To cleave or not to cleave: role of ADAM17 in cell proliferation in PKD

Alexander Staruschenko
Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin
Submitted 17 June 2014; accepted in final form 9 July 2014

A MAJORITY of growth factors, including members of the epidermal growth factors (EGF) family, are synthesized as proproteins, requiring cleavage for the mediation of some of their functions. This pro-protein cleavage of the EGF family members is performed by disintegrin and metalloprotease (ADAM) family members and matrix metalloproteinases (MMPs) and is tightly regulated by various factors (9). There is increasing evidence that under certain conditions ADAMs may be able to cleave a large set of substrates (2, 7, 9). Multiple studies identified critical roles of members of both ADAM and MMP families in the control of kidney function. Thus chronic administration of MMP inhibitors delays the progression of, and may even reverses, hypertension and diabetic nephropathy (12). Another example is a recent study by Guo et al. (6), who reported that peptidase ADAM10 is involved in the regulation of cell fates in the renal collecting ducts by changes in the distribution of water channel aquaporin-2 between principal and intercalated cells (6). Importantly, ADAM-dependent EGFR ligand shedding can be induced by activation of G protein-coupled receptors (GPCRs), such as angiotensin (ATR), endo-}

Editorial Focus


crinin (BK2R), or serotonin (5-HT2A) receptors (GPRCs), such as angiotensin (ATR), endothelin-1 (ETR), bradykinin (BK2R), or serotonin (5-HT2A) receptors (3, 5, 7). Thus it was shown that angiotensin II causes induction and redistribution of ADAM17 (also known as TACE for tumor necrosis factor-α converting enzyme) to the apical membrane and plays a role in cleaving the surface-localized transforming growth factor (TGF)-α precursor (7). It was also reported that both ADAM10 and ADAM17 are capable of shedding the antiaging transmembrane protein Klotho from the plasma membrane and that insulin can stimulate Klotho shedding (2).

The work of Beck Gooz and colleagues (1) in a recent issue of the American Journal of Physiology-Renal Physiology investigated the effects of ADAM17 on EGF family growth factors and cell proliferation in autosomal recessive polycystic kidney disease (ARPKD). The authors concluded that ADAM17 serves as a key regulator of cell proliferation via shedding of HB-EGF, amphiregulin, and TGF-α (1). While it was previously shown that ADAM17 cleavage mediates the shedding of several EGF family members, including those tested in this manuscript (HB-EGF, amphiregulin, and TGF-α), it would be important to know which members of ADAM/MMP families are involved in the control of the shedding of other members of the EGF family. It was shown that most of identified epidermal growth factors receptors (EGFR) ligands (including EGF, the best studied member of this family) are expressed in the kidney and play a critical role in the control of various processes in the kidney such as cell proliferation, differentiation, renal electrolyte homeostasis, etc. (9, 10, 13, 14). Identification of specific members of the EGF family as well as respective metalloproteinases appears to be highly critical since it can potentially allow us to target explicit mechanisms in the kidney as well as in other organs.

In the study, using several complementary approaches, the authors first identified that ADAM17 is highly expressed in ARPKD cells. They further determined that excessive expression and activity of ADAM17 promoted cell proliferation via the ERK pathway. Conditional IFT88 knockout (Ift88fl/fl) mice and collecting duct epithelia cells from Ift88fl/fl mice were used to define the role of ADAM17 in ARPKD. However, at least two main questions require further studies. First, it would be important to move these studies from in vitro and ex vivo to in vivo to test the study compound (TMI-005) used in live animals to see whether inhibition of ADAM17 will result in reduction of cyst growth. Furthermore, additional studies should be performed to determine whether a proposed mechanism is specific to ARPKD or is common for all forms of PKD and present in the autosomal dominant form of PKD (ADPKD) as well. These should be relatively straightforward studies, considering that this compound is orally active and was previously used in clinical trials. TMI-005 (also known as apratastat) was used in a phase II study for the treatment of rheumatoid arthritis (8). Importantly, this drug was safe since no hepatotoxicity was found. However, the efficacy results were discouraging and the development of TMI-005 by Wyeth was terminated (11). Although this study showed that dual inhibition of ADAM17 and MMPs was not beneficial for the treatment of rheumatoid arthritis, it did provide an impetus for the use of TACE inhibitors for other diseases, such as ARPKD. However, special precaution should be taken with regard to specific metalloproteinases mediating these effects, since TMI-005 used in current study is a relatively broad-spectrum ADAM/MMP inhibitor and not as highly selective for ADAM17 as described by the authors. To complement the pharmacological observations, the authors used a genetic approach with small interfering RNA vs. ADAM17. Since a gene-silencing approach supports the data obtained with TMI-005, this suggests that in the particular model ADAM17 is responsible for the increased cell proliferation.

Importantly, the authors also have provided some mechanistic information for how ADAM17 mediates its effects in PKD cells. They demonstrated that ADAM17 increased lactate formation and extracellular acidification (1). ARPKD cells released threefold more lactate than control cells, and treatment with TMI-005 decreased lactate production of PKD cells, indicating that ADAM17 not only is involved in cell proliferation but also regulates glycogenesis. Recent studies in the kidney cortex of type 1 diabetic (OVE26) mice identified that the activation of ADAM17 is responsible at least partially for the increase in NADPH oxidase 4 (Nox4) expression, resulting in oxidative stress in the diabetic kidney cortex (4). It would be interesting to see whether the mechanism described by Gooz and colleagues (1) is unique for cystic kidneys or if other

Address for reprint requests and other correspondence: A. Staruschenko, Dept. of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226 (e-mail: staruschenko@mcw.edu).
pathways such as oxidative stress might be also involved in cell proliferation in PKD. It is also critical, as noticed by the authors, "to analyze ADAM17-related metabolic changes regarding mitochondrial bioenergetics and to identify metabolic enzymes upregulated by increased ADAM17 activity” (1).

Briefly summarizing, ADAM and MMPs inhibitors appear to have great potential in treatment of PKD. Specific inhibition of proteolytic actions of ADAMs/MMPs, and ADAM17 in particular, may offer a novel therapeutic approach to prevent PKD. There are several potential pathways involved, and a further understanding of how ADAM/MMP-family members contribute to disease development and progression (including their role in GPCR-mediated transactivation of EGFRs) will provide opportunities to develop novel treatments for kidney disease, and PKD in particular. With the consideration that development of ADAM/MMP inhibitors is of great interest to several major drug companies, some of these newly developed compounds might be highly beneficial for treatment of ARPKD (and potentially ADPKD as well).

ACKNOWLEDGMENTS

Dr. Matthew R. Hodges and Dr. Andrey Sorokin (both at the Medical College of Wisconsin) are greatly appreciated for a critical reading of the manuscript.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grant R01 HL108880.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: A.S. drafted manuscript; A.S. edited and revised manuscript; A.S. approved final version of manuscript.

REFERENCES