cells is necessary. CD14 is expressed on monocytes, macrophages, and dendritic cells (DCs). The following data support the importance of macrophages: Histology demonstrated that M2 polarized F4/80+/CD206+ macrophages were increased in mice subjected to endotoxin preconditioning. Moreover, when TRIF signaling was restored in the CD14/KO bone marrow chimeric mice by administering the TLR3 agonist poly(I:C), a partial recovery of protection was observed. Hato et al. elegantly utilized intravital 2P imaging to show that fluorescent poly(I:C) localized specifically to green fluorescent protein (GFP)+ macrophages in the preconditioned kidneys of CX3CR1-eGFP reporter mice but not other mononuclear phagocytes such as DCs. On the basis of the intermediate GFP expression, it is likely that this subset represents the Ly-6C+ macrophages.

Using poly(I:C) as a “labeling” agent, macrophages were tracked in vivo and clustered around S1 proximal tubule segments. The subsequent events and mediators of this interaction (e.g., cytokines) remain to be investigated. A finding that might shed light on the biochemical pathways activated by macrophages in endotoxin preconditioning is the upregulation of heme oxygenase-1 and Sirtuin 1 (SIRT1), proteins involved in iron metabolism, in both macrophages and renal tubular cells. The sequelae of this observation remain to be tested; however, it is critical to highlight that an increase in heme oxygenase-1 and SIRT1 solely in renal tubules of TLR4KO/WT chimeric mice failed to mediate protection.

This work provides researchers with a pivotal macrophage-controlled pathway involved in protection from sepsis-induced AKI. Because patients with sepsis usually cannot be identified beforehand, new treatment strategies during the early disease stage are needed. Németh et al. have shown that giving bone marrow stromal cells ameliorates sepsis-induced organ dysfunction via reprogramming of host macrophages.8 In this study, kidney function was significantly improved after bone marrow stromal cell administration. Targeting macrophages or the involved signaling pathways could prove to be a more specific therapeutic approach.

In conclusion, Hato et al. have demonstrated in vivo that low-dose endotoxin administration is protective against sepsis-induced AKI in mice and that macrophages are the principal mediators of this effect. Better understanding of the mechanism by which macrophages mediate their protective effect, the involved signaling pathways, and the role of redox and iron-handling proteins may lead to novel treatment options not only for sepsis-induced AKI but also potentially for other insults that can be alleviated by cross-tolerance after preconditioning.

DISCLOSURES
None.

REFERENCES


Apolipoprotein L1-Associated Nephropathy and the Future of Renal Diagnostics

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Apolipoprotein L1 (APOL1)-associated nephropathies comprise a spectrum of related nondiabetic kidney diseases strongly associated with the G1 and G2 coding risk variants in populations with recent African ancestry.1 The spectrum is extremely
heterogeneous, ranging from nephrotic syndrome with collapsing glomerulopathy in patients with HIV-associated nephropathy to slowly progressive renal failure with minimal proteinuria that clinically and histologically mimics hypertension-related nephropathy. The genetic contribution or absence of proteinuria that clinically and histologically mimics non-African Americans who have FSGS and proteinuria above 1 g/d. Collapsing glomerulopathy is the most widely recognized biopsy finding in APOL1-associated nephropathy, and not surprisingly, Kopp et al. found that it was significantly more common in those with two copies of APOL1 nephropathy risk alleles compared with those with fewer than two risk alleles. However, collapsing glomerulopathy is not the most common variant of FSGS in this cohort; 70% of participants with two APOL1 renal risk alleles had histologic evidence of a noncollapsing FSGS variant. As such, it does not seem advisable to screen for APOL1 nephropathy variants simply based on the finding of collapsing glomerulopathy on kidney biopsy in African Americans. Screening in this manner would have detected only 22% of participants with two risk alleles in this cohort.

The outcome data from the FSGS Clinical Trial, although informative, are not encouraging. Approximately 60% of participants had a transient partial or lack of response to cyclosporin or mycophenolate/dexamethasone treatment. Those with two APOL1 renal risk alleles were significantly more likely to progress to ESRD than those with fewer than two alleles. It has been reported that genetic alterations predict a lack of treatment response in patients with steroid-resistant nephrotic syndrome. However, this may not be the case for APOL1.

Little is known about the pathogenic mechanism(s) by which APOL1 renal risk alleles confer susceptibility to kidney disease with the resultant lesions of FSGS; even the primary kidney cell types involved remain uncertain. Although the effect size of renal risk alleles is quite high, the fact remains that most individuals who inherit two APOL1 renal risk variants do not develop kidney disease. For this reason, the working hypothesis is that those who ultimately manifest clinical kidney disease possess additional genetic alterations that contribute to disease (APOL1 gene–second gene interactions) or are exposed to additional modifying risk factors (APOL1 gene–environment interactions). There is no doubt that environmental conditions play a major role in several subtypes of APOL1-associated kidney disease; these disorders are labeled by modifiers, such as sickle cell nephropathy, HIV-associated nephropathy, and SLE-associated collapsing glomerulopathy. There were no clear modifiers that contributed to disease in the population described by Kopp et al., because the FSGS Clinical Trial excluded participants with secondary conditions. Cohorts such as this provide a unique opportunity for investigation of potential novel disease modifiers that may interact with APOL1 risk alleles to produce (or prevent) CKD. Possibilities include interactions between APOL1 and second genes, which were recently described for podocin (NPHS2), serologically defined colon cancer antigen 8 (SDCCAG8), and bone morphogenetic protein 4 (BMP4), or as yet undiscovered inciting non-HIV viral triggers.

Like in idiopathic FSGS, APOL1-associated focal global glomerulosclerosis with prominent interstitial and vascular changes, typically reported as arterionephrosclerosis, currently lacks known modifying factors. We reported renal histologic findings in African Americans with arterionephrosclerosis on the basis of their APOL1 genotypes. This sample universally lacked nephrotic syndrome to exclude idiopathic FSGS and provides an interesting contrast to FSGS Clinical Trial participants. African Americans with two APOL1 renal risk alleles and arterionephrosclerosis more often lacked obsolescent glomerulosclerosis, which is the result of renal microvascular disease with reduced glomerular perfusion, subsequent ischemic collapse, and wrinkling of the glomerular basement membrane. Instead, they possessed greater degrees of solidified and disappearing glomerulosclerosis, thyroidization-type tubular atrophy, and microcystic tubular dilation relative to African Americans with fewer than two renal risk variants. Because APOL1 is felt to convey a higher risk for progression of nondiabetic nephropathy, the prominent tubulointerstitial changes may prove to be important in this disease spectrum. Similar to our report, FSGS Clinical Trial participants also displayed prominent tubular atrophy/interstitial fibrosis. As such, renal tubular cells are highly likely to be affected by APOL1 variant proteins, perhaps just as likely as the podocyte.

No existing treatments have proven efficacy for patients with progressive APOL1-associated nephropathy. Kopp et al. reported that the presence of two APOL1 renal risk alleles in study participants with biopsy-proven FSGS does not predict a response to immunosuppressive treatment. However, the vast majority in this report showed little (or no) response to the treatment regimens used. Unfortunately, this outcome currently exists for many subtypes of APOL1-associated nephropathy. Treatment and/or prevention of disease is possible in HIV-associated nephropathy, where effective antiretroviral therapy halts nephropathy progression. Although not proven, preventing acute flares in patients with SLE might have benefits.
in SLE-associated collapsing glomerulopathy. However, the vast majority of African Americans with lupus nephritis-associated ESRD who possessed two APOL1 renal risk variants in a recent report previously failed cytotoxic therapy. This may suggest limited effects of cytotoxic therapy in patients with two APOL1 nephropathy risk variants.

Recent clues concerning the possible pathogenesis of APOL1-associated nephropathy may have implications for future therapies. The lack of nephropathy in individuals with null mutations in APOL1 suggests that the renal risk alleles confer a toxic gain of function for this protein. Additionally, cell culture experiments have shown that overexpression of the APOL1 protein is harmful to cells and that expression of the APOL1 renal risk variants is more injurious than wild-type APOL1. Antiviral pathways may be important inducers of APOL1 overexpression, because this process is regulated by innate immune pathways, including signaling by IFNs and Toll-like receptors. Thus, treatments aimed at decreasing the expression of the renal risk alleles could alter the risk for ESRD.

Definitive diagnoses of APOL1-associated nephropathy are rarely made in clinical practice, because genetic testing is not routinely performed. This may be because of the fact that detecting APOL1 renal risk alleles provides no immediately actionable management strategy. Additionally, we practice in an increasingly pragmatic health care environment, where many payers will not reimburse molecular diagnostics that lack direct treatment implications. As a result, affected patients are often given vague diagnoses; many are mistaken for kidney disease resulting from the effects of essential hypertension and categorized as hypertensive or arteriolar nephrosclerosis. Those who have a kidney biopsy are often placed in the category of FSGS; a nonspecific lesion recognized historically that can have myriad pathogenic etiologies.

Moving forward, patients with common complex forms of severe nephropathy deserve precise diagnoses whenever possible. Precision medicine is rapidly paving the way. Affected individuals should be informed of what led to their renal diagnosis if they desire such information. As specific treatments (or clinical trials) become available for devastating forms of APOL1-associated nephropathy, patients and their physicians would then know that they are eligible to participate. Additionally, although no specific treatments are presently available, the diagnosis of APOL1-associated nephropathy provides prognostic information and will likely be important in evaluating suitable kidney donors who possess recent African ancestry.

The report by Kopp et al. enhances our understanding of a common etiology of the FSGS lesion seen on kidney biopsy in African Americans, and APOL1 is the most common etiology in this ethnic group. FSGS was first recognized on the kidney biopsy approximately 90 years ago. Despite subsequent advances in diagnostic technology, the most commonly used classification scheme of FSGS continues to rely largely on light microscopy. We practice in an exciting era in medicine, when diagnostic pathology is rapidly evolving with the incorporation of powerful technologies, such as next generation sequencing, allowing the simultaneous evaluation of thousands of potentially associated genes. Routine use of these new technologies will allow for more accurate pathogenesis-based classification schemes in FSGS. This will ultimately enable precise treatment options and likely improve the outcomes for many patients with CKD.

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DISCLOSURES

None.

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Transplant Glomerulopathy: The View from the Other Side of the Basement Membrane

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Transplant glomerulopathy (TG) is a morphologic lesion of renal allografts that is characterized histologically by duplication and/or multilayering of the glomerular basement membrane (GBM). TG is well documented to be associated with the presence of donor-specific antibodies (DSAs), most notably against HLA class II antigens, and in the majority of cases is felt to represent a morphologic manifestation of chronic antibody-mediated rejection (ABMR). However, TG is not specific for chronic ABMR, and in one-fourth to one-third of cases appears to have a different etiology, including hepatitis C, thrombotic microangiopathy (TMA), and possibly T cell-mediated rejection (TCMR). For ABMR and TMA, the pathogenesis of TG clearly involves injury to the glomerular endothelium, and this may also be the case for TG secondary to hepatitis C, which has been shown in five cases to involve a lesion of TMA and anticardiolipin antibodies. Indeed, the combination of moderate to severe margination of leukocytes in glomerular capillaries with associated endothelial cell swelling, GBM double contours, and the presence of DSAs is diagnostic for chronic, active ABMR according to the 2013 Banff classification.2

TG is well documented to be an important predictor of poor allograft survival, and is also manifest by proteinuria that can be in the nephrotic range, particularly in advanced lesions. In a study of graft outcomes in 36 patients with TG, John et al.8 found a mean level of proteinuria of 2.1 g/d, with >3 g/d or $3+ by dipstick in 15 (42%). Proteinuria was not different in C4d-positive and C4d-negative cases, but levels of >1 g/d or $2+ by dipstick were associated with a trend toward worse graft survival.8

In this context, the article in this issue of JASN by Yang et al. found from the laboratory of Roger Wiggins at the University of Michigan represents an interesting and unique approach to the study of TG. The authors examine podocyte density and related glomerular parameters in renal allograft biopsies taken at different times post-transplantation in patients with and without TG, and correlate these findings with urinary excretion of podocytes and of protein. Podocytes, with their complex structure that includes foot processes and slit diaphragms, are a vital element of the glomerular filtration barrier to protein. Not surprisingly, Yang et al. found that transplantation of a single kidney resulted in an approximately 20% increase in glomerular volume and podocyte volume by 3 months post-transplantation, with a similar, corresponding decrease in podocyte nuclear density within glomeruli. However, somewhat surprisingly, they found that although the transplant patients had only a single functioning kidney, their urinary podocin/creatinine ratio (UPod/Cr; an estimate of podocyte excretion) at 3 months post-transplantation was on average approximately 6-fold higher than that of control patients with two kidneys and normal renal function, and this remained elevated beyond 5 years post-transplantation. Yang et al. also found that although acute rejection (mainly TCMR), acute tubular injury, calcineurin inhibitor toxicity, and BK virus nephropathy were not associated with a significant increase in UPod/Cr above levels seen in transplant recipients with biopsies showing no histologic lesions, TG was associated with an additional 5- to 10-fold increase in UPod/Cr, signifying a marked acceleration of podocyte detachment from GBMs.

What is especially interesting about these findings in patients with TG is that similar elevations in UPod/Cr were seen in