Kidney–Gut Crosstalk in AKI

Sang Kyung Jo

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).
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 CX3CR1 expression (Ly6c^low CX3CR1^int macrophages). In contrast, the differentiation process is known to be arrested during inflammation with increased proportions of Ly6c^low CX3CR1^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 CX3CR1^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 Ly6Clow/CX3CR1high 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

S.K. Jo reports being a member of the Korean Society of Nephrology.

Funding

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (2017R1A2B1002734).

Acknowledgments

The author would like to thank Dr. Won Yong Cho, Myung Gyu Kim, and Ji Hyun Yang for their feedbacks and advice.

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

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

References

1. Pasolli E, Asnicar F, Manara S, Zollo M, Karcher N, Armanini F, Beghini F, Manghi P, Tett A, Ghensini P, Collado MC, Rice BL, DuLong C, Morgan XC, Golden CD, Quince C, Huttenhower C, Segata N: Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. *Cell* 176: 649–662.e20, 2019 https://doi.org/10.1016/j.cell.2019.01.001

2. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI: The effect of diet on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med* 1: 6ra14, 2009 https://doi.org/10.1126/scitranslmed.3000322

3. Dethlefsen L, Huse S, Sogin ML, Relman DA: The pervasive effects of an antibiotic on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med* 1: 6ra14, 2009 https://doi.org/10.1126/scitranslmed.3000322

4. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen X, Wu X, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falorny G, Okuda S, Almeida M, Le Chatelier E, Renault P, Pons N, Battot-M, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J: A metagencode-wide association study of gut microbiota in type 2 diabetes. *Nature* 490: 55–60, 2012 https://doi.org/10.1038/nature11450

5. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI: Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 106: 11466–11469, 2009 https://doi.org/10.1073/pnas.0907166106
Gut bacteria products prevent AKI induced by ischemia-reperfusion. J Am Soc Nephrol 26: 1877–1888, 2015 https://doi.org/10.1681/ASN.2014030288

10. Al-Harbi NO, Nadeem A, Ahmad SF, Alotaibi MR, AlAsmari AF, Alonazi WA, Al-Harbi MM, El-Sherbeeny AM, Ibrahim KE: Short chain fatty acid, acetate ameliorates sepsis-induced acute kidney injury by inhibition of NADPH oxidase signaling in T cells. Int Immunopharmacol 58: 24–31, 2018 https://doi.org/10.1016/j.intimp.2018.02.023

11. Nakade Y, Iwata Y, Furuichi K, Mita M, Hamase K, Konno R, Miyake T, Sakai N, Kitajima S, Toyama T, Shinozaki Y, Sagara A, Hattori M, Umesaki Y, Honda K: Th17 cell induction by adhesion of microbes to intestinal epithelial cells. Int Immunol 25: 567–579, 2013 https://doi.org/10.1093/intimm/dxs070

12. Li J, Moturi KR, Wang L, Zhang K, Yu C: Gut-derived-endotoxin contributes to inflammation in severe ischemic acute kidney injury. BMC Nephrol 20: 16, 2019 https://doi.org/10.1186/s12882-018-1199-4

13. Zhang J, Ankawi G, Sun J, Digivijay K, Yin Y, Rosner MH, Ronco C: Gut-kidney crosstalk in septic acute kidney injury. Crit Care 22: 117, 2018 https://doi.org/10.1186/s13054-018-2040-y

14. Bain CC, Schriddel A: Origin, differentiation, and function of intestinal macrophages. Front Immunol 9: 2733, 2018 https://doi.org/10.3389/fimmu.2018.02733

15. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Litman DR: Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 139: 485–498, 2009 https://doi.org/10.1016/j.cell.2009.09.033

16. Atarashi K, Tanoue T, Ando M, Kamada N, Nagano Y, Narushima S, Suda W, Imaoka A, Setoyama H, Nagamori T, Ishikawa E, Shima T, Hara T, Kado S, Jinnehara T, Ohno H, Kondo T, Toyooka K, Watanabe E, Yokoyama S, Tokoro S, Mori H, Noguchi Y, Morita H, Ivanov II, Sugiyama T, Nuñez G, Camp JG, Hattori M, Umesaki Y, Honda K: Th17 cell induction by adhesion of microbes to intestinal epithelial cells. Cell 163: 367–380, 2015 https://doi.org/10.1016/j.cell.2015.08.058

17. Krebs CF, Paus H-J, Krohn S, Koyro T, Brix SR, Riedel-H, Bartsch P, Wiech T, Meyer-Schwesinger C, Huang J, Fischer N, Busch P, Mittrücker-H, Steinhoff U, Stockinger B, Perez LG, Wenzel UO, Janneck M, Steinmetz OM, Gagliani N, Stahl RAK, Huber S, Turner-J, Panzer U: Autoimmune renal disease is exacerbated by STP-receptor-1-dependent intestinal Th17 cell migration to the kidney. Immunity 45: 1078–1092, 2016 https://doi.org/10.1016/j.immuni.2016.10.020

18. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, Haase S, Mahler A, Balogh A, Markó L, Vvedenskaya O, Kleiner FH, Tsvetkov D, Klug L, Costea PI, Sunagawa S, Maior L, Rakova N, Schatz V, Neubert P, Fratzler C, Kranich A, Gollasch M, Grohme DA, Courte-Real BF, Gerlach RG, Basic M, Tsuchiya T, Wu C, Titze JM, Jantsch J, Boschmann M, Dechend R, Kleinsteinfeld M, Kempa S, Bork P, Linker RA, Alm EJ, Müller DN: Salt-responsive gut commensal modulates Tlr17 axis and disease. Nature 551: 585–589, 2017 https://doi.org/10.1038/nature24628

19. Park SW, Kim M, Kim SY, Ham A, Brown KM, Mori-Akiyama Y, Ouellette AJ, D’Agati VD, Lee HT: Paneth cell-mediated multiorgan dysfunction after acute kidney injury. J Immunol 189: 5421–5433, 2012 https://doi.org/10.4049/jimmunol.1200581

20. Lee T-H, Park D, Kim YJ, Lee I, Kim S, OhC-T, Kim J, Yangl-Y, JoS-K: Lactobacillus salivarius BP121 prevents cisplatin-induced acute kidney injury by inhibition of uremic toxins such as indoxyl sulfate and p-cresol sulfate via alleviating dysbiosis. Int J Mol Med 45: 1130–1140, 2020 https://doi.org/10.3892/ijmm.2020.4495

Received: December 28, 2020 Accepted: February 19, 2021