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REVIEW

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Exploring the mechanistic role of epidermal growth factor receptor activation in non-cancer kidney disease

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Abstract: The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that plays a crucial role in signal transduction and cellular responses. This review explores the function of EGFR in kidney physiology and its implications for various kidney diseases. EGFR signaling is essential for kidney function and repair mechanisms, and its dysregulation significantly impacts both acute and chronic kidney conditions. The review discusses the normal distribution of EGFR in kidney tubular segments, the mechanism of its activation and inhibition, and the therapeutic potential of EGFR-targeting antagonists and ligands. Additionally, it explores the pathophysiological characteristics observed in rodent models of kidney diseases through pharmacological and genetic inhibition of EGFR, highlighting therapeutic challenges and limitations such as species differences, variability in disease models, and potential adverse effects. Overall, the findings underscore the multifaceted role of EGFR in kidney diseases, influencing inflammation, fibrosis, and tissue injury. This complex involvement suggests that targeting EGFR may be a beneficial therapeutic strategy for managing these conditions, potentially mitigating inflammation and fibrosis while promoting tissue repair.

Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein composed of 1186 amino acids, first identified in 1986 [1,2]. As illustrated in Fig. 1, it consists of several domains: an extracellular domain (621 amino acids) with ligand-binding sites, a single hydrophobic transmembrane domain (23 amino acids) that anchors the receptor to the cell membrane, and an intracellular domain (542 amino acids) responsible for signaling [3,4]. The intracellular domain includes a juxtamembrane segment, a tyrosine kinase domain, and a COOH-terminal tail [5,6]. As depicted in Fig. 2, ligand binding to the extracellular domain of EGFR induces homodimerization or heterodimerization of the bound receptor [7,8]. This dimerization activates the intrinsic tyrosine domain, resulting in the autophosphorylation of other tyrosine kinase residues in the COOH-terminal tail [9,10]. Autophosphorylation generates docking sites for various intracellular signaling proteins, subsequently initiating multiple downstream signaling cascades [11,12]. Therefore, the dimerization and autophosphorylation of EGFR are crucial steps in its role in signal transduction and cellular response.

Interest in the role of EGFR in kidney physiology has significantly increased in recent decades [13,14]. Numerous studies indicate that EGFR signaling is crucial for the progression of various kidney diseases [13,15]. This signaling pathway is central to regulating kidney function and the repair mechanisms essential for maintaining kidney health [14,16]. Dysregulation of EGFR has a profound impact on both acute and chronic kidney conditions [13,15]. This review aims to clarify the role of EGFR in kidney physiology and to introduce EGFR-targeting antagonists and ligands. Additionally, it explores the pathophysiological characteristics of EGFR observed in rodent models of various kidney diseases through pharmacological and genetic inhibition of EGFR.

Normal Distribution of EGRF in Kidney Tubular Segments

Distribution and activation of EGFR in kidney tubular segments

The kidney tubular apparatus in mammals comprises several distinct segments, each performing an indispensable function

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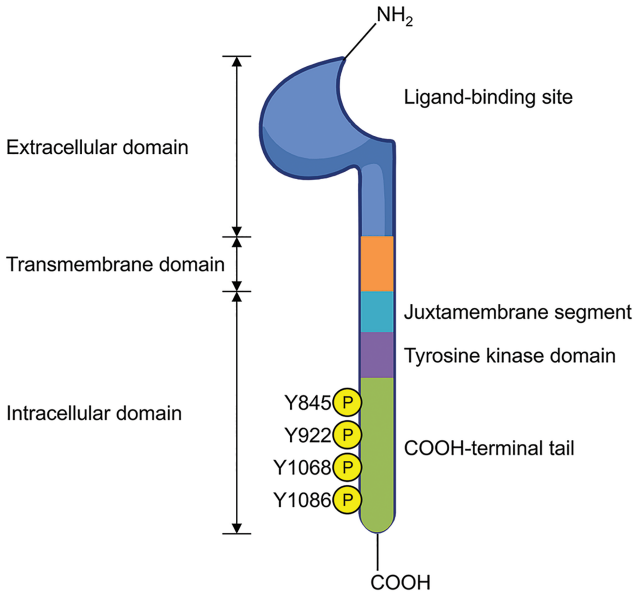

FIGURE 1. EGFR structure. The figure illustrates the extracellular domain, which contains the ligand-binding site; the transmembrane domain; and intracellular domain, which includes the juxtamembrane segment, the tyrosine kinase domain, and the COOH-terminal tail featuring autophosphorylated tyrosine residues. Created in BioRender.com.

in kidney physiology [17,18]. These segments include the proximal tubule, loop of Henle, distal tubule, connecting tubule, and collecting duct, each characterized by specific structural and functional attributes [19,20]. The proximal tubule, which consists of convoluted and straight portions, features cuboidal epithelial cells with a brush border [21,22]. The loop of Henle includes the proximal tubule's pars recta, descending thin limb, ascending thin limb, and thick ascending limb (TAL) [23,24]. The distal tubule consists of the TAL, macula densa, distal convoluted tubule (DCT), and connecting tubules [25,26]. Finally, the collecting duct, which comprises various segments, contains principal and intercalated cells.

EGFR expression is observed in normal kidneys, where it is widely distributed across various segments, including proximal tubule, thin limb of the loop of Henle, TAL, DCT, and collecting duct, and glomerulus. Specifically, within the glomerulus, EGFR expression is found in podocytes, endothelial cells, mesangial cells, and along the glomerular basement membrane [27,28] (Table 1). Additionally, EGFR expression is present in medullary interstitial cells, peritubular capillaries, and arterioles in the kidneys [27,28]. In tubular epithelial cells, EGFR is predominantly localized to the basolateral membrane and the cytoplasm adjacent to the basal membrane [27,29]. Upon binding of a EGFR ligand, EGFR activation through tyrosine phosphorylation significantly increases at the basolateral membrane across all segments of the kidney tubules, including proximal tubules, where EGFR expression is faint under normal conditions [30–32]. Notably, EGFR activation is highest in proximal straight tubules, followed by proximal convoluted tubules, collecting ducts, and DCT [31,32].

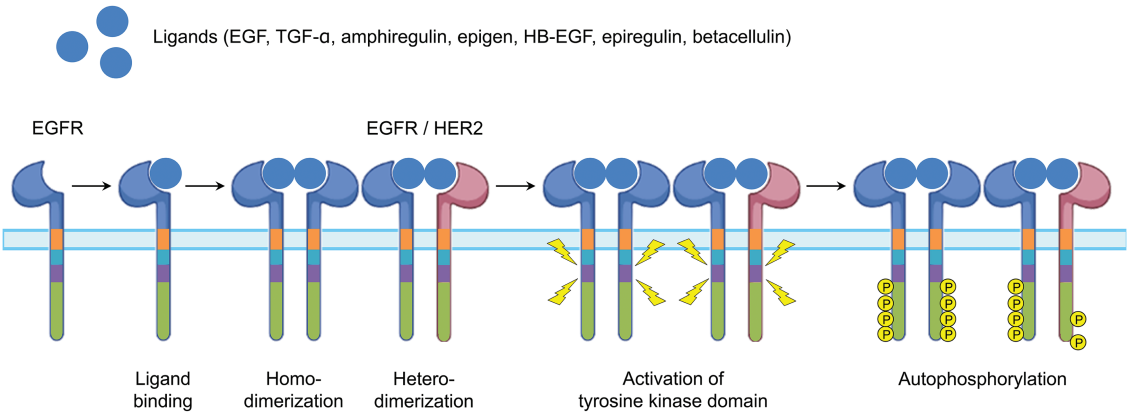

FIGURE 2. Flux of EGFR activation. Abbreviations: HB-EGF, heparin-binding EGF-like growth factor; HER2, human epidermal growth factor receptor 2; TGF-α, transforming growth factor-α. Created in BioRender.com.

TABLE 1

Expression of EGFR protein and mRNA in normal kidneys

Species	Expression	Glom	PST	PCT	TLH	TAL	DCT	CNT	CD	Ref.
Human	mRNA	+	ND	ND	ND	+	+	ND	ND	[27]
Human	Protein	+	–	–	++	++	++	ND	ND	[27]
Human	Protein	+	ND	ND	ND	ND	+	ND	+	[28]
Mouse	Protein	ND	+	+	ND	ND	ND	ND	+	[29]

Note: The symbols –, +, and ++ represent faint, moderate, and strong expression, respectively. Abbreviations: CD, collecting duct; CNT, connecting tubule; DCT, distal convoluted tubule; Glom, glomerulus; ND, not determined; PCT, proximal convoluted tubule; PST, proximal straight tubule; Ref, reference; TAL, thick ascending loop of Henle; TLH, thin limb of loop of Henle.

EGFR Activation and Inhibition from Ligands to Inhibitors

EGFR ligands

The first ligand discovered for the EGFR was epidermal growth factor (EGF) [33,34]. This ligand was initially characterized by Nobel laureate Dr. Stanley Cohen and his colleagues, who identified it in an extract from the submaxillary gland [35,36]. In addition to EGF, several other ligands interact with EGFR, including transforming growth factor-α (TGF-α), amphiregulin, epigen, heparin-binding EGF-like growth factor (HB-EGF), epiregulin, and betacellulin [37,38]. These ligands can be categorized into two groups [39]: the first group, which includes EGF, TGF-α, amphiregulin, and epigen, binds specifically to EGFR, while the second group, comprising HB-EGF, epiregulin, and betacellulin, binds to both EGFR and human epidermal growth factor receptor 4 (HER4). Connective tissue growth factor (CTGF), recognized as a ligand for integrins and TGF-β receptors, can also bind to and activate EGFR [40,41]. Among these ligands, EGF, TGF-α, HB-EGF, and betacellulin are considered high-affinity ligands [42,43], whereas amphiregulin, epigen, and epiregulin are classified as low-affinity ligands [43,44].

All endogenous EGFR ligands, with the exception of CTGF, are initially expressed as type I transmembrane proteins. These ligands are then converted into their mature, soluble forms, which are released into the extracellular environment through proteolytic cleavage by metalloproteinases, particularly members of the a disintegrin and metalloproteinase (ADAM) family [45,46]. Most EGFR ligands are produced in the kidney. EGF is primarily found in the TAL and DCT, with immunoreactivity observed along the apical membrane and in the cytoplasm [27,47]. In the connecting tubule and cortical collecting duct, EGF exhibits membranous staining, particularly in intercalated cells, which display a distinctive octopus-like morphology [47]. TGF-α is predominantly localized in the proximal tubules of the kidney cortex [47,48], with additional presence in the DCT [48]. HB-EGF is mainly localized in the proximal tubule, especially in the S3 segment of the outer stripe of the outer medulla [49]. Amphiregulin is expected to be primarily expressed in the proximal and distal tubules, as demonstrated by its upregulation following kidney injuries [50,51], although detailed distribution along various tubular segments is limited. Epigen has been detected in mouse kidney tissues [52], epiregulin is expressed in primary cultured human glomerular mesangial cells [53], and betacellulin is expressed in bovine kidney epithelial cell [54]. However, there are no reports detailing the expression of these proteins along specific tubular segments.

Mechanisms of EGFR activation

Activation of the EGFR depends on its ligands, which promote the formation of either homo- or heterodimers at the cellular membrane, ultimately leading to receptor internalization. Upon ligand binding, EGFR can dimerize with another EGFR molecule (homodimerization) or with a different receptor of the human epidermal growth factor receptor (HER) family (heterodimerization) [7,8]. Although EGFR has also been shown to heterodimerize with receptors for hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF) [55,56], the biologic significance of these interactions remains unclear. Following internalization, the dimerized receptors undergo autophosphorylation within their intracellular tyrosine kinase domains, generating binding sites for signaling molecules and initiating downstream intracellular signaling cascades [8,10]. Multiple post-translational modifications of EGFR, including methylation of the extracellular domain [57,58], phosphorylation on Serine and Threonine residues [57,59], SUMOylation [57,60], and ubiquitination [61,62], have been identified as regulatory factors that influence EGFR functionality and may serve as potential therapeutic targets to overcome drug-resistance mutations [63,64].

EGFR plays a crucial role in various signaling pathways that regulate cell growth, differentiation, and survival, particularly in kidney disease [30]. Following EGFR autophosphorylation, it activates downstream pathways such as mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), which promote cell proliferation, and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), which enhances cell survival by inhibiting apoptosis [2,65]. Additionally, HER2, a member of the EGFR family, can form heterodimers with EGFR, intensifying signaling and contributing to kidney injury and fibrosis [30,66]. EGFR signaling is critical in kidney development and repair processes, promoting the proliferation of kidney epithelial cells and facilitating recovery following acute kidney injury (AKI) [30,67]. However, dysregulation of EGFR signaling is linked to chronic kidney disease (CKD), where it can exacerbate inflammation and fibrosis [13,68]. Consequently, targeting EGFR has been explored as a therapeutic strategy for various kidney diseases, particularly those associated with fibrosis. Dual targeting of EGFR and HER2 may offer potential benefits in conditions where both pathways are implicated.

EGFR inhibitors

Small molecules inhibit the activity of EGFR tyrosine kinase by binding to the ATP-binding site within the receptor's intracellular domain [69]. EGFR tyrosine kinase inhibitors (TKIs) specifically target this domain of EGFR, competing with ATP for binding [69]. This inhibition prevents the activation of tyrosine kinase and the autophosphorylation of EGFR, thereby disrupting EGFR signal transduction pathways [69,70]. By preventing receptor phosphorylation, which is essential for the activation of downstream signaling pathways, TKIs effectively inhibit EGFR activation [70,71] (Table 2). As shown in, these inhibitors can selectively interfere with EGFR alone or with other human epidermal growth factor receptor (HER) family receptors in addition to EGFR. Numerous TKIs currently in clinical development have demonstrated potential antitumor activity. Furthermore, TKIs have shown protective effects against various kidney diseases in animal studies. These inhibitors can be further categorized based on whether their effects are reversible or irreversible [4,72].

TABLE 2

General clinical use of EGFR tyrosine kinase inhibitors and their application in animal models of kidney disease

Name	Target	General clinical use	Animal experiment for kidney disease
Reversible EGFR tyrosine kinase inhibitors			
Gefitinib	EGFR	First-generation inhibitor	Glomerulonephritis [73]
		NSCLC with EGFR L858R mutation	Hyperuricemia [74]
		Advanced or metastatic NSCLC	Sepsis [75]
			UUO [76]
Erlotinib	EGFR	First-generation inhibitor	Diabetic nephropathy [77]
		NSCLC with EGFR L858R mutation	Glomerulonephritis [78]
		Pancreatic cancer (combined with gemcitabine)	Kidney IRI [79]
			Sepsis [80]
Lapatinib	EGFR	Second-generation inhibitor	Lupus nephritis [81]
	HER2	Advanced or metastatic HER2-positive breast cancer (combined with letrozole)	
Osimertinib	EGFR	Third-generation inhibitor	
		NSCLC with EGFR T790M mutation	
		First-line treatment of EGFR-mutanted NSCLC	
Icotinib	EGFR	First-generation inhibitor (used in only China)	
		NSCLC with EGFR L858R mutation	
AG-1478	EGFR		Diabetic nephropathy [82]
			Glomerulonephritis [78]
			Obesity nephropathy [83]
PKI-166	EGFR		Diabetic nephropathy [84]
Epertinib	EGFR		
	HER2/4		
Rociletinib	EGFR		
Varlitinib	EGFR		
	HER2/4		
Irreversible EGFR tyrosine kinase inhibitors			
Dacomitinib	EGFR	NSCLC with EGFR L858R & T790M mutations	
	HER2/4		
Afatinib	EGFR	Second-generation inhibitor	
	HER2/4	NSCLC with EGFR L858R & G719X mutations	
Neratinib	EGFR	HER2-positive breast cancer	
	HER2		
CL-387785	EGFR		
Pelitinib	EGFR		
Tesevatinib	EGFR		
	HER2		
	VEGFR		
Canertinib	EGFR		
	HER2/4		
Poziotinib	EGFR		
	HER2/4		

Note: Abbreviations: IRI, ischemia and reperfusion injury; NSCLC, non-small cell lung cancer; UUO, unilateral ureteral obstruction; VEGFR, vascular endothelial growth factor.

TABLE 3

Animal models of kidney disease with EGFR-targeted inhibition

Year	Disease model + EGFR inhibition	Outcome	Ref.
Ischemic kidney disease			
2013	AKI by unilateral IRI in mice	↑ NGAL expression	[85]
	+ *Waved-2* mutation	↑ histopathological injury	
		↑ TUNEL-positive apoptosis in tubules	
		↓ p-EGFR, PAX-2, vimentin, PCNA, p-STAT3, and p-AKT expression	
2018	AKI by bilateral IRI in mice	↓ p-EGFR (Y1068), p-AKT, YAP, amphiregulin, cyclin D, and p-Rb expressions	[67]
	+ erlotinib		
	+ proximal tubular *Egfr* KO		
2023	AKI by bilateral IRI in mice	↓ CD64-positive macrophage infiltration	[86]
	+ erlotinib	↓ *Ptprc*, *Adgre1*, *Ccr2*, *Lyz2*, *Itgae*, *C5*, *Selp*, *Tnf*, *Ifng*, *Serpine1* mRNA expressions	
2012	CKD by bilateral IRI in mice	↑ BUN and creatinine concentrations in serum	[79]
	+ erlotinib	↑ histopathological injury in tubules	
	+ proximal tubular *Egfr* KO	↓ Ki67-positive cell proliferation in tubules	
		↓ p-EGFR, p-ERK1/2, and p-AKT expressions	
2013	CKD by unilateral IRI in mice	↓ Masson's trichrome-positive collagen deposition	[85]
	+ *Waved-2* mutation	↓ both α-SMA- and p-EGFR-positive cells	
		↓ both α-SMA- and PCNA-positive cells	
		↓ both α-SMA- and p-STAT3-positive cells	
		↓ both α-SMA- and p-AKT-positive cells	
		↓ p-EGFR, fibronectin, α-SMA, collagen I, PCNA, p-histone H3, p-STAT3, and p-AKT expressions	
2014	CKD by transplantation in rats	↓ Masson's trichrome-positive collagen deposition in tubulointerstitial area, glomeruli, and arteries	[87]
	+ erlotinib	↓ CD4- and CD8-positive lymphocytes	
		↓ EGF expression in tubulointerstitial area	
		↓ EGFR expression in tubulointerstitial area and tubules	
2023	CKD by bilateral IRI in mice	↓ Sirius red-positive collagen deposition	[86]
	+ erlotinib	↓ fibronectin, α-SMA, p-EGFR expressions	
Septic AKI			
2015	Septic AKI by LPS	↓ Mortality	[80]
	+ erlotinib	↓ *Il6* and *Tnf* mRNA amounts in plasma	
		↓ *Il6*, *Tnf*, and *Cxcl1* mRNA expressions in splenocytes	
2017	Septic AKI by LPS	↓ BUN and creatinine concentrations in serum	[75]
	+ gefitinib	↓ histopathological injury in tubules	
		↓ macrophage infiltration	
		↓ p-EGFR, p-STAT3, p-ERK, COX-2, and eNOS expressions	
		↓ *Icam1*, *Tnf*, and *Tgfb1* mRNA expressions	
2017	Septic AKI by CLP	↓ BUN and creatinine concentrations in serum	[75]
	+ *Waved-2* mutation	↓ histopathological injury in tubules	
		↓ TUNEL-positive and cleaved caspase-3-positive cells	
		↓ macrophage infiltration	
		↓ p-EGFR, p-ERK1/2, p-STAT3, COX-2, and eNOS expressions	
		↓ *Icam1*, *Tnf*, and *Tgfb1* mRNA expressions	

(Continued)

Table 3 (continued)

Year	Disease model + EGFR inhibition	Outcome	Ref.
Metabolic kidney disease			
2015	Hyperuricemia by adenine and potassium oxonate in rats	↓ albuminuria	[74]
	+ gefitinib	↓ creatinine, BUN, uric acid, and XOD concentrations in serum	
		↑ uric acid concentration in urine	
		↓ histopathological injury in tubules	
		↓ Masson's trichrome-positive collagen deposition	
		↓ p-EGFR (Y1068 and Y1173), lipocalin-2, fibronectin, collagen I, α-SMA, TGF-β1, p-Smad3, p-p65 NF-κB, TNF-α, IL-1β, CCL2, and CCL5 expressions	
		↑ OAT1 and OAT3 expressions	
2004	DN by STZ in rats	↓ kidney weight and glomerular volume	[84]
	+ PKI-166	↓ the number of PCNA- and BrdU-positive cells	
		↑ the number of TUNEL-positive cells	
		↑ cleaved caspase-3-positive area	
2011	DN by STZ in rats	↓ albuminuria	[88]
	+ PKI-166	↓ kidney weight and glomerular volume	
		↑ the number of WT1-positive podocytes	
		↓ the number of $p27^{Kip1}$-positive podocyte at cell cycle arrest	
2012	DN by STZ in mice	↓ p-EGFR (Y845), EGFR, Src, TGF-β, and p-Smad2/3 expressions	[89]
	+ proximal tubular *Egfr* KO		
2014	DN by STZ in *Nos3* KO mice	↓ albuminuria	[77]
	+ erlotinib	↓ mesangial expansion, mesangiolysis, and glomerulosclerosis	
		↓ F/80-positive macrophage infiltration ↓ p-EGFR (Y845, Y1068, and Y1173), p-ERK, CTGF, collagen I, collagen IV, CHOP, p62, p-ULK1 (S757), PERK, BiP, p-mTOR, p-RAPTOR, p-p70 S6 kinase, p-eIF4B, 3-nitrotyrosine expressions	
		↑ ATG12, beclin, LC3AII, p-ULK1 (S317), p-AMPKα, and p-AMPKβ expressions	
2015	DN by STZ in mice	↓ albuminuria	[90]
	+ podocyte-specific *Egfr* KO	↑ the number of synaptopodin-positive podocytes	
		↓ p-EGFR (Y845, Y1068, and Y1173), p-ERK1/2, TGF-β1, p-Smad2/3, fibronectin, and cleaved caspase-3 expressions in glomeruli	
		↑ Bcl-2 expression in glomeruli	
2016	DN by STZ in mice	↓ kidney weight	[91]
	+ proximal tubule-specific *Egfr* KO	↓ YAP, p-YAP, p-AKT, CTGF, and amphiregulin expressions	
	+ erlotinib	↑ TAZ expression	
2017	DN induced by STZ in mice	↓ albuminuria	[82]
	+ AG-1478	↓ Masson's trichrome-positive collagen deposition	
		↓ TUNEL-positive apoptosis	
		↓ DHE-positive suproxide production	
		↓ p-EGFR, p-AKT, Bax, ATF4, CHOP, and 3-nitrotyrosine expressions	
		↓ *Col4* and *Tgfb* mRNA expressions	
2018	DN in *Nos3* KO *db/db* mice	↓ blood glucose concentration	[92]
	+ erlotinib	↓ albuminuria	
		↓ glomerulosclerosis	
		↑ the number of podocytes in glomeruli	
		↓ Sirius red-positive collagen deposition	
		↓ F4/80-positive macrophage infiltration	

(Continued)

Table 3 (continued)

Year	Disease model + EGFR inhibition	Outcome	Ref.
		↓ CD8α-positive T cell infiltration	
		↓ Urinary F2-isoprostane and 4-hydroxynonenal	
		↓ p-EGFR (Y845 and Y1173), p-ERK, KIM-1, and CHOP expressions	
		↓ *Col1*, *Col3*, *Ctgf*, *Fn1*, *Tgfb*, *Adgre1*, Cd1a, *Irf5*, *Nos2*, *Tnf*, *Infg*, and *Il6* mRNA expressions	
2018	DN in *Nos3* KO *db/db* mice	↓ blood glucose concentration	[92]
	+ *Waved-2* mutation	↓ glomerulosclerosis	
		↓ macrophage infiltration in glomeruli	
2021	DN in *Nos3* KO *db/db* mice	↓ albuminuria	[93]
	+ podocyte-specific *Egfr* KO	↓ creatinine concentration in serum	
		↓ Sirius red-positive collagen deposition	
		↓ mesangial expansion and glomerulosclerosis	
		↑ the number of WT-1-positive podocytes	
		↓ Collagen I, Collagen IV, α-SMA, CTGF, Rubicon, p62, p-RPS6, and p-S6K expressions	
		↑ Beclin-1 and LC3B expression	
		↓ *Col1a1*, *Col4a1*, *Tgfb1*, Irf5, *Nos2*, *Il23*, *Il6*, *Il1a*, *Il1b*, *Ccl3*, and *Tnf* mRNA expressions	
		↑ *Nphs2* mRNA expression	
2016	Obesity by diet in *ApoE* KO mice	↓ Masson's trichrome-positivie collagen deposition	[83]
	+ AG-1478	↓ p-EGFR, p-AKT, p-ERK, TGF-β, collagen IV, Bax, VCAM-1 expressions	
		↑ Bcl-2 and IκB-α expression	
		↓ *Col1*, *Tgfb*, *Ccn2*, *Il6*, and *Il1b* mRNA expressions	
		↑ *Nfe2l2* and *Nqo1* mRNA expressions	
Inflammatory kidney disease			
2011	GN by anti-GBM in mice	↓ BUN concentration in serum	[78]
	+ AG-1478	↓ abuminuria and mortality	
	+ erlotinib	↓ crescent formation in glomeruli	
	+ podocyte-specific *Egfr* KO	↓ p-EGFR expression	
2016	GN by anti-Thy1.1 in rats	↓ creatinine concentration in serum	[94]
	+ erlotinib	↓ mesangial expansion in glomeruli	
		↓ CD4-positive T cell, CD8-positive T cell, and CD169-positive macrophage infiltrations in glomeruli	
		↓ EGF and EGFR expressions	
2023	GN by nephrotoxic serum in mice	↑ GFR	[73]
	+ macrophage-specific *Egfr* KO	↓ protein concentration in urine	
	+ gefitinib	↓ fibrinoid necrosis, crescent formation, and galectin-3-positive macrophage in glomeruli	
		↑ p56 expression in macrophages	
2018	Lupus nephritis in *Fcgr2b* KO mice	↓ BUN concentration in serum	[95]
	+ erlotinib	↓ tubulointerstitial injury	
		↓ p-EGFR and p-ERK expressions	
		↓ *Ctgf* and *Col1a1* mRNA expressions	
2022	Lupus nephritis by pristane in mice	↑ glomerular abnormality and hypertrophy	[96]
	+ $CD4^+$ T cell-specific *Egfr* KO	↑ tubulointerstitial injury and splenomegaly	
		↑ deposition of IgG and C3 in glomeruli	
		↑ CD3-positive T cell infiltration in glomeruli	
		↑ IL-17A, IFNγ, and IL-14 expressions in CD4-positive T helper effector cells	

(Continued)

Table 3 (continued)

Year	Disease model + EGFR inhibition	Outcome	Ref.
2024	Lupus nephritis by IFNα in mice	↑ proteinuria and mortality	[81]
	+ lapatinib	↑ collagen I and α-SMA expressions	
2013	Inflammation by TWEAK in mice	↓ F4/80-positive macrophage infiltration	[97]
	+ erlotinib	↓ CD3-positive T cell infiltration	
		↓ p-EGFR (Y1068 and Y1173), IL-6, CCL2, CCL5, CCL20, CXCL10, CCR2, ICAM1, and osteopontin expressions	
Obstructive kidney disease			
2012	UUO in mice	↓ Masson's trichrome-positive collagen deposition	[76]
	+ gefitinib	↓ p-EGFR, collagen I, fibronectin, α-SMA, p-Smad3, p-histone H3, lipocalin-2, p-STAT3 and p-ERK1/2 expressions	
	+ *Waved-2* mutation	↓ *Tgfb1*, *Tnf*, and *Ccl2* mRNA expressions	
2019	UUO in mice	↓ Masson's trichrome-positive collagen deposition	[98]
	+ EGFR mimotope	↓ F4/80-positive macrophage infiltration	
		↓ CD9 and CD95 expressions in F4/80-positive macrophages	
		↓ fibronectin, collagen I, α-SMA, p-STAT3, p-ERK, and TGF-β1 expressions	
2023	UUO in mice	↓ EGFR, PDGFRβ, collagen IV, fibronectin, and α-SMA expressions	[68]
	+ fibroblast *Egfr* KO	↓ *Col1a1* mRNA expression	
		↓ Sirius red-positive collagen deposition	
		↓ TGF-β signaling in fibroblasts and myofibroblasts	

Note: Abbreviations: AMPK, AMP-activated protein kinase; α-SMA, alpha-smooth muscle actin; ATF4, activating transcription factor 4; ATG12, autophagy related 12; BiP, binding immunoglobulin protein; BrdU, bromodeoxyuridine; BUN, blood urea nitrogen; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; CHOP, C/EBP homologous protein; CLP, cecal ligation and puncture; COX-2, cyclooxygenase-2; CTGF, connective tissue growth factor; CXCL, C-X-C motif chemokine ligand; DHE, dihydroethidium; DN, diabetic nephropathy; EDA, ectodysplasin A; eIF4B, eukaryotic translation initiation factor 4B; eNOS, endothelial nitric oxide synthase; Fcgr2b, Fc gamma receptor Iib; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; ICAM1, intercellular adhesion molecule 1; IκBα, nuclear factor-kappa B inhibitor alpha; IL, interleukin; Irf5,interferon regulatory factor 5; IRI, ischemia and reperfusion injury; KIM-1, kidney injury marker-1; KO, knockout; LC3, light chain 3; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NGAL, neutrophil gelatinase-associated lipocalin; NOS2, nitric oxide synthase 2; NQO1, NAD(P)H quinone dehydrogenase 1; OAT, organic anion transporter; p27Kip1, cyclin-dependent kinase inhibitor 1B; PAX-2, paired box gene 2; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PERK, protein kinase RNA-like ER kinase; RAPTOR, regulatory associated protein of mTOR; Rb, retinoblastoma protein; Ref, reference; RPS6, ribosomal protein S6; S6K, ribosomal protein S6 kinase; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TGF-β1, transforming growth factor-beta1; TNF-α, tumor necrosis factor-alpha; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; ULK1, unc-51 like autophagy activating kinase 1; UUO, unilateral ureteral obstruction; VCAM-1, vascular cell adhesion protein 1; WT1, Wilm's tumor gene 1; XOD, xanthine oxidase.

Role of EGFR in Kidney Diseases

Animal models of kidney disease

Several studies have highlighted the role of EGFR in various animal models of kidney disease (Table 3), encompassing a wide range of conditions. These include ischemic kidney disease such as AKI and CKD induced by unilateral or bilateral kidney ischemia and reperfusion injury (IRI); septic AKI triggered by lipopolysaccharide or cecal ligation and puncture; metabolic kidney disease such as hyperuricemia, diabetic nephropathy, and obesity-induced nephropathy; inflammatory kidney disease such as glomerulonephritis, lupus nephritis, and inflammation induced by tumor necrosis factor-like weak inducer of apoptosis (TWEAK); and obstructive kidney disease such as unilateral ureteral obstruction (UUO).

EGFR inhibition in ischemic kidney diseases

IRI contributes to the development of AKI, characterized by a sudden decline in kidney function, tubular injury, and inflammation [99–101]. In cases where recovery is maladaptive, the initial AKI can progress to CKD due to chronic inflammation and tubulointerstitial fibrosis [86,102,103]. Bilateral kidney IRI induces kidney dysfunction and tubular injury; however, pharmacological and proximal tubule-specific inhibition of EGFR does not significantly affect kidney dysfunction and tubular injury in AKI induced by bilateral kidney IRI [79,86]. Conversely, unilateral kidney IRI exacerbates tubular injury and apoptosis in the tubules when EGFR is inhibited due to a point mutation in the *Egfr* gene (*Waved-2* mutation) [85]. Pharmacological inhibition of EGFR has been demonstrated to reduce the pro-inflammatory response, as evidenced by decreased infiltration of macrophages and lymphocytes, as well as lower levels of pro-inflammatory mRNA expression following bilateral kidney IRI [86] and kidney transplantation [87]. Additionally, EGFR inhibition has been found to decrease IRI-induced activation of AKT and ERK [79,85], which may contribute to delayed recovery of kidney function and tubular morphology [79]. Generally, EGFR

inhibition effectively reduces tubulointerstitial fibrosis following IRI and kidney transplantation [85–87].

EGFR inhibition in septic AKI

Sepsis can lead to AKI through mechanisms such as hypotension, which impairs kidney perfusion and causes ischemia [104,105]. Additionally, the systemic inflammatory response in sepsis releases pro-inflammatory cytokines and mediators that can directly damage kidney tissues [104,106]. In mouse models of septic AKI induced by lipopolysaccharide or cecal ligation and puncture (CLP), studies have demonstrated that inhibiting EGFR, either pharmacologically or genetically, offers protection against the pro-inflammatory response [75,80]. This protective effect is evidenced by a reduction in macrophage infiltration, decreased pro-inflammatory mRNA expression [75,80]. This protection is associated with less severe kidney dysfunction, tubular injury [75], and mortality [80].

EGFR inhibition in metabolic kidney disease

Numerous animal studies have explored EGFR-targeted inhibition in diabetic nephropathy [82,92,93]. Both genetic and pharmacological inhibition of EGFR ultimately improve Type 2 diabetes by reducing blood glucose levels [92], but this effect is not observed in Type 1 diabetes [77,82,93]. In both types of diabetes, EGFR inhibition consistently reduces albuminuria [82,92,93], leading to the amelioration of diabetes-induced kidney dysfunction. In diabetic mice subjected to EGFR inhibition, the kidneys exhibit reduced histopathological injury in the tubules, decreased collagen deposition in the interstitial areas [82,92,93], and reduced infiltration of leukocytes, including macrophages [77,92] and T lymphocytes [92]. Glomeruli also show improvements, including reduced loss of podocytes [90,92,93], decreased cell cycle arrest [88], reduced macrophage infiltration [92], less mesangial expansion [93], and diminished glomerulosclerosis [77,92,93] during diabetic nephropathy. Interestingly, specific deficiencies of *Egfr* in podocytes [93] and proximal tubules [90] completely mitigate tubulointerstitial fibrosis. However, conflicting results exist regarding the effect of EGFR inhibition on tubular apoptosis [82,84,90]. Diabetic rats treated with PKI-166 exhibit increased apoptotic cell death in the tubules [84], while diabetic mice treated with AG-1478 show decreased apoptotic cell death in the tubules [82]. This controversy underscores the necessity for further research into the relationship between EGFR and apoptosis in diabetic kidneys. Treatment with gefitinib attenuates kidney dysfunction, histopathological injury in the tubules, and tubulointerstitial fibrosis induced by hyperuricemia from adenine and potassium oxonate [74]. Additionally, obesity-induced nephropathy is characterized by increased apoptosis and fibrosis, but treatment with AG-1478 effectively mitigates these symptoms [83].

EGFR inhibition in inflammatory kidney disease

In inflammatory kidney diseases, the role of EGFR has been primarily studied in models of glomerulonephritis and lupus nephritis [107,108]. Pharmacological inhibition of EGFR effectively enhances kidney function in cases of glomerulonephritis [73,78,94]. This inhibition also reduces crescent formation and macrophage infiltration in the glomeruli affected by glomerulonephritis [78,94]. Notably, specific deficiencies of *Egfr* in podocytes [78] and macrophages [73] protect against these symptoms during glomerulonephritis. In contrast, the effects of pharmacological EGFR inhibition in lupus nephritis models remain controversial. Treatment with erlotinib has been shown to reduce kidney dysfunction and tubulointerstitial fibrosis in lupus nephritis induced by *Fcgr2b* deficiency [95]. Conversely, treatment with lapatinib exacerbates kidney dysfunction and tubulointerstitial fibrosis in lupus nephritis induced by interferon-α administration [81]. Additionally, *Egfr* deficiency in CD4-positive T cells worsens glomerular and tubulointerstitial injuries in pristane-induced lupus nephritis [96]. On the other hand, treatment with erlotinib alleviates inflammation by decreasing macrophage and T cell infiltrations, as well as reducing the expression of cytokines and chemokines in kidneys affected by inflammation induced by TWEAK [97]. Further studies are necessary using animal models of lupus nephritis to gain a deeper understanding of the varying effects based on the type of disease model and the inhibition strategy employed.

EGFR inhibition in obstructive kidney disease

Obstructive kidney disease occurs when a blockage in the urinary tract impedes urine flow, leading to increased pressure in the kidneys [109,110]. Over time, this obstruction can damage the kidneys, potentially resulting in CKD [111,112]. UUO is a specific type of obstructive kidney

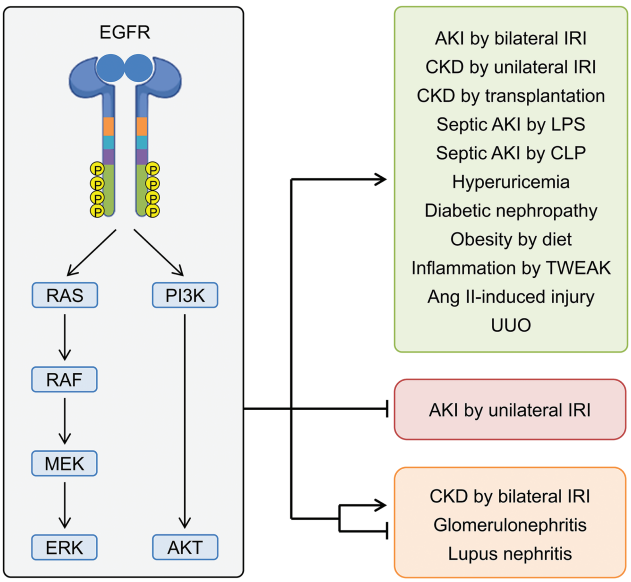

FIGURE 3. Outline of the roles of EGFR in rodent models of kidney disease. Abbreviations: AKI, acute kidney injury; AKT, protein kinase B; CKD, chronic kidney disease; CLP, cecal ligation, and puncture; ERK, extracellular signal-regulated kinase; IRI, ischemia and reperfusion injury; LPS, lipopolysaccharide; MEK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; UUO, unilateral ureteral obstruction. Created in BioRender.com.

disease characterized by the obstruction of one ureter [110,113,114]. UUO can be caused by various factors, including kidney stones, tumors, or congenital abnormalities [111,113]. This condition leads to increased collagen deposition and the expression of pro-fibrotic proteins, resulting in tubulointerstitial fibrosis [112,113]. However, EGFR inhibition through treatment with gefitinib, EGFR point mutations, or EGFR mimotopes has been shown to effectively reduce fibrosis [68,76,98]. Additionally, these interventions mitigate kidney inflammation, as indicated by reduced macrophage infiltration and lower levels of pro-inflammatory mRNA expression during UUO [68,76,98].

Conclusion and Perspectives

The EGFR plays a multifaceted role in kidney diseases, influencing both acute and chronic conditions through its effects on inflammation, fibrosis, and tissue injury (Fig. 3). In AKI, EGFR inhibition can either exacerbate or mitigate injury, depending on the type and severity of ischemia, while consistently reducing fibrosis and inflammation. In CKD, EGFR inhibition shows promise in alleviating symptoms of diabetic nephropathy and obesity-induced nephropathy, although results can vary based on specific conditions and the inhibitors used. Despite these advances, the effects of EGFR inhibition in inflammatory conditions like lupus nephritis and vascular diseases are mixed, suggesting that while targeting EGFR can be beneficial, its application must be carefully tailored to the specific disease context. Future research should focus on elucidating the mechanisms underlying these varied responses to optimize therapeutic strategies and enhance the efficacy of EGFR inhibition in managing kidney diseases.

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