involving activation of TRPC6 because DAG production likely falls in the setting of PLCε1 loss-of-function mutations. Alternatively, deficiency of AA containing PA species might be a plausible unifying hypothesis because one would predict reduced levels of this end product from loss of function of either DGKE or PLCε1.

Additional evidence connecting lipid second messengers and glomerular injury comes from a recent study by Soda et al. demonstrating heavy proteinuria and podocyte foot process effacement in mice lacking synaptojanin 1, a phosphoinositide phosphatase that normally dephosphorylates PIP₂. The authors of that study implicated altered actin nucleation and defective clathrin-mediated endocytosis as the basis for podocyte dysfunction in this model. These findings raise further intrigue regarding the contributions of aberrant lipid signaling to glomerular injury. Clearly, additional work is needed to resolve these pathophysiological mechanisms. For future investigations of DGKE-associated glomerular disease, perhaps exploiting a previously described Dgke null mouse, would be informative.

Beyond the obvious questions related to the underlying molecular mechanisms, the report by Ozaltin and colleagues describes an interesting new entity along the spectrum of glomerular microangiopathies. Unlike other forms of glomerular disease with an MPGN histologic pattern, the glomerular syndrome described in this report does not appear to involve overt complement activation or extensive Ig deposition. The three families described in this article exhibit steroid- and immunosuppressant-resistant nephrotic syndrome, further evidence for a nonimmunologic basis. Collectively, these findings support the existence of a novel mechanism for glomerular microangiopathy. Whether the clinical and pathologic features described in this article are shared by other genetic or acquired conditions will hopefully be revealed in the future.

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DISCLOSURES

None.

REFERENCES


A New Look at Tubulointerstitial Communication with Exosomes

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Various CKDs, regardless of initial insult, progress by a common pathway leading to renal fibrosis consisting of...
fibroblast accumulation and extracellular matrix deposition in the interstitium surrounding sclerotic glomeruli and atrophic tubules.\textsuperscript{1,2} In that process, it is assumed that tubular epithelial and interstitial cells such as resident/precursor fibroblasts and infiltrating immune cells communicate with each other to promote renal fibrogenesis in parallel with the functional deterioration in CKD.\textsuperscript{1,2} Traditionally, after glomerular damage, proteinuria appears and transfers the pathologic milieu in the glomerulus to the tubules by direct toxicity as well as protein-bound substances such as cytokines, growth factors, and fatty acids.\textsuperscript{3} In addition, glomerular capillary damage itself and the downstream vascular endothelial cell injury by cytokine/vasoactive substance spillage from the glomerulus into the effenter arterioles reduces peritubular capillary flow and results in tissue ischemia or hypoxia.\textsuperscript{4} Proteinuria and hypoxia likely cause tubular epithelial cells to trigger a spectrum of signaling cascades such as mitogen-activated protein kinases, Rho kinases, and Toll-like receptors and activate nuclear transcription factors such as NF-κB and AP-1.\textsuperscript{3,4}

These responses drive transcription of proinflammatory/profibrotic cytokines and growth factors, which are released to the interstitium and mediate recruitment of immune cells and activated fibroblasts to generate renal fibrosis. Renal fibrosis itself causes peritubular capillary rarefaction and facilitates tissue hypoxia, generating a vicious cycle of hypoxia-fibrosis.\textsuperscript{4} Direct tubular damage was recently shown to initiate renal fibrosis in animal models of AKI. In ischemic, toxic, and obstructive models of AKI, tubular epithelial cells with aberrant incomplete repair remain at cell cycle G2/M arrest, and activate c-Jun NH2-terminal kinase signaling, which upregulates production of profibrotic cytokines and growth factors, such as TGF-β1, and promotes renal fibrosis.\textsuperscript{5} Such accelerated progression of kidney disease from AKI to CKD was also demonstrated by using a highly selective model of sublethal tubular epithelial injury with Six2-Cre-LoxP technology to induce expression of diphertheria toxin receptor in renal epithelia.\textsuperscript{6} In that model, during repeated damage, regenerating renal tubular epithelial cells remain dedifferentiated and activate NF-κB to produce plasminogen activator inhibitor-1 and cytokines/growth factors such as monocytic chemotactic protein-1, TNF-α, and TGF-β1 in autocrine/paracrine fashion, resulting in aggravation of renal fibrosis in parallel with incomplete tubular repair.\textsuperscript{6}

All of these studies, however, simply considered that liquid cytokines/growth factors moved from tubules to interstitium to transfer proinflammatory/profibrotic signals, and neglected details in support of this hypothesis.

In this issue of JASN, Borges \textit{et al.} propose exosomes as a brand new candidate for tubulointerstitial communication in the diseased kidney.\textsuperscript{7} Cells release different types of vesicular carriers of membrane and cytosolic components into the extracellular space. Exosomes are vesicles with a diameter of 40–100 nm that are secreted upon fusion of multivesicular endosomes with the cell surface.\textsuperscript{8,9} Exosomes were first characterized during reticulocyte maturation, and then for the immune response and in cancer biology. They transfer not only membrane components but also protein and lipid mediators as a vectorized signaling system operating from inside a donor cell toward either the periphery or the cytosol of target cells.\textsuperscript{8,9} Borges \textit{et al.} observed that injured tubular epithelial cells in response to hypoxia generated exosomes containing TGF-β1 mRNA and released them to promote proliferation, α-smooth muscle actin expression, and type I collagen production in neighboring fibroblasts.\textsuperscript{7} Previously, cancer exosomes were shown to trigger the differentiation of fibroblasts to myofibroblasts and stromal remodeling to recruit cancer cells, in which the exosomes expressed TGF-β1 protein on their outer surface.\textsuperscript{10} In the case of AKI, exosome-mediated transportation of mRNA encoding TGF-β1, instead of TGF-β1 protein, can likely initiate rapid tissue repair/regenerative responses because of a deterioration of the translational process in injured tubular epithelial cells.

Although mechanisms for sorting of contents in exosomes during their biogenesis remain to be clarified, not only injured tubular epithelial cells but also other cells deliver genetic materials by exosomes. Mast cells secrete exosomes that contain mRNA from approximately 1300 genes and >100 different microRNAs (miRNAs), the transfer of which rapidly initiates translation in the recipient cells.\textsuperscript{11} Similarly, glioblastoma cells release exosomes containing mRNA, miRNA, and angiogenic proteins to stimulate angiogenesis by brain microvascular endothelial cells.\textsuperscript{12} In these studies, including one by Borges \textit{et al.} now reported here, how exosomes gain access to appropriate target cells within the extracellular matrix or beyond the basement membrane and/or how target cells capture these exosomes remains uncertain.

The work of Borges \textit{et al.} opens a new window for focusing on exosome-mediated intercellular communication in the diseased kidney, although its actual contribution is not yet known.\textsuperscript{7} Recently, the T cell Ig and mucin domain-containing molecules (Tim-1 and Tim-4) were identified as phosphatidylserine receptors that are able to bind exosomes by phosphatidylserine.\textsuperscript{13} Tim-1 expression (also known as Kim-1 in the kidney) is induced with a phagocytic property in tubular epithelial cells during the early phase of AKI.\textsuperscript{14} This suggests another notion that exosomes may be involved in the intercellular communication between injured tubular epithelial cells in AKI.

Urine also contains exosomes secreted by cells from all nephron segments, and they may carry proteins, mRNAs, and miRNAs reflecting renal dysfunction and structural injury, which may be kidney disease biomarkers.\textsuperscript{15} In tumor cells, Rab GTPases, Rab27a and Rab27b, seem to play important roles in regulating exosome secretion, and may be therapeutic targets for cancer progression.\textsuperscript{16} Further investigations are needed to explore the diagnostic and therapeutic applicability of exosomes in the progression of kidney diseases, and the mechanisms of biogenesis and secretion/capture of exosomes by tubular epithelial and interstitial cells.
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DISCLOSURES

None.

REFERENCES


In this issue of JASN, the Spanish hemodiafiltration study is published.1 What new information has become available and what might be its relevance?

Today, most patients with ESRD in the United States are treated with hemodialysis (HD). During low-flux HD, small uremic toxins are removed by diffusion, whereas larger solutes are retained within the body. When a high-flux dialyzer is used, the higher membrane permeability, and a certain amount of convection, increases the overall clearance of uremic molecules. Convection can be achieved by ultrafiltration; in high-flux HD, the amount of ultrafiltration is uncontrollable, immeasurable, and unpredictable. The volume of ultrafiltration generally exceeds the desired weight loss, and back-filtration automatically compensates for the excess.

In hemodiafiltration (HDF), diffusion and convective transport are also combined. With HDF, convective transport is obtained by filtering, through a high-flux dialyzer, amounts of plasma water considerably in excess of those required to achieve dry weight. Fluid balance is maintained by simultaneously infusing sterile substitution fluid directly into the patient’s bloodstream. The substitution fluid can be administered before (predilution), within (mid-dilution), or after (postdilution) the dialyzer. Clearance of middle- and large-molecular-weight substances is substantially greater during HDF than during high-flux HD. When HDF was introduced in the late 1970s, substitution fluid was supplied in bags, which made HDF an expensive and labor-intensive procedure and limited the magnitude of the infusion volumes and thus of convection. Today, sterile substitution fluid is prepared online,

See related article, “TGF-β1–Containing Exosomes from Injured Epithelial Cells Activate Fibroblasts to Initiate Tissue Regenerative Responses and Fibrosis,” on pages 385–392.