higher concentrations of plasma sPRR, indicating a more significant effect of diabetic kidney disease on plasma sPRR levels in female patients with OSAS (Nishijima et al., 2016). The reasons for this sex difference are unclear, but it may be related to sex hormones due to the presence of sex differences in OSAS (Lin 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 come 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.

Authorship Contributions

Participated in research design: Xu.
Performed data analysis: Qin, Xu.
Wrote or contributed to the writing of the manuscript: Qin, Xu, Yu.

References

Akhtar S and Siragy HM (2019) Pro-renin receptor suppresses mitochondrial biogenesis and function via AMPK/SIRT-1/ PGC-1α pathway in diabetic kidney. *PLoS One* **14**:e0225728.

Amari Y, Morimoto S, Iida T, Takimoto H, Okuda H, Yurugi T, Oyama Y, Aoyama N, Nakajima F, and Ichihara A (2020) Association between serum soluble (pro)renin receptor level and worsening of cardiac function in hemodialysis patients: A prospective observational study. *PLoS One* **15**:e0233312.

Amari Y, Morimoto S, Nakajima F, Ando T, and Ichihara A (2016) Serum Soluble (Pro)Renin Receptor Levels in Maintenance Hemodialysis Patients. *PLoS One* **11**:e0158068.

Avila-Ramírez MA, Esteban-Martínez RL, López-Moctezuma E, Anguiano-Robledo L, Hernández-Campos ME, and López-Sánchez P (2019). (Pro)renin/renin receptor expression during normal and preeclamptic pregnancy in rats. *Life Sci* **216**:22–28.

Beitia M, Solano-Iturri JD, Errarte P, Calvete-Candenas J, Loizate A, Etxezarraga MC, Sanz B, and Larrinaga G (2019) (Pro)renin receptor expression increases throughout the colorectal adenoma-adenocarcinoma sequence and it is associated with worse colorectal cancer prognosis. *Cancers (Basel)* **11**:881.

Binger KJ, Neukam M, Tattikota SG, Qadri F, Puchkov D, Willmes DM, Wurmsee S, Geisberger S, Dechend R, Raile K, et al. (2019) *Atp6ap2* deletion causes extensive vacuolation that consumes the insulin content of pancreatic β cells. *Proc Natl Acad Sci USA* **116**:19983–19988.

Biswas KB, Nabi AN, Arai Y, Nakagawa T, Ebihara A, Ichihara A, Inagami T, and Suzuki F (2011) Qualitative and quantitative analyses of (pro)renin receptor in the medium of cultured human umbilical vein endothelial cells. *Hypertens Res* **34**:735–739.

Bonakdaran S, Azami G, Tara F, and Poorali L (2017) Soluble (pro) renin receptor is a predictor of gestational diabetes mellitus. *Curr Diabetes Rev* **13**:555–559.

Chen W, Chang B, Saha P, Hartig SM, Li L, Reddy VT, Yang Y, Yechoor V, Mancini MA, and Chan L (2012). Berardinelli-seip congenital lipodystrophy 2/seipin is a cell-autonomous regulator of lipolysis essential for adipocyte differentiation. *Mol Cell Biol* **32**:1099–1111.

Chen Y, Xu C, Hu J, Deng M, Qiu Q, Mo S, Du Y, and Yang T (2021). Diuretic action of apelin-13 mediated by inhibiting cAMP/PKA/sPRR pathway. *Front Physiol* **12**:642274.

Cousin C, Bracquart D, Contrepas A, Corvol P, Muller L, and Nguyen G (2009) Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. *Hypertension* **53**:1077–1082.

Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, and Niehrs C (2010) Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt signaling. *Science* **327**:459–463.

Endo M, Ohba K, Sato S, Yokota Y, and Takahashi K (2020) Increased soluble (pro)renin receptor protein by autophagy inhibition in cultured cancer cells. *Genes Cells* **25**:483–497.

Fang H, Deng M, Zhang L, Lu A, Su J, Xu C, Zhou L, Wang L, Ou JS, Wang W, et al. (2018) Role of (pro)renin receptor in albumin overload-induced nephropathy in rats. *Am J Physiol Renal Physiol* **315**:F1759–F1768.

Fang H, Xu C, Lu A, Zou CJ, Xie S, Chen Y, Zhou L, Liu M, Wang L, Wang W, et al. (2017) (Pro)renin receptor mediates albumin-induced cellular responses: role of site-1 protease-derived soluble (pro)renin receptor in renal epithelial cells. *Am J Physiol Cell Physiol* **313**:C632–C643.

Feng Y, Peng K, Luo R, Wang F, and Yang T (2021) Site-1 protease-derived soluble (pro)renin receptor contributes to angiotensin ii-induced hypertension in mice. *Hypertension* **77**:405–416.

Fu Z, Hu J, Zhou L, Chen Y, Deng M, Liu X, Su J, Lu A, Fu X, and Yang T (2019) (Pro)renin receptor contributes to pregnancy-induced sodium-water retention in rats via activation of intrarenal RAAS and α-ENaC. *Am J Physiol Renal Physiol* **316**:F530–F538.

Fu Z, Wang F, Liu X, Hu J, Su J, Lu X, Lu A, Cho JM, Symons JD, Zou CJ, et al. (2021) Soluble (pro)renin receptor induces endothelial dysfunction and hypertension in mice with diet-induced obesity via activation of angiotensin II type 1 receptor. *Clin Sci (Lond)* **135**:793–810.

Fukushima A, Kinugawa S, Homma T, Masaki Y, Furihata T, Abe T, Suga T, Takada S, Kadoguchi T, Okita K, et al. (2013) Increased plasma soluble (pro)renin receptor levels are correlated with renal dysfunction in patients with heart failure. *Int J Cardiol* **168**:4313–4314.

Gatineau E, Arthur G, Poupeau A, Nichols K, Spear BT, Shelman NR, Graf GA, Temel RE, and Yiannikouris FB (2021) The prorenin receptor and its soluble form contribute to lipid homeostasis. *Am J Physiol Endocrinol Metab* **320**:E609–E618.

Gatineau E, Cohn DM, Poglitsch M, Loria AS, Gong M, and Yiannikouris F (2019a) Losartan prevents the elevation of blood pressure in adipose-PRR deficient female mice while elevated circulating sPRR activates the renin-angiotensin system. *Am J Physiol Heart Circ Physiol* **316**:H506–H515.

Gatineau E, Gong MC, and Yiannikouris F (2019b) Soluble prorenin receptor increases blood pressure in high fat-fed male mice. *Hypertension* **74**:1014–1020.

Geisberger S, Maschke U, Gebhardt M, Kleinewietfeld M, Manzel A, Linker RA, Chidgey A, Dechend R, Nguyen G, Daumke O, et al. (2015) New role for the (pro)renin receptor in T-cell development. *Blood* **126**:504–507.

Gokulakrishnan K, Maheswari K, Mahalakshmi MM, Kalaiyarasi G, Bhavadharini B, Pandey GK, Ramesh J, Ram U, and Mohan V (2015) Association of soluble (pro) renin receptor with gestational diabetes mellitus. *Endocr Pract* **21**:7–13.

Gong L, Zhang S, Li L, Gao X, Wang D, Wu D, Wang K, and Liu Y. (2019). Elevated plasma soluble (pro)renin receptor levels are associated with left ventricular remodeling and renal function in chronic heart failure patients with reduced ejection fraction. *Peptides* **111**:152-157.

Gonzalez AA, Lara LS, Luffman C, Seth DM, and Prieto MC (2011) Soluble form of the (pro)renin receptor is augmented in the collecting duct and urine of chronic angiotensin II-dependent hypertensive rats. *Hypertension* **57**:859–864.

Guo X, Shi Y, Du P, Wang J, Han Y, Sun B, and Feng J (2019). HMGB1/TLR4 promotes apoptosis and reduces autophagy of hippocampal neurons in diabetes combined with OSA. *Life Sci* **239**:117020.

Hamada K, Taniguchi Y, Shimamura Y, Inoue K, Ogata K, Ishihara M, Horino T, Fujimoto S, Ohguro T, Yoshimoto Y, et al. (2013) Serum level of soluble (pro)renin receptor is modulated in chronic kidney disease. *Clin Exp Nephrol* **17**:848–856.

Hirose T, Mori N, Totsune K, Morimoto R, Maejima T, Kawamura T, Metoki H, Asayama K, Kikuya M, Ohkubo T, et al. (2009) Gene expression of (pro)renin receptor is upregulated in hearts and kidneys of rats with congestive heart failure. *Peptides* **30**:2316–2322.

Ichihara A and Yatabe MS (2019) The (pro)renin receptor in health and disease. *Nat Rev Nephrol* **15**:693–712.

Ikeda Y, Tsutsui K, Yamada Y, Kato R, Muramatsu T, and Senbonmatsu T (2020) Relationship between soluble (pro)renin receptor and renin activity in patients with severe heart failure. *J Clin Med* **9**:4110.

Kinouchi K, Ichihara A, Sano M, Sun-Wada GH, Wada Y, Kurauchi-Mito A, Bokuda K, Narita T, Oshima Y, Sakoda M, et al. (2010) The (pro)renin receptor/ATP6AP2 is essential for vacuolar H+-ATPase assembly in murine cardiomyocytes. *Circ Res* **107**:30–34.

Kinouchi K, Ichihara A, Sano M, Sun-Wada GH, Wada Y, Ochi H, Fukuda T, Bokuda K, Kurosawa H, Yoshida N, et al. (2013) The role of individual domains and the significance of shedding of ATP6AP2/(pro)renin receptor in vacuolar H(+)-ATPase biogenesis. *PLoS One* **8**:e78603.

Kouchi M, Shibayama Y, Ogawa D, Miyake K, Nishiyama A, and Tamiya T (2017) (Pro)renin receptor is crucial for glioma development via the Wnt/β-catenin signaling pathway. *J Neurosurg* **127**:819–828.

Kreienbring K, Franz A, Richter R, Dragun D, Heidecke H, Dechend R, Muller DN, Sehouli J, and Braicu EI (2016). Predictive and prognostic value of sPRR in patients with primary epithelial ovarian cancer. *Anal Cell Pathol (Amst)* **2016**:6845213.

Li C and Siragy HM (2014) High glucose induces podocyte injury via enhanced (pro)renin receptor-Wnt-β-catenin-snail signaling pathway. *PLoS One* **9**:e89233.

Li C, Matavelli LC, Akhtar S, and Siragy HM (2019) (Pro)renin receptor contributes to renal mitochondria dysfunction, apoptosis and fibrosis in diabetic mice. *Sci Rep* **9**:11667.

Li W, Sullivan MN, Zhang S, Worker CJ, Xiong Z, Speth RC, and Feng Y (2015) Intracerebroventricular infusion of the (Pro)renin receptor antagonist PRO20 attenuates deoxycorticosterone acetate-salt-induced hypertension. *Hypertension* **65**:352–361.

Li Z, Zhou L, Wang Y, Miao J, Hong X, Hou FF, and Liu Y (2017) (Pro)renin receptor is an amplifier of Wnt/β-catenin signaling in kidney injury and fibrosis. *J Am Soc Nephrol* **28**:2393–2408.

Lin CM, Davidson TM, and Ancoli-Israel S (2008) Gender differences in obstructive sleep apnea and treatment implications. *Sleep Med Rev* **12**:481–496.

Lu X, Meima ME, Nelson JK, Sorrentino V, Loregger A, Scheij S, Dekkers DH, Mulder MT, Demmers JA, M-Dallinga-Thie G, et al. (2016a) Identification of the (pro)renin receptor as a novel regulator of low-density lipoprotein metabolism. *Circ Res* **118**:222–229.

Lu X, Wang F, Liu M, Yang KT, Nau A, Kohan DE, Reese V, Richardson RS, and Yang T (2016b) Activation of ENaC in collecting duct cells by prorenin and its receptor PRR: involvement of Nox4-derived hydrogen peroxide. *Am J Physiol Renal Physiol* **310**:F1243–F1250.

Lu X, Wang F, Xu C, Soodvilai S, Peng K, Su J, Zhao L, Yang KT, Feng Y, Zhou SF, et al. (2016c) Soluble (pro)renin receptor via β-catenin enhances urine concentration capability as a target of liver X receptor. *Proc Natl Acad Sci USA* **113**:E1898–E1906.

Luo R, Yang K, Wang F, Xu C, and Yang T (2020) (Pro)renin receptor decoy peptide PRO20 protects against adriamycin-induced nephropathy by targeting the intrarenal renin-angiotensin system. *Am J Physiol Renal Physiol* **319**:F930–F940.

Mahmud H, Silljé HH, Cannon MV, van Gilst WH, and de Boer RA (2012) Regulation of the (pro)renin-renin receptor in cardiac remodelling. *J Cell Mol Med* **16**:722–729.

Maruyama N, Segawa T, Kinoshita N, and Ichihara A (2013). Novel sandwich ELISA for detecting the human soluble (pro)renin receptor. *Front Biosci (Elite Ed)* **5**:583–590.

Mikami Y, Takai Y, Narita T, Era S, Ono Y, Saitoh M, Baba K, Matsuoka K, and Seki H. (2017). Associations between the levels of soluble (pro)renin receptor in maternal and umbilical cord blood and hypertensive disorder of pregnancy. *Placenta* **57**:129–136.

Mohammad AH, Assadian S, Couture F, Lefebvre KJ, El-Assaad W, Barrès V, Ouellet V, Boulay PL, Yang J, Latour M, et al. (2019) V-ATPase-associated prorenin receptor is upregulated in prostate cancer after PTEN loss. *Oncotarget* **10**:4923–4936.

Mohammad AH, Kim SH, Bertos N, El-Assaad W, Nandi I, Smith H, Yang J, Chen OJ, Gamache I, Rao T, et al. (2020) Elevated V-ATPase activity following PTEN loss is required for enhanced oncogenic signaling in breast cancer. *Mol Cancer Res* **18**:1477–1490.

Morimoto S, Ando T, Niiyama M, Seki Y, Yoshida N, Watanabe D, Kawakami-Mori F, Kobori H, Nishiyama A, and Ichihara A (2014) Serum soluble (pro)renin receptor levels in patients with essential hypertension. *Hypertens Res* **37**:642–648.

Morosin SK, Delforce SJ, Lumbers ER, and Pringle KG. (2020). Cleavage of the soluble (pro)renin receptor (sATP6AP2) in the placenta. *Placenta* **101**:49–56.

Nakagawa P, Gomez J, Grobe JL, and Sigmund CD (2020) The renin-angiotensin system in the central nervous system and its role in blood pressure regulation. *Curr Hypertens Rep* **22**:7.

Nakagawa T, Suzuki-Nakagawa C, Watanabe A, Asami E, Matsumoto M, Nakano M, Ebihara A, Uddin MN, and Suzuki F (2017) Site-1 protease is required for the generation of soluble (pro)renin receptor. *J Biochem* **161**:369–379.

Narita T, Ichihara A, Matsuoka K, Takai Y, Bokuda K, Morimoto S, Itoh H, and Seki H. (2016). Placental (pro)renin receptor expression and plasma soluble (pro)renin receptor levels in preeclampsia. *Placenta* **37**:72–78.

Narumi K, Hirose T, Sato E, Mori T, Kisu K, Ishikawa M, Totsune K, Ishii T, Ichihara A, Nguyen G, et al. (2015) A functional (pro)renin receptor is expressed in human lymphocytes and monocytes. *Am J Physiol Renal Physiol* **308**:F487–F499.

Nguyen G, Blanchard A, Curis E, Bergerot D, Chambon Y, Hirose T, Caumont-Prim A, Tabard SB, Baron S, Frank M, et al. (2014) Plasma soluble (pro)renin receptor is independent of plasma renin, prorenin, and aldosterone concentrations but is affected by ethnicity. *Hypertension* **63**:297–302.

Nguyen G, Delarue F, Burcklé C, Bouzhir L, Giller T, and Sraer JD (2002) Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* **109**:1417–1427.

Nguyen G and Muller DN (2010) The biology of the (pro)renin receptor. *J Am Soc Nephrol* **21**:18–23.

Nishijima T, Ohba K, Baba S, Kizawa T, Hosokawa K, Endo F, Yamashiro Y, Suwabe A, Sasaki A, Takahashi K, et al. (2018) Decrease of plasma soluble (pro)renin receptor by bariatric surgery in patients with obstructive sleep apnea and morbid obesity. *Metab Syndr Relat Disord* **16**:174–182.

Nishijima T, Tajima K, Takahashi K, and Sakurai S (2014). Elevated plasma levels of soluble (pro)renin receptor in patients with obstructive sleep apnea syndrome: association with polysomnographic parameters. *Peptides* **56**:14–21.

Nishijima T, Tajima K, Yamashiro Y, Hosokawa K, Suwabe A, Takahashi K, and Sakurai S (2016) Elevated plasma levels of soluble (pro)renin receptor in patients with obstructive sleep apnea syndrome in parallel with the disease severity. *Tohoku J Exp Med* **238**:325–338.

Obradovic D, Loncar G, Radenovic S, Tahirovic E, Heidecke H, Schulze-Forster K, Muller D, Busjahn A, Buttner P, Veskovic J, et al. (2020). Soluble (pro)renin receptor in elderly chronic heart failure patients. *Front Biosci (Landmark Ed)* **25**:1839–1853.

Ohashi N, Isobe S, Ishigaki S, Suzuki T, Iwakura T, Ono M, Fujikura T, Tsuji T, Otsuka A, Ishii Y, et al. (2016) Plasma soluble (pro)renin receptor reflects renal damage. *PLoS One* **11**:e0156165.

Ohba K, Endo M, Sato S, Kashio-Yokota Y, Hirose T, and Takahashi K (2020) (Pro)renin receptor/ATP6AP2 is required for autophagy and regulates proliferation in lung adenocarcinoma cells. *Genes Cells* **25**:782–795 10.1111/gtc.12812.

Ohba K, Suzuki T, Nishiyama H, Kaneko K, Hirose T, Totsune K, Sasano H, and Takahashi K (2014) Expression of (pro)renin receptor in breast cancers and its effect on cancercell proliferation. *Biomed Res* **35**:117–126.

Oshima Y, Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Bokuda K, Narita T, Kurosawa H, Sun-Wada GH, Wada Y, et al. (2011) Prorenin receptor is essential for normal podocyte structure and function. *J Am Soc Nephrol* **22**:2203–2212.

Peng H, Wu ZB, Kong SS, and Li L (2013) Role of (pro)rennin receptor in cardiomyocytes of heart failure rat model. *J Huazhong Univ Sci Technolog Med Sci* **33**:640–643.

Peng K, Lu X, Wang F, Nau A, Chen R, Zhou SF, and Yang T (2017) Collecting duct (pro)renin receptor targets ENaC to mediate angiotensin II-induced hypertension. *Am J Physiol Renal Physiol* **312**:F245–F253.

Prieto MC, Reverte V, Mamenko M, Kuczeriszka M, Veiras LC, Rosales CB, McLellan M, Gentile O, Jensen VB, Ichihara A, et al. (2017) Collecting duct prorenin receptor knockout reduces renal function, increases sodium excretion, and mitigates renal responses in ANG II-induced hypertensive mice. *Am J Physiol Renal Physiol* **313**:F1243–F1253.

Quadri S and Siragy HM (2016) (Pro)renin receptor contributes to regulation of renal epithelial sodium channel. *J Hypertens* **34**:486–494, discussion 494.

Quadri SS, Culver S, Ramkumar N, Kohan DE, and Siragy HM (2018) (Pro)renin receptor mediates obesity-induced antinatriuresis and elevated blood pressure via upregulation of the renal epithelial sodium channel. *PLoS One* **13**:e0202419.

Rahman A, Matsuyama M, Ebihara A, Shibayama Y, Hasan AU, Nakagami H, Suzuki F, Sun J, Kobayashi T, Hayashi H, et al. (2020) Antiproliferative effects of monoclonal antibodies against (pro)renin receptor in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* **19**:1844–1855.

Ramkumar N, Stuart D, Calquin M, Quadri S, Wang S, Van Hoek AN, Siragy HM, Ichihara A, and Kohan DE (2015) Nephron-specific deletion of the prorenin receptor causes a urine concentration defect. *Am J Physiol Renal Physiol* **309**:F48–F56.

Ramkumar N, Stuart D, Mironova E, Abraham N, Gao Y, Wang S, Lakshmipathi J, Stockand JD, and Kohan DE (2018) Collecting duct principal, but not intercalated, cell prorenin receptor regulates renal sodium and water excretion. *Am J Physiol Renal Physiol* **315**:F607–F617.

Ramkumar N, Stuart D, Mironova E, Bugay V, Wang S, Abraham N, Ichihara A, Stockand JD, and Kohan DE (2016) Renal tubular epithelial cell prorenin receptor regulates blood pressure and sodium transport. *Am J Physiol Renal Physiol* **311**:F186–F194.

Ramkumar N, Stuart D, Peterson CS, Hu C, Wheatley W, Cho JM, Symons JD, and Kohan DE (2021) Loss of soluble (pro)renin receptor attenuates angiotensin-II induced hypertension and renal injury. *Circ Res* 10.1161/CIRCRESAHA.1120.317532 [published ahead of print].

Rao R, Zhang MZ, Zhao M, Cai H, Harris RC, Breyer MD, and Hao CM (2005) Lithium treatment inhibits renal GSK-3 activity and promotes cyclooxygenase 2-dependent polyuria. *Am J Physiol Renal Physiol* **288**:F642–F649.

Riediger F, Quack I, Qadri F, Hartleben B, Park JK, Potthoff SA, Sohn D, Sihn G, Rousselle A, Fokuhl V, et al. (2011) Prorenin receptor is essential for podocyte autophagy and survival. *J Am Soc Nephrol* **22**:2193–2202.

Rose-John S, Scheller J, Elson G, and Jones SA (2006) Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol* **80**:227–236.

Shamansurova Z, Tan P, Ahmed B, Pepin E, Seda O, and Lavoie JL (2016) Adipose tissue (P)RR regulates insulin sensitivity, fat mass and body weight. *Mol Metab* **5**:959–969.

Shibayama Y, Fujimori T, Nguyen G, Hirose T, Totsune K, Ichihara A, Kitada K, Nakano D, Kobori H, Kohno M, Masaki T, Suzuki Y, Yachida S, and Nishiyama A. (2015). (Pro)renin receptor is crucial for Wnt/beta-catenin-dependent genesis of pancreatic ductal adenocarcinoma. *Sci Rep* **5**:8854.

Suda C, Yatabe J, Yatabe M, Yarita M, and Ichihara A (2020) Soluble (pro)renin receptor increased by hypoxia maintains oxidative metabolism in trophoblasts. *J Mol Endocrinol* **64**:145–154.
Sugulle M, Heidecke H, Maschke U, Herse F, Danser AHJ, Mueller DN, Staff AC, and Dechend R (2017) Soluble (pro)renin receptor in preeclampsia and diabetic pregnancies. *J Am Soc Hypertens* **11**:644–652.
Takabatake Y, Kimura T, Takahashi A, and Isaka Y (2014) Autophagy and the kidney: health and disease. *Nephrol Dial Transplant* **29**:1639–1647.
Takahashi K, Ohba K, Tajima K, Nishijima T, and Sakurai S (2017) Soluble (pro)renin receptor and obstructive sleep apnea syndrome: oxidative stress in brain? *Int J Mol Sci* **18**:1313.
Tamada S, Mitsui T, Ohira A, Tani K, Maki J, Eguchi T, Eto E, Hayata K, and Masuyama H (2019) Relationship between intracellular signaling of the (pro)renin receptor and the pathogenesis of preeclampsia. *Acta Med Okayama* **73**:433–440.
Tamura Y, Mori N, Xu B, Nakamura T, Yamakoshi S, Hirose T, Ito O, Totsune K, Takahashi K, and Kohzuki M (2016) Water deprivation increases (pro)renin receptor levels in the kidney and decreases plasma concentrations of soluble (pro)renin receptor. *Tohoku J Exp Med* **239**:185–192.
Tan P, Blais C, Nguyen TM, Schiller PW, Gutkowska J, and Lavoie JL (2016) Prorenin/renin receptor blockade promotes a healthy fat distribution in obese mice. *Obesity (Silver Spring)* **24**:1946–1954.
Tan P, Shamansurova Z, Bisotto S, Michel C, Gauthier MS, Rabasa-Lhoret R, Nguyen TM, Schiller PW, Gutkowska J, and Lavoie JL (2014) Impact of the prorenin/renin receptor on the development of obesity and associated cardiometabolic risk factors. *Obesity (Silver Spring)* **22**:2201–2209.
Terada T, Urushihara M, Saijo T, Nakagawa R, and Kagami S (2017) (Pro)renin and (pro)renin receptor expression during kidney development in neonates. *Eur J Pediatr* **176**:183–189.
Thomason J, Reyes M, Allen SR, Jones RO, Beeram MR, Kuehl TJ, Suzuki F, and Uddin MN (2015) Elevation of (pro)renin and (pro)renin receptor in preeclampsia. *Am J Hypertens* **28**:1277–1284.
Tracey D, Klareskog L, Sasso EH, Salfeld JG, and Tak PP (2008) Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* **117**:244–279.
Trepiccione F, Gerber SD, Grahammer F, López-Cayuqueo KI, Baudrie V, Păunescu TG, Capen DE, Picard N, Alexander RT, Huber TB, et al. (2016) Renal Atp6ap2/(pro)renin receptor is required for normal vacuolar H+-ATPase function but not for the renin-angiotensin system. *J Am Soc Nephrol* **27**:3320–3330.
Visniauskas B, Arita DY, Rosales CB, Feroz MA, Luffman C, Accavitti MJ, Dawkins G, Hong J, Curnow AC, Thethi TK, et al. (2021) Sex differences in soluble prorenin receptor in patients with type 2 diabetes. *Biol Sex Differ* **12**:33.
Wang F, Lu X, Liu M, Feng Y, Zhou SF, and Yang T (2015). Renal medullary (pro)renin receptor contributes to angiotensin II-induced hypertension in rats via activation of the local renin-angiotensin system. *BMC Med* **13**:278.
Wang F, Lu X, Peng K, Fang H, Zhou L, Su J, Nau A, Yang KT, Ichihara A, Lu A, et al. (2016) Antidiuretic action of collecting duct (pro)renin receptor downstream of vasopressin and PGE2 receptor EP4. *J Am Soc Nephrol* **27**:3022–3034.
Wang F, Luo R, Peng K, Liu X, Xu C, Lu X, Soodvilai S, and Yang T (2020) Soluble (pro)renin receptor regulation of ENaC involved in aldosterone signaling in cultured collecting duct cells. *Am J Physiol Renal Physiol* **318**:F817–F825.
Wang F, Luo R, Zou CJ, Xie S, Peng K, Zhao L, Yang KT, Xu C, and Yang T (2019a) Soluble (pro)renin receptor treats metabolic syndrome in mice with diet-induced obesity via interaction with PPARγ. *JCI Insight* **5**:e128061.
Wang F, Xu C, Luo R, Peng K, Ramkumar N, Xie S, Lu X, Zhao L, Zuo CJ, Kohan DE, et al. (2019b) Site-1 protease-derived soluble (pro)renin receptor targets vasopressin receptor 2 to enhance urine concentrating capability. *JCI Insight* **4**:e124174.
Wang J, Shibayama Y, Zhang A, Ohsaki H, Asano E, Suzuki Y, Kushida Y, Kobara H, Masaki T, Wang Z, et al. (2019) (Pro)renin receptor promotes colorectal cancer through the Wnt/beta-catenin signalling pathway despite constitutive pathway component mutations. *Br J Cancer* **120**:229–237.
Watanabe D, Morimoto S, Morishima N, Kato Y, Nagashima Y, Shibata N, and Ichihara A (2020). Adrenal (pro)renin receptor expression and serum soluble (pro)renin receptor concentration in primary aldosteronism. *Int J Endocrinol* **2020**:9640103.
Watanabe N, Bokuda K, Fujiwara T, Suzuki T, Mito A, Morimoto S, Jwa SC, Egawa M, Arai Y, Suzuki F, et al. (2012) Soluble (pro)renin receptor and blood pressure during pregnancy: a prospective cohort study. *Hypertension* **60**:1250–1256.
Watanabe N, Morimoto S, Fujiwara T, Suzuki T, Taniguchi K, Ando T, Kimura T, Sago H, and Ichihara A (2013a) Association between soluble (Pro)renin receptor concentration in cord blood and small for gestational age birth: a cross-sectional study. *PLoS One* **8**:e60036.
Watanabe N, Morimoto S, Fujiwara T, Suzuki T, Taniguchi K, Mori F, Ando T, Watanabe D, Kimura T, Sago H, et al. (2013b) Prediction of gestational diabetes mellitus by soluble (pro)renin receptor during the first trimester. *J Clin Endocrinol Metab* **98**:2528–2535.
Wendling O, Champy MF, Jaubert S, Pavlovic G, Dubos A, Lindner L, Jacobs H, Mark M, Combe R, Da Cruz IG, et al. (2017) Atp6ap2 ablation in adult mice impairs viability through multiple organ deficiencies. *Sci Rep* **7**:9618.
Wu CH, Mohammadmoradi S, Thompson J, Su W, Gong M, Nguyen G, and Yiannikouris F (2016) Adipocyte (pro)renin-receptor deficiency induces lipodystrophy, liver steatosis and increases blood pressure in male mice. *Hypertension* **68**:213–219.
Wu JP, Chen AM, Luo XY, and Liu JJ (2019) [Correlation between(Pro) renin receptor levels and gender and disease severity in patients with obstructive sleep apnea syndrome]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* **33**:619–624.
Xie S, Su J, Lu A, Lai Y, Mo S, Pu M, and Yang T (2020) Soluble (pro)renin receptor promotes the fibrotic response in renal proximal tubule epithelial cells in vitro via the Akt/β-catenin/Snail signaling pathway. *Am J Physiol Renal Physiol* **319**:F941–F953.
Xu C, Fang H, Zhou L, Lu A, and Yang T (2016) High potassium promotes mutual interaction between (pro)renin receptor and the local renin-angiotensin-aldosterone system in rat inner medullary collecting duct cells. *Am J Physiol Cell Physiol* **311**:C686–C695.
Xu C, Lu A, Lu X, Zhang L, Fang H, Zhou L, and Yang T (2017a) Activation of renal (pro)renin receptor contributes to high fructose-induced salt sensitivity. *Hypertension* **69**:339–348.
Xu C, Lu A, Wang H, Fang H, Zhou L, Sun P, and Yang T (2017b) (Pro)renin receptor regulates potassium homeostasis through a local mechanism. *Am J Physiol Renal Physiol* **313**:F641–F656.
Xu C, Wang F, Chen Y, Xie S, Sng D, Reversade B, and Yang T (2020) ELABELA antagonizes intrarenal renin-angiotensin system to lower blood pressure and protects against renal injury. *Am J Physiol Renal Physiol* **318**:F1122–F1135.
Yang KT, Wang F, Lu X, Peng K, Yang T, and David Symons J (2017) The soluble (Pro) renin receptor does not influence lithium-induced diabetes insipidus but does provoke beiging of white adipose tissue in mice. *Physiol Rep* **5**:e13410.
Yang T and Xu C (2017) Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. *J Am Soc Nephrol* **28**:1040–1049.
Ye Q, Wu Y, Gao Y, Li Z, Li W, and Zhang C (2016) The 'selfish brain' is regulated by aquaporins and autophagy under nutrient deprivation. *Mol Med Rep* **13**:3842–3848.
Yoshikawa A, Aizaki Y, Kusano K, Kishi F, Susumu T, Iida S, Ishiura S, Nishimura S, Shichiri M, and Senbonmatsu T (2011) The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space. *Hypertens Res* **34**:599–605.
Zhao K, Wang M, and Wu A (2020). ATP6AP2 is overexpressed in breast cancer and promotes breast cancer progression. *Cancer Manag Res* **12**:10449–10459.

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