Receptor-Mediated Endocytosis Is a Trojan Horse in Light-Chain Nephrotoxicity

Karl A. Nath
Division of Nephrology and Hypertension, Department of Medicine, and Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota


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Chronic kidney disease can arise from the misappropriation of processes that normally promote tissue homeostasis in health. Such is the case when certain Ig light chains use megalin-cubilin receptors to enter proximal tubular epithelial cells. These receptors, apically located on the proximal tubule, form complexes with any one of a number of plasma proteins that escape into the urinary space. After endocytosis, the receptors disengage from the complexes and cycle back to the apical surface, whereas the ligands are processed and catabolized by lysosomes. In health, the function of such receptor-mediated endocytosis in the kidney is truly substantial: This endocytic process restrains urinary loss of proteins, recovers filtered vitamins and nutrients derived from protein catabolism, recovers filtered vitamins, and influences the fate of hormones by either degrading them or activating their precursors. The incorporation and catabolism of Ig light chains by the proximal tubule would seem, at first glance, a beneficial renal response in myeloma and light-chain proteinuria. Clearance of light chains by the proximal tubule would reduce their downstream delivery and their interaction with Tamm-Horsfall protein, thereby decreasing the risk for cast nephropathy; however, as made clear by a number of studies, the uptake of light chains by the proximal tubule triggers a vigorous inflammatory response. The studies of Basnayake et al. in this issue of JASN examine the basis for this inflammatory behavior by exposing human proximal tubular epithelial cells to pathophysiologically relevant concentrations of light chains derived from patients with myeloma and kidney disease. Their findings demonstrate that light-chain uptake by megalin-cubilin receptors increases cellular generation of hydrogen peroxide, the latter activating c-Src, which in turn induces the chemokine monocyte chemoattractant protein 1 (MCP-1).

The activation of c-Src by nephrotoxic light chains is a significant observation, because c-Src, a nonreceptor tyrosine kinase family member, is a critical hub in cell signaling networks. Not only is c-Src activated upon receptor binding of certain growth factors, but also c-Src itself can facilitate the transactivation of growth factor receptors; c-Src recruits such signaling species as mitogen-activated protein kinase members, Akt, Stat3, and PGC-1α. c-Src can also activate transcription factors such as NF-κB and AP-1. In view of these broad effects of c-Src on cell signaling, it is not surprising that c-Src is increasingly implicated in renal processes, including those that are physiologic (e.g., acid-base homeostasis), renal hypertrophy, and those that are pathophysiologic (e.g., podocyte proliferation and dedifferentiation, cystic kidney disease, albumin-induced cytokine expression). The findings of Basnayake et al. are important for several reasons: First, they identify another disease instigated by the activation of c-Src; second, they provide an explanation for the recruitment of mitogen-activated protein kinase–dependent signaling and activation of NF-κB described in previous studies of light-chain–exposed renal epithelial cells; and third, they direct attention to c-Src as an inducer of MCP-1, a chemokine strongly upregulated and broadly implicated in kidney injury.

Previous studies by Sanders’ laboratory demonstrated that Ig light chains, quite remarkably, generate substantial amounts of hydrogen peroxide (H2O2) in cell-free solutions. In the study by Basnayake et al., the addition of catalase, a scavenger of H2O2, to the light-chain–containing medium did not reduce the cellular production of MCP-1. These findings led to the plausible conclusion that H2O2, accounting for the induction of MCP-1, originates in the intracellular, not the extracellular, compartment. It would
be of interest to determine the specific intracellular site and biochemical mechanism accounting for increased production of \( \mathrm{H}_2\mathrm{O}_2 \), because such oxidant generation links cellular uptake of light chains and activation of c-Src. The role of the hydroxyl radical and labile cellular iron would also be of interest: DMTU, used as a trap for \( \mathrm{H}_2\mathrm{O}_2 \) in the study by Basnayake et al., is also a hydroxyl radical scavenger, and \( \mathrm{H}_2\mathrm{O}_2 \) can generate the hydroxyl radical in the presence of iron.\(^6\) Defining the role of labile cellular iron is clinically relevant, because such involvement can be blocked by iron chelators. Finally, the failure of extracellular catalase to reduce cellular production of MCP-1 suggests that extracellular catalase did not scavenge intracellular \( \mathrm{H}_2\mathrm{O}_2 \), an oxidant that diffuses across cell membranes. This raises the intriguing possibility that in the extracellular medium, nephrotoxic light chains, either directly or in concert with the \( \mathrm{H}_2\mathrm{O}_2 \) they generate therein, denature catalase; if so, then this would indicate that light chains impose oxidative stress not only by generating oxidants but also by disabling mechanisms that scavenge them.

Further exploration of the elegant in vitro analyses of Basnayake et al.\(^6\) would be facilitated by the availability of a relevant in vivo model of light-chain–induced kidney disease; however, the absence of such a model is a challenging issue in this field. Approximately 20 years ago, it was shown that administration of certain Bence Jones proteins to mice induced renal lesions resembling those observed in patients from whom these Bence Jones proteins were obtained.\(^14\) More recently, systemic infusion of nephrotoxic light chains over 3 days to rats increased renal production of TNF-\( \alpha \), but it is uncertain whether structural and functional effects accompany such TNF-\( \alpha \) production.\(^15\) Although a transgenic light-chain–overexpressing mouse has been described, the renal lesions that develop are those of crystalline light-chain deposits in tubules.\(^16\) Nonetheless, the observations of Basnayake et al.\(^6\) can be readily pursued by translational analyses in patients with monoclonal gammapathies. For example, expression of oxidant stress markers, c-Src, and MCP-1 can be assessed in kidney biopsies. Urine normally contains micromolar amounts of \( \mathrm{H}_2\mathrm{O}_2 \) and it would be of interest to determine whether increased urinary excretion of \( \mathrm{H}_2\mathrm{O}_2 \) and MCP-1 anticipate the appearance of paraproteinemic kidney disease, or a decrease in such excretory rates predicts the remission of such kidney disease. Urinary content of \( \mathrm{H}_2\mathrm{O}_2 \) and MCP-1 thus may serve as biomarkers for light-chain–induced kidney disease.

By defining the concatenation of steps that culminate in Ig light-chain–induced renal production of MCP-1 and the particular role of c-Src activation in this process, the findings of Basnayake et al.\(^6\) are of therapeutic significance. There is a substantial need for new therapies for kidney disease caused by monoclonal gammapathies,\(^18\) and germane to the findings of Basnayake et al.\(^6\) is that inhibitors of c-Src are under considerable investigation as a therapy for cancer.\(^7\) Such targeting of c-Src may mitigate Ig light-chain–induced kidney disease and thus offers a novel therapeutic approach in this disorder.

**REFERENCES**


See related article, “Immunoglobulin Light Chains Activate Tubular Epithelial Cells through Redox Signaling,” on pages 1165–1173.