suggest the need for further animal studies of IL-33 before testing in humans.

ILCs occupy an interesting area immunologically between the adaptive immune system of T and B cells and the innate immune system. The ability of ILCs to present antigen to T cells through MHC class-II) allows engagement with both Th2 and Tregs. The expression of CD80 and CD86 costimulatory molecules also acts to activate CD4 T cell subsets. Recent work has identified human ILC precursors that are epigenetically set to become ILCs. These migrate to tissues, where they then develop into ILCs and proliferate locally. This paper adds a new regulatory or protective immune cell in kidney disease after previous studies have shown protection by adaptive immune cells, CD4 and CD8 Tregs, and γδT cells in kidney disease as well as certain innate cells, including macrophage subsets.

These studies show the potential contribution of renal ILCs in human kidney disease, and a mouse model shows that expansion of ILC2 cells using IL-33 ameliorates AN. This report suggests several new therapeutic avenues for kidney disease on the basis of ILCs. However, the potential for alternate immune activation by IL-33 or the activation of Th2 effectors by ILC2s may be limiting. It also raises the possibility of a role for ILC2s in other renal conditions.

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DISCLOSURES

None.

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See related article, “IL-33-Mediated Expansion of Type 2 Innate Lymphoid Cells Protects from Progressive Glomerulosclerosis,” on pages 2068–2080.

Uromodulin in the Bloodstream: Old Wine in a New Wineskin

Daniel Kraus and Christoph Wanner

Department of Internal Medicine I, Division of Nephrology, Würzburg University Hospital, Würzburg, Germany

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“What is man, when you come to think upon him, but a minutely set, ingenious machine designed to turn, with infinite

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Correspondence: Prof. Christoph Wanner, Department of Internal Medicine I, Division of Nephrology, Würzburg University Hospital, Oberdurfbrucker Str. 6, 97080 Würzburg, Germany. Email: wanner_cd@ukw.de

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artfulness, the red wine of Shiraz into urine?,” wrote Karen Blixen (1885–1962) under her pen name, Isak Dinesen, in Seven Gothic Tails.1 Urine, of course, is much more than just red wine turned yellow. As early as 1895, Karl Mörner2 of Karolinska Institute described glycoproteins in the urine. The glycoprotein that is most abundant in the urine of healthy individuals was initially characterized in 1950 by Tamm and Horsfall.3 In 1985, Muchmore and Decker4 reported the presence of an immunoospressurive protein in the urine of pregnant women, which they named uromodulin. It was later determined that Tamm–Horsfall protein and uromodulin share the same amino acid sequence.5 The terms Tamm–Horsfall protein and uromodulin have been used interchangeably ever since.

Uromodulin is expressed solely in the thick ascending limb of the loop of Henle. It has been called enigmatic,6,7 because its physiologic role cannot be easily defined. Uromodulin is a pleiotropic molecule with numerous seemingly unrelated functions. After release into the urine, it facilitates uric acid excretion and protects from urinary tract infections and the formation of renal calculi. It is the major constituent of hyaline casts. In the tubular epithelial cells, uromodulin regulates the activity of the sodium-potassium–chloride cotransporter NKCC2, an important element of sodium and BP homeostasis.8 Furthermore, mutations in the uromodulin gene cause tubulointerstitial disease.9

Some 25 years into the research of Tamm–Horsfall protein/ uromodulin, it was discovered that this protein is also released into the bloodstream, albeit at much lower concentrations than in the urine.10,11 Unlike other markers of renal function, such as creatinine or cystatin C, serum uromodulin levels correlate directly, rather than inversely, with kidney function.11–13 The physiologic role of circulating uromodulin remains enigmatic.

Two new studies, accepted for publication within a few weeks of one another, now establish serum uromodulin as an independent risk factor for cardiovascular mortality.14,15 In this issue of the Journal of the American Society of Nephrology, Delgado et al.14 report an analysis of the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study in Germany. In 3057 patients with stable or unstable angina who were referred for coronary angiography, serum uromodulin was measured using a commercially manufactured ELISA, details of which have been published previously.13 Over a median follow-up period of 10 years, serum uromodulin levels correlated inversely with all-cause and cardiovascular mortality; the lower the serum uromodulin, the higher the risk. This association remained significant after adjustments for age, sex, body mass index, diabetes mellitus, hypertension, smoking, levels of high-sensitivity C-reactive protein and N-terminal probrain natriuretic peptide, and even GFR estimated using the Chronic Kidney Disease Epidemiology Collaboration equation with combined creatinine and cystatin C measurements.

In the other, independent study, Leiherer et al.15 also report the association of serum uromodulin with overall mortality. Using an ELISA from a different commercial manufacturer than that used by Delgado et al.,14 they analyzed serum uromodulin levels in 529 Austrian patients who were also referred for coronary angiography.15 The median follow-up was 6.5 years. As in the German study, uromodulin predicted survival independent of age, sex, body mass index, diabetes, hypertension, C-reactive protein, brain natriuretic peptide, and eGFR. Additional variables that also did not confound the association were smoking status, coronary artery disease, HDL, LDL, and the neutrophile-to-lymphocyte ratio. Of note, although the inverse relationship of serum uromodulin with mortality was not confounded by diabetes, Leiherer et al.15 reported elsewhere that serum uromodulin independently predicts type 2 diabetes and is associated with several markers of impaired glucose metabolism in the same cohort.16

An association with mortality was previously shown for urinary uromodulin.17 It should be noted, however, that measurement of uromodulin in the urine poses a preanalytic challenge,18 and serum measurements seem to be more reliable.

The regulation of the NKCC2 transporter (responsible for sodium and potassium reabsorption in the loop of Henle and the target of loop diuretics) by uromodulin implies a link with hypertension. Indeed, genome-wide association studies have identified several common single-nucleotide polymorphisms in the uromodulin promoter that are associated with hypertension and renal function.8 The major alleles of two of them, rs12917707 and rs4293393, are correlated with uromodulin gene expression, urinary excretion, CKD, and the development of salt-sensitive hypertension.8 Both rs12917707 and rs4293393 are located in the uromodulin promoter, and the rs4293393 mutation was directly shown to affect uromodulin gene expression in cultured cells.19 Delgado et al.14 tested a subgroup of the LURIC Study cohort for the presence of rs12917707 and also found that the major allele is associated with significantly higher (serum) uromodulin levels and lower eGFR than the minor allele. In the total cohort, the polymorphism did not affect overall survival. However, in patients younger than 67 years old, those with one or two of the uromodulin-lowering minor alleles lived longer.

This is puzzling. On the one hand, the two current studies as well as previous studies show that higher serum and urine uromodulin levels are beneficial in terms of better renal function and better survival.12,14,15,17 On the other hand, genetic predisposition for higher uromodulin expression and release is harmful in terms of higher BP and impaired renal function.19,20 How can this paradox be resolved? Uromodulin concentrations in serum and urine reflect the aggregate of release from the kidney and may decline despite increased expression in individual nephrons if not all nephrons are functional.21 As such, uromodulin is a marker of working nephron mass,21 independent of glomerular function. Indeed, 24-hour uromodulin excretion in the urine is increased with beginning diabetic nephropathy, and it decreases as nephrons are lost with more advanced disease.21 This and the relative loss of kidney function that is associated with the major high-uromodulin alleles as well as the
development of hypertension and nonhypertensive nephropa-thy in uromodulin-overexpressing mice point to a pathogenic role of uromodulin in CKD. However, there is also a large body of evidence that uromodulin has a protective role in modulating the immunologic response to kidney injury. In this regard, it is noteworthy that Delgado et al. observed significant inverse correlations of serum uromodulin with markers of inflammation.

Whether the association of lower serum uromodulin with higher risk of death that is now reported by Delgado et al. and Lehirer et al. is due to a protective effect of circulating uromodulin itself or rather, reflects the vital role of healthy kidneys is entirely unknown at this point. However, for many decades, research was focused on uromodulin in the renal tubuli. With the recognition of low serum uromodulin as an independent cardiovascular risk factor, this old molecule now takes center stage in a different vessel, if not to say in a new (proverbial) wineskin, and the physiology of circulating uromodulin will certainly be elucidated by future studies.

DISCLOSURES

None.

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Balancing Anticoagulation
Decisions in Patients on Dialysis with Atrial Fibrillation

Eli N. Deal and Jerrica E. Shuster
Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri

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For over 20% of 678,000 patients with ESRD in the United States, the diagnosis of atrial fibrillation (AF) presents a


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