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Mini Review

Return of the (Pro)renin Receptor: A Vacuolar H^+-ATPase and Just not a Receptor of (Pro)renin/Renin?

Chuanming Xu*

Translational Medicine Centre, Jiangxi University of Chinese Medicine, Nanchang, Jiangxi, China

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Abstract

(Pro)renin receptor (PRR), a tissue-specific gene, exhibits hypertensive actions and plays an essential role in the pathogenesis of kidney injuries through the renin-angiotensin system (RAS) -dependent and -independent mechanisms. Saigo *et al*. recently demonstrated that PRR may be irrelevant to RAS but functions as a vacuolar H^+-ATPase (V-ATPase) in renal tubules using transgenic mice overexpressing the tubular epithelial PRR gene. This may challenge the initial concept that PRR works as a receptor of (pro)renin/renin and the idea that PRR is directly involved in intracellular signaling. This mini-review comments on the report by Saigo *et al*. and provides several opinions on the roles of PRR. The investigator considers that PRR functions as a V-ATPase that controls the V-ATPase activity, whereas whether the link between PRR and RAS truly occurs in vivo still awaits future investigation.

Introduction

The renin-angiotensin system (RAS) plays an important role in the maintenance and regulation of extracellular volume homeostasis and blood pressure (BP). Inappropriate activation of the RAS not only leads to various cardiovascular abnormalities including vasoconstriction, vascular remodeling, and the elevation of BP, but also contributes to the progress of kidney diseases.[1] Apart from the well-established systemic RAS, increasing evidence suggests the existence of a local RAS in the local organs/tissues, such as the intrarenal RAS, as evidenced by the observation that expression/production of multiple RAS components, has been found in the kidney.[2] Impairments of the intrarenal RAS have been known as an essential mechanism for the pathogenesis of hypertension and renal disease.[2] Furthermore, abundant evidence has established the dissociation and differential regulation of the intrarenal and systemic RAS. For example, in response to chronic angiotensin II (AngII) infusion, plasma and renal cortical renin are significantly suppressed, whereas urinary and renal medullary renin is dramatically upregulated,[3] strongly supporting the notion that the intrarenal and systemic RAS are independent of each other.

(Pro)renin receptor (PRR), also known as ATPase, H^+-transporting, and lysosomal accessory protein 2 (ATP6AP2) or ATPase, H^+-transporting, and lysosomal-interacting protein 2 (ATP6IP2), is a single transmembrane protein encoded by ATP6AP2 or ATP6IP2 gene on the short arm of the X chromosome. ATP6AP2 was initially discovered as an accessory protein of membrane-bound vacuolar H^+-ATPase (V-ATPase) in 1998.[4] Later, in 2002, PRR was identified as a specific receptor for (pro)renin and renin that contributes to AngII generation.[5]

PRR functions as a tissue-specific gene

Current evidence indicates that PRR is ubiquitously expressed but functions as a tissue-specific gene that controls renin activity and intracellular signaling in the local tissues. Firstly, mice with tissue-specific PRR deletion exhibit antihypertensive actions. For example, both collecting duct-[6,7] and renal tubule-[8] specific deletion of PRR attenuated AngII-induced elevation of BP with reduced uri-

Keywords: (Pro)renin receptor; Vacuolar H^+-ATPase; (Pro)renin/renin; Renin-angiotensin system; Hypertension; Kidney injury.

Abbreviations: AngII, angiotensin II; AQP_2, aquaporin 2; ARB, angiotensin II blocker; ARen2-TG, alternative renin transgenic mice; ATP6AP2, ATPase, H^+-transporting, and lysosomal accessory protein 2; ATP6IP2, ATPase, H^+-transporting, and lysosomal-interacting protein 2; AVP, arginine vasopressin; BP, blood pressure; DRI, direct renin inhibitor; DT-TG, double transgenic; ENaC, epithelial sodium channel; PRR, (pro)renin receptor; PRR-TG, tubular epithelial PRR gene; RAS, renin-angiotensin system; sPRR, soluble PRR; TG, transgenic; V-ATPase, vacuolar H^+-ATPase; V_2R, vasopressin receptor 2.

***Correspondence to:** Chuanming Xu, Translational Medicine Centre, Jiangxi University of Chinese Medicine, Nanchang 330002, Jiangxi, China. ORCID: https://orcid.org/0000-0001-7082-2833. Tel: +86-791-87119895, Fax: +86-791-87119895, E-mail: xuchuanming2008@163.com

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nary renin and blunted epithelial sodium channel (ENaC) and neuron-specific PRR deletion abolished intracerebroventricular (pro) renin infusion-induced elevation of BP in mice.[9] Secondly, tissue-specific, but not whole-body, PRR activation contributes to hypertension. In this case, whole-body overexpression of murine PRR in mice did not result in hypertension or cardiac and renal fibrosis,[10] while mice with smooth muscle tissue-specific overexpression of human PRR in rats were hypertensive with an elevation of plasma aldosterone.[11] Although neuron-specific overexpression of human PRR in rats did not cause hypertension, it enhanced the hypertensive response to intracerebroventricular (pro)renin infusion.[12]

However, the above notion was challenged by the studies from Trepiccione *et al*. that renal tubule-specific PRR deletion did not affect the increase of BP in mice with chronic AngII infusion accompanied by no changes in intrarenal AngII levels.[13] They concluded that PRR is required for the V-ATPase but not the RAS. Although discrepancies in the above findings might be due to differences in the AngII dosage used in these models, it is still controversial whether the (pro)renin/renin-PRR interaction and the link between PRR and local RAS truly occur in vivo, and needs to be further studied.

Emerging roles of PRR as a V-ATPase

Recently, Saigo *et al*.[14] investigated the roles of PRR in BP and tubular electrolyte homeostasis using transgenic mice overexpressing the tubular epithelial PRR gene (PRR-TG). They generated these PRR-TG mice by harboring the PRR gene with the Ksp-Cadherin promoter. PRR-TG mice were maintained and analyzed in individual metabolic cages and were administered angiotensin II blocker (ARB), direct renin inhibitor (DRI), and bafilomycin, followed by BP measurement using the tail-cuff method. They reported that (1) PRR-TG mice were hypertensive with no significant changes in plasma renin activity and the increased BP in these mice can be concurrently blocked by ARB and DRI but not bafilomycin; (2) PRR-TG mice had alkalized urine, which was restored by bafilomycin treatment; (3) PRR-TG mice had lower water intake but higher urine volume with lower osmolality and Na^+ excretion.[14] Thus, they suggest that PRR functions as a V-ATPase in renal tubules independently of intrarenal RAS but not a receptor of (pro)renin/renin,[14] consistent with previous theories stated by Trepiccione *et al*.[13] and challenge the initial concept given by Nguyen *et al*.[5] This has the potential to be a breakthrough advance in the PRR field but requires further investigation.

It is well-known that PRR works as an accessory subunit of the V-ATPase in the kidney, controlling the normal V-ATPase activity and subsequent acid-base homeostasis and urine acidification, independently of RAS.[15] Renal tubule-specific deletion of PRR caused distal renal tubular acidosis due to a defect in H^+ excretion, as a result of V-ATPase dysfunction and subsequent defects in autophagy.[13] In contrast, renal tubule-specific overexpression of PRR resulted in an alkalized urine, which was restored by bafilomycin treatment,[14] indicating the activation of V-ATPase in the renal tubules of these mice. These two reports confirm each other and jointly provide evidence for the importance of PRR on V-ATPase activity that PRR may function as a V-ATPase in renal tubules. However, whether or not the enhanced V-ATPase activity correlates to the extensive tubular degeneration in the cortico-medullary junction in DT-TG mice is unclear.

Indeed, accumulating evidence supports the notion that PRR may be a V-ATPase. Firstly, cryo-electron microscopy analysis demonstrated that part of the PRR belongs to the Vo domain of V-ATPase.[16,17] PRR directly binds to the V-ATPase subunit Ac45 (also known as ATP6AP1, ATPase H^+ transporting accessory protein 1),[16,17] which requires the extracellular domain and the transmembrane domain of PRR.[18,19] Secondly, several clinical studies have shown that PRR mutation caused X-linked Parkinsonism as a result of V-ATPase dysfunction and autophagy deficits.[20–22] Lastly, due to the dysfunctional V-ATPase and impaired autophagy, mice with embryonic ablation of PRR exhibited embryo lethality, and PRR ablation in adult mice caused multiple organ deficiencies that lead to rapid lethality,[23] mice with podocyte- or renal tubule-specific PRR deletion displayed kidney failure,[13,24] and cardiomyocyte-specific PRR deletion resulted in heart failure and premature death.[25] Thus, these results consistently indicate the functional importance of PRR in controlling normal V-ATPase activity.

PRR may act in a renin-dependent and -independent manner

Saigo *et al*. generated double transgenic (DT-TG) mice by mating PRR-TG mice with alternative renin transgenic mice (ARen2-TG) expressing intracellular renin.[14] In this case, they found that (1) DT-TG mice, but not PRR-TG mice or ARen2-TG mice, had a large proportion of offspring die shortly after birth and (2) DT-TG, but not PRR-TG or ARen2-TG, resulted in lethal kidney dysfunction, as evidenced by the observations that kidney sections from DT-TG mice, but not PRR-TG mice or ARen2-TG mice, exhibited extensive tubular degeneration in the cortico-medullary junction.[14] Thus, they concluded that intracellular renin other than conventional (pro)renin/renin may be involved in PRR signaling.[14] This may challenge the idea that PRR is directly involved in intracellular signaling.

However, the cellular mechanism of how DT-TG causes lethal renal tubular damage is still unclear. It is also unknown whether DT-TG activates intracellular RAS in tubular epithelial cells in mice. PRR has been reported to interact with wnt/β-catenin signaling that contributes to the activation of intrarenal RAS thereby regulating kidney injury and BP.[26,27] Inappropriate activations of the wnt/β-catenin signaling can cause kidney injury and hypertension via intrarenal RAS activation.[28,29] Similarly, DT-TG results in lethal renal tubular damage[14] possible due to the activation of intracellular wnt/β-catenin/RAS signaling in tubular epithelial cells. Therefore, inhibitors of the wnt/β-catenin signaling are warranted to address the involvement of this pathway in DT-TG mice. Furthermore, severe hypertension may be an indirect cause of renal injury. Questions regarding the BP in these DT-TG mice and whether DT-TG further increases or maintains the BP compared to PRR-TG alone also await future clarification.

In addition, it is well-known that PRR not only participates in megalin-mediated endocytosis of renin and (pro)renin,[30–32] but also controls the synthesis and release of renin and (pro)renin.[26,33,34] This raises the question of how the intracellular (in the cytoplasm) and extracellular (in the tubular fluid) renin and (pro)renin in PRR-TG mice compares to that of wide-type mice, and whether DT-TG affects the expression and endocytosis of the conventional (pro)renin and renin. To this effect, the hypothesis on the possible involvement of the intracellular renin other than the conventional (pro)renin/renin in PRR signaling should be further verified.

Renal PRR exhibits hypertensive action possible in an intrarenal RAS-dependent and -independent mechanism

Saigo *et al*. reported that PRR-TG significantly increased BP in

mice.[14] This raises the question of what the cellular mechanism of BP elevation in the presence of tubular epithelial-specific PRR overexpression is. There are multiple well-known mediators downstream of PRR, including intrarenal RAS, NCC (Na^+-Cl^- cotransporter), ENaC, the wnt/β-catenin signaling, the COX-2 (cyclooxygenase-2)/PGE_2 (prostaglandin E_2) signaling, and the NOX_4 (NADPH oxidase 4)/H_2O_2 signaling.[15,35] However, it is unclear which of these mediators is responsible for the hypertensive action of PRR-TG. Saigo *et al*. showed that there are no significant differences between wide-type and PRR-TG mice in plasma renin activity and PRR-TG mice exhibited lower Na^+ excretion.[14] The decreased urinary Na^+ excretion may contribute to the elevation of BP in PRR-TG mice.[14] However, whether the intrarenal renin, including the expression of (pro)renin/renin in the collecting duct and renin activity in the tubular fluid, contributes to the elevation of BP in PRR-TG mice, remains unclear. To better address the involvement of intrarenal RAS, the classical AngII infusion model is recommended employing these PRR-TG mice.

Saigo *et al*. also showed that both olmesartan (results in positive feedback enhanced (pro)renin/renin activity) and the direct renin inhibitor aliskiren (results in a decrease of (pro)renin/renin activity) abolished the increase of BP in PRR-TG mice.[14] Of note, PRR-TG may elevate BP via soluble PRR (sPRR) generation[34–37] by binding to low-density lipoprotein receptor-related protein 6 and frizzled 8 to activate wnt/β-catenin signaling[18,38] or type 1 AngII receptor (AT1R) to directly activate AT1R signaling.[39] Thus, the results from PRR-TG mice may not be enough to negate previous views that PRR functions as a receptor of (pro)renin/renin and a regulator of RAS; PRR-TG in tubular epithelial elevated BP possible due to intrarenal RAS-dependent and -independent mechanisms. Similarly, several other signaling pathways such as the wnt/β-catenin signaling and the NOX_4/H_2O_2 signaling, activated by the sPRR in the cytoplasm or the tubular fluid, may contribute to the elevation of BP in PRR-TG mice. In particular, studies have demonstrated the differential regulation of sPRR on NCC and ENaCs that sPRR suppresses NCC in the distal convoluted tubule[40] but stimulates ENaCs in the collecting duct.[41] Thus, the status of sPRR in the tubular fluid within the kidney should be determined, although its generation is enhanced in principle in PRR-TG mice.

Regulation of renal PRR on urine concentrating capability

It has been reported that collecting duct-[42] and renal tubule-[43] specific deletion of PRR causes polyuria and polydipsia by impairing the arginine vasopressin (AVP)/vasopressin receptor 2 (V_2R)/aquaporin 2 (AQP_2) signaling, while sPRR enhanced urine concentrating capability by activating the AVP/V_2R/AQP_2 signaling[44] or the β-catenin/AQP_2 signaling.[38] Saigo *et al*.[14] showed that mice with PRR-TG in the tubular epithelium exhibited lower water intake and higher urine volume with lower osmolality. It is unusual that the mice exhibited the phenotype of fluid loss and were under dehydration but maintained normal body weight. It is also interesting that both renal tubule-specific deletion[43] and overexpression of PRR[14] caused similar polyuria with the exact opposite water intake. The polyuria phenotype in mice with renal tubule-specific PRR deletion may be due to the inhibition of the V_2R/AQP_2 signaling,[43,44] while the increased BP may contribute to the polyuria phenotype in PRR-TG mice. However, the detailed mechanism of how tubular epithelial-specific PRR overexpression causes the above contradictory phenomena, plasma osmolality and blood volume or hematocrit in these mice, whether PRR-TG in the tubular epithelium leads to the redistribution of body fluids in mice, and whether there is any effect of PRR-TG in the tubular epithelium on the AVP/V_2R/AQP_2 signaling, including the expression of V_2R and AQP_2 in the kidney and the AVP sensitivity are all unanswered questions which await future investigation.

Future directions

Based on the previous findings, researchers can consider PRR as a V-ATPase, while the association between PRR and RAS requires further experimental studies. In particular, the renin activity in the tubular fluid, (pro)renin/renin levels in the collecting duct, and the other intracellular signals such as sPRR-regulated wnt/β-catenin signaling, NOX_4/H_2O_2 signaling, and AT1R signaling should be determined in PRR-TG mice. The application of some pathological models, such as AngII-, aldosterone/salt-, and DOCA/salt-induced hypertension and kidney injury models, in PRR-TG mice, can preliminarily clarify the relationship between PRR and RAS, especially the intrarenal RAS.

Conclusions

Compelling evidence demonstrates a hypertensive role of renal PRR as well as its essential role in the pathogenesis of kidney injury. Although the renin-regulatory role of PRR may be still controversial, strong evidence supports the control of PRR on V-ATPase activity that PRR may be a V-ATPase. Along this line, renal tubule-specific overexpression of PRR activates V-ATPase, resulting in alkalized urine in mice. However, renal tubule-specific overexpression of PRR may cause the activation of intrarenal RAS and several intracellular signals such as wnt/β-catenin and NOX_4/H_2O_2 signaling in the kidney, resulting in a decrease in urinary Na^+ excretion and subsequently an elevation of BP, which may further contribute to the polyuria in mice (Fig. 1). This hypothesis awaits future investigation.

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Conflict of interest

Dr. Chuanming Xu has been an editorial board member of *Exploratory Research and Hypothesis* since February 2022. The author has no other conflicts of interest to note.

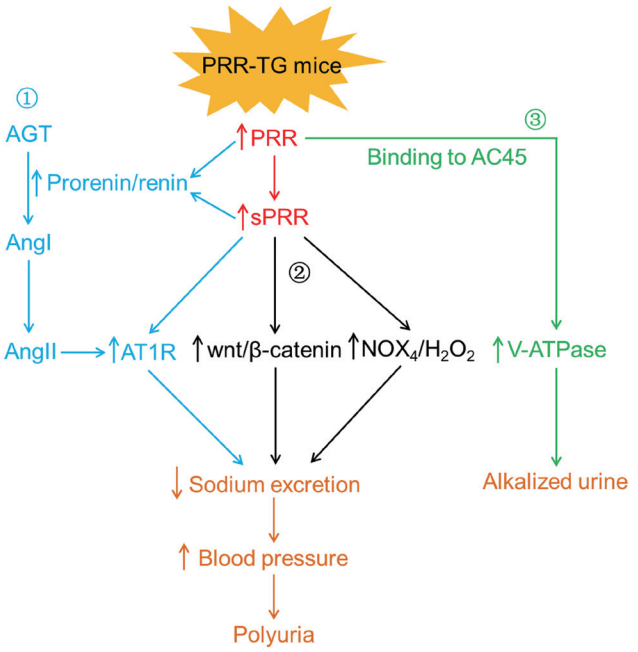

Fig. 1. The potential roles of (pro)renin receptor (PRR) in mice with renal tubule-specific overexpression of PRR (PRR-TG). In PRR-TG mice, renal PRR expression and soluble PRR (sPRR) generation are enhanced in principle. The increased PRR/sPRR may activate 1 the intrarenal renin-angiotensin system via stimulating (pro)renin/renin expression/activity in the collecting ducts or direct binding and activating type 1 AngII receptor (AT1R), and 2 several intracellular signals such as wnt/β-catenin and NOX_4/H_2O_2 signaling in the kidney, both may result in a decrease in urinary Na^+ excretion and subsequent an elevation of BP and further polyuria. 3 The enhanced PRR in the renal tubules may also activate vacuolar H^+-ATPase (V-ATPase) by binding Ac45 (also known as ATP6AP1, ATPase H^+ transporting accessory protein 1), resulting in alkalized urine.

Author contributions

CX was the sole author.

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