Gut Feeling in AKI: The Long Arm of Short–Chain Fatty Acids

Ian R. Barrows,* Ali Ramezani,† and Dominic S. Raj‡

*George Washington University School of Medicine, Washington, DC; and †Division of Renal Diseases and Hypertension, George Washington University, Washington, DC

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In 1907, Elie Metchnikoff hypothesized that “autointoxication” by “putrefactive” bacteria accelerated aging and caused disease. Emerging science from the Human Microbiome Project and the Metagenomics of Human Intestinal Tract projects has brought in a paradigm shift in our perception about the gut microbiome. The human microbiome has coevolved with the host and established a symbiotic relationship, which has expanded our metabolic and biosynthetic capabilities well beyond what is coded in our genomes. Numbers of signaling molecules, receptors, and effectors from the microbiome that regulate host functions are being constantly unraveled. Short–chain fatty acids (SCFAs) are organic fatty acids with one to six carbons, which are products of bacterial fermentation of complex polysaccharides in the colon. The most abundant SCFAs are acetate, propionate, and butyrate. SCFAs are shown to have physiologic functions and beneficial effects on the human host, but they are essentially waste products to the microbes, which are required to balance redox in the anaerobic environment of the colon. These molecules are partly metabolized by colonic epithelial cells, and a proportion enters the portal and peripheral circulation, where they exert their systemic effects through the G protein–coupled receptors, such as GPR41 and GPR43.

An observation that has intrigued researchers is that germfree mice have increased susceptibility to ischemia and reperfusion injury (IRI), which is reversed by colonization with commensal bacteria. The mechanism by which the gut microbiome confers protection against IRI is the focus of the study by Andrade-Oliveira et al., which appears in this issue of JASN. In this exciting study, Andrade-Oliveira et al. have expanded the role of SCFAs beyond their well known role as nutrient for colonic epithelium and regulators of intracellular pH, ion transport, and cell proliferation to explain the gut-kidney connection in IRI. In a series of well designed in vivo and in vitro experiments, Andrade-Oliveira et al. show that treatment with SCFAs reduces IRI–induced kidney injury. Among the SCFAs, acetate treatment offered the best protection. Andrade-Oliveira et al. believe that the key mechanism that confers protection against AKI is reduction in inflammation mediated by an epigenetic mechanism. Andrade-Oliveira et al. also noticed an increase in autophagy, a reduction in apoptosis, and an improvement in mitochondrial biogenesis in response to treatment with SCFA. Furthermore, treatment with acetate-producing bacteria protected the mice kidneys from IRI. This study clearly shows that SCFA protects against IRI through convergence of multiple mechanisms, but it also provokes a number of questions. Considering the complexity of the communication between microbiome, cells, genes, and the ecosystem, it is often challenging to clearly define the role of individual components, which is the case in this study.

Inflammation plays a critical role in induction, maintenance, and resolution of AKI. Innate pattern recognition receptors, including Toll-like receptors (TLRs) and the inflammasome, trigger inflammation in response to tissue injury and pathogens. The composition of the microbiome influences the balance between immune regulatory (Treg) and proinflammatory (TH17) T cells. For instance, segmented filamentous bacteria residing in the terminal ileum in mice recruits CD4 T helper cells that produce IL-17 and IL-22 (Th17 cells) in the lamina propria. Another commensal bacteria in the gut, Bacteroides fragilis, induces accumulation of Foxp3 Treg cells. This effect was dependent on the expression of a capsular polysaccharide known as polysaccharide A by the bacteria. Smith et al. showed that feeding germfree mice with SCFAs, acetate, propionate, and butyrate increased the abundance of Foxp3 Treg cells in the large intestine in a GPR43–dependent manner. Immune cells express the SCFA receptors GPR41 and GPR43. SCFAs may modulate the magnitude and direction of the immune responses by influencing the differentiation and proliferation of T cells and reducing proinflammatory cytokine expression initiated by TLR signaling. In the study by Andrade-Oliveira et al., acetate treatment reduced inflammatory cell infiltration and expression of TLR-4 and its endogenous ligand, Biglycan. However, among the SCFAs, acetate is not the most potent activator of these receptors.

Immune response is a highly coordinated multistep process that involves sequential epigenetic changes. Transition from euchromatin to transcriptionally silent heterochromatin is mediated by histone deacetylases (HDACs). Butyrate plays a role in modulating immune responses of intestinal macrophages by inhibiting HDAC, leading to a decreased production of proinflammatory mediators, such as NO, IL-6, and IL-12.
HDAC also plays an important role in cell survival and cell proliferation. Recent studies have shown that a significant proportion of surviving, proliferating renal tubular epithelial cells undergo G2/M arrest after injury, which delays recovery from AKI. Hypermethylation of renin-angiotensin system protein activator like-1, which encodes renin-angiotensin system oncogene, perpetuates fibroblast activation and fibrogenesis in the kidney, and thus, it may lead to progressive loss of kidney function. In vitro studies have shown that butyrate regulates expression of genes that arrest growth and induces cellular differentiation. Furthermore, in the HT-29 carcinoma cell line, butyrate inhibited proliferation and increased apoptosis but had no effect on the normal epithelial cell line, suggesting that the action of SCFAs may depend on the state of activation of the target cells. Future studies should consider examining the effect of different SCFAs at different stages of IRI injury.

The hallmark of IRI is profound depletion of intracellular ATP content. In fact, adenine nucleotides infusion enhanced recovery from AKI after an ischemic insult. Mitochondria are the principal generators of cellular ATP. Two mechanistically distinct forms of programmed cell deaths (apoptosis and autophagy) may be induced by cellular stress. Mitochondria regulate the transition between apoptosis and autophagy, with low-intensity stress favoring autophagy and high intensity of cellular stress leading to apoptosis. Autophagy is an evolutionarily conserved cell survival mechanism that recycles cellular constituents to sustain bioenergetics. Jiang et al. showed that hypoxia induces autophagy in cultured renal proximal tubular cells. Blocking autophagy by 3-methyladenine or knockdown of autophagic genes (Beclin-1 and ATG5) sensitized the cells to apoptosis. Providing butyrate or colonizing with butyrate-producing bacteria (Butyrivibrio fibrisolvens) improved oxidative phosphorylation and ATP synthesis and prevented autophagy. It is important to remember that autophagy is the lesser of two evils. The decrease in apoptosis and increase in autophagy observed in the study by Andrade-Oliveira et al. may be caused by improved mitochondrial energetics with acetate treatment. Although the increase in mitochondrial DNA content reported in the study is promising, caution must be exercised when extrapolating the results from the study are encouraging, caution must be exercised when in vitro and animal studies are extrapolated to human disease.

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REFERENCES

5. Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJF, de Almeida DC, Bassi EJ, Moraes-Vieira PM, Hiyane MI, Rodas
From Patient to Dish and Back Again: Are We There Yet?

Uta Kunter and Marcus J. Moeller
Division of Nephrology and Clinical Immunology, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen University, Aachen, Germany


Chronic kidney disease affects significant parts of the general population, and novel treatment strategies are warranted. In this issue, Lazzeri et al.1 explore the use of exfoliated cells in the urine of children affected by proteinuric kidney diseases for diagnostic and therapeutic purposes (from patient-to-dish-to-patient). The authors investigate whether the isolated cells represent putative renal progenitor cells (RPCs) and test whether they are similar to a previously isolated putative progenitor population. They find that both cell populations ameliorate doxorubicin-induced nephritis in severe combined immunodeficiency mice. The controversial identity of the isolated cells and their potential use for diagnostic purposes or stem cells therapy are discussed.

Chronic kidney disease affects an estimated 5% of the general population. It represents a major risk factor for cardiovascular disease and increased mortality at least as potent as smoking or arterial hypertension. Glomerular diseases are still the most common causes of ESRD. It is time to translate recent advances in our understanding of glomerular diseases into novel improved diagnostic and therapeutic strategies.

Several approaches can be used. One is to search for unique intrinsic cells depending on specific signaling pathways, which can be manipulated by specific pharmacologic interventions in situ/in vivo. Alternatively, renal cell populations can be isolated to then be used for diagnostic purposes. Moreover, isolated cells can be expanded in culture and/or manipulated to then be returned back into the diseased organism (i.e., from patient to dish to patient).

In this issue of JASN, this latter strategy was explored by Lazzeri et al. The authors established cultures of rare exfoliated cells from the urine of children affected by different proteinuric disorders of the kidney. The authors noted that cultured cells expressed a certain combination of markers (CD133+, CD24+, CD106− [VCAM–1], and uroplakin III negative). In addition, cells coexpressing this combination of markers showed a higher proliferative index and expressed RNA transcripts similar to previously isolated cultures of adult parietal epithelial multipotent progenitor cells (APEMPs). The authors propose that the cultured cells represent the previously postulated fixed intrinsic population of progenitor cells (urinary renal progenitor cells [u-RPCs]). To substantiate this, the authors repeated an experiment where doxorubicin-induced renal disease in immunodeficient mice was treated by intra-venous injection of human APEMPs, u-RPCs, or cultured cells expressing other markers.2 Only the APEMPs and u-RPCs engrafted into the kidney and ameliorated proteinuria. In addition, the u-RPCs engrafted to regenerate podocytes and proximal tubule cells. Finally, the authors explored the tool of cultured u-RPCs for personalized investigations of genetic kidney disorders. They found that u-RPCs from patients with homozgyous podocin mutations expressed lower levels of podocin. In a patient with a mutated LMX1B gene, authors found that filamentous actin distribution was altered in cultured u-RPCs. The authors concluded that

See related article, “Gut Bacteria Products Prevent AKI Induced by Ischemia-Reperfusion,” on pages 1877–1888.

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Uta Kunter and Marcus J. Moeller
Division of Nephrology and Clinical Immunology, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen University, Aachen, Germany


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Correspondence: Dr. Marcus J. Moeller, Medizinische Klinik II, University Hospital of the RWTH Aachen University, Pauwelsstrasse 30, D-52074 Aachen, Germany. Email: m.moeller@ukaachen.de

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