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The EGF Receptor Axis and Kidney Fibrosis

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Abstract

Purpose of review—To summarize recent findings about the role of the epidermal growth factor receptor (EGFR) in acute kidney injury and in progression of chronic kidney injury.

Recent findings—There is increasing evidence that EGFR activation occurs as a response to either ischemic or toxic kidney injury and EGFR signaling plays an important role in recovery of epithelial integrity. However, with incomplete recovery or in conditions predisposing to progressive glomerular and tubulointerstitial injury, aberrant persistent EGFR signaling is a causal mediator of progressive fibrotic injury. New studies have implicated activation of HIPPO/YAP signaling as a component of EGFR's actions in the kidney. There is also new evidence for gender disparities in kidney EGFR expression and activation after injury, with a male predominance that is mediated by androgens.

Summary—There is increasing evidence for an important role for EGFR signaling in mediation of kidney injury, raising the possibility that interruption of the signaling cascade could limit progression of development of progressive kidney fibrosis.

Keywords

EGF receptor; fibrosis; diabetic nephropathy; acute kidney injury

INTRODUCTION

The EGF receptor (EGFR, also known as ErbB1 or HER1) belongs to the ErbB/HER family of receptors, which also includes ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) [1]. These receptors are all single pass receptor tyrosine kinases that share a common structure, with an extracellular ligand-binding domain, a single membrane- spanning region, a homologic cytoplasmic protein tyrosine kinase domain, and a COOH-terminal tail with multiple phosphorylation sites that are docking sites for proteins containing SH2 domains or PTB (phosphotyrosine binding) domains [2].

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CONFLICTS of INTEREST

none

EGFR is expressed in numerus cell types in the adult mammalian kidney, including podocytes, endothelial cells and mesangial cells in the glomerulus and in multiple tubule segments, including proximal tubule, loop of Henle, distal convoluted tubule and collecting duct segments [3]. It is also expressed in cells in the interstitium, including medullary interstitial cells as well as in infiltrating immune cells. There are a number of excellent recent reviews that provide up to date information about roles for EGFR in kidney development and in physiologic regulation of renal function [4]. The current review focuses on recent studies examining the pathologic role of aberrant EGFR activation to mediate progressive kidney fibrosis.

Members of the EGF-related peptide growth factor family activate the EGFR. There are 11 known ErbB ligands, which can be divided into three groups [4]. The first group includes EGF, amphiregulin (AREG), transforming growth factor alpha (TGF-α, and epigen, specifically bind to and activate EGFR. The second group includes betacellulin (BTC), heparin-binding EGF (HB-EGF), and epiregulin (EPR), not only activate EGFR but can also bind to and activate ErbB4. The third group, the neuregulins (NRG 1–4), can only bind to ErbB3 and ErbB4 and not EGFR. No ligands have been identified for ErbB2, which heterodimerizes with the other members of the ErbB family. In addition, there has been a recent study suggesting that connective tissue growth factor (CTGF) can bind to and activate EGFR [5].

All of these growth factors are expressed as membrane-bound precursors that are released by ADAM-dependent cleavage in response to stimuli. This metalloproteinase-dependent release and EGFR activation is often in response to signaling initiated by other growth factors, cytokines or hormones, so called “transactivation” [6]. In addition, a number of the EGF family members have been shown to activate EGFR in their membrane-bound form without cleavage and release of the soluble mature growth factor, termed “juxtacrine” activation [7]. Finally, EGFR can be activated by non-ligand dependent receptor activation, mediated activation by src family kinases. The receptor can dimerize either with an additional EGFR molecule (homodimerization) or with another member of the ErbB family (heterodimerization). ErbB2 is the preferred heterodimerization partner. This leads to activation of the tyrosine kinase domains of both members of the receptor dimer and subsequent autophosphorylation of tyrosine residues in the cytoplasmic tail, which serve as docking sites for signaling protein complexes, including binding sites for scaffolding and intracellular signaling molecules: Shc, Grb2, Grb7, Crk, PLC-γ, SRC, PI-3K, protein phosphatases SHP1 and SHP2, and the E3 ubiquitin ligase Cbl. In addition, Stat1, Stat3, Stat5, and PLD mediate intracellular responses to EGFR activation without binding directly to the receptor. A broad range of signaling pathways can be activated by EGFR, including ras/raf/MEK/ERK, PI3K-Akt, p38, JNK, JAK-Stat, Src, small GTPases such as Rho and Rac, PLC-γ/Ca^{2+}/PKC and PKD [4].

There are a number of mouse models available for studying the physiologic and pathologic roles of the EGFR. Although global deletion of EGFR leads to either prenatal or perinatal death depending on the mouse strain [8], mice with floxed EGFR genes are available and have been used for conditional deletion of EGFR in podocytes [9] and proximal tubules [10,11] in the kidney. In addition, the *waved2* mice contain a point mutation in

the receptor tyrosine kinase domain that reduces activity by 90–95% and thus represent a hypomorph [12]. They develop relatively normally, although they have characteristic wavy fur and abnormal whiskers. In contrast, the DSK5 mouse has a point mutation that leads to constitutive overactivity of the EGFR receptor tyrosine kinase [13]. There are also mice available for studying the effects of altered expression of EGFR ligands. *Waved1* mice represent a spontaneous deletion of TGF-α [14]. There are also mice available with both global and conditional deletions of a number of the EGFR ligands (eg., EGF, TGF-α, amphiregulin HB-EGF, epiregulin) as well as deletion of ADAM17/TACE. In addition, our group has recently developed a mouse with selective proximal tubule overexpression of HB-EGF[15].

THE ROLE OF THE EGF RECEPTOR IN ACUTE KIDNEY INJURY

In many instances, kidneys undergoing AKI caused by either ischemic or renal toxic insults can completely recover function. There is clear evidence that recovery is dependent upon surviving proximal epithelial cells undergoing dedifferentiation, proliferation, migration, and ultimately redifferentiation into mature tubular cells[16]. EGFR expression and EGFR activation increase in response to AKI. Deletion of EGFR in proximal tubule epithelial cells or administration of the EGFR tyrosine kinase inhibitor erlotinib significantly delayed kidney functional and structural recovery from ischemia reperfusion-induced AKI [17]. Similarly, in toxin-induced AKI, *waved2* exhibited more severe renal dysfunction, histologic damage, and tubular cell apoptosis after toxin-induced AKI [12].

Older studies demonstrated that administration of exogenous EGF enhances renal tubule cell regeneration and repair and accelerates the recovery of renal function in ischemia reperfusion-induced AKI and mercury chloride nephrotoxicity [18,19]. However, renal expression and urinary levels of EGF decrease in both cisplatin and ischemia reperfusion-induced AKI. Decreased renal expression and excretion of EGF is also seen in chronic kidney diseases and in both AKI and CKD and is thought to represent dedifferentiation and injury of TAL and early DCT, the sites of greatest kidney EGF expression In this regard, decreased kidney EGF production is recognized as a prognostic biomarker for CKD progression [20]. Other EGFR ligands, such as amphiregulin, HB-EGF and epiregulin, are upregulated in AKI models and may mediate renal epithelial cell proliferation although there is still not direct evidence which EGFR ligands are involved or the cellular source of the putative ligands [21].

We recently identified an important role for activation of the Hippo-YAP pathway to mediate EGFR-dependent recovery from ischemic AKI ([22]. I/R injury induced nuclear YAP translocation and interaction with TEAD transcription factors. Inducible proximal tubule deletion of YAP in the RPTCs or administration of the YAP-TEAD association with the inhibitor, verteporfin, significantly delayed renal functional and structural recovery from IRI. Of note, inducible deletion of the TAZ had no effect, indicating a selective effect of YAP in AKI recovery. Either selective renal proximal tubule EGFR deletion or an EGFR tyrosine kinase inhibitor erlotinib inhibited YAP expression and nuclear translocation in response to IRI.

THE ROLE OF THE EGF RECEPTOR IN CHRONIC KIDNEY INJURY

Although regulated EGFR activation in response to acute kidney injury has been shown to be important for effective epithelial cell regeneration, if there is incomplete recovery, persistent and dysregulated renal EGFR activation can lead to progressive fibrosis [23]x. Selective proximal tubule EGFR inhibition reduces tubulointerstitial fibrosis in response prolonged ischemia reperfusion-induced AKI as well as in progressive fibrosis induced by subtotal nephrectomy [24]. Angiotensin II-induced kidney fibrosis is also attenuated in response to EGFR tyrosine kinase inhibition or with selective deletion of EGFR from proximal tubules [11].

Inhibition of release from proximal tubule of ADAM17-mediated factors inhibited kidney fibrosis after severe ischemic injury [25]. Administration of soluble amphiregulin promoted tubulointerstitial fibrosis after either ischemic injury or unilateral ureteral obstruction (UUO), and selective proximal tubule deletion of amphiregulin ameliorated fibrosis in both conditions [26]. Similarly, selective overexpression of HB-EGF in the proximal tubule led to increased myofibroblast transformation and concentric fibrosis surrounding the proximal tubules [27], while mice with endothelial-specific HB-EGF deletion had reduced Ang-II–mediated endothelial dysfunction, renal fibrosis, and inflammation [28].

Although EGFR inhibition has minimal effects on systolic hypertension, activation of EGFR in kidney may contribute to development of kidney injury resulting from hypertension. In the kidneys of deoxycorticosterone acetate salt-induced hypertensive rats, EGFR expression is upregulated, especially in the media of afferent and efferent arterioles, and EGFR tyrosine receptor kinase inhibition inhibited aldosterone mediated fibrosis [29].

Our group recently determined that DSK5 mice, which have constitutively active expression of EGFR, develop spontaneous glomerulosclerosis and tubulointerstitial nephritis. Interestingly, there is sexual dimorphism in the response, with male DSK5 mice exhibiting significantly more injury, associated with increased expression of kidney EGFR. Similar gender differences in kidney EGFR expression can be observed in male mice and in biopsies of human kidneys without obvious disease. The increase in EGFR expression in males was found to be secondary to testosterone since prepubertal male castration decreased, and testosterone administration to females increased kidney EGFR expression [13].

Recent studies have investigated signaling responses mediating the increased fibrosis mediated by EGFR. Previous studies had shown that Integrin α1β1 (Itgα1β1) prevented kidney fibrosis by reducing collagen production through inhibition of EGFR (Ambra). In the absence of this interaction, EGFR activation leads to increased phosphorylation and nuclear translocation of the RNA-DNA binding protein fused in sarcoma (FUS), which induces collagen synthesis [30]. In addition, a recent study demonstrated an important role for FOXM1 induction by EGFR in proliferation and repair of proximal tubules after acute ischemic injury [31]. Although this study did not specifically examine effects in chronic kidney injury, FOXM1 inhibition has been shown to decrease UUO-induced kidney fibrosis and persistent EGFR activation of FOXM1 in other organs leads to fibrosis [32]

EGFR is aberrantly activated in both experimental animal and human kidneys in response to diabetes [9,33]. In a mouse model of type I diabetes with accelerated nephropathy (eNOS-streptozotocin), chronic treatment with the EGFR tyrosine kinase inhibitor, erlotinib, reduced ER stress and decreased glomerulosclerosis. In addition, inhibition of EGFR activation increased autophagy secondary to inhibition of mTORC1 and stimulation of AMP kinase [34]. Selective deletion of EGFR in podocytes also decreased glomerulosclerosis in experimental type I diabetes [9]. Similarly, in a model of accelerated type II DN (eNOS-*db/db*), selective podocyte deletion of EGFR improved autophagy and retarded development of glomerulosclerosis [34]. Similar to the responses in acute ischemic kidney injury, proximal tubule EGFR activation in diabetes activates YAP, but its persistent activation leads to increased expression of profibrotic growth factors, including CTGF and amphiregulin. Either pharmacologic or genetic inhibition of YAP markedly decreased tubulointerstitial fibrosis in models of experimental diabetic nephropathy. This activation is dependent upon PI3 kinase/AKT and RhoA/ROCK activation by EGFR [33,35]. In addition to increased amphiregulin in diabetic nephropathy, HB-EGF expression increased in kidneys of the eNOS-db/db model of diabetic nephropathy [36], and serum and urine TGF-α increases in human diabetic kidney disease, and neutralizing antibodies to TGF-α were found to slow progression in models of accelerated diabetic kidney disease [37].

Polycystic kidney disease (PKD) is inherited as autosomal recessive (ARPKD) or autosomal dominant (ADPKD) traits, and EGFR activation has been implicated in cyst development and/or growth. Levels of EGFR ligands are increased in cyst fluid and can activate EGFR a in experimental models of PKD. Although EGFR is localized to the basolateral surface of normal renal tubules, in ADPKD, it is mislocalized to the apical surface of cyst lining epithelial cells. Administration of EGFR tyrosine kinase inhibitors attenuates cyst growth in experimental models [38]. A phase two clinical trial with an EGFR kinase inhibitor, tesavatinib, is currently underway in patients with ADPKD.

Aberrant EGFR activation has also been implicated in experimental models of rapidly progressive glomerulonephritis induced by anti-GBM serum and in puromycin aminonucleoside-mediated nephropathy. EGFR has also been found to be activated in a model of hyperuricemic nephropathy that induces glomerular sclerosis and renal interstitial fibrosis, and injury could be ameliorated by an EGFR inhibitor [39]. Renal fibrosis in an experimental model of chronic allograft nephropathy was also inhibited by EGFR tyrosine kinase inhibition [40].

Of interest, unlike the other ErbB family members, whose overexpression or constitutive activation mediates progression of many types of cancers, ErbB4 expression in cancer is often associated with growth suppression and improved prognosis. ErbB4 expression increases in CKD but in human kidney biopsy samples, ErbB4 expression levels were found to accelerate a model of murine polycystic kidney disease and inversely correlate with the degree of renal fibrosis [41]. In both a UUO model and an AKI to CKD model, deletion of ErbB4 promoted excessive renal fibrosis, which was G2/M arrest and tubule dedifferentiation. It was also notable that there was increased YAP activation, suggesting that ErbB4 activation might serve as a counter regulator of the profibrotic actions of EGFR, although further studies will be necessary to investigate this possibility.

Conclusion

There is increasing evidence that aberrant activation of the EGF receptor plays an important role in progressive fibrosis in a number of chronic kidney diseases. The skin side effects seen with current EGF receptor blocking antibodies or kinase inhibitors are a potential hurdle that must be overcome before therapeutic inhibition of this pathway will be a viable option for treatment of chronic fibrotic kidney diseases.

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KEY POINTS

The epidermal growth factor receptor is expressed both the developing and the mature mammalian kidney.

In addition to its roles in physiologic regulation of the kidney, the EGFR is involved in responses to both acute and chronic injury.

Mice with selective deletion of proximal tubule EGFR have delayed recovery from acute epithelial injury.

In contrast, persistent aberrant activation of EGFR is a mediator of progressive tubulointerstitial and glomerular injury in models of diabetic injury or other experimental models that promote kidney fibrosis.