A plethora of epidermal growth factor–like proteins in polycystic kidneys

One of the first abnormalities described in cell biological studies of polycystic kidney disease pathogenesis was the abnormal apical plasma-membrane localization of the epidermal growth factor receptor (EGFR) in cyst lining epithelial cells, as opposed to the normal localization in mature kidneys on the basal membranes of proximal and nephron tubule segments [1].

Subsequent studies found this to be an extremely common feature of cystic kidney diseases, being observed not only in human adult autosomal-dominant (ADPKD) and autosomal-recessive polycystic kidney diseases (ARPKD), but also in a variety of spontaneously occurring autosomal-recessive mouse models of cystic renal disease (cpk, bpk), as well as mouse models derived by targeted mutations of the PKD1 or PKD2 genes responsible for ADPKD and in genes that inhibit kidney ciliogenesis (KIF3A and orpk) [2–4].

In addition, early studies suggested abnormalities in EGFR receptor species, number of molecules, hyperphosphorylation, and hyperactivity with regard to proliferative induction of epithelia in human ADPKD cells in vitro and in vivo [1], as well as in ARPKD mice. Importantly, both genetic manipulation and EGFR receptor tyrosine kinase inhibition have been shown to reduce cyst formation in mice, rats, and in human ADPKD cells in culture [5, 6].

Because the EGF ligand was a well-known mitogen for renal epithelia, and had been shown to exert hyperproliferative activity on human and mouse ADPKD and ARPKD cystic epithelia in vitro, it was suggested that the accessibility of apical EGFR receptor to cyst luminal EGF ligand could provide a mechanism for autocrine/paracrine stimulation of proliferation in cystic epithelia [7]. This was subsequently confirmed by identification of EGF and EGF-reactive peptide species secreted into the apical medium of cultured ADPKD epithelia, and even more compellingly by their detection in high, potentially mitogenic concentrations in cyst fluids collected from ADPKD patients [1].

Although studies in mice with ARPKD confirmed similar EGF/EGFR abnormalities associated with cyst formation [3, 8], it soon became clear that other EGF-like ligands and receptors might also play important roles. For instance, during the developmental period, when ARPKD cysts form, although renal EGFR receptor levels are high, levels of EGF ligand are low, but transforming growth factor (TGF)-α are levels are high [9]. In addition, transgenic mice overexpressing TGFα develop cystic kidneys [10].

An important article in this issue of Kidney International by MacRae Dell et al [11] helps to clarify this seemingly confusing state of affairs by systematically comparing and contrasting the roles of additional EGF-like ligands in the bpk mouse model of mouse ARPKD. Not only do the authors elucidate a hitherto unrecognized role for heparin-binding EGF-like growth factor (HB-EGF), but they also shed light on differing specificities and relative contributions of EGF ligands with regard to cyst formation.

There are five known members in the EGF ligand family of proteins: EGF, TGFα, HB-EGF, amphiregulin, and betacellulin, all of which exert their proliferative effects via phosphorylation of the cell membrane EGF receptor dimers. They are all expressed in the developing kidney: HB-EGF in the proximal tubule, EGF in thick ascending limb of Henle’s loop and distal convoluted tubule (DCT), and TGFα in the DCT and collecting ducts. The EGFR receptor is expressed in every nephron segment. The EGF ligands are synthesized as large preproforms that are inserted into cell membranes as proforms and then become cleaved by metalloproteases to derive small (approximately 5 to 6 kD) soluble active proliferative factors. Transactivation of the EGF receptor by soluble EGF, TGFα, HB-EGF, and amphiregulin have all been shown to promote MAP kinase activation, and to be part of the regulatory system that modulates cell migration and mitogenesis, whereas the membrane-bound proforms have demonstrated roles in branching morphogenesis of the developing kidney [12, 13].

MacRae Dell et al now describe results that suggest potential mechanisms regulating the different specificities of the EGF-like ligands. Although EGF, TGFα, HB-EGF, and amphiregulin were all mitogenic to cystic > control epithelia, HB-EGF showed the most marked activation of EGF receptor (> EGF > TGFα > amphiregulin), and
was seen on apical membranes of cystic epithelia, while amphiregulin was not. In addition, immunoprecipitation of EGF and TGF-α, but not HB-EGF or amphiregulin was able to significantly reduce the mitogenicity of cyst fluids. Taken together, these studies suggest that the relative potencies of growth factors in the context of cyst expansion are a function of membrane receptor and ligand trafficking, as well as ligand availability.

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REFERENCES