demonstrate a therapeutic window for CG treatment, even if multiple cell types are impacted. Podocytes in CG have a dysregulated phenotype and adopt markers of parietal epithelial cells during injury. Although the authors report histologic normalization of glomeruli, they do not assess the expression of canonical podocyte markers, which are lost in CG. The concept of cytostatic or antiproliferative therapy is well accepted in oncology, and it raises the question whether the WIP1 pathway could be modulated in other glomerular proliferative and inflammatory states such as crescentic glomerulonephritis. The authors' short-term treatments with the WIP1 inhibitor did not increase tubulointerstitial fibrosis, but the impacts of longer-term treatment on the tubulointerstitium will have to be studied more closely given that the increased TGF-β signaling is expected to potentiate the tubular atrophy and interstitial fibrosis that is often seen with CG. This study makes it clear that the interaction between p53, Wnt, and TGF-β signaling pathways is not linear, is likely dose dependent, and is highly specific to cellular context. Thus, although it opens up a new therapeutic avenue to treat human CG, an additional study is needed to understand the impacts of pharmacologic inhibition of WIP1 in the tubules and outside the kidney.

We are seeing the rapid translation of biological discoveries into treatments for patients with FSGS and nephrotic syndrome. FSGS and especially CG are still rare diseases, and given their rarity, it is a challenge to account for heterogeneity in the patient population in assigning them to the appropriate clinical trials. As we learn more about the diverse biological mechanisms that could drive FSGS from animal models, we will have to identify which of those mechanisms may be active in a given patient, so as to choose the trial or treatment with the greatest likelihood of addressing the root cause. An example of this is the NEPTUNE Match clinical trial (NCT04571658). Direct assessment of the patient's kidney biopsy not only establishes the clinical diagnosis but can now be used to deduce underlying disease-causing mechanisms and risk-stratify patients.[8] Histologically identical lesions of CG, which receive the same clinical diagnosis, may nevertheless have divergent etiologic bases and require different treatment approaches.[9] This must be tempered by the fact that while the timing of disease onset is clear in animal models, the biopsy may be obtained from the patient at any timepoint during the disease process. Although this temporal heterogeneity might seem discouraging, it can also be viewed as an opportunity to define a therapeutic opportunity that is personalized to that patient and at the time of their presentation. Is it time to incorporate molecular stratification approaches into the routine kidney biopsy evaluation of glomerular diseases?

DISCLOSURES

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Targeting immune cell glutamyl-prolyl-transfer RNA synthetase 1 (EPRS1) to prevent fibrosis after tubulointerstitial nephritis

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Glutamyl-prolyl-transfer RNA synthetase 1 is an enzyme that connects glutamic acid and proline to transfer RNA during protein synthesis. In this issue, a study by Kang *et al.* examined the role of the immune cell glutamyl-prolyl-transfer RNA synthetase 1 in toxin-induced tubulointerstitial nephritis mice. The study demonstrated that blocking glutamyl-prolyl-transfer RNA synthetase 1 may be a therapeutic target to attenuate fibrosis after toxin-induced tubulointerstitial nephritis.

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see basic research on page 997

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Tubulointerstitial nephritis (TIN) is a common cause of acute kidney injury and can lead to chronic kidney disease. TIN is characterized by immune cell infiltration in the kidney interstitium. TIN can be drug induced (e.g., immune checkpoint

inhibitors and nonsteroidal anti-inflammatory drugs), infectious, idiopathic, genetic, or related to a systemic inflammatory condition such as inflammatory bowel disease or IgG4-associated immune complex multiorgan autoimmune disease.[1] Corticosteroids are often used but with variable effects. Recent studies have suggested that the immunosuppressant mycophenolate mofetil may have a potential therapeutic role.[1] Targeting immune/inflammatory cells is an attractive approach.

A potential modifier of kidney immune cell functions is glutamyl-prolyl-transfer RNA synthetase 1 (EPRS1). EPRS1 is a multifunctional enzyme involved in protein synthesis and non-canonical functions within cells. Its primary role lies in the aminoacylation of transfer RNA, specifically charging transfer RNA with proline and glutamine, an essential step in translation.[2] Several studies have highlighted the involvement of EPRS1 in promoting fibrosis.[2] One mechanism of EPRS1 action involves activating transforming growth factor-β signaling, a central pathway in fibrosis development. EPRS1 has been shown to interact with transforming growth factor-β receptors and facilitate its downstream signaling cascade, leading to the expression of profibrotic genes and collagen production.[3] EPRS1 has also been associated with the epithelial-to-mesenchymal transition, a process whereby epithelial cells acquire a fibroblast-like phenotype, contributing to tissue fibrosis.[3]

EPRS1 in tubulointerstitial nephritis

In this issue, Kang *et al.*[4] presented exciting data on the pathophysiological role of EPRS1 in TIN inflammation-induced fibrosis. They fed mice a diet containing 2% adenine (Figure 1).[4] This simulated TIN, leading to kidney immune cell infiltration and subsequent fibrosis. They observed an increased EPRS1-positive area with immunohistochemical localization in interstitial cells on day 14. Single-cell RNA sequencing was performed to study the subset of EPRS1 "high" cells linked to TIN progression. The TIN kidneys had more γδ T cells expressing interleukin-17a. EPRS1 expression was highest in γδ T cells and proliferating T cells, with low expression in other T and natural killer cell subsets. EPRS1 had the highest expression in TIN compared with 20 other aminoacyl-transfer RNA synthetases. They studied heterozygous knockout ($Eprs1^{+/-}$) mice because the homozygous knockout is lethal at the preweaning period and demonstrated a correlation of EPRS1 expression with fibrotic transformation after TIN. Elegant adoptive transfer studies of $CD3^{+}CD62L^{+}$ T cells from $Eprs1^{+/+}$ or $Eprs1^{+/-}$ into T cell– and B cell–deficient $Rag1^{-/-}$ mice 1 day before TIN-induced nephritis led to more T cell infiltration and fibrosis in $Eprs1^{+/+}$ than in $Eprs1^{+/-}$.

To begin to translate mouse results into humans, they found that EPRS1 increased in human T cells during the proliferation of naive $CD4^{+}$ or $CD8^{+}$ T cells and *ex vivo* expansion of peripheral blood–derived γδ T cells. Amphiregulin (a member of the epidermal growth factor family, a type II cytokine that primarily regulates inflammation and enhances regulatory T cell function[5]) was also induced in both conventional T cells and γδ T cells that were actively proliferating. There was also a positive correlation between the expression of EPRS1 and the development of fibrosis in human kidneys, studying fibrotic parameters including collagen I and fibronectin. TIN cases had more fibrotic material in the interstitium. EPRS1 induction was higher in human kidneys with interstitial inflammation such as toxin- and drug-induced TIN, but not in minimal change disease. EPRS1 correlated with Sirius red–positive fibrotic areas in human TIN cases.

The authors studied the effects of an inhibitor of EPRS1, bersiporocin, in mice. Bersiporocin binds to the PRS component of EPRS1 and decreases the production of proline-rich collagen. T cell proliferation decreased with the increase in the inhibitor dose, and kidney fibrosis was attenuated. When the inhibitor was administered to γδ T cells, the production of interleukin-17A decreased while CD44 expression remained unchanged. Amphiregulin production was also reduced when the inhibitor was given during γδ T cell activation.

Unanswered questions

Kang *et al.* have provided valuable insights into the mechanisms of toxin-induced TIN and the important role of the immune cell EPRS1. This study generates optimism for novel potential therapeutic applications. However, it also raises several points:

(i) Although the adenine-induced model is used to simulate TIN, studying EPRS1 in other models using drugs that commonly cause human TIN might be more relevant for patients.

(ii) Use of conditional knockouts instead of EPRS1 heterozygous mice would help dissect the kinetics of the effects on TIN.

(iii) Performing direct glomerular filtration rate measurement, now relatively simple in mice, would provide more precise data on kidney function than blood urea nitrogen and creatinine measurements.

(iv) Although they found that interleukin-17 production by γδ T cells was reduced, it would also have been interesting to study interleukin-17 secretion by $CD4^{+}$ T cells.[6]

(v) What is the origin of these γδ T cells—within the kidney, in the tertiary lymphoid tissues,[7] or are migrating from distant sites?[8]

(vi) Because there was an increase in the expression of EPSR1 in human peripheral blood–derived γδ T cells during *ex vivo* expansion, could there also be fibrosis in distant organs such as heart, blood vessels, and lung? Distant organ T cell effects have been demonstrated in acute kidney injury.[9]

(vii) To further dissect the role of EPRS1 in immune/inflammatory cells versus resident kidney cells, bone marrow chimera studies could be quite revealing.

(viii) The details of the etiology of TIN are not provided in patients, and so does the cause of TIN affect the tissue findings?

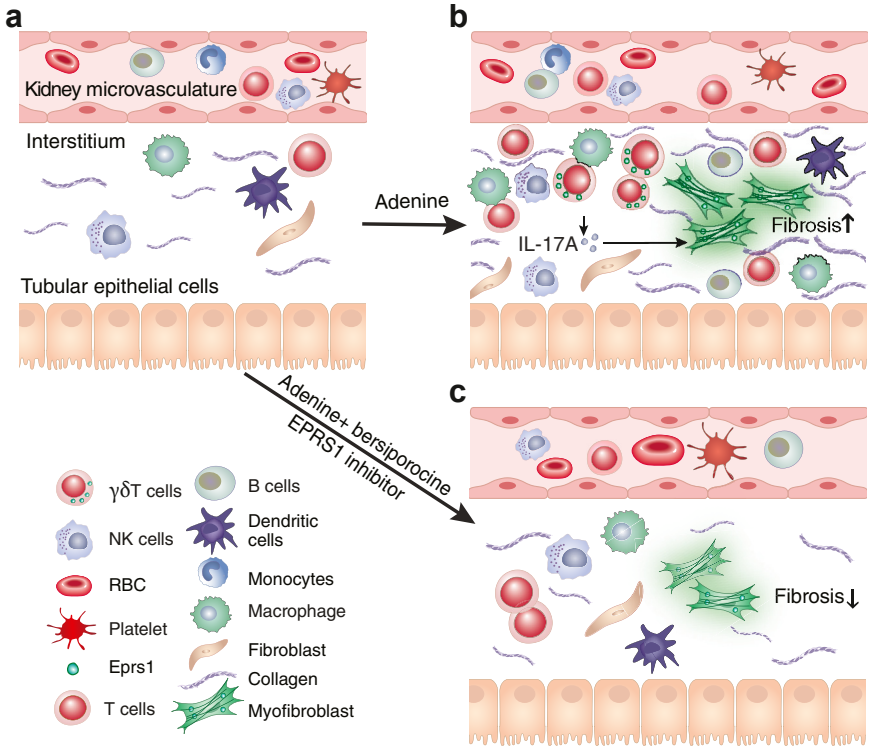

Figure 1 | Effect of the immune cell glutamyl-prolyl-transfer RNA synthetase 1 (EPRS1) and its inhibitor bersiporocin on experimental tubulointerstitial nephritis. (**a**) Normal kidney with limited numbers of inactivated resident immune cells in the kidney microvasculature and interstitium. (**b**) After adenine, there are increased numbers of total T cells, γδT cells, B cells, and natural killer (NK) cells. There is also an increase in pro-inflammatory cytokines, such as interleukin-17A (IL-17A), and EPRS1 mediated activation of transforming growth factor-β signaling that orchestrates tissue injury, maladaptive repair, and drives kidney fibrosis. (**c**) EPRS1 inhibitor bersiporocin targets the catalytic activity of EPRS1, reduces the production of collagen and fibronectin, reduces proline and glutamine, and decreases the release of IL-17. RBC, red blood cell.

(ix) What is the specificity and off-target effects of the EPRS1 inhibitor bersiporocin?

Overall, the present article is a scientific *tour de force*, with murine *in vivo* data, cell culture studies, use of modern single-cell technology, and thoughtfully selected human kidney tissue analysis. Further studies in both experimental models and humans with TIN will be required to ascertain the potential impact of this discovery.

DISCLOSURE

All the authors declared no competing interests.

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