consideration factors such as frailty, comorbidities and albuminuria."

The marked decrease in both cardiovascular events and all-cause mortality outweighs the increased risk of acute kidney injury that was seen in a very small proportion of SPRINT participants. In order to achieve this lower blood pressure goal, patients will likely require, on average, at least 1 additional antihypertensive agent. To minimize the risk of acute kidney injury, eGFR should be monitored after the addition of an antihypertensive agent or an increase in dose of an existing antihypertensive agent. It seems prudent to follow the KDIGO recommendations for blood pressure management in elderly persons with CKD,[4] in particular the suggestion that there be "gradual escalation of treatment with close attention to adverse events related to treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects," in all CKD patients in whom antihypertensive medications are titrated to a goal blood pressure of <120 mm Hg.

Notably, more than half of the participants in the intensive therapy arm of SPRINT had systolic blood pressure greater than 120 mm Hg after 1 year, highlighting the challenges of achieving and maintaining a lower target blood pressure. Future studies should consider the feasibility and cost–benefit of intensive blood pressure control in real-world clinical practice, where providers must balance blood pressure control with the management of comorbid risk factors for cardiovascular disease and all-cause mortality.

DISCLOSURE

All the authors declared no competing interests.

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translational science

Epithelial-to-mesenchymal transition of tubular epithelial cells in renal fibrosis: a new twist on an old tale

Madhav C. Menon[1] and Michael J. Ross[2]

[1]*Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA*
[2]*James J. Peters VA Medical Center, Bronx, NY, USA*
Correspondence: *Michael Ross, Division of Nephrology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1243, New York, NY 10029 USA.*
E-mail: michael.ross@mssm.edu

Recent publications have questioned whether epithelial-to-mesenchymal transition of tubular epithelial cells is an important contributor to renal fibrosis. Two recent publications describe an intratubular epithelial-to-mesenchymal transition-like program of epithelial cell dedifferentiation that may contribute to the recruitment or proliferation of interstitial myofibroblasts after kidney injury.

Refers to: Lovisa S, LeBleu VS, Tampe B, et al. Epithelial-to-mesenchymal transition induces cell cycle arrest and parenchymal damage in renal fibrosis. *Nat Med* 2015;21:998–1009.
Grande MT, Sanchez-Laorden B, Lopez-Blau C, et al. Snail1-induced partial epithelial-to mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease. *Nat Med* 2015;21:989–997.

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Renal interstitial fibrosis is closely associated with progression of most types of chronic kidney disease.[1] Myofibroblasts are critical mediators of renal fibrosis and are responsible for the secretion of excess extracellular matrix components. A key topic of controversy in the study of renal fibrosis has been the relative contributions of renal parenchymal cells versus nonrenal cells to the myofibroblast population. Numerous publications have incriminated epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells (TECs) as a key source of myofibroblasts that drive fibrosis, demonstrating that TECs lose their epithelial markers and apicobasal polarity, acquire mesenchymal markers, and undergo morphologic changes. EMT normally occurs during development and has pathogenic roles in cancer, in which it promotes vascular and local invasion, organ fibrosis, metastasis, and drug resistance.[2] Cells that complete EMT degrade the basement membrane and transmigrate into the interstitium.[3] In the setting of renal fibrosis, acquired expression of mesenchymal proteins such as vimentin, together with reduced expression of epithelial cytokeratins in TECs, has often been used as evidence that EMT has occurred. Although earlier studies suggested that a high proportion of renal myofibroblasts arise from complete TEC EMT, with migration into the interstitium,[4] more recent studies have cast doubt on whether EMT is responsible for generating a significant proportion of renal myofibroblasts.[5,6] In a recent issue of *Nature Medicine*, 2 articles by Lovisa *et al.*[7] and Grande *et al.*[8] describe an intratubular EMT-like dedifferentiation program of TECs that may contribute to renal fibrosis.

Both teams studied the role of EMT in renal fibrosis by generating mice with TEC-specific knockout of key transcriptional regulators of EMT, using slightly different approaches. Grande *et al.*[8] knocked out *Snai1* in cortical and medullary tubules, whereas Lovisa *et al.*[8] knocked out *Snai1* or *Twist* specifically in proximal tubules. Both groups found significant reductions in interstitial fibrosis in tubular *Snai1* and *Twist* knockout mice. Importantly, reduced fibrosis was noted in several kidney injury models, including unilateral ureteral obstruction, folic acid nephropathy, and nephrotoxic serum nephritis (Figure 1). Lovisa *et al.*[7] also found that reduced fibrosis in *Snai1* and *Twist* knockout mice was associated with improved renal function, and analyses of gene expression in kidneys suggested preserved tubular function and metabolism in knockout mice after injury. These data were further supported by *in vitro* functional assays of tubular transport in cell lines and expression of tubular transporters in a cohort of humans with chronic kidney disease, in whom increased expression of EMT markers in kidney biopsy samples (RNA and protein) correlated with reduced expression of tubular transport proteins.

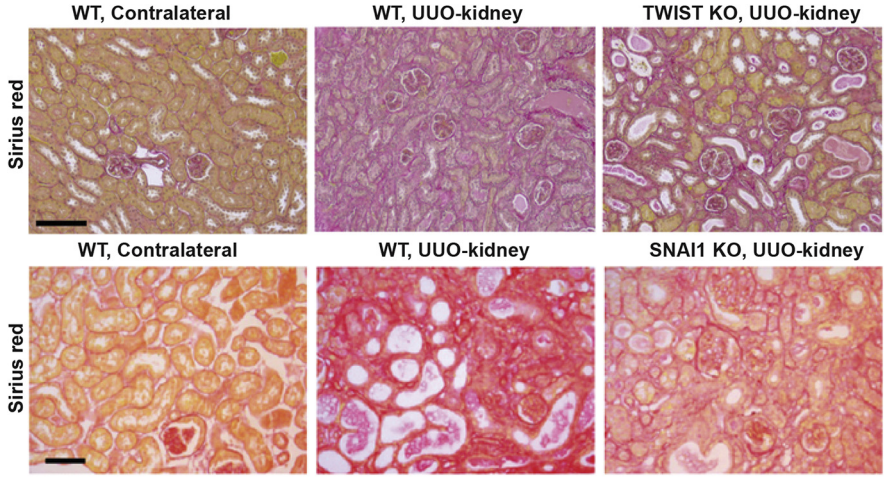

Figure 1 | Tubule-specific knockout of Snai1 or Twist decreased unilateral ureteral obstruction–induced renal fibrosis as determined by picrosirius red staining.[4,5] KO, knockout; UUO, unilateral ureteral obstruction; WT, wild type. Adapted by permission from Lovisa S, LeBleu VS, Tampe B, et al. Epithelial-to-mesenchymal transition induces cell cycle arrest and parenchymal damage in renal fibrosis. *Nat Med.* 2015;21:998–1009[7] and Grande MT, Sanchez-Laorden B, Lopez-Blau C, et al. Snail1-induced partial epithelial-to-mesenchymal transition drives renal fibrosis in mice and can be targeted to reverse established disease. *Nat Med*. 2015;21:989–997.[8]