The (pro)renin receptor: what's in a name?

Matias Simons, Michael Bader and Dominik N. Müller

We read with interest the recent Review by A. Ichihara and M. S. Yatabe (The (pro)renin receptor in health and disease. *Nat. Rev. Nephrol.* **15**, 693–712 (2019))[1]. The (pro)renin receptor (PRR; also known as ATP6AP2) was first discovered in 1998 in a biochemical purification approach that yielded a 8.9 kDa fragment of a membrane-associated protein. This fragment associated with the proton pump V-ATPase and was hence given the gene name *ATP6AP2* (REF.[2]). However, in 2002, a seminal paper by Nguyen and colleagues[3] suggested that the fragment belonged to a larger protein — the PRR — that can bind to prorenin, the precursor of renin, on the cell surface, thereby facilitating its processing to renin. The circulatory levels of renin are normally ten times lower than those of prorenin. Moreover, elevated prorenin levels correlate with the microvascular complications of diabetes and hypertension, suggesting that prorenin may contribute to the extra-renal effects of renin. The PRR therefore represented a promising drug target to prevent end-organ damage mediated by the renin–angiotensin system (RAS). As a result, the PRR attracted a lot of attention, which was aided to a large extent by its flashy name.

Despite almost two decades of PRR research, it is still far from clear how prorenin is processed and, most importantly, whether this processing is physiologically relevant for the RAS. Unlike previous reviews of this research area[4,5], the article by Ichihara and Yatabe[1] and another recent review by N. Ramkumar and D. E. Kohan published in *Kidney International*[6] do not acknowledge this uncertainty.

A major issue plaguing the field is that deletion of the *ATP6AP2* gene causes embryonic lethality. For this reason, most loss-of-function studies either use a blocking peptide against the handle region or conditional mouse knockouts. Whereas the efficiency of the peptide approach remains controversial[7], the conditional knockout approach has so far mainly revealed V-ATPase-dependent effects, as reflected by reduced lysosomal acidification and/or impaired cell homeostasis in the targeted cell types and tissues. Importantly, impairment of cell homeostasis and even slow death of PRR-deficient cells can easily be missed if researchers do not specifically look for these effects[8,9]. Therefore, it is likely that putative RAS-related phenotypes reported in mice[10,11] are influenced or even caused by impaired cell homeostasis.

Studies of the effects of mutations in the *ATP6AP2* gene in humans have failed to identify any evidence of a role of the encoded protein in the RAS[12,13]. Instead, one report provided evidence for a causal relationship of *ATP6AP2* missense mutations with steatohepatitis, immunodeficiency and psychomotor impairment[14]. The most prominent cellular phenotypes were lysosomal and/or autophagic defects. The similarity of these phenotypes with phenotypes that are associated with deficiencies of endoplasmic reticulum (ER)-resident V-ATPase assembly factors as well as cell biological studies focusing on an ER retention motif in the cytosolic tail led to the proposal that the PRR could be a true component of the assembly machinery[14,15]. Defects in V-ATPase assembly may explain decreased endolysosomal acidification in the setting of human *ATP6AP2* mutations as well as Wnt signalling phenotypes reported for model organisms with reduced ATP6AP2 (REFS[16,17]). However, the ER localization of V-ATPase assembly is difficult to reconcile with any prorenin-binding activity for the PRR at the cell surface.

William Shakespeare's Juliet famously asks "what's in a name?". In the case of the PRR, the name has had a profound impact on the development of an entire research field. Although the two recent reviews clearly point out that the PRR has pleiotropic functions, noncritical use of this name could be misleading for the research community.

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Competing interests

The authors declare no competing interests.