

Editorial

*Corresponding author

Shi-Bin Cheng, MD, PhD

Assistant Professor

Department of Medicine

Warren Alpert Medical School

of Brown University

Providence, RI 02903, USA

E-mail: shibin_cheng@brown.edu

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The Epidermal Growth Factor Receptor: A Potential Therapeutic Target in Chronic Kidney Disease

Zijun Liu, MD, PhD¹; Na Liu, MD, PhD²; Shi-Bin Cheng, MD, PhD^{3*}

¹Nanjing First Hospital, Nanjing Medical University, Nanjing, China

²Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

³Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI 02903, USA

Chronic kidney disease (CKD) is a clinical syndrome characterized by a gradual loss of kidney function that persists for >3 months with health implications and affects nearly 500 million people worldwide. Diabetes and hypertension are the 2 most common causes of CKD, which account for up to two-thirds of the cases.¹⁻³ Accumulating evidence has shown that hyperuricemia is tightly associated with the pathogenesis of CKD.¹⁻⁴ Hyperuricemic nephropathy is a condition characterized by glomerular hypertension, arteriosclerosis, and tubule interstitial fibrosis. Prior studies demonstrate that decreasing uric acid levels delays the development of CKD and slows its progression and uric acid is an independent predictor of future development of CKD.¹⁻⁴ The mechanistic processes by which hyperuricemia induces chronic renal injury involve deposition of uric acid crystals in the collecting duct of the kidney, renal angiotension system activation, oxidative stress, tubular epithelial cell transition and inflammation.⁴⁻⁷

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptors. EGFR is activated by binding of its specific ligands such as epidermal growth factor (EGF) and transforming growth factor α (TGF α). Additionally, EGFR can be transactivated by cytokines, oxidants as well as indirectly *via* activation of G protein-coupled receptors such as angiotension II receptor and G protein-coupled estrogen receptor-1 (GPER-1).⁸⁻¹⁰ Upon activation, EGFR undergoes dimerization, a transition from an inactive monomeric form to an active homodimer. EGFR dimerization promotes its intrinsic intracellular protein-tyrosine kinase activity, which results in autophosphorylation of several tyrosine residues in the C-terminal domain of EGFR. This autophosphorylation initiates several signal transduction cascades such as the mitogen-activated protein kinases (MAPK), protein kinase B (PKB) also known as Akt and Jun amino-terminal kinases (JNK) pathways, regulating cell migration, adhesion, and proliferation.^{8,9}

Numerous studies have shown that EGFR activation contributes to chronic renal injury and glomerular sclerosis.^{4,10} Intriguingly, a recent study by Liu et al⁴ reported that EGFR activation was critically involved in uric acid-induced chronic renal injury in a rat model of hyperuricemic nephropathy. Using this model, they demonstrated that blockage of EGFR by gefitinib, a drug that specially inhibits EGFR activation and is clinically used for treating various cancers, alleviated renal fibrosis and renal tubular injury and inhibited activation of renal interstitial fibroblast, a pathological process that initiates the development of renal fibrosis and promotes its progression.⁴ Mechanistically, inhibition of EGFR abrogated the expression of TGF- β and phosphorylation of Smad3 (a downstream molecule of TGF- β), and blocked NF- κ B pathway activation and macrophage infiltration in the kidney of hyperuricemic rat.⁴ In addition, gefitinib treatment decreased release of various proinflammatory cytokines/chemokines including TGF α , interleukin 1 beta (IL-1 β), monocyte chemoattractant protein-1 (MCP-1) and RANTES.⁴ Furthermore, blockage of EGFR reduced serum uric acid levels through inhibiting the activity of the enzyme xanthine oxidase, a key enzyme for the production of uric acid, as well as through preventing the downregulation of urate transporters, organic anion transporter

1 (OAT1) and OAT3.⁴ Collectively, Liu and colleagues⁴ have demonstrated for the first time that EGFR activity contributes to the pathogenesis of hyperuricemic nephropathy and that EGFR blockage alleviates development of hyperuricemia-induced nephropathy through blocking TGF- β signaling pathway, inhibiting inflammatory response, and reducing uric acid production. Thus, EGFR may serve as a therapeutic target for treating uric acid-associated CKD.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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