Emerging evidence points to epidermal growth factor receptor (EGFR) overstimulation as a key player in the progression of chronic kidney disease (CKD) associated with hypertension. Angiotensin II (Ang II) has a well-recognized role in the development of renal fibrotic lesions. Compelling in vitro studies showed that the heparin-binding EGF-like growth factor (HB-EGF) ligand is a key mediator in the EGFR transactivation observed during chronic Ang II type 1 receptor (AT1R) stimulation. This editorial focus highlights the first evidence for the HB-EGF role in vivo using an inducible Cre-mediated recombination to generate a mouse model lacking HB-EGF in the vascular endothelial cells. This recent publication provides strong evidence for the role of HB-EGF mediating the Ang II/AT1R transactivation of the EGFR-mediated renal tissue damage during hypertension. Absence of endothelial HB-EGF in Ang II-infused mice showed a significant attenuation of the tissue fibrosis and damage, particularly in but not limited to the kidney.

One in 10 American adults, more than 20 million people, has some level of CKD (3a, 4). Among the comorbidities associated with CKD, diabetes and hypertension are the most prevalent conditions (5, 6, 23). As such, prevention and early intervention in patients undergoing CKD are instrumental steps in reducing the alarming end-stage renal disease projections. In this regard, clinical and experimental studies have investigated a number of potential mechanisms implicated in the generation and progression of renal tissue damage during different physiological and pathophysiological conditions.

One common insight to address is how the whole kidney (comprised of nephrons, tubules, and vasculature) responds to mechanical and hemodynamic strains during the development of CKD. On one hand, chronic low shear is known to promote endothelial dysfunction in arteries, which is typically associated with increased reactive oxygen species generation, reduced bioavailability of nitric oxide, and increased proinflammatory factors (14, 26). On the other hand, overactivation of G protein-coupled receptor (GPCR) signaling stimulates proliferation of the vascular smooth muscle cells (SMC) and renal interstitial tissue (2, 7), although this is initially displayed as an adaptive mechanism.

Specifically, Ang II has a well-recognized role in the development of renal fibrotic lesions (19). The use of angiotensin-converting enzyme inhibitors or Ang II type 1 receptor (AT1R) blockers benefits the traditional approach to ameliorate the progression of CKD (1, 18). Nevertheless, the exact molecular mechanism underlying the renoprotective effects of these approaches is not fully understood.

Emerging evidence points to epidermal growth factor receptor (EGFR) overstimulation as a key player in the progression of CKD associated with hypertension (20). Specifically, GPCRs such as the AT1R were shown to stimulate the processing and release of heparin-binding epidermal-like growth factor (HB-EGF) followed by transactivation of the EGFR (11, 12, 17, 24), the potency of which is comparable with platelet-derived growth factor-B and occurs in various kidney cell types and in vascular smooth muscle cells (29). First identified in the conditioned media of human macrophage-like cells, HB-EGF is a membrane-anchored acid glycoprotein cleaved by the metalloproteinase ADAM17 (the major sheddase for HB-EGF in renal tissue) and matrix metalloproteinases (15, 17). Soluble HB-EGF binds EGFR, influencing mutagenicity and chemotactic factors for smooth muscle cells and fibroblasts.

Compelling in vitro studies showed that HB-EGF ligand is a key mediator in the EGFR transactivation. Nevertheless, the first evidence for its role in vivo has been reported by Zeng et al. (28) in a recent issue of *AJP-Renal Physiology*, who utilized HB-EGF floxP and tamoxifen-inducible endothelial Cre mouse model (HBendo+/− mice) (28). This well-designed study provides strong evidence for the role of HB-EGF mediating the Ang II/AT1R transactivation of the EGFR-induced renal damage during hypertension. Absence of endothelial HB-EGF in Ang II-infused mice showed a significant attenuation of the tissue fibrosis and damage predominantly in but not limited to the kidney. These mice feature less albuminuria and glomerulosclerosis during Ang II-induced hypertension. Also, HBendo+/− mice show preserved endothelial and podocyte integrity, with attenuated VEGF expression in both glomeruli and vasculature. These studies nicely complement their own previous reports showing that specific deletion of HB-EGF expression in the vascular endothelium improves the renal injury status of diabetic nephropathy in mice lacking the eNOS, a model that may be related to high-circulating Ang II levels as well (13). Taken together, mice without endothelial HB-EGF present a much-attenuated response to the chronic Ang II-induced hypertension and renal tissue damage without blood pressure being lowered. These data reveal that neither EGFR transactivation nor HB-EGF ligand is the sole contributor to the vasoactive effects of chronic Ang II infusions.

Importantly, the local actions appear to respond to a predominant expression of HB-EGF in renal glomeruli and peritubular capillaries rather than in larger blood vessels.

Another important lesson from the studies by Ohtsu et al. (17) and Zeng et al. (28) is the promising approach by which ADAM17 inhibition combined with the lack of EGFR activation by HB-EGF abrogation could serve as a powerful strategy to augment the effectiveness of the beneficial renovascular outcomes. This assumption is based in the high levels of the ADAM17 sheddase in response to Ang II, although the ADAM17 levels were similarly elevated in HBlox/lox and HBendo+/− mice.

Can we fight chronic kidney disease by targeting endothelial HB-EGF?

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Divergent effects were found in response to EGFR activation by exogenous EGF or HB-EGF, with evidence of accelerated renal recovery from acute ischemic injury (8). Increased expression of HB-EGF was also identified in the kidney after acute tubular injury induced by multiple insults. In a mouse strain that has a point mutation in EGFR that displays a 90% reduction in receptor tyrosine kinase activity (waved-2 mice), renal function recovery was delayed after acute renal injury. Similarly, renal function recovery was significantly impaired in response to ischemia and reperfusion injury in mice with a certain EGFR deletion in the renal proximal tubule or treated with specific EGFR inhibitors (3, 25). These data provide substantial evidence that EGFR is somewhat involved in promoting kidney recovery from acute injury. This intriguing counterbalance seems to have its origins in the EGF/EGFR developmental functions. During organogenesis in fetal life, renal mesenchymal cells are dedifferentiated and extremely proliferative, a process that is actively regulated by numerous growth factors such as EGFR ligands (27). Whereas the inactivation of EGFR kinase activity inhibits the branching of cultured ureteric bud, EGFR knockout mice display impaired epithelial development in several organs, including the kidney (22). Overall, EGFR activation may promote renal recovery by enhancing renal regeneration. Not exclusive to the kidney, EGFR also plays a critical role during cardiac valve tissue development (9). This is another important reason to take advantage of inducible knockout models allowing a normal renal vascular and epithelial development due to the presence, for instance, of HB-EGF ligand.

In summary, a certain basal level of EGFR activity appears to be required to recover from detrimental insults (25). Therefore, although EGFR signaling may initially promote tissue repair during acute processes, the excess of tissue fibrosis and functional deterioration overcome the reparative actions contributing to a progressive decline in function. Also deserving attention is the use of EGFR inhibition for the treatment of kidney-unrelated tumors. In these patients, EGFR inhibition was associated with minor renal imbalance in electrolyte homeostasis. It is noteworthy that high rates of patients treated with EGFR inhibitors for colorectal tumors developed hypomagnesemia secondary to a reduced activity of EGFR-dependent renal Mg2 channels. However, induced collapsing glomerulonephritis, focal segmental glomerulosclerosis, and acute tubular necrosis were observed in a reduced group (10, 21). In addition, several experimental studies demonstrated that the use of a neutralizing antibody to EGFR reduces medial SMC proliferation and intimal hyperplasia. These after-effects further confirm that physiological EGFR signaling is required for renal electrolyte homeostasis and maintenance of an optimal kidney function. This supports the notion that systemic EGFR targeting may have a high-risk/high-benefit outcome.

Altogether, these new findings suggest that HB-EGF may be a link among vascular trophic responses to chronic elevations of blood pressure, endothelial dysfunction, and kidney injury, validating the therapeutic value of tissue-specific EGF and HB-EGF/EGFR inhibition in the context of renal fibrotic disorders. In this respect, the implementation of genetically engineered mice to target endothelial EGFR signaling provides the first known in vivo evidence of a novel opportunity for drug development.

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AUTHOR CONTRIBUTIONS

A.S.L. conception and design of research; A.S.L. analyzed data; A.S.L. interpreted results of experiments; A.S.L. prepared figures; A.S.L. drafted manuscript; A.S.L. edited and revised manuscript; A.S.L. approved final version of manuscript.

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