**Activated protein C protects against diabetic nephropathy**

Renal abnormalities in early diabetic nephropathy include increases in glomerular filtration rate and albuminuria, which are due, at least in part, to glomerular capillary damage. It is well documented that podocyte integrity, an important determinant of the permselective properties of the glomerular filtration barrier, is impaired in subjects with diabetic nephropathy. The glomerular endothelium also contributes to the permselective properties of the glomerular barrier, but it is unknown whether endothelial dysfunction is causally related to impairment of the glomerular filtration barrier in diabetic nephropathy.

Protein C is a vitamin K-dependent plasma proenzyme. Its partial or complete genetic deficiencies cause venous thrombosis or neonatal purpura fulminans, respectively. It has long been known that activated protein C (APC) inactivates factors Va and VIIIa to downregulate thrombin generation. More recent work has shown that APC has direct cytoprotective effects that involve gene expression profile alterations, anti-inflammatory and antiapoptotic activities, and endothelial barrier stabilization. In unperturbed endothelial cells, activation of protein C that is dependent on thrombomodulin (encoded by Thbd) inhibits coagulation, inflammation, and apoptosis. Function of the endothelial thrombomodulin–protein C system is impaired in diabetic individuals, as shown by increased levels of soluble thrombomodulin, thought to reflect loss of thrombomodulin from the endothelium, and decreased levels of APC. Thus, perturbation of the thrombomodulin–protein C system resulting in reduced levels of APC is a potential mechanism of glomerular capillary dysfunction in diabetes.

In a recent manuscript, Isermann et al. examined the role of APC in endothelial and glomerular capillary dysfunction. They found that persistent hyperglycemia reduced thrombomodulin expression and APC formation in wild-type mice in vivo (Figure). To determine whether the loss of thrombomodulin-dependent protein C activation and diabetic nephropathy are causally linked, they tested genetically engineered mice in which APC formation was either impaired or enhanced. Diabetic nephropathy was worse in mice with genetically imposed losses of protein C activation; conversely, mice with increased APC formation were protected from diabetic nephropathy. The authors discovered that this protection was not due to different thrombomodulin expression levels, and that APC was renoprotective independently of blood clotting. APC prevented endothelial-cell (and podocyte) apoptosis by modulating the mitochondrial apoptosis pathway via the protease-activated receptor PAR-1 and the endothelial protein C receptor EPCR in glucose-stressed cells. These elegant experiments establish a new pathway in which hyperglycemia impairs endothelial thrombomodulin-dependent APC formation and causes glomerular apoptosis and diabetic nephropathy. Conversely, maintaining high APC levels during long-term diabetes protects against diabetic nephropathy. (Nat Med 2007; 13: 1349–1358; doi:10.1038/nm1667)

Juan Oliver

**Benefits of frequent nocturnal versus conventional hemodialysis on left ventricular mass and quality of life**

Prior cohort studies demonstrate improvements in multiple measures, including blood pressure control, phosphorus control, and quality of life, among patients moving toward more frequent dialysis (either daily or nocturnal). Although results have been compelling, the lack of control groups and potential Hawthorne effect arguably diminish the strength of these conclusions.

Culleton et al. reported the results of a trial of 52 prevalent hemodialysis patients randomized to frequent nocturnal hemodialysis versus conventional dialysis. Frequent nocturnal dialysis improved mean left ventricular mass as compared with
conventional dialysis (difference 15.3 g, \( P = 0.04 \)). Frequent dialysis also improved mineral metabolism (a decrement in serum phosphate of 1.5 mg/dl between groups \( P < 0.01 \)) with a concurrent decrease in elemental calcium use as a binder in the frequent-dialysis group \( P < 0.001 \). Although changes in overall quality of life were not different between groups, those subjects in the frequent-dialysis group experienced improvements in selected kidney-specific domains.

The results of this trial clearly provide an optimistic outlook on the improved delivery of renal replacement therapies, which could improve cardiovascular outcomes or survival in patients with end-stage renal disease. In addition to providing valuable information for the confirmation of prior observational studies and the estimation of treatment effect to perform or confirm power calculations for larger studies, this study provides a practical message. Although larger trials likely will confirm the beneficial effect on intermediate and/or hard clinical outcomes, widespread use of this modality needs to be considered. Only one subject in the frequent-dialysis arm discontinued participation because of technical problems with home dialysis, indicating that this modality was successfully performed. However, in the enrollment of this trial, only about 10% of available patients were interested in nocturnal dialysis. Hopefully, the Frequent Hemodialysis Network trials, sponsored by the National Institutes of Health, will demonstrate additional benefits. Our challenge as a renal community is to determine how to implement these therapies in countries such as the United States, where home therapies such as peritoneal dialysis are not given to a large proportion of patients. \( JAMA 2007; 298: 1291–1299 \)

Lynda Szczech

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**T cells are involved in angiotensin II-induced hypertension and vascular dysfunction**

Angiotensin II is a potent vasoconstrictor and salt-retaining hormone whose excess can cause hypertension. Reactive oxygen species (ROS) produced by the Nox-based nicotinamide adenine dinucleotide phosphate (NADPH) oxidases have recently been implicated in several models of experimental hypertension. These multisubunit enzymes are similar to the neutrophil oxidases that are present in vascular cells, kidney, and central nervous system. Angiotensin II can activate these enzymes; the superoxide \( \left( \text{O}_2^{-*} \right) \) that is produced can react with the endogenous vasodilator nitric oxide (NO), thereby promoting vasoconstriction. This can increase systemic vascular resistance and elevate blood pressure. It has also been proposed that \( \text{O}_2^{-*} \) and related ROS can increase renal sodium reabsorption, which could also contribute to hypertension. T lymphocytes contain a functional NADPH oxidase and an angiotensin type I receptor. Angiotensin II stimulates T-cell proliferation and is known to stimulate ROS production via NADPH oxidase in several cells. Moreover, perturbation of immune function by thymectomy or by pharmacological interventions prevents hypertension in several experimental models. Infusion of alloactivated T cells for treatment of cancer increases blood pressure in humans. Activation of both humoral and cellular immunity occurs in women with preeclampsia. Conversely, suppression of the adaptive immune system can inhibit hypertension in experimental animals and humans. All these studies suggest that adaptive immunity contributes to hypertension via yet undefined mechanisms.

In a recent study, Guzik et al. addressed this question and found that hypertension due to angiotensin II infusion was blunted in mice lacking T and B cells (RAG-1\(^{-/-}\) mice). They also found that the mice did not develop abnormalities of vascular function. Adoptive transfer of T, but not B, cells restored the hypertension and the vascular abnormalities. When the authors transferred T cells lacking the angiotensin type I receptor or a functional NADPH oxidase, the angiotensin II-dependent hypertension was blunted and aortic \( \text{O}_2^{-*} \) production decreased. Additionally, angiotensin II increased T-cell markers of activation and tissue homing in wild-type, but not in NADPH oxidase-deficient, mice. Angiotensin II also increased T cells in the perivascular adipose tissue and the adventitia (Figure). These cells expressed high levels of CC chemokine receptor 5 and were commonly double negative (CD3\(^+\)CD4\(^-\)CD8\(^-\)). This infiltration was associated with an increase in intercellular adhesion molecule-1 and RANTES in the aorta. Hypertension also increased T-lymphocyte production of tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)). Further, treatment with the TNF-\( \alpha \) antagonist etanercept prevented the hypertension and increase in vascular \( \text{O}_2^{-*} \) caused by angiotensin II. In addition, RAG-1\(^{-/-}\) mice had blunted hypertensive response to the administration of deoxycorticosterone acetate plus salt, indicating that their lymphocytes play a role in other causes of hypertension. These studies identify a previously undefined role for T cells and inflammation in the pathogenesis of hypertension. T cells might represent a novel therapeutic target for the treatment of high blood pressure. \( J \text{ Exp Med} 2007; 204: 2449–2468; \text{doi:10.1084/jem.20070657} \)

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