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The evolving complexity of the collecting duct renin–angiotensin system in hypertension

Minolfa C. Prieto[1,2,✉], **Alexis A. Gonzalez**[3], **Bruna Visniauskas**[1], **L. Gabriel Navar**[1,2]

[1]Department of Physiology, Tulane University School of Medicine, New Orleans, LA, USA.

[2]Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, LA, USA.

[3]Instituto de Química, Pontificia Universidad Católica de Valparaíso, Valparaiso, Chile.

Abstract

The intrarenal renin–angiotensin system is critical for the regulation of tubule sodium reabsorption, renal haemodynamics and blood pressure. The excretion of renin in urine can result from its increased filtration, the inhibition of renin reabsorption by megalin in the proximal tubule, or its secretion by the principal cells of the collecting duct. Modest increases in circulating or intrarenal angiotensin II (ANGII) stimulate the synthesis and secretion of angiotensinogen in the proximal tubule, which provides sufficient substrate for collecting duct-derived renin to form angiotensin I (ANGI). In models of ANGII-dependent hypertension, ANGII suppresses plasma renin, suggesting that urinary renin is not likely to be the result of increased filtered load. In the collecting duct, ANGII stimulates the synthesis and secretion of prorenin and renin through the activation of ANGII type 1 receptor (AT1R) expressed primarily by principal cells. The stimulation of collecting duct-derived renin is enhanced by paracrine factors including vasopressin, prostaglandin E2 and bradykinin. Furthermore, binding of prorenin and renin to the prorenin receptor in the collecting duct evokes a number of responses, including the non-proteolytic enzymatic activation of prorenin to produce ANGI from proximal tubule-derived angiotensinogen, which is then converted into ANGII by luminal angiotensin-converting enzyme; stimulation of the epithelial sodium channel (ENaC) in principal cells; and activation of intracellular pathways linked to the upregulation of cyclooxygenase 2 and profibrotic genes. These findings suggest that dysregulation of the renin–angiotensin system in the collecting duct contributes to the development of hypertension by enhancing sodium reabsorption and the progression of kidney injury.

The renin–angiotensin system (RAS) is essential for the regulation of blood pressure and extracellular fluid volume and composition[1]. However, when inappropriately activated

✉ mprieto@tulane.edu .

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it contributes to the development and progression of hypertension, inflammation and tissue injury[2]. The systemic RAS is primarily controlled by the production of renin by juxtaglomerular cells in the kidney, which acts on angiotensinogen (AGT) produced by the liver to initiate a tightly regulated enzymatic cascade, resulting in the production of angiotensin II (ANGII)[3]. However, in the kidneys of human, rat and mouse, renin is also synthesized by mesangial cells, arteriolar smooth muscle cells, pericytes and tubuloepithelial cells[4,5]. In addition, the proenzyme prorenin is produced by the principal cells of the connecting tubule and collecting duct of the adult human, rat and mouse kidney[6,7]. In this Review, we refer to prorenin produced in the collecting duct as 'collecting duct-derived renin'.

The mechanisms that regulate the production of collecting duct-derived renin differ from those that control juxtaglomerular-derived renin. An increasing body of evidence indicates that the production of collecting duct-derived renin is regulated by hormones that target the distal nephron segments[8–11] but is not influenced by blood pressure[12]. Rather, studies in animal models suggest that collecting duct-derived renin might enhance the ability of the kidneys to conserve sodium and is upregulated in pathophysiological models of ANGII-induced hypertension, 2K1C Goldblatt hypertension and type 1 diabetes mellitus[13–16]. The expression of the prorenin receptor (PRR) by cells of the collecting duct enhances the formation of intratubular ANGII by activating prorenin and increasing local renin catalytic activity[17], leading to the activation of signals that mediate kidney fibrosis, at least partially via mechanisms that are independent of ANGII[18]. In this Review, we discuss the key mechanisms that regulate the production of collecting duct-derived renin and describe the local interactions between renin and the PRR that underlie the contributions of the distal nephron RAS to the pathogenesis of hypertension and kidney injury. The novel roles of renin and PRR beyond their hypertensive effects and fibrosis-inducing mechanisms, such as in kidney development, urine concentration and inflammation, are also considered.

2K1C Goldblatt hypertension

The two-kidney, one-clip (2K1C) Goldblatt hypertensive rat is an experimental model for studying renovascular hypertension, whereby one renal artery is clipped to decrease renal blood flow, and the other kidney remains unaffected.

Renin in the kidney

Juxtaglomerular-derived renin

Renin synthesis by juxtaglomerular cells is regulated by the actions of Gs protein-coupled receptors, including prostaglandin E2 (PGE_2) receptor EP4 and β1 adrenergic receptor, resulting in the activation of protein kinase A (PKA), phosphorylation of cAMP response element binding protein, and the induction of cAMP response element (CRE) on the renin gene[19] (FIG. 1). Renin synthesis and secretion by juxtaglomerular cells involves the processing of the non-active proenzyme, prorenin, to active renin by enzymes such as cathepsin G, kallikrein and tonin[19]. Although both prorenin and renin are secreted by juxtaglomerular cells, only the active serine protease renin can cleave AGT to form

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biologically inactive ANGI[19]. Activation of ANGI requires its conversion to the octapeptide, ANGII, by the action of angiotensin-converting enzyme (ACE), which is abundantly produced by the endothelial cells of many organs, including the endothelial cells of the lungs[19]. Increased circulating levels of ANGII inhibit further renin synthesis by juxtaglomerular cells through activation of ANGII type 1 receptors (AT1Rs) via protein kinase C (PKC) and cytosolic Ca^{2+}, which decrease cAMP synthesis and promote its degradation. By contrast, the effects of ANGII on AT1R in the collecting duct are the opposite, acting to stimulate renin, as described in detail later[20,21]. The activation of AT1R by ANGII also induces aldosterone release from adrenal glands[22]. Fine tuning of sodium reabsorption and homeostasis then occurs in the distal nephron via activation of the aldosterone-dependent mineralocorticoid receptor (MR), which stimulates the expression of the sodium chloride symporter (NCC) and the epithelial sodium channel (ENaC), thereby promoting sodium reabsorption by the kidneys[23] (FIG. 1). ANGII also acts on ANGII type 2 receptors (AT2Rs), which are abundantly expressed during kidney development but are markedly reduced in the adult kidney[24] and exert diuretic and anti-proliferative effects[25].

Collecting duct-derived renin

In contrast to the regulation of juxtaglomerular-derived renin, which has been extensively studied, the mechanisms regulating collecting duct-derived renin are less well understood. All components of the RAS are expressed in the kidney[26–29]. Specifically, in the collecting duct, AT1R are widely expressed on the luminal as well as the basolateral sides of principal and intercalated cells[30], and may have a role in canonical regulation of the *REN* gene in the principal cells (FIG. 2). In contrast to the inhibitory effects of ANGII on juxtaglomerular-derived renin, in vitro studies of collecting duct cells have shown that ANGII directly increases expression levels of *REN*, protein levels of prorenin and renin, as well as renin activity in cell culture supernatant[9,31,32]. Furthermore, in vivo studies have demonstrated that ANGII upregulates renin protein levels in collecting duct cells independent of changes in blood pressure[12], distal sodium reabsorption or mineralocorticoid receptor activation[9]. In Goldblatt rats with 2K1C ANGII-dependent hypertension, perfusion pressure is elevated only in the non-clipped kidney, whereas it is low or normal in the clipped kidney[33]. Despite the differences in kidney perfusion pressure, upregulation of collecting duct-derived renin occurs in both the clipped and the non-clipped kidneys[12]. Moreover, administration of the ENaC inhibitor amiloride to Sprague-Dawley rats chronically infused with ANGII attenuated the increase in blood pressure without affecting the ANGII-associated induction of collecting duct-derived *Ren* mRNA levels in the renal inner medulla, which is devoid of juxtaglomerular–renin component[9]. In addition to the effects of ANGII on aldosterone release and mineralocorticoid receptor-mediated Na^+ reabsorption[22], activation of AT1R in the distal nephron also increases Na^+ reabsorption via the direct stimulation of ENaC[22,34–37] (FIGS 1,2). Although AT1R activation increases the open probability of ENaC independent of aldosterone[34,36], the finding that ENaC inhibition with amiloride does not alter the synthesis of ANGII-induced renin synthesis by collecting duct cells, despite attenuated increases in blood pressure, supports the hypothesis that the AT1R stimulates the synthesis of collecting duct-derived renin independent of aldosterone[9]. This finding is relevant because renin protein expression in the connecting tubule and collecting duct is not influenced by a high salt diet[38]. By contrast, a low-salt diet for 7 days increases *Ren* mRNA

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and renin protein levels in the renal inner medulla in parallel with increases in plasma and intrarenal ANGII levels[39]. Thus, it seems that AT1R in the collecting duct contributes to the regulation of sodium homeostasis under conditions of low salt intake and chronic ANGII infusions[39]. The exact mechanisms responsible for the regulation of collecting duct-derived renin synthesis remain unclear and seem to involve complex intracellular signalling pathways other than ENaC and/or mineralocorticoid receptor activation.

Regulation by angiotensin II

As described above, the effects of ANGII on renin synthesis in the collecting duct are contrary to the well-known inhibitory effect of ANGII–AT1R signalling on renin synthesis in juxtaglomerular cells[19]. Whereas AT1R activation inhibits renin expression via PKC and Ca^{2+} in juxtaglomerular cells[21], in the collecting duct, the same mechanisms act to promote renin expression[31]. In collecting duct cells, the activation of AT1R by ANGII stimulates PKC and enhances cAMP–PKA–CREB signalling[10,40]. In freshly isolated rat inner medullary collecting duct (IMCD) cells, activation of PKC with PMA (Phorbol 12-myristate 13-acetate) stimulates renin synthesis, whereas inhibition of PKC with calphostin C blunts this effect[9]. Similarly, in M-1 cells[31] — a mouse epithelial cortical collecting duct cell line that contains mainly principal cells — the inhibition of PKC and depletion of Ca^{2+} impaired ANGII-mediated CREB phosphorylation and upregulation of renin[41]. Adenylyl cyclase type 6 (AC6), the main isoform expressed in collecting duct cells, is required in this process. In M-1 cells, forskolin stimulates AC6-dependent cAMP production and upregulates renin expression, whereas small interfering RNA (siRNA)-mediated inhibition of AC6 partially prevents ANGII-mediated upregulation of *Ren1c*[31]. PKC-dependent accumulation of cAMP has also been described in Chinese hamster ovary (CHO) cells transfected with AT1R and the arginine–vasopressin (AVP) V2 receptor (V2R), as discussed later[42].

Renin enzymatic activity is required to cleave AGT to form ANGI. An extensive body of evidence demonstrates that the liver is the predominant source of AGT in the kidney[43]. Increased *Agt* mRNA levels in proximal tubule cells contribute to the maintenance of endogenous intrarenal ANGII formation in ANGII-infused hypertensive rats[44]. Indeed, the increase in AGT filtration underlies the enhanced synthesis of intratubular ANGII that is observed in models of glomerular permeability, such as nephrotic syndrome[45]. This notion is further supported by studies in NEP25 mice — a model of podocyte injury and progressive glomerular sclerosis — in which increased glomerular permeability enhanced AGT filtration and the formation of intrarenal ANGII[46]. Treatment of hypertensive rat models with liver-directed antisense oligonucleotides against AGT led to a robust and durable reduction in blood pressure[47,48]. Similarly, maximal blockade of the RAS with valsartan plus administration of a liver-targeted siRNA against AGT yielded a greater reduction in blood pressure and cardiac hypertrophy in spontaneously hypertensive rats, than AGT-lowering or conventional RAS inhibition alone[49]. Of note, inhibition of the endocytic receptor, megalin, by antisense oligonucleotides reduced levels of AGT and renin within proximal tubule cells of mice, whereas urinary levels of AGT were increased[50]. Together, these findings suggest that liver-derived AGT is a key source of AGT in the kidney and that its levels in the kidney are dependent on glomerular permeability and uptake by megalin.

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Antisense oligonucleotides

Short DNA or RNA molecules that regulate gene expression by blocking the transcription or translation of target genes.

The formation of AGT by proximal tubule cells is stimulated by glucose entry via sodium–glucose cotransporter 2 (SGLT2), independent of the AT1R[51]. These findings are supported by a study of mice with high fat diet-induced type 2 diabetes mellitus, in which augmented urinary excretion of AGT occurred prior to the development of the diabetes, and in the absence of microalbuminuria or other markers of kidney damage[52]. The augmentation of AGT in those mice paralleled increases in systolic blood pressure as measured by telemetry[52]. Thus, the formation of de novo intratubular ANGII is the result of concomitant increases in AGT derived from both the kidney and the liver and its subsequent cleavage by intrarenal renin. This process is of relevance because in rodent models of ANGII-dependent hypertension, newly formed ANGII in the lumen of distal nephron segments[53,54] directly stimulates local sodium reabsorption, contributing to the development and maintenance of hypertension[34–36]. Under conditions of low salt intake, renin levels in the kidney are increased in both juxtaglomerular cells and collecting duct principal cells; however, despite elevated plasma and intrarenal levels of ANGII, urinary AGT and ANGII excretion rates are not augmented[39]. Moreover, despite the fact that AGT formation is stimulated by chronic ANGII infusion[27], elevations of plasma and intrarenal ANGII levels caused by physiological stimulation of the RAS in response to low salt intake neither stimulate AGT formation in the proximal tubules nor increase urinary excretion of AGT or ANGII[39,55].

ANGII levels in the kidney are the result of glomerular filtration, luminal internalization of the ligand–AT1R complex in the proximal tubule cells, and de novo synthesis[53]. The localization and cellular processing of RAS components supports the concept of a self-contained renal RAS within the proximal tubules[56] and distal nephron[57–60]. In various models of ANGII-dependent hypertension, intrarenal levels of ANGII increase substantially more than circulating levels, and despite the decreased synthesis of juxtaglomerular-derived renin[53,61–63]. This dissociation between the circulating and intrarenal RAS during the development and maintenance of ANGII-dependent hypertension could potentially be advantageous by conserving Na^+ and water during long periods of water deprivation to ensure an euvolaemic status. However, increased circulating and intrarenal ANGII in the context of hypertension elicits deleterious effects, including vasoconstriction of renal arteries and enhanced tubular sodium reabsorption, thereby propagating the hypertensive response and promoting the development of kidney injury. The enhanced intrarenal ANGII activity seen in experimental models of ANGII-dependent hypertension is the result of both AT1R-mediated uptake of filtered ANGII as well as AT1R-mediated synthesis and secretion of AGT in proximal tubule cells and liver. Thus, ANGII-dependent augmentation of AGT excretion in urine to some extent represents an index of intrarenal RAS activation. In human studies, increased urinary excretion of AGT has been demonstrated in patients with hypertension[27,64], type 1 and type 2 diabetes mellitus[65], and chronic kidney disease[66]. Stimulation of renin production by cells of the collecting duct in response to AT1R activation would further favour the cleavage of AGT derived from the proximal tubule to

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promote the formation of ANGI, providing further substrate for conversion into ANGII by local ACE.

As mentioned above, and in contrast to the inhibitory effect of ANGII–AT1R signalling on juxtaglomerular-derived renin, ANGII stimulates renin production and secretion by principal cells of the collecting duct and contributes to the formation of intratubular ANGII[7,12,28]. Although renin can be freely filtered by the glomerulus and reabsorbed by the proximal tubule via megalin[13], experimental models of ANGII-dependent hypertension, including rodent models of chronic ANGII infusion, 2K1C-induced hypertension and the transgenic *Ren2* (Cyp1a1-Ren2) rat, show increased urinary renin despite suppression of plasma renin activity (PRA) owing to the inhibition of juxtaglomerular-derived renin[7,12,28,32]. This finding suggests that low levels of filtered juxtaglomerular-derived renin are unlikely to markedly contribute to the increase in intratubular renin in these models[16,32]. In support of a physiological role for collecting duct-derived renin, mice deficient in collecting duct-derived renin demonstrated an attenuated hypertensive response to dietary salt and chronic infusion of ANGII compared with that of similarly treated wild-type mice; this attenuated response in the transgenic mice was associated with decreased expression of ENaC[67].

Further complexity arises in the context of diabetes mellitus. A study of patients with and without type 2 diabetes mellitus reported that prorenin was undetectable in the urine of patients with diabetes and that increased levels of urinary renin more closely reflected intrarenal RAS activity than did urinary AGT or aldosterone[15]. Given that principal cells of the collecting duct predominantly release prorenin[16,32], it is possible that prorenin is either taken up by tubule cells after binding to the PRR, thereby allowing selective secretion of renin in urine, and/or that collecting duct-derived prorenin is converted to renin before it is excreted in urine[15]. The co-expression of *Ren1c* gene with *Aqp2* in kidney sections from mice indicates that renin is expressed exclusively by principal cells[31] but not by intercalated cells — which is the main cell type that expresses PRR in the distal nephron[68,69].

Regulation of renin by other hormones

Various hormones that are involved in blood pressure regulation and body fluid homeostasis also contribute to the regulation of collecting duct-derived renin. In addition, renin synthesis and release within the collecting duct are also regulated by prostaglandin E2 (PGE_2) via E prostanoid receptors (EPs) (FIG. 2).

Prostaglandin E2

Four EP receptor subtypes are expressed in the different regions of the kidney[70]. EP4 receptors are mainly expressed by macula densa cells, EP3 receptors are more abundant in cells of the thick ascending limb[71], whereas the collecting duct expresses primarily EP1 and EP4 receptors[71]. EP1 and EP4 differ by the type of intracellular signals they evoke when activated. EP1 is a Gq protein-coupled receptor that activates PKC and increases intracellular Ca^{2+}, EP2 and EP4 are Gs protein-coupled receptors and increase cAMP levels, whereas EP3 is a Gi protein-coupled receptor that decreases cAMP levels[70,71]. Treatment of M-1 cells (which express EP1, EP3 and EP4 but not EP2 receptors) with PGE_2 increases *Ren1c* transcript levels, as well as the abundance of prorenin and renin proteins in a

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dose-dependent manner, responses that are blunted by EP1 receptor antagonists[72]. These findings further support the concept that PKC activity in collecting duct cells stimulates intracellular renin content in contrast to the inhibitory effect that PKC exerts on renin in juxtaglomerular cells. The effect of PGE_2 might be of relevance during the first 3–5 days of chronic ANGII infusion (the early phase) in Sprague-Dawley rats, as reflected by increases in urine PGE_2. concentration over this time[73]. After 7 days of ANGII infusion (late phase), the expression of PGE_2 and its upstream regulator, cyclooxygenase 2 (COX2), returns to basal levels in urine and kidney tissues. Available evidence suggests that during the early phase of ANGII-induced hypertension, PGE_2 stimulates prorenin synthesis and secretion by the principal cells of the collecting duct via the PKC–cAMP–CREB pathway, which subsequently boosts the formation of intratubular ANGII[8,74]. The presence of PRR in intercalated cells of the collecting duct further influences the ability of prorenin and renin to form ANGII and thereby enhances the effects of PGE_2 signal transduction[8,74].

Chronic infusions of ANGII also increase urinary renin activity and total renin content in the renal medulla via EP4-dependent upregulation of the PRR via a mechanism mediated by the ERK1/2 pathway[75]. These findings are intriguing because EP4 receptors also mediate PGE_2 vasodilatory responses by coupling with eNOS[76] and promote salt and water excretion by reducing the activity of the Na-K-2Cl (NKCC2) transporter when NCC and ENaC transporters are blocked[77]. The net result of EP4 receptor activation in the collecting duct cells therefore likely depends on the balance between its prohypertensive and antihypertensive actions[75]. Furthermore, ANGII upregulates COX2 in the renal medulla[69], which, together with PGE_2, might stimulate the production of renin in the collecting duct via activation of the EP1–PKC–cAMP–CREB pathway[8,78]. The local production of renin by activation of the PRR may further stimulate COX2 synthesis by the neighbouring intercalated cells[72], thus maintaining PGE_2 production and the activation of PRR via EP4-mediated signalling[79]. Moreover, newly formed intrarenal ANGII stimulates ENaC-dependent sodium transport in the collecting duct[36]. Accordingly, PGE_2 may act not only to buffer the effects of ANGII but also to temporally stimulate the production of collecting duct-derived renin.

Vasopressin

The antidiuretic hormone AVP also regulates renin production by principal cells of the collecting duct. The activation of luminal V2R by AVP in rat IMCD cells induces the PKA–CREB pathway to regulate water reabsorption[80]. Treatment of M-1 cells with the V1R and V2R agonist desmopressin induced a marked increase in CREB phosphorylation followed by renin upregulation. This effect is prevented by the selective V2R antagonist tolvaptan, supporting a role for V2R–PKA–CREB signalling in the production of collecting duct-derived renin[10]. Mice deprived of water for 48 h to increase AVP levels augmented prorenin and renin production in renal inner medullary tissues, even during concomitant RAS blockade[10].

Crosstalk between AT1R and V2R signalling has been described in CHO cells, vascular smooth muscle cells and fibroblasts[42]. In CHO cells transfected with AT1R and V2R cDNA, concomitant treatment with ANGII and AVP potentiated the production of cAMP by V2R

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in the presence of intracellular Ca^{2+}. However, concomitant treatment of these cells with ANGII and forskolin did not modify the production of cAMP[42]. Moreover, activation of PKC by administration of PMA in AT1R and V2R-transfected CHO cells emulated the effect of concomitant ANGII and AVP treatment on intracellular cAMP accumulation, but inhibition of PKC by staurosporine partially prevented cAMP accumulation. Therefore, PKC contributes to the cross-talk between AT1R and V2R, in which activation of AT1R by ANGII potentiates the effects of V2R signalling through an intracellular signalling pathway involving Ca^{2+}-dependent PKC activation coupled to adenylyl cyclase[42].

Bradykinin

Bradykinin, the main effector of the kallikrein–kinin system, is also involved in the regulation of collecting duct-derived renin. The kallikrein–kinin system and RAS interact in multiple physiological and pathological conditions, including the regulation of blood pressure and sodium reabsorption. Bradykinin acts via B2 receptor (B2R), which is linked to the Gq/G11, Gs, and Gi/Go heterotrimeric G proteins[11]. In M-1 cells, activation of B2Rs by bradykinin promotes renin synthesis via stimulation of diacylglycerol-dependent PKC signalling and nitric oxide release; inhibition of nitric oxide production blunted renin synthesis[11].

Natriuretic versus anti-natriuretic regulation

Renin in the collecting duct likely contributes to the regulation of volume homeostasis and blood pressure control. However, the production of collecting duct-derived renin can be stimulated by both natriuretic (PGE_2 and bradykinin) and anti-natriuretic (ANGII and AVP) hormones. The response of renin to these two types of hormone in the collecting duct likely reflects underlying physiological processes. For example, the collecting duct harbours feed-forward mechanisms to sustain renin production in which ANGII–AT1R is the main regulator of its synthesis and secretion, whereas other hormone-mediated pathways, including AVP–V2R, PGE_2–EP1 receptor and bradykinin –B2R signalling, acting through similar intracellular pathways, can modulate crosstalk between PKC–Ca^{2+} and cAMP–PKA–CREB pathways (FIG. 2). Ostensibly, the anti-natriuretic mechanisms of renin production serve to further increase ANGII formation through the stimulation of renin synthesis, whereas natriuretic hormones seem to be linked to renin and prorenin-mediated production of PRR and COX2, primarily in the early phases of hypertension[69,81].

The prorenin receptor

The PRR, encoded by *ATP6AP2*, was first identified as an accessory subunit of the H^+-ATPase and was initially thought to have a primary role in enhancing RAS activity[82]. However, an increasing body of evidence suggests that the PRR has important roles beyond the regulation of RAS activity, including the regulation of acid–base balance, kidney development and lysosomal function[83].

The PRR protein is expressed in brain, lung, placenta, pancreas and kidney[82]. In the kidney, the PRR is expressed in the macula densa, mesangial cells, podocytes, interstitium, proximal tubule and cells of the collecting duct[68,69,82,84]. In the collecting duct, the

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PRR is primarily expressed on the luminal side of type-A intercalated cells where it has a vital role in regulating intracellular pH and cell survival[68]. Mutation of *ATP6AP2* causes functional alterations in the H^+-ATPase, which results in intracellular pH imbalance, podocyte anomalies, proteinuria, and abnormal nephron development[55,73,85] as a result of altered Wnt–β-catenin signalling[86]. However, the PRR might also contribute to kidney sodium and water balance by regulating the expression of AQP2 channels in principal cells[59]. Water deprivation in mice induces sequential activation of the EP4 receptor and PRR, leading to upregulation of AQP2 (ReF.[79]). Although the PRR is primarily expressed in intercalated cells, it is also expressed in principal cells (in which AQP2 is expressed) at lower, but sufficient levels to influence AQP2 expression[68,87] (FIG. 2); however, further studies are needed to elucidate the mechanisms underlying the regulation of AQP2 by the PRR.

Renin and PRR in kidney development

The PRR is essential for proper embryonic development and nephrogenesis, and is critical for normal kidney function. During kidney development, the nephric duct elongates to form the ureteric bud, which leads to the formation of the renal collecting duct, pelvis and ureters. Loss of PRR during development leads to functional alterations in the H^+-ATPase, as well as intracellular pH imbalances, podocyte anomalies, abnormal nephron development and proteinuria in the adult mice[88]. Furthermore, the ablation of PRR in mouse $Six2^+$ nephron progenitor cells leads to reduced numbers of developing nephrons, small cystic kidneys and podocyte anomalies, resulting in reduced kidney function and massive proteinuria in adult mice[83]. These findings are important because emerging evidence shows that the PRR is required for acidification through Wnt–β-catenin signalling during embryonic development[86].

PRR activation and kidney injury

Studies in rats with streptozotocin-induced diabetes suggest that the renoprotective effects of AT1R blockade are in part mediated through suppression of PRR activity[89]. PRR is thought to contribute to the development of diabetic kidney disease not only by enhancing inflammation[90] and renal ANGII formation[91] but also through activation of ANGII-independent MAPK pathways and profibrotic genes, as discussed below. Mice with collecting duct-specific knockout of PRR demonstrate reduced ANGII content in urine[92].

In addition to stimulating intrarenal ANGII content, rats fed a low-salt diet also demonstrate augmented expression of the PRR in glomeruli, proximal tubules and medullary collecting duct cells, via cGMP-mediated activation of PKG[93,94]. In addition, IMCD cells cultured under low-salt conditions, display PRR upregulation via the activation of the GSK–3β–NFAT5–SIRT1 pathway[95] suggesting that PRR is induced by low salt through two independent mechanisms. Also of note is the finding that the upregulation of PRR by low salt is further enhanced in response to ANGII treatment[93], which induces PRR signalling following the upregulation of profibrotic genes such as fibronectin, type I collagen and connecting tissue growth factor (CTGF)[18,89,96,97], thus likely contributing to the development of kidney fibrosis. In male Sprague-Dawley rats fed a low-salt diet, the augmentation of intrarenal ANGII content was associated with collagen deposition in the

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absence of other markers of kidney injury[39]. An excessively low-salt diet also accelerates cardiac fibrosis via the ERK1/2–p-HSP27–p-38MAPK and TGFβ1 pathways, in which PRR is downstream[98].

On the other hand, rats fed a high-salt diet for 4 weeks also display PRR upregulation in glomeruli, proximal tubules and medullary collecting duct cells[99]. The upregulation of PRR in response to a high-salt diet is mediated via activation of NF-κB[100], and may contribute to the activation of prorenin in principal cells. In this scenario, ANGII is expected to upregulate PRR through the production of COX2 and PGE2 and activation of EP4 and EP1 receptors in the renal inner medulla[75,79] (FIG. 2). Collectively, the paracrine interactions involving PRR–COX2–PGE_2–renin signalling contribute to a feed-forward amplification mechanism that regulates the synthesis and release of collecting duct-derived renin under physiological and pathological conditions.

In addition to the membrane-bound form of the PRR, a soluble form (sPRR) results from the cleavage of PRR by several intracellular proteases: site-1 protease (S1P), a disintegrin and metalloprotease 19 (ADAM19) and furin[101–104]. The sPRR is present in kidney tissues, urine[17] and plasma[102], and plasma levels of sPRR are elevated in patients with kidney damage, gestational diabetes, essential hypertension and preeclampsia[60,105–107]. The sPRR contributes to intratubular activation of the RAS in chronic ANGII-infused hypertensive rats by enhancing distal tubule renin activity and ANGII levels, as measured by urinary levels of ANGII[17]. In vitro studies of renal medullary collecting duct cells show that recombinant sPRR also increases AQP2 protein expression via sequential activation of the frizzled 8–β-catenin pathway and activation of cAMP-PKA[108]. In addition to the influence of PRR and sPRR on AQP2 regulation, emerging evidence suggests that PRR and sPRR are involved in regulating vasopressin signalling in the collecting duct, as demonstrated by the ability of recombinant sPRR to attenuate the nephrogenic diabetes insipidus induced by V2R antagonism, but not by lithium, in mice[109]. The central and renal actions of PRR and sPRR in regulating vasopressin provide insights into the roles of PRR in central and nephrogenic diabetes insipidus and urine concentration. However, further understanding of the signalling pathways activated by the sPRR is needed to better understand the relevance of the sPRR to cardiovascular and renal pathophysiology.

Renin and PRR in fibrosis and inflammation.—Activation of ERK1/2–PI3K–AKT signalling following stimulation of membrane-bound PRR promotes cell proliferation and fibrosis via the induction of transforming growth factor-β1 (TGFβ1), plasminogen-activator inhibitor 1 (PAI1), CTGF, fibronectin, type I collagen and COX2 (REFS[72,97,110,111]) (FIG. 3). In mice chronically infused with prorenin, the induction of profibrotic factors and ROS is dependent on COX2-derived PGE2 and activation of EP4 and Smad[97]. PRR knockdown in clipped kidneys during ischaemia–reperfusion significantly reduces the expression of PRR, TNF, COX2, p-NF-κB, MCP1 and type I collagen, supporting the concept that PRR has a relevant role in inflammation and fibrosis during renal ischaemia[112].

In line with the profibrotic role of PRR, treatment of M-1 cells with nanomolar concentrations of recombinant prorenin induces epithelial-to-mesenchymal transition and the formation of ROS along with upregulation of CTGF, α-smooth muscle actin (αSMA)

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and PAI1, and phosphorylation of ERK1/2 (REF.[18]). These responses are blunted by ROS scavengers and inhibition of the ERK1/2 pathway. Thus, nanomolar concentrations of prorenin might contribute to tubuloepithelial cell damage via PRR activation[18]. Nonetheless, one study found that physiological augmentation of renin in a mouse model of PRR overexpression did not induce cardiac tissue damage in the presence of AT1R blockade[113]. Of note, the concentrations of prorenin used in in vitro studies are in the nanomolar range, which are higher than those in systemic circulation (in the picomolar range)[58,114] and lower than the pharmacological threshold for PRR activation[115]. However, as mentioned earlier, pathophysiological conditions such as ANGII-dependent hypertension stimulate the production of prorenin and renin in principal cells of the collecting duct[12,28] and upregulate PRR expression in intercalated cells of the collecting duct[69]. It is possible that under these pathological conditions, intratubular levels of prorenin could be high enough to activate the PRR in the distal nephron. In support of this notion, physical interaction between renin or prorenin and sPRR has been demonstrated in co-immunoprecipitation studies using urine samples from rats with chronic ANGII-induced hypertension[17]. Although similar interactions between intrarenal renin and/or prorenin with the PRR or sPRR may occur in the diabetic kidney[16,116], increased glomerular filtration of plasma prorenin and renin is likely to occur in this setting[13,117,118], making it difficult to determine the origin of intrarenal renin. Filtered prorenin and renin is normally fully reabsorbed by megalin in the proximal tubule[119]. However, impairment of megalin-mediated endocytic uptake is a hallmark of many forms of kidney diseases, including diabetic kidney disease[120], and is also likely to affect the amount of filtered renin reaching the distal tubule.

Renin and PRR in hypertension.—Available evidence suggests that augmentation of intrarenal ANGII levels may contribute to the development and maintenance of hypertension. In models of experimental hypertension[121,122], the stimulation of PRR[75,99] favours the formation of ANGI[92], which is converted into ANGII by ACE[26,123].

A body of evidence supports a functional role of collecting duct-derived renin in the regulation of blood pressure. Levels of sPRR and renin are augmented in the urine of ANGII-infused rats[9], and transgenic mice with collecting duct-specific overexpression of renin have elevated blood pressure compared with controls on a high-sodium diet[124]. Furthermore, mice with distal nephron-specific deletion of renin demonstrate an attenuated response to ANGII-induced hypertension through a reduction in ENaC expression[67]. These findings indicate that collecting duct-derived renin might be as important as juxtaglomerular-derived renin in the development of hypertension. However, studies that have used rodent models with deletion of PRR suggest that the PRR exerts pleiotropic effects on the regulation of RAS, blood pressure and the renal handling of sodium and water[87,125]. Mice with inducible panepithelial cell deletion of PRR using a PAX8 promoter developed interstitial hypotonicity in response to chronic ANGII infusion (1,000 ng/kg/min for 14 days), with impaired countercurrent multiplication and autophagic defects in the epithelial cells of medullary tubules[126]. However, these mice did not show alterations in intrarenal ANGII production or blood pressure[126]. Conversely, another study that used similar PRR-null mice with recombinase activity driven by the PAX8 promoter demonstrated reduced Na^+ retention and an attenuated hypertensive response to chronic

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ANGII infusion (600 ng/kg/min)[127]. Moreover, mice with specific deletion of PRR in collecting duct cells have alterations in kidney function, such as their ability to concentrate the urine and an attenuated hypertensive response to chronic ANGII infusion (400 ng/kg/min), associated with reduced Na^+ retention[92]. These collecting duct-specific PRR-null mice exhibited attenuated systolic and diastolic blood pressure responses, diminished expression of a cleaved α-ENaC isoform and decreased ANGII and renin contents in urine. Interestingly, patch clamp studies in freshly isolated collecting ducts from these mice demonstrated reduced ANGII-dependent stimulation of ENaC activity owing to the presence of fewer active channels and lower open probabilities[92]. The different responses of these transgenic models to ANGII infusion could be due to differences in the doses of ANGII infused. A 2010 study demonstrated that modest, but not excessive, increases in circulating ANGII stimulated intrarenal ANGII, associated with augmentation of intrarenal AGT and the production of RAS components along the nephron[128]. Together, however, these data suggest that the PRR in the collecting duct cells may be important for kidney function and the regulation of blood pressure responses during chronic ANGII infusion by enhancing renin activity, increasing ANGII and activating ENaC in the distal nephron segments.

As mentioned earlier, PRR in the collecting duct is primarily expressed by intercalated cells; however, low levels of *Atp6ap2* have been detected in principal cells[87]. Deletion of *Atp6ap2* specifically in principal cells reduced Na^+ and water reabsorption in the distal tubule through altered regulation of ENaC activity[87]. The regulatory effect of PRR on ENaC may be mediated by enhanced distal luminal production of ANGII and activation of AT1R[53,92] or via a direct effect on ENaC. Other mechanisms that regulate PRR-dependent ENaC activity include the activation of PKA–Akt signalling, NADPH oxidase-dependent stimulation of H_2O_2 (REF.[129]) and activation of SGK1–NEDD4–2 pathways[95]. In addition, single-cell transcriptomics and lineage-tracing analyses have highlighted the role of Notch signalling in regulating the interconversion of intercalated cells and principal cells[130], suggesting that collecting duct cell plasticity might also contribute to differences in PRR signalling observed in the different PRR-knockout mouse models.

Overexpression of PRR in the kidney leads to kidney injury[131]. However, the extent to which plasma prorenin can reach and activate collecting duct PRR is unclear[114]. Studies using the PRR blocker, handle region peptide (HRP), have shown conflicting results in models of cardiovascular and kidney diseases. The HRP is a peptide composed of 10 amino acids[132] that inhibits the binding of prorenin to PRR[85,133], and decreases the formation of intrarenal ANGI and ANGII in diabetic rats[131,134]. Nonetheless, the effects of augmented intrarenal ANGII on blood pressure have been questioned by studies showing that HRP does not mitigate kidney injury in rats with renovascular hypertension[135] and does not improve the effects of renin inhibition when used concomitantly with aliskiren in spontaneously hypertensive rats[73]. Furthermore, in diabetic hypertensive rats, renin inhibition with aliskiren improved vascular dys-function, whereas HRP did not[136]. A newer PRR antagonist, PRO20, which is composed of 20 amino acids[137], was effective in reducing kidney inflammation and injury in a model of chronic ANGII-dependent hypertension[75]. The conflicting results achieved using HRP and PRO20 could be due to technical inconsistences in the experimental approaches, such as differences in delivery routes, which might affect their concentration and ability to reach the apical side of the collecting duct cell to block the

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actions of prorenin and renin, or could be due to differences in their mechanisms of actions. Further studies are needed to enhance our knowledge of the mechanism of action and the pharmacokinetic properties of this novel antagonist.

Remaining controversies

The availability of knockout animal models in which a particular component of the RAS can be eliminated either globally or in a specific segment of the kidney has provided insights into the roles and interactions of these components in a model system. These studies support the concept that excessive activity of the intrarenal RAS leads to a deleterious cycle that perpetuates the progression of hypertension and kidney diseases such as diabetic kidney disease. However, human studies are in general limited to measurements of RAS components in plasma and urine[15]. Patients with type 1 and type 2 diabetes treated with either ACE inhibitors or AT1R blockers exhibit an increase in PRA and decreased plasma AGT levels in the absence of alterations in plasma aldosterone levels. These drugs also decrease urinary renin and aldosterone levels without affecting urinary AGT excretion, suggesting that urinary renin more closely reflects renal RAS activity than urinary AGT or aldosterone[15]. The observation that AGT excretion parallels albuminuria in humans but that urinary renin levels relative to albumin excretion are much higher than urinary AGT, suggests that urinary renin levels reflect not only the release of renin by the collecting duct but also renin that is filtered and incompletely reabsorbed by the proximal tubules[138]. Under normal circumstances, the reabsorption of renin and prorenin by the proximal tubule is extensive — potentially close to 100% — suggesting that very little filtered renin and prorenin escapes into the urine[139]. Given this extensive reabsorption of renin and prorenin by the proximal tubule, the finding that prorenin is not detectable in urine[15,116], despite the fact that renin and prorenin are filtered in larger amounts than albumin, indicates that urinary renin may not reflect the conversion of prorenin to renin in tubular fluid and rather reflects intrarenal renin production[119,139]. One study[13] showed that renin was increased in the urine of patients with type 1 diabetes mellitus and kidney disease, as well in mice with streptozotocin-induced diabetes[13]. The lack of difference in *Ren1c* transcript levels in microdissected collecting duct led to the conclusion that the increased urinary renin in diabetic mice is attributable to increased renin filtration and impaired proximal tubular reabsorption, as evidenced by a reduction in megalin mRNA in the kidney cortex[13]. Unfortunately, commercially available ELISA kits rely on prorenin as their standard, and do not provide reliable measurements of renin levels[140]. The extent to which these assays may have contributed to contradictory findings in the field is unknown.

Conclusions

The discovery that renin is produced and secreted by principal cells of the collecting duct where it interacts with the local PRR, which is expressed mainly by intercalated cells, has contributed to a better understanding of the regulation of blood pressure by the collecting duct. Many studies have attempted to unravel the mechanisms that regulate renin synthesis and release and the impact of its interaction with the PRR in the collecting duct. These mechanisms are more complex than anticipated as a consequence of the various hormones and receptors that target distal transport and interact with RAS components. In this part

of the nephron, increased luminal ANGII leads to the upregulation of renin and PRR, which contributes to further increases in intratubular ANGII formation. In states of high intrarenal ANGII, despite PRA suppression, upregulation of renin and PRR occurs in the collecting duct, which enables the de novo formation of intratubular ANGII. In addition to the activation of PRR by its natural agonists, prorenin and renin, PRR may contribute to the stimulation of profibrotic factors, independent of ANGII. Thus, targeting the PRR could be beneficial in the prevention of tubulointerstitial fibrosis in the context of hypertension and diabetic kidney disease. In addition, the interactions of RAS components with paracrine hormones within the collecting duct enables tubular compartmentalization of the RAS to orchestrate complex mechanisms underlying increases in intratubular ANGII concentrations, augmented Na^+ reabsorption and increased blood pressure. New therapeutic modalities that target renin and/or the PRR in the collecting duct have the potential to decrease the intratubular ANGII concentration and its impact on pathological processes such as kidney fibrosis.

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References

1. Ferrario CM & Schiavone MT The renin angiotensin system: importance in physiology and pathology. Cleve. Clin. J. Med 56, 439–446 (1989). [PubMed: 2663229]
2. Sparks MA, Crowley SD, Gurley SB, Mirotsou M & Coffman TM Classical renin-angiotensin system in kidney physiology. Compr. Physiol 4, 1201–1228 (2014). [PubMed: 24944035]
3. Stokes GSThe renin angiotensin system — its physiology and role in disease states. Anaesth. Intensive Care11, 369–376 (1983). [PubMed: 6316802]
4. Sequeira-Lopez MLSet al.The earliest metanephric arteriolar progenitors and their role in kidney vascular development. Am. J. Physiol. Reg308, R138–R149 (2015).
5. Brunskill EWet al.Genes that confer the identity of the renin cell. J. Am. Soc. Nephrol22, 2213–2225 (2011). [PubMed: 22034642]
6. Rohrwasser Aet al.Elements of a paracrine tubular renin-angiotensin system along the entire nephron. Hypertension34, 1265–1274 (1999). [PubMed: 10601129]
7. Prieto-Carrasquero MCet al.AT(1) receptor-mediated enhancement of collecting duct renin in angiotensin II-dependent hypertensive rats. Am. J. Physiol. Renal Physiol289, F632–F637 (2005). [PubMed: 15870381]
8. Gonzalez AA, Salinas-Parra N, Leach D, Navar LG & Prieto MC PGE2 upregulates renin through E-prostanoid receptor 1 via PKC/cAMP/CREB pathway in M-1 cells. Am. J. Physiol. Renal Physiol 313, F1038–F1049 (2017). [PubMed: 28701311]
9. Gonzalez AAet al.Angiotensin II stimulates renin in inner medullary collecting duct cells via protein kinase C and independent of epithelial sodium channel and mineralocorticoid receptor activity. Hypertension57, 594–599 (2011). [PubMed: 21282553]
10. Gonzalez AAet al.Vasopressin/V2 receptor stimulates renin synthesis in the collecting duct. Am. J. Physiol. Renal Physiol310, F284–F293 (2016). [PubMed: 26608789]
11. Lara LS, Bourgeois CRT, El-Dahr SS & Prieto MC Bradykinin/B-2 receptor activation regulates renin in M-1 cells via protein kinase C and nitric oxide. Physiol. Rep 5, e13211 (2017). [PubMed: 28373410]
12. Prieto-Carrasquero MCet al.Collecting duct renin is upregulated in both kidneys of 2-kidney, 1-clip Goldblatt hypertensive rats. Hypertension51, 1590–1596 (2008). [PubMed: 18426992]

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13. Tang Jet al.Urinary renin in patients and mice with diabetic kidney disease. Hypertension74, 83–94 (2019). [PubMed: 31079532]
14. Saito T, Urushihara M, Kotani Y, Kagami S & Kobori H Increased urinary angiotensinogen is precedent to increased urinary albumin in patients with type 1 diabetes. Am. J. Med. Sci 338, 478–480 (2009). [PubMed: 19884815]
15. van den Heuvel Met al.Urinary renin, but not angiotensinogen or aldosterone, reflects the renal renin-angiotensin-aldosterone system activity and the efficacy of renin-angiotensin-aldosterone system blockade in the kidney. J. Hypertens29, 2147–2155 (2011). [PubMed: 21941204]
16. Kang JJet al.The collecting duct is the major source of prorenin in diabetes. Hypertension51, 1597–1604 (2008). [PubMed: 18413493]
17. Gonzalez AA, Lara LS, Luffman C, Seth DM & Prieto MC 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 (2011). [PubMed: 21321306]
18. Gonzalez AAet al.(Pro)renin receptor activation increases profibrotic markers and fibroblast-like phenotype through MAPK-dependent ROS formation in mouse renal collecting duct cells. Clin. Exp. Pharmacol. Physiol44, 1134–1144 (2017). [PubMed: 28696542]
19. Castrop Het al.Physiology of kidney renin. Physiol. Rev90, 607–673 (2010). [PubMed: 20393195]
20. Muller MWH, Todorov V, Kramer BK & Kurtz A Angiotensin II inhibits renin gene transcription via the protein kinase C pathway. Pflugers Arch. 444, 499–505 (2002). [PubMed: 12136269]
21. Klar Jet al.Calcium inhibits renin gene expression by transcriptional and posttranscriptional mechanisms. Hypertension46, 1340–1346 (2005). [PubMed: 16286572]
22. Beutler KTet al.Long-term regulation of ENaC expression in kidney by angiotensin II. Hypertension41, 1143–1150 (2003). [PubMed: 12682079]
23. Náray-Fejes-Tóth A & Fejes-Tóth G The sgk, an aldosterone-induced gene in mineralocorticoid target cells, regulates the epithelial sodium channel. Kidney Int. 57, 1290–1294 (2000). [PubMed: 10760056]
24. Siragy HMThe angiotensin II type 2 receptor and the kidney. J. Renin Angiotensin Aldosterone Syst11, 33–36 (2010). [PubMed: 19861347]
25. Matavelli LC & Siragy HM AT2 receptor activities and pathophysiological implications. J. Cardiovasc. Pharm 65, 226–232 (2015).
26. Redublo Quinto BMet al.Expression of angiotensin I-converting enzymes and bradykinin B-2 receptors in mouse inner medullary-collecting duct cells. Int. Immunopharmacol8, 254–260 (2008). [PubMed: 18182236]
27. Kobori H, Harrison-Bernard LM & Navar LG Expression of angiotensinogen mRNA and protein in angiotensin II-dependent hypertension. J. Am. Soc. Nephrol 12, 431–439 (2001). [PubMed: 11181790]
28. Prieto-Carrasquero MCet al.Enhancement of collecting duct renin in angiotensin II-dependent hypertensive rats. Hypertension44, 223–229 (2004). [PubMed: 15226276]
29. Rohrwasser Aet al.Renin and kallikrein in connecting tubule of mouse. Kidney Int. 64, 2155–2162 (2003). [PubMed: 14633138]
30. HarrisonBernard LM, Navar LG, Ho MM, Vinson GP & ElDahr SS Immunohistochemical localization of ANGII AT(1) receptor in adult rat kidney using a monoclonal antibody. Am. J. Physiol 273, F170–F177 (1997). [PubMed: 9249605]
31. Gonzalez AAet al.PKC-alpha-dependent augmentation of cAMP and CREB phosphorylation mediates the angiotensin II stimulation of renin in the collecting duct. Am. J. Physiol. Renal Physiol309, F880–F888 (2015). [PubMed: 26268270]
32. Liu Let al.Increased renin excretion is associated with augmented urinary angiotensin II levels in chronic angiotensin II-infused hypertensive rats. Am. J. Physiol. Renal Physiol301, F1195–F1201 (2011). [PubMed: 21865264]
33. Vonthun AM, Eldahr SS, Vari RC & Navar LG Differential expression of intrarenal renin-angiotensin system genes in angiotensin-II-induced and 2-kidney, one-clip (2K1C) hypertension. Hypertension 21, 601–601 (1993).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

34. Peti-Peterdi J, Warnock DG & Bell PD Angiotensin II directly stimulates ENaC activity in the cortical collecting duct via AT_1 receptors. J. Am. Soc. Nephrol 13, 1131–1135 (2002). [PubMed: 11960999]
35. Mamenko M, Zaika O, Ilatovskaya DV, Staruschenko A & Pochynyuk O Angiotensin II increases activity of the epithelial Na^+ channel (ENaC) in distal nephron additively to aldosterone. J. Biol. Chem 287, 660–671 (2012). [PubMed: 22086923]
36. Mamenko Met al.Chronic angiotensin II infusion drives extensive aldosterone-independent epithelial Na^+ channel activation. Hypertension62, 1111–1122 (2013). [PubMed: 24060890]
37. Sun P, Yue P & Wang WH Angiotensin II stimulates epithelial sodium channels in the cortical collecting duct of the rat kidney. Am. J. Physiol. Renal Physiol 302, F679–F687 (2012). [PubMed: 22169010]
38. Lantelme Pet al.Effects of dietary sodium and genetic background on angiotensinogen and renin in mouse. Hypertension39, 1007–1014 (2002). [PubMed: 12019284]
39. Shao W, Seth DM, Prieto MC, Kobori H & Navar LG Activation of the renin-angiotensin system by a low-salt diet does not augment intratubular angiotensinogen and angiotensin II in rats. Am. J. Physiol. Renal Physiol 304, F505–F514 (2013). [PubMed: 23303412]
40. Lee YJet al.Increased AQP2 targeting in primary cultured IMCD cells in response to angiotensin II through AT_1 receptor. Am. J. Physiol. Renal Physiol292, F340–F350 (2007). [PubMed: 16896188]
41. Stoos BA, Narayfejestoth A, Carretero OA, Ito S & Fejestoth G Characterization of a mouse cortical collecting duct cell-line. Kidney Int. 39, 1168–1175 (1991). [PubMed: 1654478]
42. Klingler Cet al.Angiotensin II potentiates vasopressin-dependent cAMP accumulation in CHO transfected cells. Mechanisms of cross-talk between AT1A and V2 receptors. Cell Signal. 10, 65–74 (1998). [PubMed: 9502119]
43. Matsusaka Tet al.Liver angiotensinogen is the primary source of renal angiotensin II. J. Am. Soc. Nephrol23, 1181–1189 (2012). [PubMed: 22518004]
44. Ingelfinger JRet al.Rat proximal tubule cell line transformed with origin-defective SV40 DNA: autocrine ANGII feedback. Am. J. Physiol276, F218–F227 (1999). [PubMed: 9950952]
45. Koizumi Met al.Podocyte injury augments intrarenal angiotensin ii generation and sodium retention in a megalin-dependent manner. Hypertension74, 509–517 (2019). [PubMed: 31352823]
46. Matsusaka Tet al.Podocyte injury enhances filtration of liver-derived angiotensinogen and renal angiotensin II generation. Kidney Int. 85, 1068–1077 (2014). [PubMed: 24284520]
47. Wu CHet al.Antisense oligonucleotides targeting angiotensinogen: insights from animal studies. Biosci. Rep39, BSR20180201 (2019). [PubMed: 30530571]
48. Mullick AEet al.Blood pressure lowering and safety improvements with liver angiotensinogen inhibition in models of hypertension and kidney injury. Hypertension70, 566–576 (2017). [PubMed: 28716988]
49. Uijl Eet al.Strong and sustained antihypertensive effect of small interfering RNA targeting liver angiotensinogen. Hypertension73, 1249–1257 (2019). [PubMed: 31030610]
50. Ye Fet al.Angiotensinogen and megalin interactions contribute to atherosclerosis-brief report. Arterioscler. Thromb. Vasc. Biol39, 150–155 (2019). [PubMed: 30567480]
51. Satou Ret al.Blockade of sodium-glucose cotransporter 2 suppresses high glucose-induced angiotensinogen augmentation in renal proximal tubular cells. Am. J. Physiol. Renal Physiol318, F67–F75 (2020). [PubMed: 31682172]
52. Reverte Vet al.Urinary angiotensinogen increases in the absence of overt renal injury in high fat diet-induced type 2 diabetic mice. J. Diabetes Complications34, 107448 (2020). [PubMed: 31761419]
53. Navar LG, Kobori H, Prieto MC & Gonzalez-Villalobos RA Intratubular renin-angiotensin system in hypertension. Hypertension 57, 355–362 (2011). [PubMed: 21282552]
54. Navar LG, Prieto MC, Satou R & Kobori H Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension. Curr. Opin. Pharmacol 11, 180–186 (2011). [PubMed: 21339086]
55. Satou R, Penrose H & Navar LG Inflammation as a regulator of the renin-angiotensin system and blood pressure. Curr. Hypertens. Rep 20, 100 (2018). [PubMed: 30291560]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

56. Pohl Met al.Intrarenal renin angiotensin system revisited: role of megalin-dependent endocytosis along the proximal nephron. J. Biol. Chem285, 41935–41946 (2010). [PubMed: 20966072]
57. Eladari D, Chambrey R & Peti-Peterdi J A new look at electrolyte transport in the distal tubule. Annu. Rev. Physiol 74, 325–349 (2012). [PubMed: 21888509]
58. Batenburg WW & Danser AJ Prorenin and the (pro)renin receptor: binding kinetics, signalling and interaction with aliskiren. J. Renin Angiotensin Aldosterone Syst 9, 181–184 (2008). [PubMed: 18957390]
59. Tamura Yet al.Water deprivation increases (Pro) renin receptor levels in the kidney and decreases plasma concentrations of soluble (Pro)renin receptor. Tohoku J. Exp. Med239, 185–192 (2016). [PubMed: 27350190]
60. Li Zet al.(Pro)renin receptor is an amplifier of wnt/beta-catenin signaling in kidney injury and fibrosis. J. Am. Soc. Nephrol28, 2393–2408 (2017). [PubMed: 28270411]
61. Fox J, Guan S, Hymel AA & Navar LG Dietary Na and Ace inhibition effects on renal tissue angiotensin-I and angiotensin-II and ACE activity in rats. Am. J. Physiol 262, F902–F909 (1992). [PubMed: 1317125]
62. Navar LG, Harrison-Bernard LM, Nishiyama A & Kobori H Regulation of intrarenal angiotensin II in hypertension. Hypertension 39, 316–322 (2002). [PubMed: 11882566]
63. Harrison-Bernard LM, El-Dahr SS, O'Leary DF & Navar LG Regulation of angiotensin II type 1 receptor mRNA and protein in angiotensin II-induced hypertension. Hypertension 33, 340–346 (1999). [PubMed: 9931127]
64. Kobori H, Nishiyama A, Abe Y & Navar LG Enhancement of intrarenal angiotensinogen in Dahl salt-sensitive rats on high salt diet. Hypertension 41, 592–597 (2003). [PubMed: 12623964]
65. Kamiyama Met al.Detailed localization of augmented angiotensinogen mRNA and protein in proximal tubule segments of diabetic kidneys in rats and humans. Int. J. Biol. Sci10, 530–542 (2014). [PubMed: 24910532]
66. Mills KTet al.Increased urinary excretion of angiotensinogen is associated with risk of chronic kidney disease. Nephrol. Dial. Transpl27, 3176–3181 (2012).
67. Ramkumar Net al.Collecting duct-specific knockout of renin attenuates angiotensin II-induced hypertension. Am. J. Physiol. Renal Physiol307, F931–F938 (2014). [PubMed: 25122048]
68. Advani Aet al.The (Pro) renin receptor site-specific and functional linkage to the vacuolar H^{+}-ATPase in the kidney. Hypertension54, 261–269 (2009). [PubMed: 19546380]
69. Gonzalez AA, Luffman C, Bourgeois CR, Vio CP & Prieto MC Angiotensin II-independent upregulation of cyclooxygenase-2 by activation of the (Pro)renin receptor in rat renal inner medullary cells. Hypertension 61, 443–449 (2013). [PubMed: 23184385]
70. Breyer RM, Bagdassarian CK, Myers SA & Breyer MD Prostanoid receptors: subtypes and signaling. Annu. Rev. Pharmacol. Toxicol 41, 661–690 (2001). [PubMed: 11264472]
71. Hebert RL, Breyer RM, Jacobson HR & Breyer MD Functional and molecular aspects of prostaglandin-E receptors in the cortical collecting duct. Can. J. Physiol. Pharm 73, 172–179 (1995).
72. Gonzalez AAet al.Renal medullary cyclooxygenase-2 and (pro)renin receptor expression during angiotensin II-dependent hypertension. Am. J. Physiol. Renal Physiol307, F962–F970 (2014). [PubMed: 25143455]
73. te Riet Let al.Deterioration of kidney function by the (pro)renin receptor blocker handle region peptide in aliskiren-treated diabetic transgenic (mRen2)27 rats. Am. J. Physiol. Renal Physiol306, F1179–F1189 (2014). [PubMed: 24694588]
74. Salinas-Parra N, Reyes-Martinez C, Prieto MC & Gonzalez AA Prostaglandin E2 induces prorenin-dependent activation of (Pro)renin receptor and upregulation of cyclooxygenase-2 in collecting duct cells. Am. J. Med. Sci 354, 310–318 (2017). [PubMed: 28918839]
75. Wang Fet al.Prostaglandin E-prostanoid4 receptor mediates angiotensin II-induced (pro)renin receptor expression in the rat renal medulla. Hypertension64, 369–377 (2014). [PubMed: 24866147]
76. Audoly LPet al.Identification of specific EP receptors responsible for the hemodynamic effects of PGE2. Am. J. Physiol277, H924–H930 (1999). [PubMed: 10484412]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

77. Nüsing RMet al.Dominant role of prostaglandin E2 EP4 receptor in furosemide-induced salt-losing tubulopathy: a model for hyperprostaglandin E syndrome/antenatal Bartter syndrome. J. Am. Soc. Nephrol16, 2354–2362 (2005). [PubMed: 15976003]
78. Gonzalez AAet al.Renal cyclooxygenase-2 expression and hemodynamic role during angiotensin II-dependent hypertension. Hypertension62, A413 (2013).
79. Wang Fet al.Antidiuretic action of collecting duct (Pro)renin receptor downstream of vasopressin and PGE2 receptor EP4. J. Am. Soc. Nephrol27, 3022–3034 (2016). [PubMed: 27000064]
80. Chou CL, Rapko SI & Knepper MA Phosphoinositide signaling in rat inner medullary collecting duct. Am. J. Physiol. Renal Physiol 274, F564–F572 (1998).
81. Gonzalez AA & Prieto MC Renin and the (pro) renin receptor in the renal collecting duct: role in the pathogenesis of hypertension. Clin. Exp. Pharmacol. Physiol 42, 14–21 (2015). [PubMed: 25371190]
82. Nguyen Get al.Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J. Clin. Invest109, 1417–1427 (2002). [PubMed: 12045255]
83. Song Ret al.Prorenin receptor is critical for nephron progenitors. Dev. Biol409, 382–391 (2016). [PubMed: 26658320]
84. Nguyen G, Delarue F, Berrou J, Rondeau E & Sraer JD Specific receptor binding of renin on human mesangial cells in culture increases plasminogen activator inhibitor-1 antigen. Kidney Int. 50, 1897–1903 (1996). [PubMed: 8943472]
85. Uddin MNet al.Non-proteolytic activation of prorenin: activation by (pro)renin receptor and its inhibition by a prorenin prosegment, “decoy peptide”. Front. Biosci13, 745–753 (2008). [PubMed: 17981584]
86. Cruciat CMet al.Requirement of prorenin receptor and vacuolar H^+-ATPase-mediated acidification for Wnt signaling. Science327, 459–463 (2010). [PubMed: 20093472]
87. Ramkumar Net al.Collecting duct principal, but not intercalated, cell prorenin receptor regulates renal sodium and water excretion. Am. J. Physiol. Renal Physiol315, F607–F617 (2018). [PubMed: 29790390]
88. Song RF, Preston G, Ichihara A & Yosypiv IV Deletion of the prorenin receptor from the ureteric bud causes renal hypodysplasia. PLoS ONE 8, e63835 (2013). [PubMed: 23704941]
89. Zhang Let al.Inhibition of (pro)renin receptor contributes to renoprotective effects of angiotensin II type 1 receptor blockade in diabetic nephropathy. Front. Physiol8, 758 (2017). [PubMed: 29056916]
90. Matavelli LC, Huang JQ & Siragy HM (Pro) renin receptor contributes to diabetic nephropathy by enhancing renal inflammation. Clin. Exp. Pharmacol. Physiol 37, 277–282 (2010). [PubMed: 19769609]
91. Ichihara A, Kaneshiro Y & Suzuki F Prorenin receptor blockers: effects on cardiovascular complications of diabetes and hypertension. Expert Opin. Inv. Drug 15, 1137–1139 (2006).
92. Prieto MCet al.Collecting duct prorenin receptor knockout reduces renal function, increases sodium excretion, and mitigates renal responses in ANGII-induced hypertensive mice. Am. J. Physiol. Renal Physiol313, F1243–F1253 (2017). [PubMed: 28814438]
93. Gonzalez AA, Womack JP, Liu L, Seth DM & Prieto MC Angiotensin II increases the expression of (Pro)renin receptor during low-salt conditions. Am. J. Med. Sci 348, 416–422 (2014). [PubMed: 25250989]
94. Huang J & Siragy HM Sodium depletion enhances renal expression of (pro)renin receptor via cyclic GMP-protein kinase G signaling pathway. Hypertension 59, 317–323 (2012). [PubMed: 22203739]
95. Quadri S & Siragy HM (Pro)renin receptor contributes to regulation of renal epithelial sodium channel. J. Hypertens 34, 486–494 (2016). [PubMed: 26771338]
96. Clavreul N, Sansilvestri-Morel P, Magard D, Verbeuren TJ & Rupin A (Pro)renin promotes fibrosis gene expression in HEK cells through a Nox4-dependent mechanism. Am. J. Physiol. Renal Physiol 300, F1310–F1318 (2011). [PubMed: 21411480]
97. Reyes-Martinez C, Nguyen QM, Kassan M & Gonzalez AA (Pro)renin receptor-dependent induction of profibrotic factors is mediated by COX-2/EP4/NOX-4/Smad pathway in collecting duct cells. Front. Pharmacol 10, 803 (2019). [PubMed: 31396082]

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98. Okamoto Cet al.Excessively low salt diet damages the heart through activation of cardiac (pro) renin receptor, renin-angiotensin-aldosterone, and sympatho-adrenal systems in spontaneously hypertensive rats. PLoS ONE12, e0189099 (2017). [PubMed: 29220406]
99. Rong Ret al.Expression of (pro)renin receptor and its upregulation by high salt intake in the rat nephron. Peptides63, 156–162 (2015). [PubMed: 25555681]
100. Su Jet al.NF-κB-dependent upregulation of (pro)renin receptor mediates high-NaCl-induced apoptosis in mouse inner medullary collecting duct cells. Am. J. Physiol. Cell Physiol313, C612–C620 (2017). [PubMed: 29021196]
101. Zhu Q & Yang T Enzymatic sources and physio-pathological functions of soluble (pro)renin receptor. Curr. Opin. Nephrol. Hypertens 27, 77–82 (2018). [PubMed: 29346132]
102. Cousin Cet al.Soluble form of the (Pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. Hypertension53, 1077–1082 (2009). [PubMed: 19380613]
103. Yoshikawa Aet al.The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space. Hypertens. Res34, 599–605 (2011). [PubMed: 21270819]
104. Nakagawa Tet al.Site-1 protease is required for the generation of soluble (pro)renin receptor. J. Biochem161, 369–379 (2017). [PubMed: 28013223]
105. Morimoto Set al.Serum soluble (pro)renin receptor levels in patients with essential hypertension. Hypertens. Res37, 642–648 (2014). [PubMed: 24646643]
106. Watanabe Net al.Prediction of gestational diabetes mellitus by soluble (pro)renin receptor during the first trimester. J. Clin. Endocrinol. Metab98, 2528–2535 (2013). [PubMed: 23720787]
107. Watanabe Net al.Soluble (pro)renin receptor and blood pressure during pregnancy: a prospective cohort study. Hypertension60, 1250–1256 (2012). [PubMed: 23045457]
108. Lu Xet al.Soluble (pro)renin receptor via beta-catenin enhances urine concentration capability as a target of liver X receptor. Proc. Natl Acad. Sci. USA113, E1898–E1906 (2016). [PubMed: 26984496]
109. Yang KTet al.The soluble (Pro)renin receptor does not influence lithium-induced diabetes insipidus but does provoke beiging of white adipose tissue in mice. Physiol. Rep5, e13410 (2017). [PubMed: 29138356]
110. Ichihara A, Itoh H & Inagami T Critical roles of (pro)renin receptor-bound prorenin in diabetes and hypertension: sallies into therapeutic approach. J. Am. Soc. Hypertens 2, 15–19 (2008). [PubMed: 20409880]
111. Kaneshiro Yet al.Increased expression of cyclooxygenase-2 in the renal cortex of human prorenin receptor gene-transgenic rats. Kidney Int. 70, 641–646 (2006). [PubMed: 16807542]
112. Quadri SS, Culver S & Siragy HM Prorenin receptor mediates inflammation in renal ischemia. Clin. Exp. Pharmacol. Physiol 45, 133–139 (2018). [PubMed: 28980339]
113. Peters Jet al.Lack of cardiac fibrosis in a new model of high prorenin hyperaldosteronism. Am. J. Physiol. Heart Circ. Physiol297, H1845–H1852 (2009). [PubMed: 19749160]
114. Danser AHThe role of the (Pro)renin receptor in hypertensive disease. Am. J. Hypertens28, 1187–1196 (2015). [PubMed: 25890829]
115. Nabi AHet al.Binding properties of rat prorenin and renin to the recombinant rat renin/prorenin receptor prepared by a baculovirus expression system. Int. J. Mol. Med18, 483–488 (2006). [PubMed: 16865234]
116. Siragy HM & Huang JQ Renal (pro)renin receptor upregulation in diabetic rats through enhanced angiotensin AT_1 receptor and NADPH oxidase activity. Exp. Physiol 93, 709–714 (2008). [PubMed: 18192338]
117. Sun Yet al.Megalin: a novel endocytic receptor for prorenin and renin. Hypertension75, 1242–1250 (2020). [PubMed: 32200675]
118. Lee JW, Chou CL & Knepper MA Deep sequencing in microdissected renal tubules identifies nephron segment-specific transcriptomes. J. Am. Soc. Nephrol 26, 2669–2677 (2015). [PubMed: 25817355]
119. Roksnoer LCet al.On the origin of urinary renin: a translational approach. Hypertension67, 927–933 (2016). [PubMed: 26928805]

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120. Peruchetti DB, Silva-Aguiar RP, Siqueira GM, Dias WB & Caruso-Neves C High glucose reduces megalin-mediated albumin endocytosis in renal proximal tubule cells through protein kinase B O-GlcNAcylation. J. Biol. Chem 293, 11388–11400 (2018). [PubMed: 29871929]
121. Kobori H, Harrison-Bernard LM & Navar LG Enhancement of angiotensinogen expression in angiotensin II-dependent hypertension. Hypertension 37, 1329–1335 (2001). [PubMed: 11358949]
122. Shao W, Seth DM & Navar LG Augmentation of endogenous angiotension if levels in Val5-ANGII infused rats. J. Invest. Med 56, 419–419 (2008).
123. Komlosi Pet al.Angiotensin I conversion to angiotensin II stimulates cortical collecting duct sodium transport. Hypertension42, 195–199 (2003). [PubMed: 12835330]
124. Ramkumar N, Ying J, Stuart D & Kohan DE Overexpression of renin in the collecting duct causes elevated blood pressure. Am. J. Hypertens 26, 965–972 (2013). [PubMed: 23702969]
125. Ramkumar Net al.Nephron-specific deletion of the prorenin receptor causes a urine concentration defect. Am. J. Physiol. Renal Physiol309, F48–F56 (2015). [PubMed: 25995108]
126. Trepiccione Fet al.Renal Atp6ap2/(Pro)renin receptor is required for normal vacuolar H^+-ATPase function but not for the renin-angiotensin system. J. Am. Soc. Nephrol27, 3320–3330 (2016). [PubMed: 27044666]
127. Ramkumar Net al.Renal tubular epithelial cell prorenin receptor regulates blood pressure and sodium transport. Am. J. Physiol. Renal Physiol311, F186–F194 (2016). [PubMed: 27053687]
128. Gonzalez-Villalobos RAet al.Intrarenal mouse renin-angiotensin system during ANGII-induced hypertension and ACE inhibition. Am. J. Physiol. Renal Physiol298, F150–F157 (2010). [PubMed: 19846570]
129. Lu Xet al.Activation of ENaC in collecting duct cells by prorenin and its receptor PRR: involvement of nox4-derived hydrogen peroxide. Am. J. Physiol. Renal Physiol310, F1243–F1250 (2016). [PubMed: 26697985]
130. Humphreys BDMechanisms of renal fibrosis. Annu. Rev. Physiol80, 309–326 (2018). [PubMed: 29068765]
131. Ichihara Aet al.Contribution of nonproteolytically activated prorenin in glomeruli to hypertensive renal damage. J. Am. Soc. Nephrol17, 2495–2503 (2006). [PubMed: 16885412]
132. Suzuki Fet al.Human prorenin has “gate and handle” regions for its non-proteolytic activation. J. Biol. Chem278, 22217–22222 (2003). [PubMed: 12684512]
133. Nabi AHMN & Suzuki F Biochemical properties of renin and prorenin binding to the (pro)renin receptor. Hypertens. Res 33, 91–97 (2009). [PubMed: 19942927]
134. Kaneshiro Yet al.Slowly progressive, angiotensin ii-independent glomerulosclerosis in human (Pro)renin receptor-transgenic rats. J. Am. Soc. Nephrol18, 1789–1795 (2007). [PubMed: 17494887]
135. Muller DNet al.(Pro) renin receptor peptide inhibitor “handle-region” peptide does not affect hypertensive nephrosclerosis in Goldblatt rats. Hypertension51, 676–681 (2008). [PubMed: 18212268]
136. Batenburg WWet al.The (pro)renin receptor blocker handle region peptide upregulates endothelium-derived contractile factors in aliskiren-treated diabetic transgenic (mREN2)27 rats. J. Hypertens31, 292–302 (2013). [PubMed: 23303354]
137. Li Wet al.Intracerebroventricular infusion of the (Pro)renin receptor antagonist PRO20 attenuates deoxycorticosterone acetate-salt-induced hypertension. Hypertension65, 352–361 (2015). [PubMed: 25421983]
138. Roksnoer LCWet al.Urinary markers of intrarenal renin-angiotensin system activity in vivo. Curr. Hypertens. Rep15, 81–88 (2013). [PubMed: 23296471]
139. Sun Y, Lu X & Danser AHJ Megalin: a novel determinant of renin-angiotensin system activity in the kidney? Curr. Hypertens. Rep 22, 30 (2020). [PubMed: 32172431]
140. Roksnoer LCWet al.Methodologic issues in the measurement of urinary renin. Clin. J. Am. Soc. Nephrol9, 1163–1167 (2014). [PubMed: 24742480]

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Key points

- Renin-expressing cells are present in various components of the nephron, including the juxtaglomerular apparatus, glomeruli, proximal tubules, connecting tubules and collecting ducts.
- Collecting duct-derived renin is stimulated by a number of factors, including angiotensin II, prostaglandin E_2, bradykinin and vasopressin, which contribute to the paracrine control of sodium reabsorption in the distal nephron.
- Binding of prorenin and renin to the prorenin receptor, expressed by collecting duct cells, enhances the formation of intratubular angiotensin II and promotes kidney fibrosis.
- In models of angiotensin II-dependent hypertension, components of the renin–angiotensin system, including proximal tubule-derived angiotensinogen, collecting duct-derived renin and the prorenin receptor expressed in the collecting duct, together facilitate the sustained formation of intratubular angiotensin II and stimulation of profibrotic factors leading to kidney tubule damage.
- Circulating renin that is filtered and not reabsorbed by megalin in the proximal tubule may also contribute to renin in the urine.
- The renin–angiotensin system in the distal nephron is complex and not fully understood but seems to involve coordinated actions to regulate intrarenal and intratubular angiotensin II, sodium reabsorption, blood pressure and fluid–electrolyte homeostasis.

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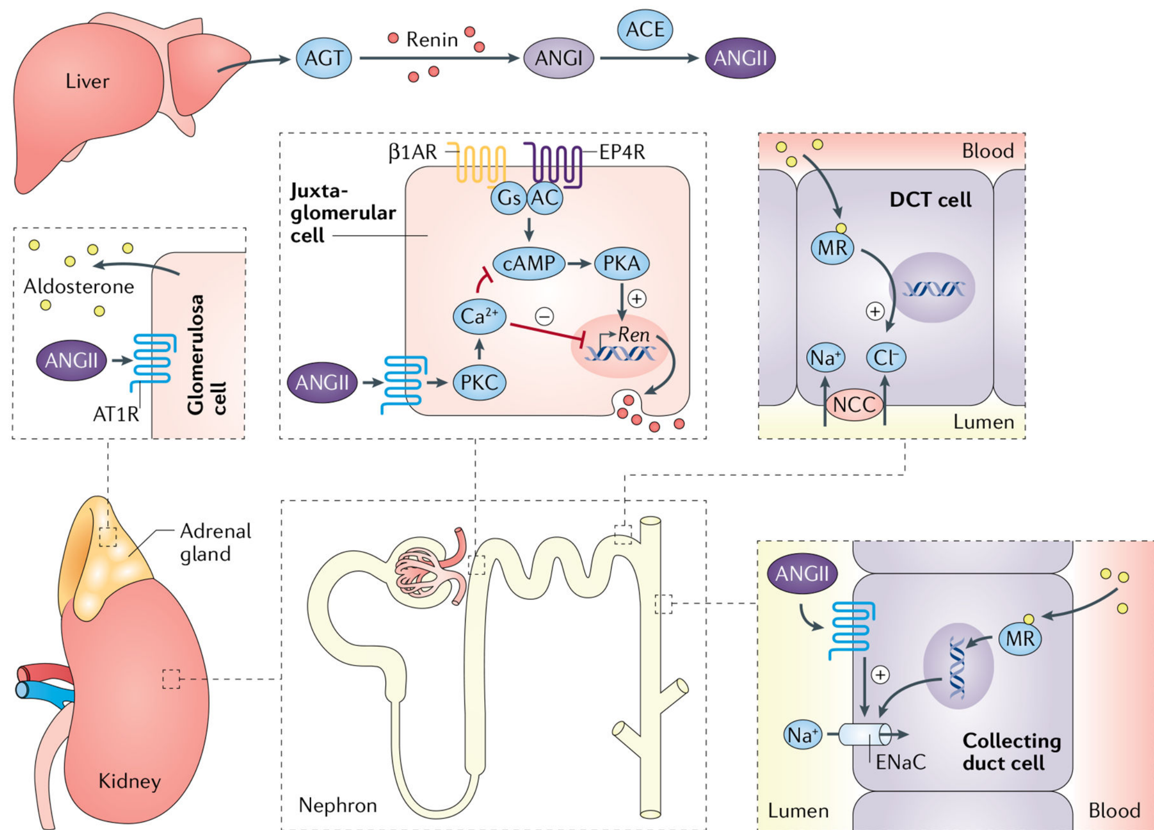

Fig. 1 |. The regulation of renin in juxtaglomerular cells.

In juxtaglomerular cells, renin expression is induced by activation of Gs-coupled receptors, such as the prostaglandin receptor EP4R and the β1 adrenergic receptor (β1AR), which increase adenylate cyclase (AC) activity, thereby increasing cAMP levels and protein kinase A (PKA) activity, which in turn activates CREB to induce expression of *Ren*. The encoded protein, renin, is secreted into blood and cleaves angiotensinogen (AGT) secreted by the liver to form angiotensin I (ANGI), which is subsequently converted to angiotensin II (ANGII) by the angiotensin-converting enzyme (ACE). ANGII is the main effector of the renin–angiotensin system, promoting aldosterone release from the adrenal glands, which stimulates sodium reabsorption by the sodium chloride symporter NCC in the distal connecting tubule (DCT) and the epithelial sodium channel ENaC in the collecting duct. ANGII also stimulates ENaC in the collecting duct. ANGII-mediated activation of ANGII type 1 receptor (AT1R) in juxtaglomerular cells suppresses *Ren1c* expression via activation of protein kinase C (PKC) and Ca^{2+}. MR, mineralocorticoid receptor.

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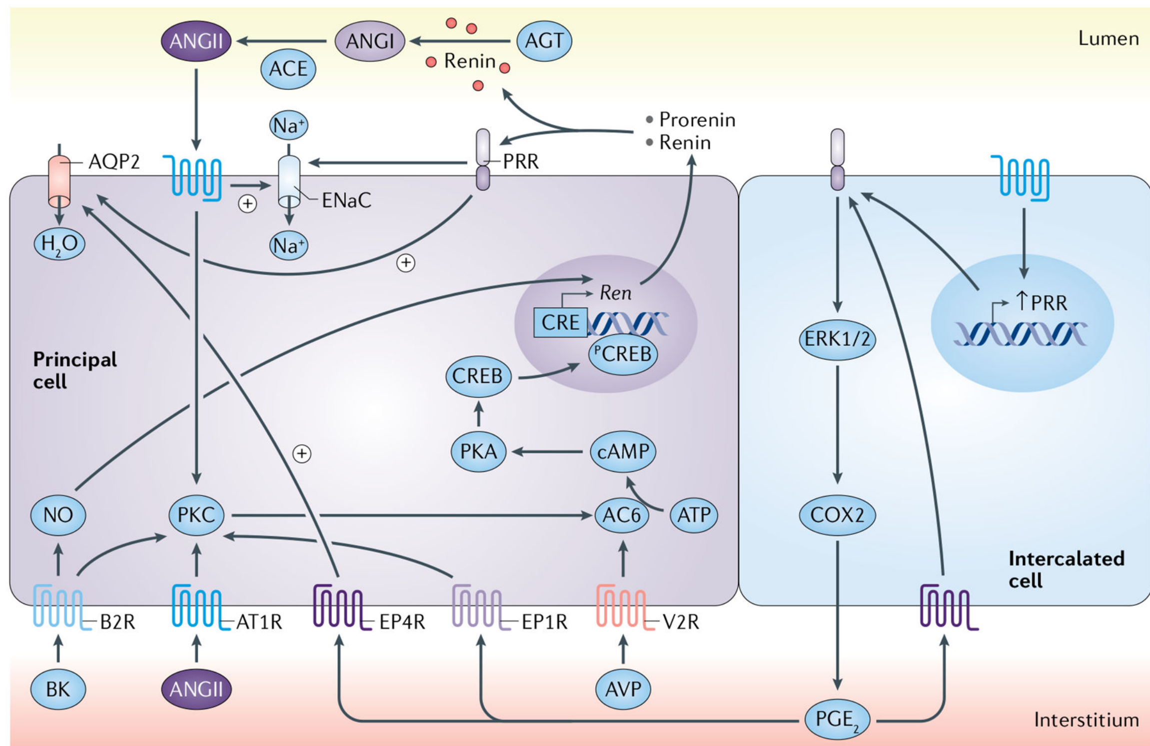

Fig. 2 |. The regulation of renin in the collecting ducts.

In the collecting ducts, angiotensin II (ANGII) activates ANGII type 1 receptors (AT1Rs) on the apical and basolateral sides of principal cells, stimulating the expression of prorenin and renin via protein kinase C (PKC)-dependent activation of the cAMP–protein kinase A (PKA)–CREB pathway. Other hormones, such as prostaglandin E2 (PGE_2), bradykinin (BK) and arginine vasopressin (AVP) also induce renin expression via activation of the EP1 receptor, the bradykinin type 2 receptor (via B2R-dependent PKC and nitric oxide (NO)–cGMP pathway activation) and the AVP type 2 receptor (V2R), respectively. The prorenin receptor (PRR), which is expressed predominantly on the luminal side of intercalated cells, binds prorenin and renin to fully activate prorenin and enhance the enzymatic activity of renin. Prorenin and renin binding to PRR also stimulates cyclooxygenase 2 (COX2) expression via activation of ERK1/2 in the intercalated cells, leading to PGE_2 synthesis. Furthermore, ANGII and PGE_2 also stimulate PRR gene expression via AT1R. The presence of renin, angiotensin-converting enzyme (ACE) in the collecting ducts, and the spill-over of angiotensinogen (AGT) from proximal tubules promote the formation of intratubular ANGII formation and distal luminal sodium reabsorption by activation of the epithelial sodium channel (ENaC). AC, adenylate cyclase type 6.

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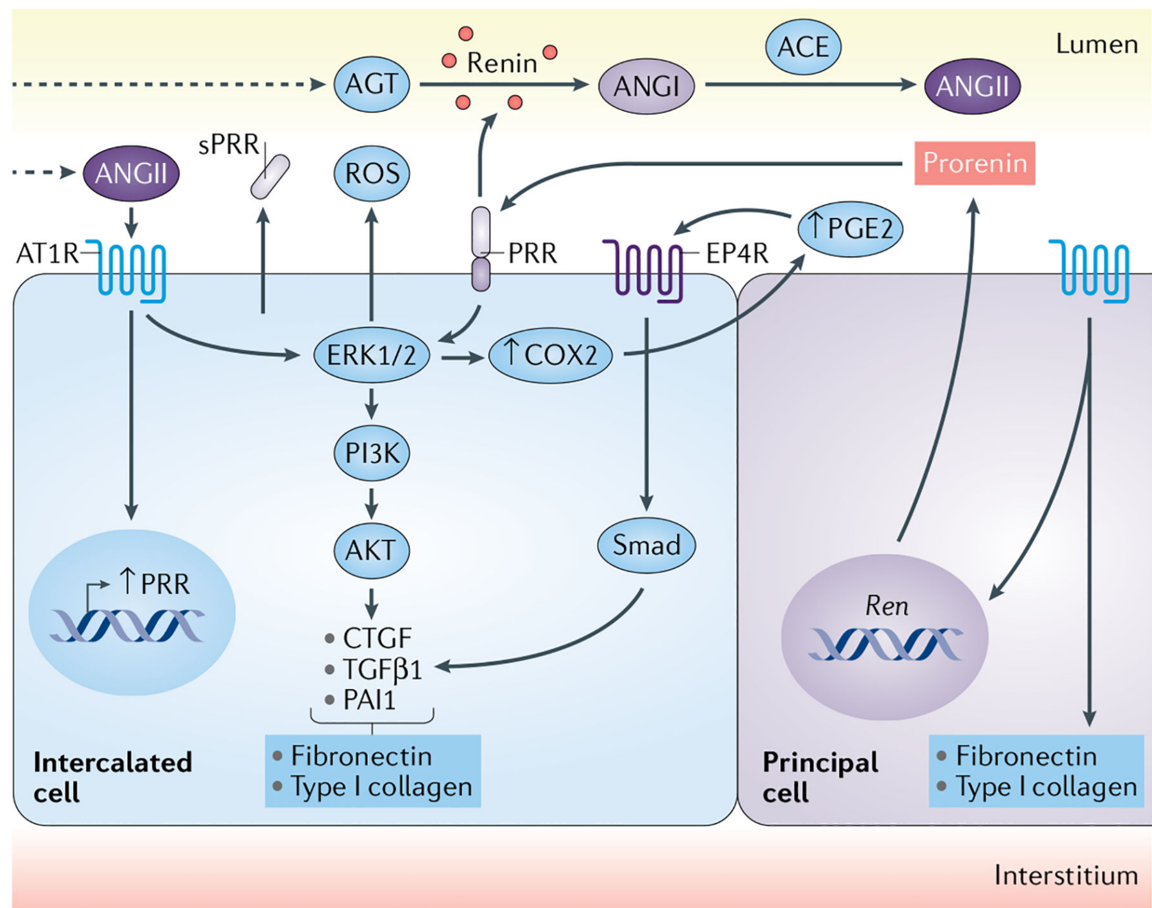

Fig. 3 |. The PRR and renin interactions in distal nephron segments enhance profibrotic pathways and the formation of intratubular ANGII.

Chronic activation of angiotensin II (ANGII) type 1 receptor (AT1R) upregulates prorenin receptor (PRR) expression in intercalated cells, prorenin and renin in principal cells but also increases the expression of fibronectin and collagen I. Binding of prorenin or renin to PRR promotes cell proliferation and the induction of profibrotic factors, including transforming growth factor-β1 (TGFβ1), plasminogen-activator inhibitor 1 (PAI1), connecting tissue growth factor (CTGF), fibronectin, type I collagen and cyclooxygenase 2 (COX2), and increases the formation of reactive oxygen species (ROS) via activation of ERK1/2, MAPK, PI3K and AKT. The prostaglandin receptor EP4R also increases Smad activity to increase expression of the above-mentioned profibrotic proteins. The soluble form of the PRR, sPRR, is formed by the cleavage of PRR by a disintegrin and metalloproteinase domain-containing protein 19 (ADAM19), site-1 protease (S1P) and furin, and is secreted into the tubular lumen where it activates prorenin and enhances renin catalytic activity. These actions contribute to the cleavage of liver and proximal tubule-derived AGT to form angiotensin I (ANGI), which further contributes to the formation of ANGII formation by angiotensin-converting enzyme (ACE), present in the collecting duct.