This Month’s Highlights

Basic Science Articles

Regulated Expression of an Ammonia Transporter in the Distal Nephron. Recent studies have identified the Mep/Amt/Rh glycoprotein family of ammonia transporters. One member of this family, Rh C glycoprotein (RhCG), transports ammonia, is expressed in the distal nephron, and has increased expression in chronic metabolic acidosi.

Han et al. performed immunoblot analysis of human renal cortical protein lysates and demonstrated RhCG protein expression with a molecular weight of approximately 52 kD. Immunohistochemistry revealed both apical and basolateral RhCG expression in the distal convoluted tubule, connecting segment, initial collecting tubule, and throughout the collecting duct. Colocalization studies with other transporters suggest that RhCG contributes to both apical and basolateral membrane ammonia transport in the human kidney. The increased expression in metabolic acidosi indicated a regulated transport pathway rather than the simple diffusive NH₄⁺ “trapping” model originally described by Pitts. See Han et al., pages 2670–2679.

Functions of Polycystin-2 in Zebrafish. The zebrafish pronephros is a useful model of kidney development and function. The zebrafish genome contains a homologue of the human PKD2 gene, and disruption of this gene produces pronephric cysts. To understand the mechanism of cyst formation, Obara et al. at the Massachusetts General Hospital generated an antibody against zebrafish polycystin-2 and immunolocalized the protein in apical cilia and intracellular membranes, which is similar to the expression in the mammalian kidney. One advantage of zebrafish is that gene expression can be inhibited experimentally using morpholino antisense oligonucleotides. Inhibition of PKD2 expression using this technique resulted in cyst formation and situs inversus. The cilia in the kidney appeared to be morphologically normal, but urine flow was reduced due to obstruction of the distal pronephric duct. Although the relevance of the latter finding to the pathogenesis of human polycystic kidney disease remains to be determined, these results highlight the causal relationship between urinary tract obstruction and cyst formation. See Obara et al., pages 2706–2718.

T Cell–Mediated Regulation of Macrophage Function in Murine Adriamycin-Induced Nephropathy. CD4⁺/CD25⁺ FoxP3-expressing T regulatory cells (Treg) control pathogenic T cell responses and are recognized as key mediators of autoimmunity and tolerance. Whether Treg can also control innate pathogenic immune reactions that lead to kidney pathology has not been well studied. In this issue of JASN, Mahajan and colleagues from Sydney, Australia, show that Treg inhibit macrophage activation and function in vitro. The authors then demonstrate that adoptive transfer of Treg limits adriamycin-induced nephropathy in immunodeficient SCID mice, a disease process that involves macrophages but no T cells. The inhibitory effect is further shown to be TGF-β-dependent. The results delineate a previously unknown role for Treg and TGF-β as modulators of macrophage function, and provide a mechanism to account for how Treg can prevent renal pathology by inhibiting innate as opposed to adaptive immunity in vivo. See Mahajan et al., pages 2731–2741.

Development of Polycystic Kidney Disease in jck Mice. The jck mutant mouse develops polycystic kidney disease (PKD) due to a missense mutation of the cell-cycle kinase, Nek8. A study published in JASN in November 2005 showed that Nek8 is located in the primary cilia of renal epithelial cells. In this issue of JASN, Smith and her colleagues studied the development of PKD in the jck mouse. They found that cysts originated from multiple nephron segments and that the EGF receptor was mislocalized, similar to human PKD. Two findings were of particular interest: First, the cilia in the kidneys of jck mice were longer than in wild-type mice, which suggests that Nek8 plays a role in controlling cilia length. Second, male mice had more aggressive disease, and administration of testosterone to female mice worsened cyst formation. Because male gender is a poor prognostic indicator in human autosomal dominant PKD, further studies of jck mice may be particularly useful for understanding this aspect of the disease. See Smith et al., pages 2821–2831.
Mutations of Developmental Genes in Renal Hypoplasia. Renal hypoplasia/dysplasia (RHD) comprises a heterogeneous group of congenital disorders characterized by small or absent kidneys and abnormal nephrogenesis often associated with kidney cysts. RHD occurs in various syndromes caused by mutations in renal developmental genes, such as TCF2, PAX2, EYA1, SIX1, and SALL1. To determine whether mutations in these genes can also cause sporadic RHD, Weber and colleagues studied 100 children enrolled in the prospective, multicenter, European ESCAPE trial. Mutations were identified in 18 children, 13 of whom were not suspected to have a clinical syndrome associated with RHD. Mutations were most commonly found in TCF2 and PAX2. TCF2 mutations were often associated with kidney cysts, whereas mutations of PAX2 were associated with renal hypoplasia and urinary tract abnormalities. Genetic testing may be helpful in children with sporadic RHD, especially those with cystic renal dysplasia or extrarenal abnormalities. See Weber et al., pages 2864–2870.

Mild Contrast Nephropathy: Worse News Than We Thought. Weisbord et al. confirm and extend the findings of adverse outcomes associated with radiocontrast nephropathy, even where the apparent severity of acute kidney injury is modest. Over a 12-yr period at a major academic medical center, data on >11,000 persons who underwent coronary angiography with pre- and postprocedure assessments of kidney function were analyzed. Fewer than 5% of patients experienced a nominal increase in serum creatinine >0.25 mg/dl on one or more of the first three days after angiography. However, even modest changes in serum creatinine (0.25 to 0.5 mg/dl) were associated with clinically and statistically significant increases in the odds of in-hospital death within 30 days (and extended lengths of stay). This study documents that acute kidney injury after radiocontrast exposure is relatively rare when examined in an unselected population of patients undergoing coronary angiography. However, when the serum creatinine “goes bump in the night,” we need to pay attention, as adverse outcomes are much more frequent. See Weisbord et al., pages 2871–2877.

The Better Survival of African-Americans with ESRD: Is It Real? The survival advantage that is consistently reported for African-American and other racial and ethnic ESRD patients has been a conundrum that can be studied only through observational study designs. Potential explanations for this preferential survival have included selection bias due to competing causes of mortality, unmeasured biologic and behavioral risk factors, and differences in the response to the treatment environment and care. The report by Robinson et al. from the US Dialysis Outcomes and Practice Patterns Study (US-DOPPS) illustrates the complexity of these analyses and sheds some additional light on possible explanations for these survival differences. The authors note that the ethnic and racial groups in the US-DOPPS varied substantially with respect to baseline characteristics and that many of these risk factors varied over follow-up, necessitating complex time-dependent models to fully capture the survival experience of the study group. Next, they found that, while no single category of risk factors could fully account for the survival differences, the magnitude of the differences was attenuated and finally no longer significant as they controlled for additional groups of risk factors. As noted by the authors, all other things being equal, the risk of death should be comparable across ethnic and racial groups. See Robinson et al., pages 2910–2918.

T Cells and Human Drug-Induced Interstitial Nephritis. Despite a significant amount of information derived from animal models, pathogenic mechanisms underlying drug-induced interstitial nephritis in humans remain poorly understood. To provide mechanistic insight into this disease process, Spanou et al. from Bern, Switzerland, studied T cell immunity in several patients with biopsy-proven, drug-induced, interstitial nephritis. Peripheral blood mononuclear cells responded specifically to the presumed inciting agent in patients with disease, and drug-specific T cell lines and clones were readily isolated and characterized from the patients. The antigen-specific T cells were CD4+, expressed a relatively restricted pattern of T cell receptor V region genes, and produced a heterogeneous cytokine profile. Immunohistochemical analysis of renal biopsies revealed T cell infiltrates, a heterogeneous cytokine expression, and an absence of cytotoxic T cell markers. The results support the notion that CD4+ T lymphocytes reactive to putative inciting agents are central mediators of human drug-induced interstitial nephritis. See Spanou et al., pages 2919–2927.