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Preamble:
In this month's Karger Blogs I comment on two papers, both published in the *American Journal of Nephrology* and both constructing a novel concept about kidney disease. One builds on strong, scientifically-based experimental observations that the intestinal barrier function is somehow altered in the course of chronic kidney disease, while the other postulates (indirectly) from clinical studies that nephron endowment at birth can have a material impact on the nature of predisposition to develop a specific kidney lesion; namely, focal and segmental glomerulosclerosis. While both papers represent an early stage of experimental or clinical investigation, they are tantalizingly attractive as they may evoke new strategies for prevention and treatment of kidney diseases.

Chronic Kidney Disease Causes Disruption of Gastric and Small Intestinal Epithelial Tight Junction

N.D. Vaziri, J. Yuan, S. Nazertehrani, Z. Ni, S. Liu

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Commentary

By Professor Richard Glassock

Prior studies have clearly shown an association of chronic kidney disease (CKD) with markers of systemic micro-inflammation and oxidative stress. This phenomenon may be involved in the pathogenesis of some of the complications of CKD, such as anemia, cardiovascular disease and nutritional disorders. But the origins of the pro-inflammatory state remain obscure. A common view is that the phenomenon rests on an imbalance of pro- and anti-inflammatory or oxidant mediators and processes. The work from Professor Vaziri's highly productive laboratory suggests a new avenue of pathogenesis; specifically CKD-induced alterations in intestinal microbial flora (the microbiome) and resultant disruption of the normal intestinal permeability barrier allowing pro-inflammatory molecules (such as bacterial endotoxin) to gain access to the circulation. Using the 56/6 nephrectomy model of CKD in outbred rats, the investigators demonstrate marked reduction in the abundance of epithelial tight-junction proteins (claudin-1, occluding and ZO-1) in the gastric and small intestinal mucosa in animals with CKD compared to sham-operated controls. Using data from prior experiments they postulate that the upper GI tract is colonized with urease-producing microflora and is enriched with urea diffusing in from the circulation, ultimately leading to an increase in luminal ammonia and ammonium concentrations (depending on local pH). The resulting high intra-luminal ammonium hydroxide concentrations can 'disassociate' the tight-junction proteins leading to the loss of intestinal permeability function. While this is a tantalizingly attractive hypothesis to explain some of the observations bearing on the pro-inflammatory state of uremia, many knowledge gaps exist that need to be closed before this mechanistic formulation can be widely accepted. Will pathogen-free, germ-free or gnotobiotic animals lack the characteristic pro-inflammatory features of CKD? Do treatments (such as oral activated charcoal adsorbents) designed to abrogate high ammonium hydroxide levels in intestine also reduce evidence of enhanced intestinal permeability, such as high circulating endotoxin levels in CKD patients? Will oral urease inhibitors (e.g. aceto-hydroxamic acid or monastrol analogues) protect the gut in CKD? These and other questions will likely be answered soon as this new avenue of research is pursued with vigor and imagination.

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