The Prorenin Receptor: What’s in a Name

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The discovery of the prorenin receptor, now nearly a decade ago, altered our view of the renin-angiotensin system (RAS).1,2 Binding of prorenin, the inactive precursor of renin, to the prorenin receptor results in full catalytic activity of prorenin through a nonproteolytic mechanism that likely involves a conformational change by which the prosegment moves out of the catalytic cleft, which then becomes available for the substrate, angiotensinogen. Binding of renin or prorenin (here together denoted as prorenin) to the prorenin receptor also activates intracellular signaling pathways in several cell models independent from angiotensin generation, which leads to increased cellular proliferation, cytoskeletal rearrangements, and the production of profibrotic and proinflammatory factors.

Plasma prorenin levels are approximately 10-fold higher than those of renin and increase even further under certain pathologic conditions, such as diabetes mellitus complicated by nephropathy. Hence, prorenin could be a source for renin (here together denoted as prorenin) to the prorenin receptor gene is an essential gene, and strategies have therefore focused on using tissue-specific null alleles. Cardiomyocyte-specific prorenin receptor ablation results in early mortality due to heart failure.3 The cardiomyocytes of these null mice are characterized by extensive vacuolarization and impaired autophagic digestion because of decreased vacuolar-type H⁺-ATPase (V-ATPase) activity. The carboxyterminal 8.9-kD fragment of the prorenin receptor co-purifies with the V-ATPase from bovine adrenal secretory vesicles6 and is therefore also referred to as ATP6AP2 (ATPase, H⁺-transporting, lysosomal accessory protein 2). V-ATPases are complex proton pumps that consist of two multisubunit domains: a peripheral V₁ domain that hydrolyzes ATP and a transmembrane V₀ pore domain that translocates protons across membranes. V-ATPases are found in virtually every cell type and are important for acidification of intracellular compartments. In some cell types, they are abundantly expressed at the plasma membrane, for example in the intercalated cells of the collecting duct, where V-ATPases secrete protons into urine. Although not a subunit of the V-ATPase, the prorenin receptor is important for V-ATPase stability, because prorenin receptor ablation in mouse embryonic fibroblasts and in cardiomyocytes results in selective downregulation of V₀, but not V₁, subunits.5

The prorenin receptor is also required for canonical Wnt/β-catenin signaling, acting as a physical adaptor between the Frizzled/LDL receptor-related protein complex and V-ATPase.7 Frizzled/LDL receptor-related protein receptor complexes become internalized into signalosomes. For downstream signaling, signalosomes have to be acidified by V-ATPases, and this process depends on the presence of the prorenin receptor. In the Wnt/planar cell polarity pathway, the prorenin receptor also interacts with Frizzled receptors and is required for the planar polarization of epithelial cells.8

In the current issue of JASN, Oshima et al.9 and Riediger et al.10 report that the prorenin receptor–V-ATPase association is also essential for podocyte function and survival. Both groups crossed prorenin receptor-floxed mice with mice that express Cre-recombinase under the podocin promoter to specifically delete prorenin receptor expression in podocytes. The conditional null mice (cKO) died within 2 to 4 weeks because of renal failure. cKO mice developed nephrotic syndrome with increased serum creatinine and cholesterol levels. Albuminuria was present as early as day 2,10 indicating a defective glomerular filtration barrier. Podocytes of cKO mice displayed massive foot-process effacements accompanying by alterations in the actin cytoskeleton, whereas the slit diaphragm proteins, nephrin and podocin, showed reduced expression and redistribution to the cytosol. Over time, cKO podocytes became highly vacuolated and showed autophagic defects.

Autophagy depends on V-ATPase activity, and ablation of the prorenin receptor gene from isolated podocytes concordantly resulted in deacidification of intracellular vesicles, altered actin cytoskeletal organization,10 and increased expres-
sion of autophagosomal markers. These abnormalities could be reproduced by treatment of wild-type podocytes with the V-ATPase specific inhibitor, bafilomycin A1. Riediger et al. found that the accumulation of undigested proteins leads to endoplasmic reticulum stress. This could ultimately result in necrosis of podocytes, explaining the progressive loss of podocytes in cKO glomeruli.

Similar to cardiomyocytes, prorenin receptor depletion in podocytes causes destabilization of the V0 domain, as witnessed by downregulation of the V0c subunit. Is V-ATPase instability and the subsequent loss of activity the sole reason for the effects of prorenin receptor depletion, or are there other functions for the prorenin receptor essential for podocyte integrity? Both groups found vesicle deacidification in cultured podocytes 6 to 8 days after prorenin receptor depletion, when expression of the V0c subunit is greatly diminished. However, at day 4, V0c subunit expression is still comparable to controls, whereas the prorenin receptor protein is completely absent. It may therefore be interesting to determine whether vesicle deacidification and podocyte dysfunction is already manifested after 3 to 4 days of prorenin receptor depletion when V-ATPase is presumably still intact. Cruciat et al. found decreased Wnt-induced lipoprotein receptor-related protein phosphorylation and promoter activity in cells 3 days after transfection with small interfering RNAs against the prorenin receptor, although they did not check for expression of V-ATPase subunits. Wnt/β-catenin signaling is required for metanephric kidney development, but cKO mice were born without detectable kidney deformations. In podocytes, a balanced amount of Wnt/β-catenin signaling seems required because both overexpression and deletion of β-catenin can cause podocyte dysfunction. Planar cell polarity signaling components are also expressed in podocytes from fetal and adult glomeruli. In cultured podocytes, knockdown of planar cell polarity signaling causes alterations in cell shape, a decreased number of actin stress fibers, and redistribution of nephrin from cell protrusions to the cytosol, similar to prorenin receptor-deficient podocytes. However, it has been suggested that planar cell polarity is more likely involved in the primary organization of podocytes in the developing, but not in the mature, glomerulus.

Because prorenin receptor depletion in podocytes cultured in a defined medium has the same effect as in cKO glomeruli, these studies provide yet another addition to a growing list of prorenin-independent functions for the prorenin receptor. One may wonder whether there is a functional relation at all between prorenin and the prorenin receptor in vivo. Transgenic animal models are as yet inconclusive.

Overexpression of the prorenin receptor in rats causes hypertension, slowly progressive glomerulosclerosis, and renal cyclooxygenase-2 (COX-2) upregulation in an angiotensin-independent manner. In mice, hepatic overexpression of prorenin causes hypertension due to angiotensin generation. The plasma prorenin levels in these animals were approximately 70-fold higher than normal, far above the elevations (usually <5-fold) that occur under pathologic conditions. Remarkably, the mice showed no sign of end-organ damage, although this was anticipated on the basis of the activation of profibrotic and proinflammatory pathways resulting from prorenin-prorenin receptor interaction. The affinities of the prorenin receptor for renin and prorenin are in the nanomolar range, far above their picomolar plasma levels. Nanomolar concentrations are also required for signaling responses in most cell-based models, with a few exceptions (e.g., in collecting duct cells, where picomolar concentrations are sufficient to induce phosphorylation of the extracellular signal-regulated kinase 1/2). At least in collecting duct cells, this may be due to cell surface expression of the prorenin receptor, allowing engagement of sufficient numbers of receptors, even at low prorenin levels, to initiate signaling responses. Interestingly, prorenin-induced extracellular signal-regulated kinase 1/2 phosphorylation in cultured collecting duct cells is completely blocked by bafilomycin A1, indicating that for prorenin signaling, V-ATPase activity is also required.

In diabetic nephropathy, renal prorenin receptor expression is increased and COX-2 exacerbates the disease by specifically increasing podocyte prorenin receptor expression. Moreover, COX-2 inhibition abrogates the prorenin receptor upregulation and reduced albuminuria, foot-process effacement, and mesangial matrix expansion in diabetic transgenic mice selectively expressing COX-2 in podocytes. Combined with the COX-2 upregulation in prorenin receptor transgenic rats, these data suggest a link between COX-2 and the prorenin receptor, eventually resulting in nephropathy. Although it is attractive to speculate that this involves upregulated prorenin synthesis in the diabetic kidney, reflected by increased renin levels in urine (but not plasma), there is one caveat to this: Wnt/β-catenin signaling is also increased in podocytes and glomeruli in diabetic kidney disease, which likely contributes to podocyte loss and subsequently albuminuria. Hence, the effects of prorenin receptor overexpression could also be due to overactivation of the Wnt/β-catenin pathway, independent from prorenin.

Clearly, the delicate balance required for Wnt/β-catenin signaling appears to also apply to the prorenin receptor because overexpression and deletion of the prorenin receptor can cause podocyte dysfunction. This balance might also underlie the conflicting results arising from prorenin receptor blockade with handle region peptide (ranging from beneficial to detrimental) in vivo. These latter studies, the studies in transgenic rodents overexpressing the prorenin receptor or prorenin, and the current cKO podocyte data argue against a link between the prorenin receptor and the RAS. Thus, although it remains attractive to speculate about such a link, rigorous in vivo data are now required to determine whether the prorenin receptor truly deserves its name. In addition, although the beneficial effect of RAS blockers with regard to podocyte injury is well established, blocking the prorenin receptor on top of RAS blockade may prove to be detrimental.
DISCLOSURES
None.

REFERENCES


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