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Podocyte ACE2 protects against diabetic nephropathy

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As new components of the renin–angiotensin system (RAS) are elucidated, our understanding of the complexities of their interactions also advances. Previous studies have determined that podocytes possess a local RAS that can generate angiotensin II. Podocytes have also been shown to express angiotensin-converting enzyme 2 (ACE2), which can decrease angiotensin II levels by generation of angiotensin-(1–9). Nadarajah et al. now show that increased podocyte ACE2 activity can attenuate the development of diabetic nephropathy.

The renin–angiotensin system (RAS) is phylogenetically ancient, and its importance in the maintenance of physiologic homeostasis is reflected by the tens of thousands of publications on the subject. However, although renin was first described in 1898 and angiotensin in 1936, investigators continue to discover new facets of the RAS. The role of the mono-carboxyl peptidase angiotensin-converting enzyme 2 (ACE2) in physiology and pathophysiology has attracted increasing interest. While ACE converts the decapetide angiotensin I to angiotensin II by removing the most distal amino acid, leading to production of angiotensin-(1–9) (Ang-1–9) and angiotensin-(1–7) (Ang-1–7), respectively. Ang-1–9 is then further metabolized by ACE to give Ang-1–7. Although ACE2 shares approximately 40% homology with the classic ACE, it is the product of a separate gene and is under separate regulatory control. Importantly, ACE inhibitors in clinical practice do not inhibit ACE2.

In general, studies have indicated that ACE2-mediated responses counteract those generated by ACE-mediated production of angiotensin II and promote vasodilation, natriuresis, and cytoprotection. Mice with global ACE2 deletion have increased responsiveness to RAS activation. Maternal ACE2 deficiency leads to fetal growth restriction, possibly secondary to increased placental concentrations of angiotensin II. ACE2 has also been implicated in regulation of oxidative stress in the paraventricular nucleus and rostral ventrolateral medulla, which may modulate sympathetic tone and blood pressure. Although in a manner that is not related to its role in regulation of the RAS, ACE2 serves as the receptor in the lung for the severe acute respiratory syndrome coronavirus, and ACE2-deficient mice do not develop lung injury upon exposure to the virus.

There remains uncertainty about exactly how ACE2’s effects are mediated. On the one hand, by conversion of both angiotensin I and angiotensin II to Ang-1–7, ACE2 modulates the amount of angiotensin II that is available to activate angiotensin II type 1 receptors, while on the other hand, Ang-1–7 is itself a ligand for the Mas receptor, activation of which has been reported to mediate vasodilation, natriuresis, and reductions in blood pressure. Depending on the tissue and the pathophysiologic condition, one or the other of these mechanisms may predominate, or they may work in concert. In any event, abnormalities in ACE2 expression and/or activity have now been implicated in a range of disorders, including hypertension, cardiovascular disease, and diabetic nephropathy.

Studies in patients with diabetic nephropathy have shown increases in the ACE/ACE2 ratio in both glomerulus and tubulointerstitium, due largely to decreased ACE2 expression. Previous studies in diabetic mice found that either global ACE2 deletion or pharmacologic ACE2 inhibition exacerbated development of diabetic nephropathy. Although these studies did not report any alterations of blood pressure with inhibition of ACE2 activity or expression, amelioration of diabetic nephropathy with systemic administration of recombinant ACE2 or increases in systemic ACE2 by adeno viral expression was associated with decreases in blood pressure, making it difficult to discern whether beneficial effects of ACE2 were a local response in the kidney or were secondary to systemic effects on blood pressure.

In the glomerulus, the podocyte expresses many components of the RAS, including the (pro)renin receptor, angiotensinogen, ACE, and the angiotensin II type 1 receptor. Podocytes also express ACE2, although glomerular expression of the Mas receptor remains uncertain. In previous studies, Mas was detected not in...
commentary

Figure 1 | The podocyte renin–angiotensin system and the mechanisms by which increased ACE2 expression can decrease local angiotensin II production. ACE2, angiotensin-converting enzyme 2; Ang-1–7, angiotensin-(1-7); Ang-1–9, angiotensin-(1-9); AT1, angiotensin II type I receptor; GBM, glomerular basement membrane.

glomeruli but only in the proximal tubule and juxtamedullary region, although global deletion of Mas induces hyperfiltration and albuminuria (Figure 1).

In order to test directly the role of local glomerular ACE2 in diabetic nephropathy, Nadarajah et al. (this issue) have developed a mouse model with selective podocyte overexpression of ACE2 by coupling the human ACE2 transcript to the nephrin promoter. The mice were on the FVB/n background, which is relatively sensitive to development of diabetic nephropathy, and when these mice were rendered diabetic by streptozotocin administration, the selective ACE2 overexpression in the podocytes delayed the onset of severe functional and structural glomerular changes. Specifically, there was a delay in the onset of significant albuminuria, a delay in development of significant mesangial expansion, a partial preservation of podocyte number, a delay in increases in glomerular expression of transforming growth factor-β (TGF-β), and preservation of expression of the podocyte markers nephrin and synaptopodin. Notably, these changes were not accompanied by any detectable differences in blood pressure between wild-type and transgenic diabetic mice, suggesting that the observed beneficial effects were due to direct, local effects at the glomerulus.

As with any well-performed study, these results raise a number of interesting questions. First and foremost of course are the exact mechanism and sites of action. Is this effect only due to relative inhibition of local podocyte angiotensin II production and angiotensin II type I receptor activation? If so, one might expect that with administration of an ACE inhibitor or an angiotensin receptor blocker, there might not be any additional benefit seen in the transgenic mice. Conversely, if increased Ang-1–7 underlies the observed beneficial effects of podocyte overexpression of ACE2, what is its site of action, as there is no evidence to date that podocytes express Mas? In this regard, this group has previously described that cultured mesangial cells do express Mas and respond to Ang-1–7. Other questions include the site of production and role of altered TGF-β in the ACE2 effects, especially since the aforementioned study in mesangial cells indicated that Ang-1–7 actually stimulated TGF-β production rather than inhibiting it. In a previous study by this group in a 5/6 nephrectomy mouse model, ACE2 inhibition worsened proteinuria, while administration of Ang-1–7 had no effect and actually increased mesangial expansion.

In summary, the study by Nadarajah et al. clearly shows that podocyte ACE2 overexpression can delay and ameliorate the development of glomerulopathy in a type 1 model of diabetes, indicating that in addition to systemic effects, ACE2 can slow diabetic nephropathy by direct effects on the glomerulus. Therefore, modulation of the ACE2 pathway represents a potentially exciting target for therapeutic intervention. Further studies to unravel the mechanisms underlying this protection will be required in order to determine whether increasing ACE2 activity or activating Ang-1–7-mediated signaling pathways will be the most successful mode of intervention (Figure 1).

DISCLOSURE

The author declared no competing interest.

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