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REVIEW

The Pathological Role of Pro(Renin) Receptor in Renal Inflammation

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Abstract: (Pro)renin receptor (PRR) is the recently discovered component of the renin-angiotensin-aldosterone system (RAS). Many organs contain their own RAS, wherein PRR can exert organ-specific localized effects. The Binding of prorenin/renin to PRR activates angiotensin-dependent and independent pathways which leads to the development of physiological and pathological effects. Continued progress in PRR research suggests that the upregulation of PRR contributes to the development of hypertension, glomerular injury, and progression of kidney disease and inflammation. In the current review, we highlight the function of the PRR in renal inflammation in pathophysiological conditions.

Keywords: prorenin receptor, renal inflammation, hypertension, diabetes, renin-angiotensin system

Introduction

Renin and prorenin were thought of as proenzymes, but recent evidence suggests that they also could act as hormones as they bind to cellular targets and mediates physiological actions.[1,2] Binding of renin/prorenin to PRR has been shown to increase the catalytic activity of renin by about four- to fivefold and induce a signal-transduction cascade leading to vasoconstriction, sodium, and water reabsorption, cell growth, proliferation, and inflammatory responses.[3–5] It is expressed in almost all of the body tissues including smooth muscle, kidney, liver, brain, testis, lung, heart, and adipose tissue,[3,6,7] and activation of PRR has been linked to upregulation and activation of mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERK).[8]

Expression/Signaling of (Pro)Renin Receptor (PRR) in the Kidney

(Pro)renin receptor (PRR), a new member of the renin-angiotensin system (RAS) encoded by ATPase H(+)-transporting lysosomal accessory protein 2 (ATP6AP2) was first cloned in mesangial cells.[2] Full length PRR is a 350-amino acid protein (Figure 1) with a single transmembrane domain consists of four different domains namely, N-terminal signal peptide, a large extracellular domain, a signal transmembrane domain, and a short cytosolic domain.[7] The extracellular domain can be cleaved to soluble PRR (sPRR) which is secreted into the blood and urine.[9] Binding of sPRR to prorenin leads to the generation of angiotensin II (Ang II) and mediating the effects of renin/prorenin.[10,11] The cytoplasmic domain complexed with V-ATPase is involved in lysosomal acidification[12] and is independent of prorenin/

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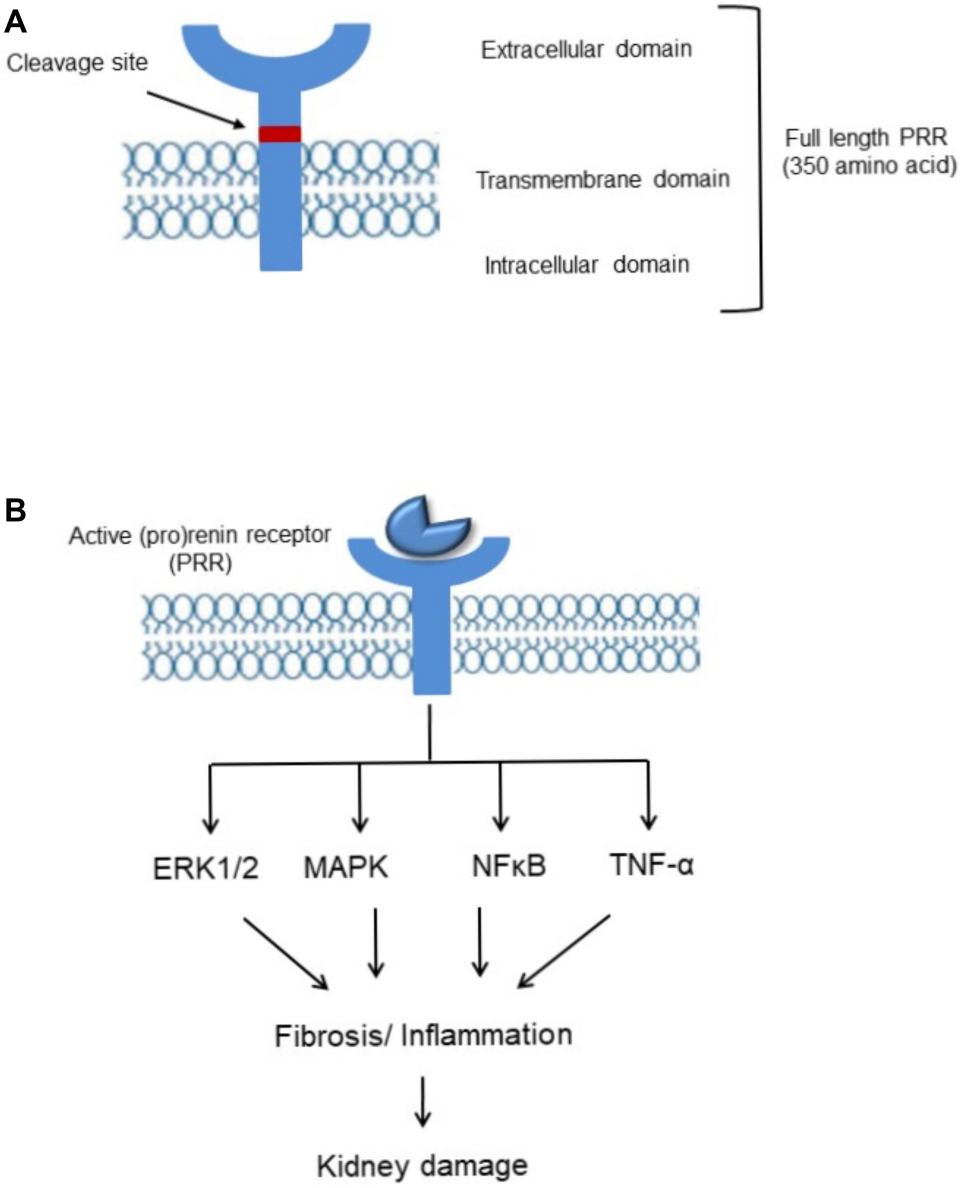

Figure 1 (**A**) Biology and signaling of (pro)renin receptor. Representative schematic organization. (**B**) (Pro)renin receptor (PRR) signaling pathways. Activation/upregulation of PRR induces kidney damage via ERK1/2, MAPK, NF-κB, TNF-α pathway.

renin binding to PRR[13] (Figure 1). Recent studies reported that PRR acts as an adaptor protein between the Wnt receptor and V-ATPase complex, resulting in activation of the Wnt-β-catenin signaling pathway which regulates physiologic embryonic development and also pathological disease[14,15] and deletion of PRR during embryogenesis caused pronounced proteinuria, renal failure, and death.[16,17]

In the kidney, PRR is mainly expressed in podocytes, mesangial cells, proximal and distal renal tubules.[2,7,18] Depending on the form of PRR, actions can be either Ang II-dependent or independent. Activation of full length PRR and soluble PRR (sPRR) mediates angiotensinogen cleavage, binds and activates prorenin/renin, and contributes to its Ras-dependent effects.[19,20] Independent of Ang II, PRR activates mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK)[21–23] signaling pathway which induces proliferation and activation of inflammatory and fibrotic molecules including transforming growth factor β (TGF-β), plasminogen activator inhibitor-1 (PAI-1), IL-1β, nuclear factor-κB (NF-κB) and COX-2, contributing to kidney dysfunction.[24]

PRR is involved in Ang II production and intracellular signaling. Activation and overexpression of PRR in

podocytes[18] contribute to the slow progressive glomerular sclerosis, increases cell albumin permeability, and autophagy causing structural and functional abnormalities.[16,18,25] Activation of ERK1/2 and PI3K-AKT signaling pathway by PRR plays a significant role in autophagosome development, induction of cell apoptosis, and organ damage.[26] PRR contribution in Ang II generation and RAS activation is a significant step in kidney damage.[27] In Goldblatt's hypertensive model PRR is increased in the clipped kidney, leading to Ang II formation in distal nephron segments, distal tubular sodium reabsorption, inflammation, and development of hypertension.[6] A novel pharmacological inhibitor of PRR successfully attenuated the RAS-mediated increase in blood pressure.[28,29] PRR knockdown in the salt-sensitive hypertension model also decreases Ang II formation.[30]

Role of PRR in Renal Dysfunction and Inflammation

The kidneys play a crucial role in regulating blood pressure, and salt and water balance. The PRR in the distal nephron is particularly of interest due to its role in stimulating sodium reabsorption and the development of hypertension.[31] The impact of PRR on the kidney is evident from the fact that the expression of PRR is increased in different hypertensive models[6,32] and the administration of PRR antagonists attenuated the hypertensive response and renal damage.[28]

PRR contributes to renal inflammation and fibrosis is a gradual process involving the RAS system in the development of hypertension and end-stage kidney damage.[6,33] Hypertension damages the glomerular filtration barrier, which interferes with the filtration of circulating angiotensinogen, prorenin, renin, angiotensin I, and Ang II and their uptake in the proximal tubules. Recent evidence indicates that uptake of major components of the circulating RAS, including prorenin, may contribute to high levels of RAS proteins in the kidney. In the glomerulus, PRR is involved in the stimulation of tyrosine phosphorylation, leading to activation of the mitogen-activated protein kinase (MAPK)[2] and subsequent increase in the expression of p-ERK, p-38, and p-JNK.[34] PRR is also credited to increase the expression of transforming growth factor-β (TGF-β) which was inhibited by blocking the prorenin receptor suggesting an independent role of PRR in renal damage.[35,36] In the Goldblatt 2-Kidney 1-clipped hypertensive model, we found that PRR expression is upregulated in the clipped kidney and activates the MAPK/ERK1/2 signaling pathway which in turn increased the expression of COX-2, NF-κB, and production of the inflammatory factors IL-1β, tumor necrosis factor -α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). Targeted knockdown of PRR in the clipped kidney attenuated the expression of IL-1β, TNF-α, COX-2, and NF-κB indicating the intricate and direct interaction between PRR and renal inflammation.[5]

PRR also plays an important role in is renal dysfunction associated with diabetes. Diabetic nephropathy is characterized by increased renal inflammation and fibrosis and is strongly associated with glomerular injury leading to the development of the end-stage renal disease.[37] The pathophysiology of diabetic nephropathy involves multiple mechanisms including the RAS dependent[38] and independent mechanisms.[39] Inflammatory cytokines, including IL-1, IL-6, and IL-18, and TNF-α, are potentially involved in the development and progression of diabetic nephropathy. In vivo and human, studies confirm the role of RAS in the development and progression of kidney disease in diabetes.[40,41] Studies have shown that the expression of PRR was significantly increased in the invivo and invitro diabetic models[18,42] along with the upregulation of oxidative stress.[43] The expression and activity of prorenin and PRR are significantly increased in the diabetic kidney[44] and together contribute to the fibrosis, cellular inflammation, proliferation, and apoptosis, and progression of diabetic nephropathy.[24,39,45] These claims are supported by the research that shows that blockade of PRR in vivo reduced albuminuria and renal production of the inflammatory cytokines TNF-α and IL-1β[39] and attenuated the development and progression of diabetic nephropathy.[46–48] These changes were independent of changes in renal production of Ang II suggesting an independent and additive contribution of PRR in the development of renal inflammation in diabetes.

Upregulation of PRR expression in the kidney has been demonstrated in the streptozotocin-induced diabetic model where it augments the expression of inflammatory cytokines including TNF- α and interleukins,[39] which activates second messenger systems, transcription factors, growth factors resulting in significant renal damage in diabetes.[49] PRR mediated upregulation of cytokines also has been shown to induce apoptosis and alterations in endothelial permeability contributing to renal damage.[50,51] The upregulation of PRR in diabetes also affects the structure and function of podocytes as evident with the reduction in podocin and nephrin through the Wnt3a-β-catenin-snail signaling

pathway.[18] Concurrent studies also showed that the PRR and cytokines prevent the formation of F-actin fibers resulting in the restructuring of the intercellular junction causing the loss of endothelial permeability, leading to podocytes injury.[52,53] Down-regulation of PRR attenuated the inflammation and improves the F-actin expression and reorganization,[18,24,26] indicating the direct role of PRR in the pathophysiology of diabetic kidney disease.

Role of Soluble PRR (sPRR) in Renal Dysfunction and Inflammation

Full length PRR can be cleaved to a soluble form of PRR (sPRR). The sPRR can either be retained inside cells and/or secreted into plasma, urine, and extracellular space.[32,54] Evidence from the literature suggests that the upregulation of sPRR reflects the activation of RAS and direct stimulation of MAPK/ERK1/2 signaling pathway which may lead to renal dysfunction.[32,55] Recent studies have identified a more specific role of sPRR in renal dysfunction which is demonstrated by the fact that sPRR activates the aquaporin 2 (AQP-2) channel in the distal nephron via frizzled-8 and β-catenin signaling pathway and increases water reabsorption.[11,56] Another study highlighted the role of sPRR in sodium reabsorption where sPRR upregulates epithelial sodium channel (ENaC) in the distal nephron and increases sodium reabsorption.[57] These findings indicate the role of sPRR in sodium and water homeostasis and the development of subsequent renal dysfunction.[58] sPRR also promotes inflammation, adhesion, and endothelial dysfunction via NOX-4/NF-κB signaling pathway and increases the expression of cytokines including IL-6, IL-8, vascular cell adhesion protein 1 (VCAM-1), and Intercellular Adhesion Molecule 1 (ICAM-1).[59] These inflammatory processes are gradual and may involve the RAS system.[60] Significance of sPRR in renal fibrosis is demonstrated by Xie et al where sPRR is shown upregulates fibronectin in human renal proximal tubular cells via activation of AKT/β-catenin/snail signaling pathway and inhibition of sPRR by selective S1P inhibitor PF429242 attenuated expression of fibronectin indicating an important role and identifying sPRR as a novel therapeutic target in renal fibrosis.[61] In addition to the renal effects, sPRR plays a role in the impairment of the sympathetic nervous system and vascular tone.[9,62] In obese mice induced with sPRR, blood pressure was increased due to elevation of leptin and sympathetic activation.[63] In obesity-related hypertension sPRR has shown to impair the morphology of adipose tissue contributing to the inflammatory process.[9] These effects were attenuated by knockdown of PRR suggesting that plasma leptin mediates the sPRR effect on sympathetic tone.[9,64] These mechanisms may be completely independent of the RAS system. However, taken together the above studies demonstrate that renal PRR plays a prominent pathophysiological role in renal dysfunction and inflammation.

Summary

In conclusion, the studies have demonstrated that PRR plays a significant role in the development of renal dysfunction, inflammation, and fibrosis. While the association between PRR and the inflammatory process is complex. These findings identify PRR as a potential therapeutic target in the management of renal complications in pathological disease.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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