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.2,5 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 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 categories1–4: (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 recovery, decreased renal tubular epithelial proliferation, and was associated with persistent expression of kidney injury markers including kidney injury molecule-1, as assessed on day 5 by morphology. Renal expression of IL-22 was upregulated and exclusively localized to the interstitium, with renal mononuclear cells (macrophages and dendritic cells) identified as a predominant source by flow cytometry. Depletion of renal mononuclear cells with an injection of clodronate liposomes eliminated renal IL-22 synthesis and reduced recovery from IRI to the same extent as treatment with antibodies to IL-22. The effect was reversed by the injection of IL-22. Finally, Kulkarni et al. showed that supernatants from necrotic renal tubular epithelial cells stimulated bone marrow–derived dendritic cells to release IL-22 in a TLR4-dependant fashion. Treatment of mice with IRI and antibodies to IL-4 mimicked the effects of anti–IL-22 antibodies. Thus, TLR4 ligands released from damaged tubules appeared to initiate the IL-22–dependent repair response.

Together these studies prove that IL-22 attenuates acute injury and initiates tissue repair in IRI, and these findings fit beautifully with the known effects of IL-22 in other contexts, including IRI-induced liver injury.22 The signaling through STAT3 and the downstream molecular consequences reported by Xu et al. are characteristic of those seen in other models of epithelial injury.3,4 The cellular source of the IL-22 and the effects of TLR ligation in upregulating its synthesis are similar to those in the intestine and lung, although the link with the release of damage-associated molecular patterns adds an entirely novel angle.

Despite the similarities in the studies by Xu et al. and Kulkarni et al., there are some interesting differences. The proximal tubular location of IL-22R1 and pSTAT3 in IL-22TG mice reported by Xu et al. contrasts with the IRI-induced pSTAT3 expression to more distal nephron segments reported by both groups, together with the protective effects on the distal tubular epithelium. More research is needed to resolve this apparent paradox, but there several possible explanations. First, IL-22 is a 33-kD protein; thus, freely filtered (when not complexed with IL-22BP) and increased circulating concentrations might selectively activate proximal tubular cells. Second, IRI might extend the expression of IL-22R1 further down the nephron. Finally, IRI increases synthesis of other cytokines that amplify the effects of IL-22 (e.g., TNF and IL-20) and others that activate STAT3 directly (e.g., IL-6), although this is less likely because pSTAT3 expression by intestinal epithelium results solely from IL-22 despite coexpression with IL-6.10

The articles by Xu et al. and Kulkarni et al. provide new insight into injury in AKI and the consistency of these results is testimony to the strength of the effects of IL-22 and its ability overcome the effects of differences in experimental protocols. These data strongly reinforce the case for IL-22 as a therapeutic target, not least because, in other preclinical situations, IL-22 markedly diminishes postinjury fibrosis, which is an increasing issue in AKI clinically.23,24 However, more data are required to ascertain whether IL-22 has similarly potent effects in humans. It should be easy to confirm whether human 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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DISCLOSURES

None.

REFERENCES


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