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Kidney–Gut Crosstalk in AKI

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Introduction

AKI is an inflammatory condition characterized by the activation of innate and adaptive immune cells, along with endothelial and epithelial injury. Despite progress in understanding the pathogenesis of AKI, the mortality associated with this condition remains high, and additional therapeutic strategies are needed. Emerging evidence has shown that more than 100 trillion microbial cells inhabiting the gastrointestinal tract affect multiple physiologic functions of their mammalian hosts. Because the intestine represents the largest reservoir of immune cells in the human body, the intestine–microbiota interaction has been shown to be important for maintaining immune homeostasis. Recent microbiome research has suggested that gut microbiota alteration, known as dysbiosis, can trigger or aggravate several immune-mediated or metabolic disorders, including diabetes, obesity, and inflammatory bowel disease. Given that immune activation plays an important role in both injury and recovery from AKI, there is a possibility that changes in intestinal microbiota and mucosal immune response have a substantial effect on AKI.

AKI, Dysbiosis, Leaky Gut, and Bacterial Translocation

Advances in high-throughput sequencing technology have offered unprecedented insights into the complex microbial communities residing in the mucosal surfaces of the human body. Although there is mounting evidence that the microbiota signature in various disease conditions is significantly different from that in healthy controls, and therefore possibly contributes to disease pathogenesis, only limited studies have examined the crosstalk between the intestine, microbiota, and AKI.

Although the intestinal microbiota in individuals remains markedly stable, it is also frequently disturbed by various environmental factors, such as geographic locations, diets, and the use of antibiotics (1–3). Similar to other disorders, such as diabetes, obesity, and inflammatory bowel disease, kidney ischemia/reperfusion injury (IRI) was recently found to provoke intestinal dysbiosis within 24 hours (4–7) (Figure 1). The intestinal microbiota structure in a mouse model of IRI was shown to be markedly different from that in control mice by principal coordinate analysis. The relative increase of *Escherichia*, *Enterobacter*, and relative decrease of *Lactobacillus* were characteristic. Further, dysbiosis on day 1 of kidney IRI was associated with significantly reduced fecal levels of short-chain fatty acids (SCFAs), including acetate and butyrate, showing that dysbiosis induced a metabolic shift in the intestine (7). SCFAs are bacterial fermentation products of indigestible dietary fibers and are known to perform pleiotropic functions, including serving as the energy source for colonocytes, induction of regulatory T cells, immune modulation, and maintenance of barrier integrity (8). These are primarily mediated by binding to several G protein-coupled receptors expressed in cells of gastrointestinal and immune system, or by inhibition of histone deacetylase (8). Acetate has been demonstrated to exert a renoprotective effect *via* its effect on dendritic cells and T cells in IRI-induced or septic AKI models (9,10). Given that SCFAs have anti-inflammatory, barrier-strengthening effects, it is possible that dysbiosis and the resultant metabolic shift toward reduced SCFA levels might play an important role in kidney IRI by aggravating inflammation (Figure 1). The recent observation that gut microbiota–derived D-serine had a renoprotective effect in IRI also shows the important interaction between gut microbiota, its metabolites, and the kidney (11).

In healthy humans, an intact epithelial barrier composed of a mucin layer, antimicrobial peptides, and various tight junctions of epithelial cells is important for maintaining nutrient absorption while preventing bacterial translocation. Loss of barrier integrity in AKI was previously demonstrated by Li *et al.* (12), who observed increased blood levels of the bacterial fermentation product D-lactate in a rat model of IRI. In a recent study, researchers demonstrated increased gut permeability, serum endotoxin levels, and the number of amplicon reads of bacterial 16s rRNA in the liver on day 1 of IRI, suggesting the breakdown of the intestinal barrier and subsequent translocation of bacteria or endotoxins (7). Given the enhanced expression of pattern recognition receptors, such as Toll-like receptor-4 in leukocytes and damaged kidneys, barrier disruption and subsequent bacterial translocation might lead to the potentiation of systemic inflammation and more severe inflammation or injury in the kidney. Zhang *et al.* (13) have also suggested the gut is an amplifier of systemic inflammation in septic AKI. The altered expression of claudin-1 or increased apoptosis of colonocytes along with dysbiosis are also thought to contribute to the breakdown of the intestinal barrier after kidney IRI (7).

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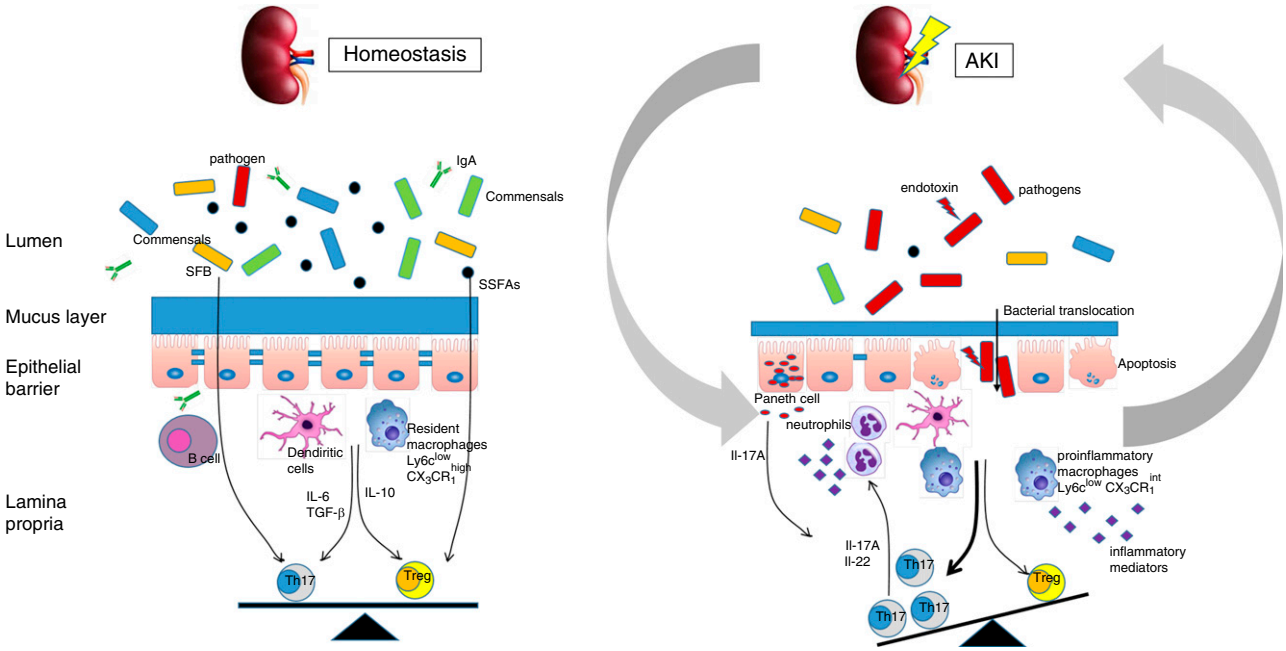

Figure 1. | **Kidney-gut-microbiota interaction during AKI.** AKI-induced dysbiosis is associated with reduced SCFA levels, loss of barrier integrity with translocation of endotoxin, or bacteria. Neutrophils, proinflammatory macrophages, and Th17 cells accumulate in the lamina propria, and are likely to contribute to intestinal inflammation that further compromise barrier integrity and bacterial translocation. IL-17A produced by Paneth cell degranulation also play an important role. Dysbiotic microbiota and altered mucosal immune response after kidney ischemia/reperfusion injury (IRI) further aggravate kidney injury by potentiating systemic inflammation. SFB, segmented filamentous bacteria; SCFAs, short-chain fatty acids.

AKI and Altered Gut Immunity

Inflammation is a well-orchestrated response initiated by host recognition of pathogen- or danger-associated molecular patterns, and it plays a critical role in both the injury and repair of AKI. Recently, dysbiosis and altered mucosal immune responses have been increasingly recognized to play important roles in many immune-mediated or metabolic disorders.

After kidney IRI, cells of the innate immune system in the intestine are activated. Neutrophils quickly appear in the lamina propria of the colon after kidney IRI and then disappear by day 3 (7). Macrophages, another effector cell type involved in innate immunity, show phenotypic changes. Through several sophisticated fate mapping studies, it has become clear that lamina propria resident macrophages originate exclusively from circulating Ly6c^{high} monocytes (14). In a steady-state condition, these cells ultimately give rise to mature resident macrophages by gradually downregulating Ly6c and upregulating CX$_3$CR$_1$ expression (Ly6c^{low}CX$_3$CR$_1^{high}$ macrophages). In contrast, the differentiation process is known to be arrested during inflammation with increased proportions of Ly6c^{low}CX$_3$CR$_1^{int}$ proinflammatory macrophages that are capable of inducing highly pathogenic Th17 cells (14). Using flow cytometry, Yang *et al.* (7) demonstrated the increase of Ly6c^{low}CX$_3$CR$_1^{int}$ proinflammatory macrophages after IRI compared with sham-operated mice. Increased inducible nitric oxide synthase and decreased arginase expression suggest these cells are M1-like proinflammatory macrophages. Accumulation of neutrophils and proinflammatory macrophages after kidney IRI is thought to contribute to intestinal inflammation, leaky gut, and bacterial translocation, which could then potentiate systemic inflammation *via* multiple inflammatory mediators (Figure 1).

In addition, cells of the adaptive immune system are also activated in the intestine after AKI. The percentage of IL17A$^+$CD4$^+$ cells significantly increases in both the small and large intestines, whereas that of IFN-γ^+CD4$^+$ cells does not change, suggesting kidney IRI results in the activation of the intestinal Th17 pathway (7) (Figure 1). Cytokines, such as TGF-β and IL-6, or specific microbes, including segmented filamentous bacteria, *Escherichia coli*, and *Staphylococcus aureus*, are known inducers of intestinal Th17 cells (15,16). The relative increase in *E. coli*, proinflammatory macrophages, and barrier disruption after IRI are likely to contribute to the activation of the intestinal Th17 pathway in AKI. Despite the well-known function of Th17 cells in inflammation and tissue destruction, there is no evidence to show the activation of intestinal Th17 cells directly affects kidney injury. However, recent studies have elucidated the important role of gut-derived Th17 cells in the pathogenesis of distant organ injury or the development of hypertension (17,18). Using *kaede* transgenic mice in which photoconverted cells can be tracked *in vivo*, Krebs *et al.* (17) showed the egress of Th17 cells from the intestine to injured kidneys in a mouse model of ANCA-associated GN. Another study showed the critical role of gut-derived Th17 cells in the development of systemic hypertension. A high-salt diet resulted in the depletion of *Lactobacillus murinus* abundance and increase in the proportion of Th17 cells, whereas treatment with *L. murinus* reduced the proportion of Th17 cells with prevention of salt-sensitive hypertension (18). The

authors also observed that sodium chloride directly inhibited the growth of several *Lactobacillus* spp. *in vitro* and salt challenge in humans led to decreased abundance of *Lactobacillus* spp., increased the proportion of circulating Th17 cells, and the development of hypertension (18). Despite these results, whether the activation of the Th17 pathway in the intestine after AKI can directly cause kidney injury remains unclear. Distinct from Th17 activation, IL-17A from Paneth cell degranulation has also been shown to be important in mediating kidney, intestine, and liver injury after AKI (19). It is also possible that IL-17A, produced by other cell types, such as neutrophils, γδT cells, and natural killer cells, might contribute to intestinal and systemic inflammation in AKI (Figure 1).

Microbiota as a Therapeutic Target in AKI

A recent study showed that administration of *Lactobacillus salivarius* reduced the severity of cisplatin-induced AKI by suppressing inflammation, oxidative stress, and the generation of uremic toxins (20). Another study that implicated the intestinal microbiota as a therapeutic target in AKI was conducted by Andrade-Oliveira *et al.* (9); they showed that pretreatment of mice with SCFAs significantly reduced the severity of kidney IRI by modulating the inflammation. However, despite these promising leads, the development of microbiota-based therapeutic strategies has not made substantial progress, because many studies have failed to show the causality of dysbiosis.

Yang *et al.* (7) recently demonstrated that intestinal dysbiosis as a whole could be causally linked to the severity of IRI by showing that germ-free mice transplanted with AKI feces developed more severe kidney injury or inflammation than those transplanted with sham feces. These observations show a unique bidirectional relationship of the kidney and intestine during AKI; AKI-induced dysbiosis and dysbiosis (as a whole) act as an important modifier of AKI. The authors further established the critical role of dysbiosis in worsening kidney injury by demonstrating that microbiota depletion by administering combination of oral antibiotics significantly mitigated kidney injury. The renoprotective effect of microbiota depletion was associated with a decrease of Th17 cells in the small intestine, increase of regulatory T cells, and $Ly6C^{low}CX3CR1^{high}$ or $CD206^{+}F4/80^{+}$ M2-like macrophages in both the colon and kidneys (7). These data further support the notion that microbiota and mucosal immune responses that are shifted toward dysbiosis and proinflammatory activity after AKI are important factors in worsening kidney injury. Moreover, these findings also suggest that strategies targeting dysbiosis and altered mucosal immunity, such as novel probiotics, could provide a new avenue for the prevention and treatment of AKI.

Conclusions

Intestinal dysbiosis, altered mucosal immune responses, and loss of barrier integrity are emerging as previously unrecognized factors responsible for injury or inflammation in AKI. However, despite advances in our understanding of the kidney–gut crosstalk, insights into the complex interplay between intestinal microbiota and immunity in the pathogenesis of AKI are rather primitive. To further develop novel intestinal microbiota-based therapeutics, several key questions need to be addressed. These include (*1*) gaining a more thorough understanding of the molecular mechanisms underlying microbiota shift-immune dysregulation, (*2*) identification of causal pathogens, (*3*) development of novel probiotic strains that exert beneficial effects, and (*4*) translation of these findings and therapeutic avenues into human models. Developing innovative methodologies and multidisciplinary approaches to answer these questions could substantially advance our understanding of host–microbiota interactions, not only in the field of AKI but also in other disease models.

Disclosures

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Author Contributions

S.K. Jo conceptualized the study, was responsible for data curation and funding acquisition, and wrote the original draft.

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