Cell and Transport Physiology

Mutations in the Human Na-K-2Cl Cotransporter (NKCC2) Identified in Bartter Syndrome Type I Consistently Result in Nonfunctional Transporters

Abnormalities of the Na-K-Cl Cotransporter in Bartter Syndrome. Bartter syndrome, an inherited disorder of renal NaCl reabsorption, can be caused by mutations of the Na-K-Cl cotransporter (NKCC2), potassium channel (ROMK), chloride channel (ClC-Kb), or Barttin. Mutations of NKCC2 produce a severe neonatal form of Bartter syndrome with polyuria, polyhydrannis, hypokalemic metabolic alkalosis, and hypercalciuria. To determine the effects NKCC2 mutations on the function of the protein, Starremans et al. expressed cRNAs encoding wild-type or mutant NKCC2 in Xenopus oocytes. Surprisingly, they found that injection of identical amounts of cRNA produced significantly lower amounts of mutant protein compared with wild-type. The small amount of mutant protein that was produced was appropriately localized in the plasma membrane but was functionally inactive. In Gitelman syndrome, by contrast, the mutant Na-Cl cotransporter (NCC) is often retained in the endoplasmic reticulum. These studies represent the first functional characterization of NKCC2 mutations in Bartter syndrome. Although the results need to be confirmed in mammalian cells, they suggest that mutations of the NKCC2 gene cause reduced expression and loss of function of the Na-K-Cl cotransporter without affecting trafficking to the plasma membrane.

Hemodynamics, Hypertension and Vascular Regulation

Lead-Induced Downregulation of Soluble Guanylate Cyclase in Isolated Rat Aortic Segments Mediated by Reactive Oxygen Species and Cyclooxygenase-2

Lead — Yet Another Culprit Causing Endothelial Cell Dysfunction by Interfering with Nitric Oxide Bioavailability and Action. Historically, lead poisoning was an important public health problem causing hypertension, gout, and renal failure. This hazard has been virtually eliminated in most (but not all) Western countries. Nevertheless, interest in the complex mechanisms of lead has continued. Recent studies have shown that lead must be added to the growing list of culprits of which action is mediated by interfering with endothelial cell—dependent, NO-mediated vasodilatation. It had been shown that lead decreases the bioavailability of NO by increasing reactive oxygen species, which scavenge and inactivate NO. The present study adds to the complexity by documenting that, independent of the NO-generating system, lead in vitro causes concentration-dependent reduction in the expression of the β1 subunit of the heterotrimeric soluble guanylate cyclase, i.e., the effector arm of NO. This was associated with increased generation of superoxide anions via NADH oxidase or other pathways and by upregulation of cyclooxygenase-2. Vitamin C partially abrogated to downregulation of soluble guanylate cyclase, and this was also found after administration of a protein kinase A inhibitor or a cyclooxygenase-2 inhibitor. The authors provide evidence that vitamin C reduced expression of Cox-2 and superoxide anion generation, while the Cox-2 inhibitor failed to affect superoxide anion production, presumably acting via modifying the availability of cAMP. The findings shed further light on the longstanding puzzle of how lead causes hypertension and renal dysfunction. In retrospect, they justify determined efforts to eliminate environmental exposure to lead.

Immunology and Pathology

Plasminogen Activator Inhibitor-1 Is a Significant Determinant of Renal Injury in Experimental Crescentic Glomerulonephritis

Another Approach to Preventing Crescents in RPGN. Crescent formation is a consequence, in large part, of intraglomerular coagulation and fibrin deposition. While some forms of anticoagulant therapy can inhibit crescent formation experimentally, systemic anticoagulation in humans has often been accompanied by unacceptable risks of bleeding. In this issue, Kitching et al. show that plasminogen activator inhibitor 1 (PAI-1), another more recently recognized component of the coagulation system, is as critical to crescent formation as fibrin. PAI-1 inhibits fibrin breakdown and thereby enhances crescent formation; mice with intact PAI-1 might therefore be expected to suffer more severe crescentic glomerulonephritis, whereas mice lacking this inhibitor would break down fibrin more rapidly and have less severe disease. The authors of this study use genetically manipulated mice to show exactly that. The documentation of a major role for PAI-1 in crescentic glomerulonephritis obviously offers another promising therapeutic target in treating rapidly progressive, crescentic glomerulonephritis. Developing inhibitors of PAI-1 could prove more useful and significantly less toxic than general anticoagulation to a level that prevents fibrin deposition.
A Gene Locus for Steroid-Resistant Nephrotic Syndrome with Deafness Maps to Chromosome 14q24.2

Mapping of a New Syndrome of Steroid-Resistant Nephrotic Syndrome and Deafness. Several genes that cause inherited forms of nephrotic syndrome in humans have been identified. Mutations of nephrin cause congenital nephrotic syndrome of the Finnish type, mutations of podocin cause steroid-resistant nephrotic syndrome, and mutations of \( \alpha \)-actinin-4 cause autosomal dominant nephrotic syndrome. In this issue, Ruf et al. identify a locus on chromosome 14 for a rare association of autosomal recessive steroid-resistant nephrotic syndrome and deafness. Using homozygosity mapping in a highly inbred Palestinian family, they localized the gene locus through a genome-wide scan and then further refined the gene interval to a segment of approximately 7 Mb containing approximately 50 candidate genes. This study is potentially of great interest because it pinpoints the existence of a gene involved in a new entity associating steroid-resistant nephrotic syndrome and deafness. Cloning of the gene promises to shed novel insights into the molecular pathogenesis of nephrotic syndrome, the structure of the glomerular slit diaphragm, and sensorineural deafness.

Pathophysiology of Renal Disease

BMP-7 Is an Efficacious Treatment of Vascular Calcification in a Murine Model of Atherosclerosis and Chronic Renal Failure

Vascular Calcification — An Active Process Susceptible to Modulation by Circulating Factors? Evidence has recently accumulated that vascular calcification in uremia is more than the passive consequence of supersaturation after transgression of a critical \( \text{Ca} \times \text{P} \) solubility product. It appears instead to be, at least in part, an active process, as indicated by the fact that vascular smooth muscle cells transdifferentiate to acquire an osteoblast-like phenotype. This line of thought is reinforced by the present observation that bone morphogenetic protein-7 (BMP-7), an important morphogen in renal development that is locally expressed in the adult kidney and is presumably present at low concentrations in the circulation, diminishes calcium deposits in the intima and media of uremic LDL-R\(^{-/-}\) mice on a high-fat diet. In parallel, the expression of osteocalcin, an osteoblastic marker, was decreased. One can hypothesize that BMP-7 maintains VSMC differentiation and precludes transdifferentiation into an osteoblast-like phenotype. Although indirect effects, e.g., via influencing ions or calcium-regulating hormones, have not yet been thoroughly excluded, the findings may point to the fascinating perspective that vascular calcification in uremia as an active process may be modulated by circulating factors.

Clinical Nephrology

The Contribution of Increased Diabetes Prevalence and Improved Myocardial Infarction and Stroke Survival to the Increase in Treated End-Stage Renal Disease

What Is Causing the Epidemic of ESRD? Some Answers and Surprises. The reasons for the continuing increase in the incidence of ESRD are poorly understood. In this issue of JASN, Muntner et al. assess three possible contributions to the epidemic increase in ESRD: increase in the US population, prevalence of diabetes, and decreased mortality due to cardiovascular disease. They estimate that 41\% of the increased incidence in ESRD observed in the US population between 1978 and 1991 could be attributed to these factors and that two thirds of the explained increase was due to the increased prevalence of diabetes. These estimates suggest that other factors may be influencing the increased risk of ESRD observed in the US population and underscore the need for continued investigation of causes for the current epidemic. Muntner et al. also report that the estimated rate of ESRD among Americans with diabetes was 2567 cases per million persons; among individuals surviving a myocardial infarction or stroke, the estimated rate was 1463 cases per million persons. This contrasts to an estimated ESRD rate of 153 cases per million persons among individuals without diabetes mellitus or a history of stroke or myocardial infarction. These estimates provide additional support for the growing interest in identifying explanatory factors for the joint occurrence of cardiovascular disease and chronic kidney disease.
Dialysis

**Ankle-Brachial Blood Pressure Index Predicts All-Cause and Cardiovascular Mortality in Hemodialysis Patients**

Can We Predict the Risk of Cardiovascular Disease and Death in Dialysis Patients with Just a Blood Pressure Cuff? Ono et al. examine the association between the ankle-brachial blood pressure index (ABPI) and mortality in a cohort of 1010 Japanese hemodialysis patients. This report extends observations that ABPI is a risk factor for all-cause and cardiovascular mortality in the general population to a hemodialysis population. Decreased ABPI was present in 16.5% of patients at baseline and was associated with increased risk of all-cause and cardiovascular disease mortality. The relationship was graded, persisted after accounting for other risk factors, and was independent of a previous history of cardiovascular disease. If these observations are supported in other populations, then low ABPI may prove useful in identifying a high-risk hemodialysis population that might be studied in clinical trials to determine the benefit of intensive interventions to modify the risk of subsequent cardiovascular disease and death.

**Change in Allograft Function among Long-Term Kidney Transplant Recipients**

Long-Term Transplant Patients Are a Major Component of the Chronic Kidney Disease Population. Although transplantation rates have not increased substantially during the last decade, the population of individuals who are alive with a transplanted kidney at any one time has nearly doubled from 56,000 individuals in 1991 to 104,000 in 2000, 27% of all patients reported in 2000 by the USRDS. This constitutes a substantial population of individuals with CKD. Gill et al. analyze renal transplant registry data to describe the pattern of posttransplant renal function in nearly 41,000 patients transplanted between 1987 and 1996. During 5 years of follow-up, variable patterns of renal function were noted, with 50% of these patients either maintaining or improving estimated GFR. The factors identified as independently associated with increased rate of loss of GFR included younger age, male gender, black race, primary cause of ESRD other than polycystic kidney disease, older donor age and cadaveric source, and HLA mismatch. The rate of loss in GFR was greater during the later posttransplant period and was associated with higher posttransplant GFR. Although the rate of loss of renal function overall was modest at 1.66 ml/min per year, there are some patients who have substantially higher rates of decline. Additional research should include studies to identify modifiable risk factors for the higher rates of loss of renal function and for the acceleration of loss with time.

Transplantation

**Regulatory CD25+ T Cells in Human Kidney Transplant Recipients**

Are Regulatory T Cells the Major Factor in Governing the Immune Response to Allografts? Salama et al. provide for the first time evidence that regulatory T cells (CD5+) are functional in human kidney transplant recipients. Using an ELISPOT assay system, these cells have been identified in the peripheral blood of approximately 50% of kidney transplant recipients who are hyporesponsive to donor HLA-DR allopeptides (indirect allorecognition pathway). Therefore, regulation is an important mechanism resulting in donor-specific hyporesponsiveness in some kidney transplant recipients. Interestingly, an accompanying article by Game et al. shows that regulation is not operative in the case of hyporesponsiveness to donor cells (direct allorecognition pathway), suggesting that T cell anergy and/or apoptosis may mediate such hyporesponsiveness. Regulatory cells therefore function to suppress the indirect but not the direct alloimmune response in human transplant recipients. These results are important for development of novel assays to monitor transplant recipients undergoing new strategies targeted at minimizing immunosuppression or inducing tolerance and for understanding the mechanisms of regulation in humans with autoimmune diseases and cancer.