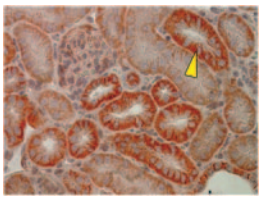
This Month's Highlights

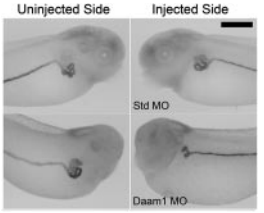
BASIC RESEARCH

Inhibiting β-catenin Signaling Benefits CKD



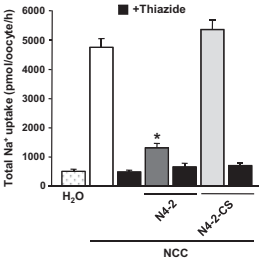
Activation of β-catenin signaling may promote renal fibrosis. Hao *et al.* studied the anti-fibrotic efficacy of the peptidomimetic small molecule ICG-001, which disrupts β-catenin-mediated gene transcription. In cultured tubular epithelial cells, ICG-001 inhibits TGF-β1-induced expression of pro-fibrotic genes in a Smad-independent manner. In a mouse model of obstructive uropathy, ICG-001 ameliorates interstitial fibrosis and suppresses genes indicative of epithelial-mesenchymal transition. These data suggest that inhibiting β-catenin signaling may hold promise as an anti-fibrotic therapy in CKD. *See Hao et al., pages 1642–1653.*

Daam1 Required for Renal Tubulogenesis



Normal development of kidney tubules requires proper planar cell polarization (PCP) and modulation of the cytoskeleton, but whether PCP components directly affect the actin cytoskeleton in renal tubulogenesis is unknown. In experiments involving *Xenopus laevis* and zebrafish, Miller *et al.* found that the developing pronephros expresses the formin protein Daam1 and its associated Rho-GEF, which compose one branch of the PCP/noncanonical Wnt pathway and modulate actin polymerization. Inhibiting the Daam1 signaling pathway reduces pronephric tubulogenesis. These data suggest that Daam1 provides a molecular link between planar-cell polarity signaling and cytoskeletal modulation in renal tubulogenesis. *See Miller et al., pages 1654–1667.*

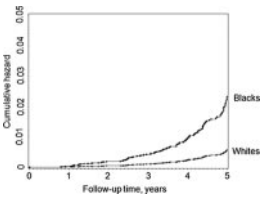
Nedd4–2 Mediates NCC Upregulation by Aldosterone



Upregulation of the Na^+-Cl^- cotransporter (NCC) in the distal convoluted tubule contributes to aldosterone-mediated Na^+ reabsorption, but the mechanism by which aldosterone increases NCC expression is unknown. In this issue, Arroyo *et al.* report that aldosterone promotes phosphorylation of Nedd4–2 by serum-glucocorticoid-regulated kinase (SGK1), which prevents the ubiquitylation and degradation of NCC. Furthermore, they found that SGK1 must phosphorylate two sites on Nedd4–2 to modulate NCC in contrast to the one site necessary to modulate ENaC. Supporting these data, Nedd4–2 deficiency in mouse renal tubules upregulates NCC. These data suggest that aldosterone increases NCC expression through a pathway involving SGK1 and Nedd4–2. *See Arroyo et al., pages 1707–1719.*

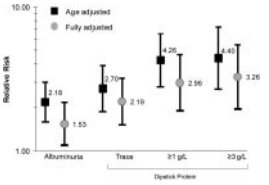
CLINICAL EPIDEMIOLOGY

Proteinuria May Explain Racial Disparities in ESRD



African Americans are at increased risk for ESRD, but the reasons for this disparity are not completely understood. McClellan *et al.* analyzed data from nearly 28,000 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study to determine whether racial differences in albuminuria may contribute. Albuminuria was more common among African Americans, and despite having better renal function at baseline, they had a fourfold greater age- and sex-adjusted risk for incident ESRD. Adjusting for albumin-to-creatinine ratio substantially attenuated this risk, suggesting that the higher prevalence of albuminuria among African Americans may underlie their excess burden of ESRD. *See McClellan et al., pages 1721–1728.*

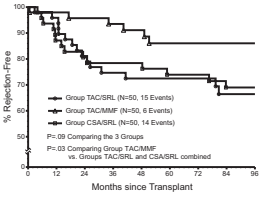
Dipstick Proteinuria Predicts Renal Decline



It is not cost-effective to repeatedly screen the general population with measurements of estimated GFR. To determine whether assessments of proteinuria could help identify a high-risk population, Clark *et al.* analyzed data from >2500 participants in a community-based prospective cohort. They found that dipstick proteinuria ≥1g/L more strongly predicts a >5% annual decline in eGFR than the presence of albuminuria. Proteinuria ≥1g/L correctly identifies 91% of those who will rapidly progress. Their data suggest that screening with a urine dipstick may allow a physician to follow fewer patients with serial eGFR measurements to identify those with rapidly declining renal function. *See Clark et al., pages 1729–1736.*

CLINICAL RESEARCH

Tacrolimus/MMF Superior to Alternatives



The optimal regimen of immunosuppression after kidney transplantation remains unknown. Guerra *et al.* report the results of a randomized trial involving 150 kidney transplant recipients assigned to regimens that included either tacrolimus/sirolimus, tacrolimus/mycophenolate mofetil (MMF), or cyclosporine/sirolimus. They found that acute rejection occurred significantly less often and mean estimated GFR was consistently higher among those treated with tacrolimus/MMF. Death with a functional graft was significantly more common among those treated with tacrolimus/sirolimus than the other groups. These results suggest that a regimen including tacrolimus/MMF is superior to either tacrolimus/sirolimus or cyclosporine/sirolimus. *See Guerra et al., pages 1758–1768.*