uPAR/suPAR expression as previously described by Wei et al.1 The resultant proteinuria in this study set could not be further exacerbated by coinjection of exogenous physiologic suPAR forms. These experiments argue that the glomerular suPAR that is generated or deposited in the kidney in response to LPS is different from the recombinant one administered by Cathelin et al.2 An appealing possibility is that the vitronectin/suPAR complex is disrupted by acute phase rises in plasminogen activator inhibitor-1. Plasminogen activator inhibitor-1 competes with uPAR for vitronectin binding3; thus, one might expect less vitronectin/suPAR during an acute phase reaction. This scenario favors vitronectin/suPAR as the active principle in integrin activation.

Overall, the study by Cathelin et al. lets us appreciate that we currently do not fully understand which suPAR forms or associated proteins (e.g., vitronectin) represent the most podocyte pathogenic ones. Given this shortcoming in knowledge regarding which of the suPARs is most relevant to FSGS, none of the animal experiments using suPAR may precisely reflect what occurs in human FSGS. From a scientific perspective, these will be very interesting questions to answer. From a clinical perspective, the removal of all suPAR forms in patients’ circulation using a specific suPAR-immunoadsorption device may provide an approach in addressing the relevance of suPAR for human FSGS, and, if successful, may suggest a therapeutic consideration in this and potentially other suPAR-mediated disorders.

DISCLOSURES
J.R. has pending or issued patents on novel kidney protective drug therapies. He stands to gain royalties from their commercialization.

REFERENCES

See related article, “Administration of Recombinant Soluble Urokinase Receptor Per Se Is Not Sufficient to Induce Podocyte Alterations and Proteinuria in Mice,” on pages 1662–1668.

Cytomegalovirus and Anemia: Not Just for Transplant Anymore

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Cytomegalovirus (CMV) is one of the most important viruses in renal transplantation that causes significant morbidity and mortality, even in the current era of effective prophylaxis and treatment. The CMV syndrome is characterized by fever, malaise, and transplant dysfunction that manifests as AKI, mortality, even in the current era of effective prophylaxis and treatment, immunosuppression reduction was the only treatment and was commonly associated with death and/or transplant failure. The introduction of effective antiviral medications, such as...
ganciclovir and valganciclovir, has significantly reduced the mortality directly attributable to CMV infection. However, despite this reduction in mortality, the indirect effects of CMV infection are still relatively common. CMV DNA has been detected in kidney transplants with chronic allograft nephropathy and subclinical CMV viremia has been associated with poor long-term transplant outcomes.1–4 In this issue of JASN, the article by Butler et al. highlights anemia as another indirect effect of CMV infection and reminds us of associations between CMV, anemia, and native CKD, of which many clinicians may not be aware.5 Butler et al. performed an exceptional translational study that began with two clinical observations that are well known to nephrologists. First, patients with native CKD demonstrate a direct correlation between the loss of kidney function, declining erythropoietin (EPO) levels, and worsening anemia. Second, kidney transplant recipients demonstrate a direct association between CMV and post-transplant anemia. The investigators sought to elucidate the mechanism of declining EPO production in CMV-affected patients with native and transplant CKD.

Anemia is an important complication of native and transplant CKD that results from loss of endogenous EPO production from the diseased kidney. It affects 70%–90% of patients with stages 4 and 5 CKD and 40%–50% of kidney transplant recipients within the first 6 months after transplantation.6,7 The findings in transplant recipients are particularly troubling because EPO deficiency and anemia occur in those individuals with normal estimated transplant function as well as decreased kidney function, highlighting the existence of additional contributors to anemia in kidney disease beyond the loss of renal function. Anemia is an important risk factor for the immense morbidity and mortality associated with CKD, including reduced exercise tolerance, left ventricular hypertrophy, and left ventricular systolic dysfunction.8–10 Patients with CKD-associated anemia experience increased hospitalization rates and length of stay in addition to higher mortality rates. Partial correction of CKD-associated anemia with recombinant EPO has improved many of these comorbidities, but there are many patients for whom recombinant EPO is ineffective. The precise mechanism of declining EPO production in native and transplant CKD and the resistance to treatment with recombinant EPO in select patients remain poorly understood. The exciting work of Butler et al. partially addresses this gap in knowledge.5

CMV targets renal glomerular, vascular, epithelial, interstitial, and tubular cells, including fibroblast-type cells in the renal cortex that activate EPO production in the setting of local tissue hypoxia. CMV DNA can be detected in asymptomatic kidney transplant recipients and its presence has been associated with severe anemia within the first 6 months after transplantation.11 Although there are no studies to date of CMV DNA in native kidneys with CKD, there are numerous reports of systemic CMV infection or reactivation in patients with CKD. Furthermore, patients with native CKD who are CMV-IgG positive require higher erythrocyte stimulating agent doses to treat anemia than patients who are CMV negative.12 However, a direct mechanism to explain the apparent association between CMV and anemia had remained a mystery.

The authors previously found CMV DNA in kidney transplants with chronic allograft nephropathy at the time of nephrectomy.1 They examined whether patients with native CKD also had CMV DNA in their kidneys even in the absence of overt CMV disease. Through carefully designed and conducted translational studies, they explored whether the presence of CMV DNA in these kidneys correlated with CMV serostatus, and if so, by what mechanism would CMV affect EPO production. The investigators effectively used human specimens and animal and cellular models to answer these questions and translate their mechanistic findings back toward the bedside. In brief, Butler et al. found that 9 of 13 (69%) kidney biopsies from patients with native stage 4 CKD tested positive for CMV-immediate early (IE) proteins despite the absence of signs or symptoms attributable to CMV infection. Importantly, although only two patients were CMV seronegative, their kidney biopsies were also negative for CMV-IE proteins. CMV serostatus was then examined in the context of hematologic data from these 13 patients. CMV-IgG levels were inversely correlated with both hemoglobin and red blood cell counts. These important findings confirm the prevalence of subclinical CMV infection in a small cohort of humans with CKD and demonstrate an association between CMV seropositivity and anemia that the authors studied further in animal and cellular models.

Next, the investigators infected BALB/c mice with murine CMV and followed them prospectively over 6 weeks. EPO levels were lower at 1 and 6 weeks in CMV-infected mice compared with uninfected controls. Unlike the human CKD cohort, hemoglobin and red blood cell counts were not affected by murine CMV infection, although the mean corpuscular hemoglobin concentration was significantly lower in the CMV-infected group. One possible explanation for these divergent findings is that in humans, CKD-associated anemia often takes weeks or months to develop after a decline in EPO levels because the lifetime of erythrocytes is 90–120 days.13 Therefore, if the CMV-infected mice had a longer follow-up period, the decline in EPO levels may have eventually produced the declines in hemoglobin and erythrocyte counts that were seen in humans with CKD. As discussed by the authors, another possibility is that the murine CMV infection was controlled by 6 weeks because EPO levels had returned to baseline by that time. The transient drop in EPO levels may have been inadequate to produce significant anemia, given the long t1/2 of existing erythrocytes.

In the cell-based models using cultured human EPO-producing cells (HEPCs), CMV inoculation resulted in increased expression of CMV-IE proteins, which were detected in kidney biopsies of native CKD patients who were CMV seropositive. When exposed to hypoxia, CMV-infected HEPCs produced significantly less EPO mRNA than control cells. Constitutive EPO production under normoxic conditions was not affected by CMV infection, which suggests a direct effect of CMV infection on the response of HEPCs to hypoxia. To show that the diminished EPO effect was not a general viral phenomenon, the investigators showed that HEPCs infected
with Kaposi’s sarcoma virus had normal EPO production under normoxic conditions and increased EPO mRNA production under hypoxic conditions, in contrast with the effects of CMV in this cell line. Further studies showed that it was the CMV-IE gene expression (identical to CMV-IE proteins detected in CMV-infected HEPCs and human kidneys with CKD) that directly mediated the lowering of the EPO mRNA. In a clinically relevant cellular study, treatment of the cells with valganciclovir, an inhibitor of CMV-late gene expression, had no effect on EPO mRNA production and supported that IE or early CMV gene expression was required to reduce EPO production. In several additional elegant experiments, the investigators showed that CMV infection reduces EPO mRNA production by inhibiting the expression of hypoxia-induced transcription factor-2α and that there was a dose response with CMV-IE gene expression. The working model shown in Figure 8 by Butler et al. is a brilliant figure synthesizing this novel mechanistic work.

A major strength of this study is the authors’ use of clinical observations, human biospecimens, animal models, and cell culture experiments to conduct true translational research that addresses an important question for clinicians. The finding of CMV-IE proteins in kidneys from humans with CKD but no overt symptoms of the CMV syndrome is important but must be confirmed in larger prospective studies. These should include studies of immunosuppressed and nonimmunosuppressed patients with native CKD, as well as the effect of CMV on resistance to recombinant EPO therapy. An intriguing extension of this mechanistic study would include a treatment arm to determine the effect of antiviral medications that target CMV on CKD-associated anemia. We applaud this innovative study that has the potential for broad applications in transplantation but more importantly in native CKD, which currently affects >20 million people in the United States.

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REFERENCES

None.

REFERENCES


Race, Class, and AKI

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If you are poor in this country that is hazardous to your health, if you are black or brown, too, and poor, it can be downright deadly.

President Barack Obama, 2007 Iowa Brown & Black Presidential Forum

In the United States, 46.5 million Americans are poor and 42.5 million do not have health insurance coverage. Income, used as a proxy for socioeconomic status, is a persistent and pervasive determinant of one’s health. Individuals with lower socioeconomic

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