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Jerry Yee

Henry Ford Health, JYEE1@hfhs.org

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The Tubulointerstitium: Dark Matter



Rellegated to a less glamorous position than the glomerulonephritides, the tubulointerstitial compartment or tubulointerstitium of the kidney has been the dark matter of the kidney universe.¹ In the same fashion that dark matter predominates over atomic matter, the tubulointerstitium does so over the glomerular compartment. In fact, dark matter and the tubulointerstitium hold their respective universes together. In this issue, some of the mysteries of kidney dark matter are revealed by Cynthia Nast and the authors she has enlisted. The tubulointerstitial compartment is featured, and several of its many aspects are brought into the light.

Interstitial nephritis or more properly tubulointerstitial nephritis (TIN) is common, yet still underdiagnosed. Indeed, hypertensive nephrosclerosis is the most common tubulointerstitial disorder. Long-term assault by uncontrolled hypertension induces rarefaction of peritubular capillaries, with subsequent attenuation of sodium excretion and an ongoing cycle of hypertension, impaired sodium excretion, and volume-dependent hypertension. This capillary rarefaction phenomenon is recapitulated in the ischemia-reperfusion model of rat acute kidney injury established by Basile.² In terms of adult acute kidney injury (AKI), acute TIN accounts for 10–27% of cases examined by kidney biopsy,³ following the two foremost etiologies of hospital-acquired AKI, prerenal azotemia and acute tubular necrosis.

The classification of acute TIN is straightforward and can be conveniently used at the bedside. Most instances of acute TIN fall into one of these categories: drug toxicity, heavy metals, metabolic disorders, hereditary disorders, miscellaneous disorders, idiopathic, immunologic mechanisms, anti-tubular basement membrane antibodies, immune complexes, hypersensitivity, and cellular pathomechanisms.⁴ Regarding the latter, recent, exciting molecular discoveries have evinced some genetic tubulointerstitial disorders such as uromodulin disease⁴ and juvenile nephronophthisis.⁵ These are extremely rare and progressive disorders, and family history and genetic analysis are crucial to diagnosis.

Because no diagnostic pattern exists for acute TIN, it is not always considered early in the differential diagnosis of AKI.^{6,7} Drugs such as proton pump inhibitors⁶ and antibiotics⁷ induce most acute cases of TIN, and the common

reflex is to suspect the most recent additions to the medical armamentarium and alter the medication regimen in hope of self-amelioration of the problem. Kidney biopsies certainly can be carried out more frequently to establish the diagnosis, but there is an inertia among most to do so. When biopsies are done, acute TIN will be evident in one-tenth of cases or more.³ After acute TIN is established, withdrawal of the putative, offending agent should be followed by glucocorticoid administration, even when no confirmatory biopsy is available. Although this maneuver may prove salutary by mitigating renal fibrogenesis and progression to chronic tubulointerstitial disease, resistance to therapy prevails here. Is this resistance due to fear of steroid-induced side effects or something else?

There are now intriguing data supporting the view that early glucocorticoid administration results in superior outcomes, and without induction of severe, untoward effects. Predecki and associates examined biopsies from 187 patients in a 14-year retrospective analysis.⁸ Eighty-four percent (n=158) received steroids and 16% (n=29) were managed conservatively. These 29 participants were matched to 29 steroid-treated individuals to avoid selection bias and before analysis. After 24 months of observation, the steroid-treated group had an estimated glomerular filtration rate of 43 mL/min/1.73 m² that was significantly greater than those untreated at 24 mL/min/1.73 m² ($P < 0.01$). In terms of dialysis dependence at the 24-month end point, only 3.2% of steroid-treated patients required maintenance dialysis vs. 20.6% ($P < 0.002$). This study is essentially a nested case-control study. Therefore, the impact of confounding or bias, particularly selection bias, on the outcomes cannot be entirely excluded. Further testing of the Predecki observations with a randomized, controlled trial is warranted.

Attenuation of renal fibrosis by glucocorticoids may retard the transition from acute to progressive and chronic tubulointerstitial inflammation with fibrosis. The inhibition of fibrogenesis promotes normal proximal tubular functions, including the secretion of toxins from peritubular capillaries, receipt of nutrients from the capillary

network, and transport of solutes to the circulation.⁹ Generally, in drug-induced acute TIN, treatment should be delayed no longer than two weeks following clinical diagnosis and withdrawal of the offending agent. Hopefully, in the near-term, small molecule-targeting of various interstitial cells such as perivascular pericytes will provide novel means to impede tubulointerstitial fibrosis.^{10,11}

Thus, a somewhat algorithmic, clinical approach to tubulointerstitial disease has emerged, but it is imperative to acknowledge the dynamic interplay of the intrinsic components of this long underappreciated and largest of kidney compartments. Combined with the kidney tubules and vascular components, the interstitium becomes the tubulointerstitium. However, the kidney interstitial compartment or interstitium has been defined by Lemley and Kriz¹² as the intertubular, extraglomerular, extravascular space of the kidney bounded topologically by tubular and vascular basement membranes. The interstitium also includes the extraglomerular mesangium, periarterial connective tissues, and lymphatics. Polkissen cells, also referred to as cells of Goormaghtigh and lacis cells, are found near the vascular pole beneath the afferent arteriolar endothelia and occupy the space between the vasculature and the macula densa. These fibrillar pericytes likely participate in kidney autoregulatory responses and possibly in erythropoietin secretion.

The periarterial connective tissue sheaths represent the scaffolding upon which the interstitial vasculature, vasa recta and veins, and lymphatics are maintained. Here, the vital solute exchanges occur that we take for granted as passage from tubular lumina to vessels attributable to the hydrostatic pressure gradient that drives solute from the interstitium to the hilum. Note that there are no medullary lymphatics, and thus, there are two kidney interstitia, cortical, and medullary. This arrangement facilitates countercurrent medullary solute trapping, thereby establishing in part the corticomedullary osmotic gradient. The glycosaminoglycan content of the interstitium is relatively high, too, and provides the microenvironment in which tubulovascular structures equilibrate with each other, that is, this is a water- and solute-restricted space.

The interstitium houses multiple cell types, extracellular matrix, and interstitial fluid.⁹ The proximal tubular cells that constitute most cells of the kidney tubular compartment may directly interact with the interstitium through paracrine and juxtacrine mechanisms. They are semiprofessional antigen-presenting cells and elaborate numerous growth factors and cytokines.¹⁰ Therefore, by virtue of their proximity to the interstitium, these cells may participate, as bystander or inciting party, in multiple types of inflammatory insults within the tubulointerstitium. Proximal tubular cells are exposed to inflammatory and immunological stimuli on their tubular and basolateral aspects. These cells are influenced by a host of autacoids and produce their own growth factors, metalloproteinases and inhibitors thereof, and cytokines, including transforming growth factor-beta.¹¹ The consequent cell-matrix interactions may ultimately determine fibroblast dynamics that hasten, stabilize, or abolish extracellular matrix produc-

tion. One of the best known and experimentally proven examples is the influence of a high-glucose environment on proximal tubular epithelia, whereby hypertrophying cells transform to a matrix-producing phenotype while experiencing apoptosis.¹¹ Less is known how the more distal cells of the tubular compartment interact with the neighboring interstitium.

Interstitial fibroblasts have been the subject of intense scrutiny for over three decades, and are considered among the prototypical "interstitial" cells. These mesenchymal, nonvascular, noninflammatory, nonepithelial cells are the most prevalent residents of the interstitium.¹³ Fibroblasts have specific cell markers and are distinguishable from non-fibroblastic cells of renal mesenchymal origin, for example, pericytes, myofibroblasts, vascular smooth muscle cells, and stem cells. Historically, this had been problematic, and fibroblasts were identified as those cells that were not the cells that had identifiable cell markers. Fibroblasts and myofibroblasts, derived from proto-myofibroblasts that differentiated from fibroblasts or from circulating fibrocytes,^{13,14} express matrix-promoting and -degrading proteins such as zinc-dependent matrix metalloproteinases and their tissue inhibitors, i.e., tissue inhibitors of metalloproteinases. The net expression of these counteracting proteins ultimately determines net matrix accumulation or degradation of fibrillar collagens I and III within the tubulointerstitium, which is the preeminent prognosticator of renal longevity—an observation first espoused by Schainuck et al.¹⁴ Nearly five decades ago, he and colleagues demonstrated in 70 kidney biopsies that alterations in glomerular, tubular, vascular, and interstitial compartments conformed to those of simultaneously measured glomerular filtration rates, effective kidney plasma flows, and concentrating and acidifying capacities, irrespective of the form of kidney disease. Quite unexpectedly, the investigators concluded that "impaired kidney function was most closely related to changes in the tubules and in the interstitium"—a truism now known to all.

In the kidney cortex, interstitial fibroblasts are considered a source of endogenous erythropoietin production, with the oxygen sensor intrinsic to these cells that express messenger RNAs for erythropoietin and hypoxia-inducible factor subunits 1-alpha and 2-alpha or another peritubular cell juxtaposed to hypoxic blood flow. (18)¹⁵ In addition, putative fibroblast adenosine production within the interstitium increases during hypoxic conditions. Fibroblasts, due to their tubular apposition, can mediate the conversion of tubular adenosine monophosphate (5'-adenylic acid) to adenosine via intrinsic ecto-5'-nucleotidase activity. The metabolic consequence of intrarenally active adenosine is to lessen overall renal workload during periods of metabolic stress by reducing sodium reclamation and afferent arteriolar vasoconstriction, with limitation of ultrafiltration.

Aside from fibroblasts and myofibroblasts the interstitium also contains resident mast cells, macrophages, lymphocytes, lymphatic endothelial cells, and dendritic cells (DCs). Mast cells are rare in the normal kidney, but have been associated with both profibrotic and antifibrotic actions. They play a vital role in the kidney fibrosis of

obstructive uropathy during rodent unilateral obstruction.¹⁶ Macrophages are the oldest cells of hematopoietic lineages. Migration of monocytes from the circulation to the kidneys provides the few interstitial macrophages of the normal kidney. Inflammatory foci and mediators recruit monocytes to the kidney in glomerular and tubulointerstitial disorders, with consequent differentiation into a prototypical inflammatory M1 or reparative M2 phenotype.¹⁷ Type II major histocompatibility complex antigen expression may ensue during the M1 transformation. Overall, the balance between M1/M2 phenotypic expression and modulating interactions with T lymphocytes, fibroblasts, and DCs via growth factors, cytokines, and other microenvironmental cues dictates in part the extent of renal fibrogenesis and progression of chronic kidney disease.

Note that fibroblasts are not fibrocytes,^{18,19} which are derived from leukocytes. Fibrocytes, following migration to the tubulointerstitium, may also participate in the processes of interstitial fibrosis and tubular atrophy. These cells are typically identified in injured kidneys and are present in nephrogenic systemic fibrosis.¹⁹ Resident kidney medullary fibroblast-like interstitial cells are found along the renal medulla among the vasa recta, Henle's thin limb, and medullary collecting ducts. Abundant lipid cytoplasmic droplets of triglycerides, cholesterol esters, and free long-chain fatty acids including arachidonic acid are contained in these cells. These medullary interstitial cells express cyclooxygenase-2 and are involved in prostanoid synthesis. Intracellular lipid droplets are altered by varying salt and water intake, implying a role for these cells in normal and aberrant kidney physiology.²⁰

The spotlight has recently been aimed at the DC. DCs are antigen-collecting cells, well-characterized in the immunology literature, mature in the interstitium following their sojourn as bone marrow-derived precursor cells, a process requiring expression of the C-X3-C motif chemokine receptor 1, CX3CR1.²¹ In the interstitial compartment, DCs serve a sentinel role in the kidney,² interacting with T cells residing within the interstitial lymphatic network and probing for foreign antigen(s). The relationship of DCs to interstitial mononuclear cells is more intimate than previously thought, and DCs may represent dichotomously differentiated cells from the same monocyte lineage. DCs may also be recipients of tubular lumen antigens presented by proximal tubular cells, which constitutively express major histocompatibility complex class II antigens.²² Migration of DCs to the glomerular compartment in nephrotoxic nephritis,²² a glomerulonephritis, represents one mechanism among many of tubuloglomerular crosstalk and injury within the tubulointerstitium following glomerular injury.¹¹

Weakly interacting massive particles have been recently theorized as the major, if not only, constituent of dark matter,¹ but the incredible, galaxial instruments such as the Laser Interferometer Gravitational-Wave Observatory housed at the California Institute of Technology and the Massachusetts Institute of Techno-

logy constructed to explore such postulates must resolve signals from distances incomprehensible and over eons. Fortunately, for us, our earth-bound kidney pathologists and scientists have begun to resolve the mysteries of tubulointerstitial dark matter. To explore and comprehend this dark matter in greater depth, you, the reader, must now engage.

About Dark Matter: "I'm sorry I know so little. I'm sorry we all know so little. But that's kind of the fun, isn't it?"

— Vera Rubin (2009)

Jerry Yee, MD
Editor-in-Chief
Henry Ford Hospital
Wayne State University
Detroit, MI

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