Endothelin 1 from the vascular endothelium contributes to blood pressure control

Kisanuki et al., Hypertension 2010; 56: 121–128; doi:10.1161/HYPERTENSIONAHA.109.138701

Endothelin 1 (ET-1) was identified as a potent vasoconstrictor agent isolated from endothelial cells, and although it is expressed by various cell types, endothelial cells are its most abundant source in the adult. ET-1 acts on two distinct G protein-coupled receptors, ET\(_A\) and ET\(_B\), which are found in various vascular and nonvascular tissues. Vascular smooth muscle cells express both ET\(_A\) and ET\(_B\), which mediate a direct vasoconstrictor action of ET-1. In contrast, endothelial cells express only ET\(_B\), which exerts vasodilator effects via the release of nitric oxide and prostacyclin. In addition to direct vascular actions, ET-1 and its receptors also affect blood pressure via activity in the collecting ducts and perhaps the brain and the adrenal gland. Renal collecting duct-specific ET-1 knockout mice or ET\(_B\) knockout mice exhibit salt retention and hypertension. The potential role of ET-1 in vascular tone has been studied with blockers of the ET\(_A\) and ET\(_B\) receptors, but the precise physiological roles of endothelial ET-1 in the regulation of blood pressure have remained unclear, as ET-1-deficient mice die shortly after birth. To address this question, Kisanuki et al. used Cre/loxP recombination (ET-1\(_{flox/flox}\); Tie2-Cre\(^{+}\) mice) to generate a mouse strain in which ET-1 is disrupted, specifically in endothelial cells. They found that ET-1 peptide levels in plasma, heart, lung, kidney, and brain homogenates were reduced by more than 65%. This reduction was associated with a blood pressure about 10 mm Hg lower than that of controls (Figure).

These results establish that endothelial-derived ET-1 is involved in blood pressure maintenance. Because collecting duct-specific ET-1 deletion causes salt retention and hypertension, it is likely that the lower blood pressure of the mice with deleted endothelial ET-1 is due to loss of a normal vasoconstrictor action by the peptide. If confirmed, these results indicate that, unlike angiotensin II, vasopressin, and atrial natriuretic peptide, ET-1 has vascular and renal sodium handling discordant actions.

Juan Oliver

A B-cell signature associated with renal transplant tolerance in humans

Newell et al., J Clin Invest 2010; 120: 1836–1847; doi:10.1172/JCI39933
Sagoo et al., J Clin Invest 2010; 120: 1848–1861; doi:10.1172/JCI39922

Most long-term practicing nephrologists have encountered or are aware of a rare patient who received a cadaveric kidney transplant that maintained allograft function despite discontinuation of immunosuppression. Needless to say, such patients have allograft tolerance, a highly desirable condition in which good allograft function is maintained in the absence of immunosuppressive therapy. Grant tolerance has been achieved in numerous animal models of kidney transplantation. Attempts to induce it in humans have been far less successful, and the fear of potential loss of the graft during immunosuppression minimization or withdrawal has not encouraged experimentation. Two recent studies have approached this issue by attempting to identify biomarkers and mechanisms active in subjects with engrafted kidneys that, despite sustained discontinuation of immunosuppression (spontaneously by the patients or because of intolerable side effects), maintained graft function. Newell et al. obtained data from 25 patients with allograft tolerance and compared them with data from kidney transplant recipients on immune suppression and from normal volunteers. With flow cytometry of lymphocyte sub-populations plus blood and urine gene expression using gene arrays and PCR validation, they found that B cell-related genes were strongly expressed in the tolerant patients. Tolerant subjects showed increased expression of multiple B-cell differentiation genes, and a set of just three of these genes distinguished tolerant from non-tolerant recipients.

Sagoo et al. screened for potential biomarkers and bioassays in 11 tolerant kidney transplant recipients and compared them with those of patients on immune suppression and exhibiting chronic allograft injury and healthy controls. They found that tolerant patients had an expansion of peripheral blood B and natural killer lymphocytes, fewer activated CD4\(^+\) T cells, a lack of donor-specific antibodies, donor-specific hyporesponsiveness of CD4\(^+\) T cells, and a high ratio of forkhead box P3 to α-1,2-mannosidase gene expression. The authors of both studies shared samples, and in cross-validation studies they confirmed a strong association between the kidney allograft-tolerant state and B cell-related genes and markers.

Although the exact significance of these results and their potential clinical application remain to be established, the two studies strongly suggest a fruitful avenue of research on the mechanisms of renal transplant survival.

Juan Oliver
Methylation determines fibroblast activation and fibrogenesis in the kidney

Bechtel et al., Nat Med 2010; 16: 544–550; doi:10.1038/nm.2135

A general hallmark of fibrosis, as opposed to physiological wound healing, is the active scarring that does not cease once the initial insult has been contained and, instead, becomes a continuous process.1,2 What perpetuates scarring in the setting of fibrosis is not yet known. Activated fibroblasts are considered principal mediators of fibrogenesis. Bechtel et al. hypothesized that epigenetic modifications cause this perpetuation of fibrogenesis. They found that hypermethylation of RASAL1, encoding an inhibitor of the Ras oncprotein, is associated with the perpetuation of fibroblast activation and fibrogenesis in the kidney. RASAL1 hypermethylation is mediated by the methyltransferase Dnmt1 in renal fibrogenesis, and kidney fibrosis is ameliorated in Dnmt1−/− heterozygous mice (Figure). These studies further highlight differences between fibrogenesis and physiological repair. Fibroblast activation is associated with transcriptional RASAL1 repression in the settings of both physiological kidney repair and pathological fibrogenesis. However, whereas reversible fibroblast activation typical of physiological repair is associated with reversible RASAL1 suppression without its hypermethylation, sustained fibroblast activation typical of fibrotic kidneys is associated with irreversible RASAL1 expression due to hypermethylation of the RASAL1 promoter. This finding suggests that hypermethylation perpetuates fibroblast activation, and ultimately fibrogenesis, by imprinting pathways of fibroblast activation that are engaged during the transient fibroblast activation typical of physiological repair. Although these elegant studies demonstrated that the RASAL1 hypermethylation correlates strongly with fibrogenesis and the absence of RASAL1 methylation correlates with physiological repair upon kidney injury, studies manipulating RASAL1 in vivo are needed to elucidate whether RASAL1 silencing alone is sufficient to induce fibrogenesis in the kidney or whether it modulates the rate at which induced fibrosis progresses.

Future studies should explain the utility of methylated genes as diagnostic markers to predict fibrosis and the possible therapeutic efficacy of methylation inhibitors in progression of fibrogenesis.

Marc De Broe


Cystatin C and contrast-induced acute kidney injury

Briguori et al., Circulation 2010; 121: 2117–2122; doi:10.1161/CIRCULATIONAHA.109.919639

Multiple epidemiologic studies have defined the utility of cystatin C in various clinical settings. Briguori et al. attempted to define the utility of changes in cystatin C and sought in the short term to identify patients with acute kidney injury (AKI) before their elevation in serum creatinine.

Patients undergoing cardiac catheterization were prospectively enrolled from January 2007 to September 2009 at a single center. Exclusion criteria were preexisting dialysis, multiple myeloma, pulmonary edema, acute myocardial infarction, recent exposure to contrast media, pregnancy, and the use of certain medications. Participating patients were treated with intravenous sodium bicarbonate and N-acetylcysteine before and after receiving their contrast media. Serum creatinine and cystatin C were measured 24 hours before and 24 hours after the administration of the contrast media. The purpose was to assess whether changes in cystatin C level could predict who would go on to have an increase in serum creatinine of at least 0.3 mg/dl more and either need dialysis or die within 12 months.

Enrolled patients had a mean age of 70 years and a median serum creatinine of 1.64 mg/dl. The cohort of 410 patients received a mean volume of contrast of 165 ml and experienced a rate of AKI (defined as an increase in serum creatinine greater than 0.3 mg/dl) of 8.2%. Changes in cystatin C and their ability to predict AKI were calculated with multiple definitions of a ‘clinically significant change.’ Any increase in cystatin C was 100% sensitive in detecting all events of AKI at the expense of a sensitivity of 65.2%. Any increase in cystatin C, therefore, gave a negative predictive value of 100%, with a positive predictive value of only 20.6%. An increase of cystatin C of at least 10% maintained the same 100% sensitivity but improved the specificity to 85.9% and the positive predictive value to 39.1%.

This analysis demonstrates some utility in the use of changes in cystatin C to predict the patients who may go on to experience a rise in serum creatinine following the administration of contrast media. The degree to which the specificity and positive predictive value may overcall the likelihood of AKI should be considered. The cost of hospitalizing and monitoring patients with a rise in cystatin C following the administration of contrast media may not justify the benefit. However, if the care and surveillance can be delivered on an outpatient basis, it may be an exceptionally useful tool to identify patients who require laboratory measures as outpatients for additional scrutiny in the short term.

Lynda Szzech