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The Role of the EGF Receptor in Kidney Disease

Raymond Harris
Vanderbilt, United States

The **Epidermal Growth Factor Receptor (EGFR)** is a member of the family of ErbB receptors, which consist of an extracellular ligand-binding domain, a single membrane-spanning region, a homologic cytoplasmic protein tyrosine kinase domain and a C-terminal tail with multiple phosphorylation sites. EGFR can be activated by a family of ligands (including EGF, TGF-a, HB-EGF, amphiregulin, epiregulin and betacellulin) that bind and induce receptor autophosphorylation and activation of intracellular signaling pathways.

Ligand binding to EGFR leads to activation of the intrinsic kinase domain and subsequent phosphorylation on specific tyrosine residues within the cytoplasmic tail. These phosphorylated residues serve as docking sites for a variety of signaling molecules whose recruitment leads to the activation of intracellular pathways controlling cell proliferation, differentiation, and apoptosis. Recent studies by us and others have uncovered important but distinctly different roles for the epidermal growth factor receptor in acute kidney injury (AKI) and chronic progressive kidney disease. Exogenous administration of EGFR ligands accelerates recovery from acute ischemic renal injury, and mice with either genetic or pharmacologic inhibition of EGFR have delayed renal functional and structural recovery after AKI, indicating that functional EGFR activity is an essential component of the kidney's ability to recover from acute injury. We have determined that an important signaling process mediating this recovery is EGFR-dependent activation of Hippo-YAP signaling.

In contrast to acute injury, persistent and aberrant activation of EGFR in chronic renal disease is an important driver of progressive fibrosis, and either genetic or pharmacologic inhibition of EGFR activation can be an effective therapeutic intervention in experimental models of kidney disease. We have found that either genetic or pharmacologic inhibition of EGFR activation can be an effective therapeutic intervention in experimental models of diabetic nephropathy. EGFR may contribute to renal injury by inhibiting autophagy, which is associated with inhibition of AMPK activity. EGFR inhibition decreases oxidative stress and mTOR activation and increases autophagy in models of both type I and type II diabetic nephropathy.

It is well known that there are gender differences in predisposition to development of both experimental and clinical progressive renal injury. Our recent studies have identified that there is increased renal EGFR expression in males, expression of which is mediated by testosterone. We have foung that this increased renal EGFR expression is a predisposing factor for increased susceptibility and progression of chronic renal injury.