Endothelial Health and Diversity in the Kidney

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The endothelial cells that line all blood vessels are essential in maintaining vascular tone, largely through the production of the vasodilators nitric oxide (NO) and prostacyclin, and antithrombogenic properties, via the production of the tissue-type plasminogen activator (t-PA) and glycoprotein. Alterations in endothelial health, as reflected by an impaired NO response (1), an increase in the presence of detached, circulating endothelial cells (2), or increased thrombogenic properties, are common in kidney diseases and may have a role in development of injury. Indeed, endothelial “dysfunction” is recognized as a key process in acute and chronic renal failure as well as ESRD of all causes. Endothelial activation plays a central role in hemolytic uremic syndrome, in various types of glomerulonephritis, in hypertension, in metabolic syndrome, and in diabetic renal disease (1–7). In addition, microalbuminuria is likely a marker of cardiovascular risk by virtue of the fact that microalbuminuria itself is reflective of endothelial dysfunction.

The mechanism by which endothelial dysfunction may promote renal progression is complex but may include the development of an inflammatory phenotype with the production of proinflammatory molecules and leukocyte chemotactic factors and adhesion molecules (9,10). Endothelial dysfunction that results in reduced NO production and development of systemic and glomerular hypertension could lead to the development of pregglomerular vascular disease (11). Endothelial dysfunction also may lead to endothelial cell detachment or death, resulting in the atrophy of capillaries that normally provide oxygen and nutrients to the tubules (12). These processes are thought to have a major role in renal progression similar to its projected role in atherosclerosis (13).

It is of interest that all endothelial cells in the kidney are not alike and that certain subpopulations may have different phenotypic characteristics. This was already known to some degree. For example, whereas both glomerular and peritubular capillary endothelial cells have pores (fenestrations), the pores of the peritubular capillary endothelial cells have a small overlying diaphragm (14). Afferent arteriolar endothelial cells express a different pattern of connexin molecules than efferent arteriolar endothelial cells, and these differences are accentuated in diabetes (15). Heterogeneity can occur within a single vessel, as in the segmental differences in capacity to produce NO and cyclooxygenase-dependent products in the aorta (16,17). Paired mesenteric arterioles and venules also have widely different NO synthase protein abundance and activities (18). Furthermore, both glomerular and peritubular capillary endothelial cells express aminopeptidase P (as identified by the JG-12 antibody), whereas arterioles and larger vessels do not express this antigen (19).

Although all of these observations suggest endothelial cell diversity, in this issue, Panzer et al. (10) present additional evidence for differences in renal endothelial cell populations with marked functional consequences. Specifically, the authors use a rodent model of thrombotic microangiopathy using injection of an anti-endothelial antibody. In this model, glomeruli are categorized by a macrophage infiltrate, whereas the interstitium is characterized by a macrophage and T cell infiltrate with T cells predominating. Using in situ hybridization, they demonstrate that the macrophage chemokine monocyte chemotactant protein-1 is expressed both in glomeruli and in tubulointerstitium, whereas the T cell chemokine IP-10 is expressed only by the peritubular capillaries. They further show that blocking IP-10 largely prevents the T cell infiltrate, while not affecting the macrophage infiltrate, and provides renal protection.

This finding highlights the importance of the diversity of the endothelial cell response in the kidney and identifies IP-10 as a major candidate for the long-sought mechanism by which T cells are attracted into the interstitium. T cells now are recognized as a major infiltrating cell type in the interstitium of the kidney in a wide variety of renal diseases, including nephrotic syndrome and glomerulonephritis, hypertension, diabetes, and chronic renal disease (20). Furthermore, T cells have been shown to have a key role in the hypertensive response in experimental models of hypertension, in the severity of renal dysfunction that occurs with acute renal failure syndromes, and in various models of acute and chronic renal disease (21–25). Although several candidates such as RANTES and osteopontin have been proposed, to our knowledge, neither molecule has been shown to have a major role in mediating the T cell infiltration in models of kidney disease.

In conclusion, studies such as that by Panzer et al. (10) in this issue provide a new understanding of the diversity of the endothelial cell populations and their phenotypic responses in kidney disease. Importantly, we must remember that the kidney is one of the most vascular organs, with two capillary beds in which normally 25% of the blood flows. Thus, just as the
Phrase “all roads lead to Rome” indicates the importance of this ancient capital in the days of the Roman Empire, we must consider that endothelial injury is the heart of the crossroads that leads to hypertension, diabetes, or non-diabetic renal disease and is a central mechanism driving the development of chronic kidney disease.

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