is critical in embryogenesis, whereas BMP7 is critical in kidney development regulating the differentiation of metanephric mesenchymal cells required for ureteric bud branching.11–13

It is tempting to speculate that BMP7 regulation of Tet3 expression and the resulting effect on the epigenome play an important role in nephrogenesis.

The study by Tampe et al.7 indicates that Rasal1 promoter hypermethylation and reduced Tet3 expression are features of renal fibrosis. BMP7 treatment resulted in normalization of Tet3 expression and consequently hydroxymethylation of the Rasal1 promoter. BMP7-mediated hydroxymethylation of the Rasal1 promoter was impaired when Tet3 expression was lost. Electrophoretic mobility shift assays confirmed binding of Tet3 to its CXXC binding motif flanking the Rasal1 CpG island promoter, further indicating the role of Tet3 in Rasal1 hydroxymethylation.

Preclinical data from this study indicate that aberrant methylation or perhaps active demethylation processes catalyzed by Tet3 determine the balance between health and CKD. These findings suggest that transient therapies targeted at amplifying or restoring Tet3 activity may prove beneficial to patients with CKD. Furthermore, analysis of methylation status (e.g., using RASAL1 as a methylation biomarker) to determine the individual risk of a patient to develop fibrosis or suitability for demethylation-based therapy appears both plausible and attractive. However, further studies in larger patient cohorts are warranted to establish these targets for both diagnosis and therapy.

Demethylation agents, such as 5-azacytidine, have already been described to rescue kidney fibrosis in experimental models3 and demethylation agents are in clinical trials for treatment of cancers; however, these drugs are cytotoxic and the long-term effects of genome-wide demethylation are unknown. It therefore seems more attractive to transiently and specifically reactivate an endogenous demethylation process and thereby readress the imbalance that results in CKD. The identification of Tet3 as a critical player in both the development and reversal of renal fibrogenesis described in the study by Tampe et al.7 may be the first step toward achieving this attractive possibility.

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DISCLOSURES

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REFERENCES


See related article, “Tet3-Mediated Hydroxymethylation of Epigenetically Silenced Genes Contributes to Bone Morphogenic Protein 7-Induced Reversal of Kidney Fibrosis,” on pages 905–912.

All of the Twos, 22—Bingo!

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IL-22 is currently a hot topic, with researchers generating approximately 400–500 related articles per year. However,
articles by Xu et al. and Kulkarni et al. in this issue of JASN are the first to describe the involvement of IL-22 in the kidney.1,2 Interest in IL-22 is growing because of its unique range of cellular targets and the power of its effects,3–4 which are generating increasing excitement about its potential as a therapeutic target.5,6 Unlike other ILs, IL-22 does not interact with leukocytes but instead targets intrinsic tissue cells—principally epithelia, hepatocytes, and some fibroblasts—and is critical for maintaining and restoring them in infection or other types of injury.2,3 The power of these protective effects has been amply demonstrated in injury models in the intestine, lung, and skin; however, until now, there have been no data about its effects in the kidney. The studies by Xu et al. and Kulkarni et al. show that IL-22 provides striking protection from AKI in the ischemia-reperfusion injury (IRI) model as well as in recovery after IRI.1–2 These findings help facilitate entirely new approaches to the prevention and management of AKI with the possibility of rapid translation to the clinic, because IL-22 therapy is currently being developed for other diseases and has already entered phase I human trials.7

IL-22 was discovered in 2000, and is a member of the IL-10 cytokine family with highly distinctive properties.8 IL-22 is produced by cells of the innate and adaptive immune systems, including multiple lymphocyte subsets of CD4- and CD8-positive T cells, such as T helper 1 (Th1) cells, Th17 cells, and newly characterized Th22 cells; γ-δ T cells, innate T cells, and natural killer cells; macrophages and dendritic cells; and some subsets of neutrophils.3,4 The generation of IL-22 by T cells is tightly controlled by the cytokine environment, whereas its secretion by macrophages and dendritic cells is more dependent on IL-1 and Toll-like receptors (TLRs).8,10 Once IL-22 is released, it binds to a two-chain receptor composed of IL-22 receptor 1 (IL-22R1), which has high affinity for IL-22, and IL-10 receptor 2, which is essential for signaling. The expression of IL-22R1 is highly restricted and accounts for its biologic effects: It is not expressed by leukocytes but is abundant in epithelial cells in the skin, intestine, and lung, as well as in hepatocytes and the pancreas and in some myofibroblasts.11 The IL-22 receptor signals predominantly through signal transducer and activator of transcription 3 (STAT3), with additional contributions from STAT1 and STAT5, as well as phosphoinositide-3-kinase and mitogen-activated protein kinase.12 IL-22 activity is modulated by IL-22BP, a binding protein that has 20- to 1000-fold greater affinity for IL-22 than the IL-22R1.13 IL-22BP is expressed on the surface of immature dendritic cells but is released from them on activation coincident with increased IL-22 expression.14 Although its major activities occur locally, IL-22 can be detected in the circulation and it stimulates hepatocytes to synthesize acute phase reactants in acute inflammatory conditions.15

IL-22 has multiple effects on epithelial cells. Although the details vary from tissue to tissue, these effects can be grouped into three broad categories3,4: (1) strengthening resistance to pathogens by stimulating the generation of antimicrobial proteins (including defensins, S100A family proteins, neutrophil gelatinase–associated lipocalin, and lipocalin) and through the release of selected chemokines; (2) protecting against cell death by increasing expression of antiapoptotic proteins (Bcl2) and decreasing expression of proapoptotic proteins (Bax and Bad); and (3) promoting repair by increasing epithelial cell proliferation and inhibiting terminal differentiation. Multiple studies using deficient mice and pharmacologic manipulation have shown that IL-22 has a major effect on tissue repair in models of acute injury to the intestine, lung, liver, skin, and pancreas.5,6 The protective effects of IL-22 have largely been confined to models of acute injury, but IL-22 also has deleterious effects when secretion by pathogenic T cells contributes to the uncontrolled proliferation of keratinocytes in psoriasis16,17 and synoviocytes in rheumatoid arthritis,18 as well as to tumor progression.19,20 In certain contexts, IL-22 can assume proinflammatory properties.21

The studies by Xu et al. and Kulkarni et al. provide convincing evidence that IL-22 reduces injury in models of ischemia-reperfusion in mice. The study by Xu et al. was founded on knowledge of the effects of IL-22 on epithelial injury in other tissues and concentrated on the acute injury after ischemia-reperfusion and its modulation by IL-22.1 Interest in IL-22 by Kulkarni et al. arose from a high-throughput in vitro screen for cytokines that enhanced renal tubular epithelial repair, which identified IL-22 as the most promising candidate.2 Consequently, the authors’ subsequent in vivo studies concentrated on tissue repair after IRI. Thus, the two studies are almost completely complementary, although with just enough overlap to reinforce the validity of each study’s conclusions.

Xu et al. first defined renal expression of IL-22R1 and showed that it was restricted to the brush border of proximal tubules. The authors confirmed that IL-22R1 was functional by demonstrating that activated STAT3 (pSTAT3) was similarly expressed in transgenic mice expressing high circulating concentrations of IL-22. Mice genetically deficient in IL-22 had subtly more severe renal injury after IRI with significantly lower serum urea and creatinine after 30 minutes of ischemia. However, increasing the circulating IL-22 concentration had more obvious effects both in mice systemically injected with IL-22 and in transgenic mice with systemically overexpressing IL-22 (IL-22TG). In both settings, high circulating IL-22 concentrations strikingly improved renal function and decreased morphologic signs of injury, even after 40 minutes of ischemia. Consistent with studies from other tissues, IL-22 activated the STAT3 and phosphoinositide-3-kinase signaling pathways and increased the expression of antiapoptotic protein Bcl-2 while decreasing proapoptotic proteins Bax and Bad. Finally, the power of the influence of IL-22 on injury was emphasized in mice subjected to unilateral IRI followed by contralateral nephrectomy. All IL-22 genetically deficient mice died within 3 days, whereas the day 7 survival rates for wild-type mice and IL-22TG mice were 28.6% and 77.8%, respectively.

Kulkarni et al. also showed that IL-22–deficient mice had significantly worse renal function on day 5 after bilateral IRI. Furthermore, the inhibition of IL-22 with specific antibodies after 48 hours of reperfusion profoundly inhibited renal
tubular epithelial cells express IL-22R1 and to ascertain whether IL-22 expression and STAT3 activation responses are similar in clinical and murine AKI. Nevertheless, nephrologists should be keenly interested in the results of the recently initiated phase I clinical studies of human recombinant IL-22.7

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Endothelin Antagonists in Diabetic Nephropathy: Back to Basics

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Endothelin Antagonists in Diabetic Nephropathy: Back to Basics

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The pivotal discovery of endothelin (ET) by Yanagisawa and colleagues1 in 1988 generated wide interest in this peptide, as evidenced by the nearly 27,000 articles published to date that have examined its role in biology. ET is now recognized as essential to the function of various organs and metabolic processes.2 The ET family consists of three 21-amino acid peptides—ET-1 (ubiquitous and most biologically active), ET-2, and ET-3—that exert their actions via two receptor subtypes: ET_A and ET_B. Activation of these receptors usually, but not always, incites opposing actions; an additional consideration is that the ET_B receptor also acts as a clearance receptor.3 Consequently, the effects of ET can vary among different organs depending on the amount being formed and on the receptor subtypes present. For instance, in the cardiovascular system ET induces vasoconstriction and growth via ET_A receptors and vasodilation and growth inhibition via ET_B receptors.3,1 The net effect results in an increase in systemic vascular resistance and BP. This potentially injurious effect is augmented by ET’s ability to stimulate growth factors and cytokines, which induce neutrophil adhesion, platelet aggregation, and formation of extracellular matrix protein.3 Together, these actions can precipitate a vicious cycle that accelerates hypertension and atherosclerosis-induced vascular disease.3

Despite its importance in the cardiovascular system, ET plays an even larger role in regulating renal function and injury. This is because the kidneys are exquisitely sensitive to ET-1 (up to 10-fold more than are other organs4) and because the components of the ET system are widely distributed throughout the kidney; ET-1 is present in the renal microvasculature, in all types of glomerular cells, and in the tubules (the renal medulla contains the highest ET-1 levels in the body5). Thus, it is no surprise that ET-1 has such a key role in regulating renal hemodynamics, salt and water homeostasis, and acid-base balance6 and in modulating cell proliferation, extracellular matrix accumulation, inflammation, and fibrosis.7 Consequently, any abnormality in the intrarenal ET system may result in renal dysfunction (e.g., salt sensitivity) and/or injury. Indeed, ET may participate in the progression of renal injury during obesity, hypertension, and diabetes.7 Because most of the deleterious effects of ET-1 appear to be mediated through the ET_A receptors, this receptor has become an attractive therapeutic target in various forms of cardiovascular and renal diseases, such as diabetes.3

Diabetic nephropathy is an attractive target for ET-1 blockade because several lines of evidence implicate ET in this disease. First, the synthesis and/or effects of ET-1 are increased in response to hyperglycemia, hypertensive glomerular injury, and insulin,8 which results in increased renal expression and systemic circulatory levels of ET-1 in experimental and clinical diabetes.9,10 Second, abnormalities in the ET system are present in the renal areas targeted by diabetes, including the microvasculature, mesangial cells, and podocytes.11 Third, overactivity of ET-1 promotes proliferation, inflammation, fibrosis, and ultimately glomerulosclerosis.9 Finally, several studies have shown that ET receptor antagonists ameliorate experimental diabetic nephropathy.5,12,13 It is within this context that two