

(Pro)renin Receptor and Vacuolar H⁺-ATPase

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(Received for publication on August 9, 2011)
(Revised for publication on September 14, 2011)
(Accepted for publication on November 17, 2011)

The (pro)renin receptor [(P)RR] is a molecule that binds prorenin and renin in tissues, leading not only to their activation, but also carrying out intracellular signaling. As a key player in the tissue renin-angiotensin system, (P)RR activation plays an important role in the development of end-organ damage in hypertension and diabetes. One fragment of (P)RR is also known as ATP6AP2 because it is associated with vacuolar H⁺-ATPase (V-ATPase). V-ATPase is a multi-subunit proton pump involved in diverse and fundamental aspects of cellular physiology, including receptor-mediated endocytosis and recycling, processing of proteins and signaling molecules, membrane sorting and trafficking, and activation of lysosomal/autophagosomal enzymes. The role of (P)RR in the function of V-ATPase has been investigated in recent studies using conditional knockout mice. Furthermore, the novel function of (P)RR as an adaptor protein between the Wnt receptor complex and V-ATPase has been demonstrated. Thus, (P)RR is a multi-functional molecule that has complex structure and functionality. This review focuses on current insights into the possibility of (P)RR acting as a modulator of V-ATPase and future perspectives in translational research. (Keio J Med 61 (3) : 73–78, September 2012)

Keywords: renin-angiotensin system, signal transduction, V-ATPase, vesicular acidification

Introduction

The (pro)renin receptor [(P)RR] was first identified as a receptor for renin and prorenin in 2002.¹ Binding with (P)RR not only induces the enzymatic activation of renin and prorenin but also induces angiotensin II-independent intracellular signaling. (P)RR has been shown to play a key role in the tissue renin-angiotensin system (RAS), and the actions induced by its own intracellular signaling play an important role in the development of end-organ damage in hypertension and diabetes.^{2–5} Recent studies revealed that (P)RR is an integral component of mammalian vacuolar-type H⁺-ATPase (V-ATPase), which is a multi-subunit proton pump involved in diverse and fundamental aspects of cellular physiology, including receptor-mediated endocytosis and recycling, processing of proteins and signaling molecules, membrane sorting and trafficking, and activation of lysosomal/autophagosomal enzymes.⁶ In addition, (P)RR works as an adaptor pro-

tein between the Wnt receptor complex and V-ATPase.⁷ Thus, (P)RR is a multi-functional molecule that exhibits complex structure and functionality. This review highlights the physiological effects of (P)RR on the function of mammalian V-ATPase.

Roles of (P)RR in Pathophysiology

Prorenin is an inactive proenzyme for active renin. Nevertheless, plasma prorenin levels are elevated in patients with diabetes mellitus compared with healthy subjects, and this elevation predicts microvascular complications in diabetic patients.^{8–10} The cause of this increase in prorenin levels is unclear, but may reflect increased prorenin gene expression and/or decreased prorenin clearance. The prorenin molecule contains a region called the prorenin prosegment, which consists of a 43-amino-acid sequence at the N-terminus of the renin molecule. The prorenin prosegment is thought to cover the enzyme ac-

tive site (the “closed” formation) and prevents access of angiotensinogen to the site. Prorenin can be activated proteolytically or nonproteolytically. The main physiological pathway for the activation of renin is proteolytic cleavage of the prorenin prosegment, which opens up the active site for angiotensinogen and its subsequent cleavage to angiotensin I. *In vivo*, proteolytic activation of prorenin occurs almost exclusively in the juxtaglomerular cells within the kidney. Nonproteolytic activation of prorenin is a reversible process and can be viewed as the prorenin prosegment unfolding from the enzymatic cleft. Nonproteolytic activation can be induced *in vitro* by low temperatures or low pH (optimal at pH 3.3).¹¹ (P)RR was found to induce nonproteolytic activation of prorenin.¹ (P)RR-bound prorenin becomes enzymatically active as a result of a conformational change without cleavage of the prosegment, and thereby becomes able to produce local angiotensin I, which subsequently generates angiotensin II. Therefore, (P)RR provides reasonable explanations of the significance and enzymatic role of prorenin in end-organ damage in diseases associated with the tissue activation of RAS, such as hypertension, diabetes, and preeclampsia.^{2–5,12} Moreover, (P)RR possesses its own intracellular signaling capability. Activated (P)RR induces the mitogen activated protein (MAP) kinases extracellular signal-regulated kinase (ERK) 1/2 and p38 pathways, leading to upregulation of profibrotic and cyclooxygenase-2 genes independent of angiotensin II generation; this upregulation contributes to the pathophysiology of end-organ damage. (P)RR blockade has been shown to attenuate end-organ damage in hypertensive and diabetic models.^{2–5}

Roles of (P)RR in Development

Previous reports have suggested a possible relationship of (P)RR with V-ATPase. Mouse embryonic stem cells deficient in (P)RR failed to generate chimeras when injected into blastocysts, in contrast to the successful birth of renin, angiotensinogen, and angiotensin type I receptor knockout mice.^{13–15} Zebrafish with mutant (P)RR display early developmental abnormalities, including eye and body hypopigmentation, as well as neuronal cell death, and die early in development, implicating the critical function of (P)RR in melanocytes and neurons.¹⁶ Zebrafish embryos with mutant V-ATPase subunits and those with mutant (P)RR share similar phenotypes,¹⁶ indicating a possible link between these two proteins. Similar phenotypes such as small heads, shortened tails, and defects in melanocyte and eye pigmentation were also observed in *Xenopus* when morpholino antisense RNA against (P)RR was injected into embryos.⁷ An exonic splice enhancer mutation of human (P)RR is associated with a family with X-linked mental retardation and epilepsy, allowing us to speculate that (P)RR may play an important role in the synaptic vesicles.^{17,18} These phenotypes related to the

mutation or deletion of (P)RR suggest essential roles for (P)RR in development.

(P)RR-deleted embryonic stem cells do not form chimeras after blastocyst injection.¹⁹ To circumvent this embryonic lethality, the tissue-specific (P)RR knockout mouse was created.⁶ Based on the roles of (P)RR under pathological conditions, the genetic ablation of (P)RR had been expected to be protective. However, cardiomyocyte-specific (P)RR knockout mice developed fulminant heart failure and inevitably died young. (P)RR-depleted cardiomyocytes displayed the perinuclear accumulation of numerous vacuoles, including multi-vesicular bodies and autophagolysosomes, which appeared to be caused by RAS-independent mechanisms. A C-terminal fragment of (P)RR was identified as vacuolar adenosine triphosphatase (V-ATPase), H⁺-transporting, lysosomal accessory protein 2 (ATP6AP2),²⁰ which plays an essential role in controlling the intracellular vesicular acid environment.²¹ Investigation of the underlying cellular mechanisms accounting for the incredible phenotypes observed in (P)RR-ablated cardiomyocytes identified a role for (P)RR in the function of V-ATPase, and disclosed that (P)RR is an accessory subunit to mammalian V-ATPase, important, in particular, for the stability and assembly of V₀ subunits.

V-ATPase-related Physiological Function of (P)RR

V-ATPase is a large multi-subunit, membrane-associated protein complex that carries out active transport of protons across the membrane, thereby affecting the acidic environment of intracellular compartments and of the extracellular space (**Fig. 1**). V-ATPase is expressed in most kinds of cells and is widely distributed in various subcellular compartments such as the trans-Golgi network, endosomes, lysosomes, secretory granules, melanosomes, synaptic vesicles, and endocytic vesicles. As shown in **Table 1**, V-ATPase-dependent acidification of organelles facilitates protein sorting, membrane trafficking and fusion, receptor-mediated endocytosis and recycling, and lysosomal/autophagosomal protein degradation.²² For instance, hydrolases responsible for protein degradation in the lysosome have optimal activity at a low pH. pH is also involved in diverse cellular processes such as phagocytosis, virus entry, metastasis, and embryonic left–right patterning.^{22,23} In intracellular vesicles, V-ATPase also serves as a pH sensor to regulate trafficking.²⁴ (P)RR might also sense the acidity levels of intracellular compartments and regulate V-ATPase activity accordingly.⁶ Mutations in V-ATPase components, including (P)RR, or pharmacological inhibition of V-ATPase activity leads to the disruption of pH homeostasis. This results in an accumulation of membrane proteins in endocytic compartments and in some cases blocks transport between the late endosome and the lysosome, leading to lethality in various organisms.^{6,25} In addition, specific V-ATPase

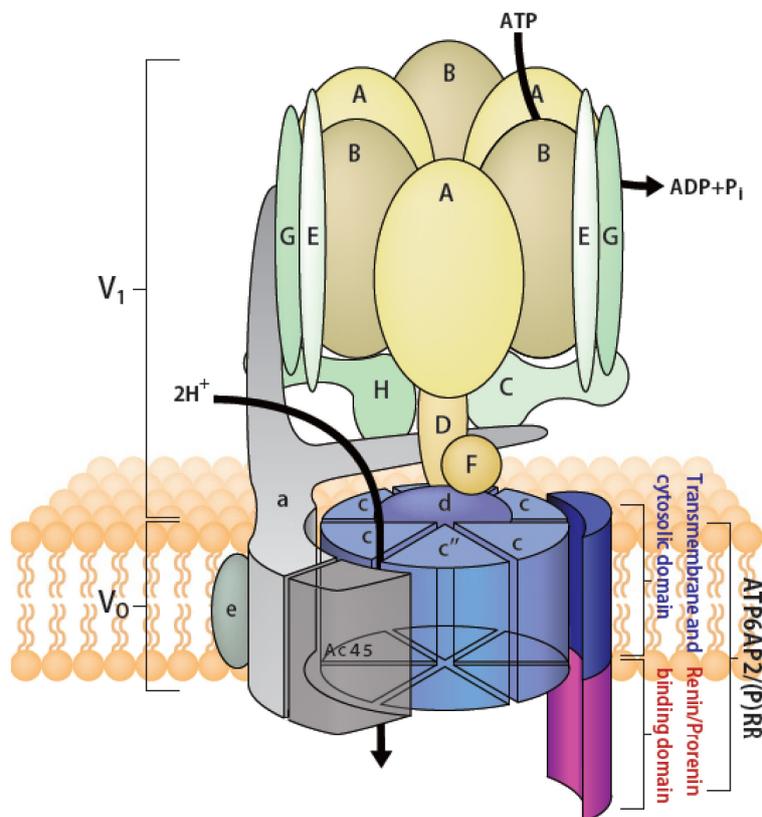


Fig. 1 Putative structure of mammalian vacuolar-type H^+ -ATPase and the (pro)renin receptor. A, B, C, D, E, F, G, H, a, c, c', d, e, AC45: subunits of vacuolar-type H^+ -ATPase. Reproduced with permission from Lippincott Williams & Wilkins.⁶

complexes participate in highly differentiated cellular and tissue functions, including urine acidification in renal intercalated cells and bone resorption in osteoclasts. V-ATPase complexes are also abundant in endocrine tissues, such as β cells in the pancreas and chromaffin cells in adrenal glands, participating in exocytosis in the regulated hormone secretion in an acidification-independent

manner.^{26,27} This ubiquitous and specific distribution of V-ATPase suggests that the enzyme is required for diverse fundamental roles in cellular physiology, and underscores the significance for the cell survival. Since the accumulation of intracellular vesicles in (P)RR-ablated cardiomyocytes was reproduced by the V-ATPase pharmacological inhibitor bafilomycin, it is clear that several

Table 1 Vacuolar H^+ -ATPase (V-ATPase)-dependent cellular mechanisms and their contributing physiological functions in mammals

V-ATPase in organelles	Examples of physiological functions
Protein sorting	Conversion of proinsulin to insulin in β cells
Membrane trafficking and fusion	Hormone secretion from endocrine cells
Receptor-mediated endocytosis and recycling	Receptor expression at plasma membranes
Lysosomal/autophagosomal degradation	Cellular recycling system
V-ATPase in plasma membranes	
Acid secretion	Urine acidification in renal intercalated cells
	Bone resorption in osteoclasts
Cell-to-cell fusion	Metastasis of malignancy
	Infection by HIV and influenzae

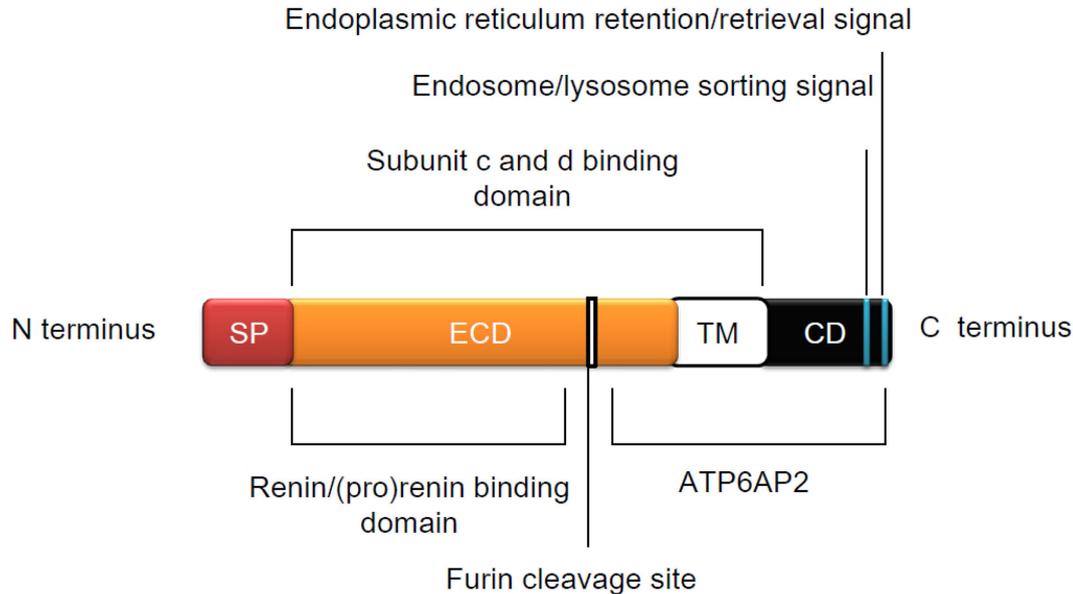


Fig. 2 The structure of the (pro)renin receptor.

SP, signal peptide; ECD, extracellular domain; TM, transmembrane domain; CD, cytosolic domain.

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physiological roles of (P)RR can be attributed to the functions of V-ATPase.

Structure, Cellular Localization, and Function of (P)RR

In humans, the (P)RR gene is located on the X chromosome at locus p11.4. (P)RR messenger RNA is 2034 base pairs long and there is no alternative splicing product. The protein is composed of 350 amino acids and has a predicted mass of 37 kDa. (P)RR contains four different domains: an N-terminal signal peptide, an extracellular domain, a single transmembrane domain, and a short cytosolic domain (**Fig. 2**).²⁸ The extracellular domain is responsible for binding with renin and prorenin, whereas the transmembrane and cytosolic domains are associated with V-ATPase. Unlike other components of RAS, the (P)RR gene is highly conserved among species, and (P)RR orthologs are found in many species, including rat, mouse, chicken, as well as in more primitive species such as frog, zebrafish, *Caenorhabditis elegans*, and *Drosophila melanogaster*,¹⁹ in which the role of RAS is unlikely to be meaningful. The degree of homology of (P)RR between human, rat, and mouse is about 95% for the nucleotide sequence and over 80% at the amino-acid level.²⁹ Thus (P)RR is an evolutionally conserved protein despite having no yeast orthologs. The highest level of homology is found in the transmembrane and cytoplasmic regions corresponding to ATP6AP2, discovered in bovine chromaffin granules.²⁰ This corroborates the most

fundamental function of (P)RR – working as a subunit of V-ATPase. In addition, the extracellular domain displays high amino acid sequence identity exclusively in vertebrates.¹⁹ Because RAS emerged relatively late in evolution, the ATP6AP2 protein may have acquired renin- and prorenin-binding properties.³⁰ Consequently, RAS could affect the intracellular vesicular environment by modulating V-ATPase function via (P)RR.

(P)RR was thought to be localized mainly on the plasma membrane. However, recent studies revealed that most (P)RR is found in the intracellular regions, particularly around the nucleus, which is in line with the subcellular localization of V-ATPase.^{31,32} In fact, sequence analysis disclosed that the cytosolic domain of (P)RR carries an endosomal/lysosomal sorting signal as well as endoplasmic reticulum retention motifs.¹⁹ Previous studies have also demonstrated that (P)RR is found in the trans-Golgi network, where it undergoes cleavage by proteases such as proprotein convertase furin and ADAM19 to generate a 28-kD N-terminal soluble fragment that is secreted outside the cell, along with a 10-kD C-terminal residue that likely represents ATP6AP2.³³ Consistent with this, the N-terminal fragment of (P)RR is present in plasma and urine.³³ However, there are still many issues to be resolved: whether V-ATPase requires full-length (P)RR or still functions with truncated (P)RR, whether (P)RR always accompanies V-ATPase or sometimes exists alone, whether the amount of soluble (P)RR reflects the state of the intracellular environment, and to what extent soluble (P)RR contributes to the local RAS. The function of (P)

RR could be determined by its cellular localization and its form. Future study must address these issues and unravel the complex behavior of this molecule.

Wnt Signals and (P)RR at Plasma Membranes

Recently, the novel function of (P)RR as an adaptor protein between the Wnt receptor complex and V-ATPase was discovered in *Drosophila* and *Xenopus* using genomewide siRNA screening.^{7,34,35} Wnt signaling is involved in virtually every aspect of embryonic development and also controls homeostatic self-renewal in a number of adult tissues; it is also implicated in tumor formation.³⁶ Wnts bind to the seven-pass transmembrane receptor Frizzled, which enables Frizzled to cooperate with single-pass transmembrane proteins LRP5 and LRP6. Currently, Wnt receptor activation is believed to activate three different pathways: the canonical Wnt/ β -catenin cascade, the noncanonical planar cell polarity (PCP) pathway, and the Wnt/ Ca^{2+} pathway.³⁶ Since Wnt signaling was disturbed by the inhibition of V-ATPase function through the knock down of either (P)RR or other V-ATPase subunits and by pharmacological inhibitors of V-ATPase, (P)RR seems to mediate the internalization of the receptors and the subsequent proper signal transduction as a hinge molecule between the Wnt receptor and V-ATPase. Furthermore, it has been shown that V-ATPase is also required for the activation of the Notch receptor in physiological and pathological settings.^{37,38} Therefore, the acidification of an intracellular compartment could be a crucial factor for a wide variety of signal transductions. Indeed, this appears to be applicable also to (P)RR-mediated signaling itself. The inhibition of V-ATPase with bafilomycin attenuates ERK 1/2 phosphorylation induced by renin and prorenin in collecting duct/distal tubule lineage Madin-Darby canine kidney cells.³¹ However, the attenuation of ERK 1/2 phosphorylation could be explained by the effects of other intracellular signal transductions rather than by the direct influence of (P)RR-mediated signaling. V-ATPase-mediated vesicular acidification is necessary for proper signal transduction by controlling receptor-mediated endocytosis and receptor recycling. Therefore, bafilomycin might have disturbed granular acidification, thereby nonspecifically suppressing various signal transductions. Future studies should address the important issue of whether ERK 1/2 phosphorylation is attributed to (P)RR-specific intracellular signaling or to ligand nonspecific signaling.

Future Perspectives

(P)RR is an accessory subunit of mammalian V-ATPase as well as the receptor for renin and prorenin. Although there is currently no explanation as to why a subunit of V-ATPase acquired the function of a receptor for renin and prorenin, tissue RAS and the intracellular environ-

ment may be interconnected and mutually regulated via (P)RR. In fact, (P)RR blockade appeared to have benefits in animal models of diabetes and hypertension by inhibiting the tissue renin–angiotensin system,^{2–5} however, several studies have reported conflicting results.^{39,40} (P)RR blockade might also have adverse effects because it affects the activity of V-ATPase. If we can discover exactly to what extent the extracellular domain of (P)RR contributes to the function of V-ATPase, then translational research regarding (P)RR might provide a new strategy for treatment of chronic kidney diseases, osteomalacia, malignancy, infection, and endocrine disorders in addition to hypertension and diabetes.

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