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The Potential Role of the Gut Microbiota in Kidney Transplantation

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Introduction

Through use of high-throughput sequencing technologies, numerous studies have revealed the multifaceted role of the gut microbiota in host immunity and infection, resulting in wide-ranging implications for patients with cancer and autoimmune diseases (1). The gut microbiota's potential to influence host immunity may be of particular importance in solid organ transplant recipients, given this population's risk for allograft rejection and increased susceptibility to infections. In this perspective article, we present recent work on the effect of the gut microbiota in kidney transplant recipients, with a focus on infectious complications and immunosuppressive drug metabolism.

Gut Microbiota in Kidney Transplant Recipients Compared with Nontransplant Recipients

The Human Microbiome Project characterized the microbiota of 242 healthy human volunteers and found the gut microbiota was dominated by the phylum Bacteroidetes (2). This is distinctly different from kidney transplant recipients, as evidenced by several studies. Fricke *et al.* (3) evaluated the gut microbiota using rectal swabs in 61 kidney transplant recipients and reported a high proportion of the phylum Firmicutes rather than Bacteroidetes. Similarly, Lee *et al.* (4) evaluated the gut microbiota using fecal specimens in 26 kidney transplant recipients and found gut dominance by Firmicutes in this cohort. Lee *et al.* further noticed the gut abundance of Proteobacteria, a phylum that includes Gram-negative bacteria such as *Escherichia coli*, increased in the first couple of weeks after transplantation. Swarte *et al.* (5) studied the gut microbiota in kidney transplant recipients several years after transplantation compared with that of healthy controls and observed they had a significantly lower microbial diversity in the gut compared with healthy controls. However, none of these studies compared the kidney transplant cohort to a nontransplant, ESKD cohort, so it is unclear whether this gut microbiota signature is unique to transplant recipients, or if it is pervasive in patients with ESKD as well. Nevertheless, the studies do find an altered species composition and lower microbial diversity in the gut microbiota of kidney transplant recipients compared with that of healthy controls.

Commensal Gut Microbiota and Inhibition of Pathobionts

Recent work has shown an intricate relationship between commensal gut bacteria and pathobionts, resident microbes with pathogenic potential that are often responsible for infectious complications. Several studies have elucidated mechanisms by which commensal bacteria inhibit the growth of common pathobionts *via* secretion of specific metabolites. Caballero *et al.* (6) studied a four-bacteria consortium that included *Blautia producta* using an antibiotic-treated mouse model and reported that administering the consortium provided colonization resistance against vancomycin-resistant *Enterococcus* (VRE), an organism that commonly causes nosocomial infections in the transplant population. The group further investigated the mechanism and reported that a specific strain of *Blautia producta* produces a lantibiotic antimicrobial peptide that inhibits VRE growth (7). Other studies have also established a role for short-chain fatty acids (SCFAs) in inhibiting the growth of Gram-negative bacteria. Sorbara *et al.* observed that ampicillin-treated mice had less abundance of SCFAs than controls and were more susceptible to carbapenem-resistant *Klebsiella pneumoniae*. They further showed that SCFAs directly inhibit *K. pneumoniae* and other common Gram-negative bacteria in the *Enterobacteriaceae* family at an acidic pH, similar to physiologic concentrations in the human gut (8). Recent studies have also established a role for secondary bile acid formation in inhibiting *Clostridioides difficile*. Buffie *et al.* (9) reported that introduction of *Clostridium scindens*, which converts primary bile acids to secondary bile acids *via* 7 alpha-dehydroxylase, provides enhanced resistance to *C. difficile* infection in a mouse model. Taken together, these studies have elegantly established how commensal organisms may inhibit the growth of pathobionts in the gut.

Gut Microbiota and Infectious Complications in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Recent investigations in allogeneic hematopoietic stem cell transplant (HSCT) recipients show the balance of commensal organisms and pathobionts in the

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gut has a significant effect on infectious outcomes. In a study of 94 patients receiving HSCT, Taur *et al.* (10) profiled serial stool specimens using 16S rRNA gene sequencing of the V4–V5 hypervariable region and found that a fecal abundance of >30% of *Enterococcus* was associated with a future risk for VRE bacteremia. A follow-up study of 696 patients receiving HSCT by this group found that a gut abundance of >30% of Gram-negative bacteria was associated with future development of Gram-negative bacteremia, and that fluoroquinolone prophylaxis decreased the risk for Gram-negative bacteremia (11). These studies suggest that intestinal domination with pathobionts in the gut can lead to the development of sepsis; however, they did not evaluate whether the bloodstream isolates came from the gut. A study by Tamburini *et al.* sought to evaluate this concept in 32 patients receiving HSCT. Using strain-level analysis, the group determined the strains in the gut before the development of bacteremia were most similar to the isolates from subsequent blood cultures (12). The gut microbiota may also have a role in the development of viral infections. Haak *et al.* (13) investigated 360 patients receiving HSCT, and noted that a gut abundance of >1% of butyrate-producing bacteria was associated with a decreased risk for the development of lower respiratory tract viral infections.

Gut Microbiota and Infectious Complications in Kidney Transplant Recipients

Similar to reports that demonstrate the gut microbiota modulate the risk of infectious complications in patients receiving HSCT, recent work suggests there may also be a relationship between commensal microbiota and infections in kidney transplant recipients. Magruder *et al.* investigated the role of the gut microbiota in the development of urinary tract infection (UTI), which is one of the most common infections that kidney transplant recipients encounter after transplantation. In a study of 168 kidney transplant recipients, they serially profiled fecal specimens using 16S rRNA gene sequencing and found gut abundance of *Escherichia* was independently associated with future development of *Escherichia* UTI (14). Detailed metagenomic sequencing of paired gut and urine specimens collected in patients with UTI revealed the *E. coli* strain in the urine was most similar to the *E. coli* strain in the gut in several patients, supporting gut bacteria as a source for UTIs. The group may have also identified protective gut bacteria; specifically, there was a trend toward significance for increased gut abundances of *Faecalibacterium* and *Romboutsia* to be associated with a decreased risk for *Enterobacteriaceae* UTI (15). Interestingly, *Faecalibacterium* and *Rombousia* produce SCFAs, which have been shown to inhibit the growth of *Enterobacteriaceae* (8). Furthermore, the abundance of these bacteria was negatively correlated with the abundance of *Enterobacteriaceae,* supporting the concept that SCFA-producing gut bacteria may be protective of *Enterobacteriaceae* UTIs *via* inhibition of *Enterobacteriaceae* growth in the gut.

Further analysis of the 168 kidney transplant recipients also revealed a potential association between gut bacteria that produce butyrate, an SCFA, and protection from respiratory viral infections (16). A relative abundance >1% of butyrate-producing gut bacteria was associated with decreased development of respiratory tract viral infections in the first 2 years after transplantation, consistent with data from Haak *et al.* in the HSCT population.

There are now limited data, albeit mostly in the form of case reports, which suggest efficacy of gut microbiota–based therapies, such as fecal microbial transplantation (FMT), for preventing infectious complications other than *C. difficile* infection. In one patient study, a heart and kidney transplant recipient had recurrent *C. difficile* infection and recurrent *Enterococcus* bacteremia and UTIs (17). After undergoing FMT for recurrent *C. difficile* infections, the patient was free not only of *C. difficile* infection but also of *Enterococcus* bacteremia and UTIs, up to the time of publication of the case report. In a study of eight patients who were nontransplant and had recurrent UTIs and received FMT for the indication of recurrent *C. difficile* infections, FMT was associated with a significant decrease in UTI recurrence (18). Further studies are needed to investigate the role of gut microbiota–based therapies for preventing infectious complications in kidney transplant recipients at high risk for non-*C. difficile* recurrent infections.

Gut Microbiota and Metabolism of Immunosuppressive Medications

The alteration of the gut microbiota due to medications, including antibiotics, has been extensively described. There is now growing interest in how the gut microbiota affects drug metabolism. Recent work by Zimmermann *et al.* (19) evaluated 76 human gut bacteria and their potential ability to metabolize 271 drugs, and found considerable gut microbiota–mediated drug metabolism *in vitro*. Recent studies have specifically elucidated the role of the gut microbiota in influencing the metabolism of two of the most commonly used immunosuppressive medications in kidney transplant recipients: tacrolimus and mycophenolate mofetil.

In a pilot study of 19 kidney transplant recipients, Lee *et al.* (20) evaluated the gut microbiome using 16S rRNA gene sequencing at 1 week after transplantation and reported a correlation between higher gut abundance of *Faecalibacterium prausnitzii* and higher tacrolimus dosage at 1 month after transplantation. The mechanism behind this association was not initially understood. However, a follow-up study by Guo *et al.* (21) found *in vitro* evidence that *F. prausnitzii* and more than 20 commensal gut bacteria directly metabolize tacrolimus into a metabolite, M1, that is 15-fold less immunosuppressive than parent tacrolimus. They also found that M1 is a bacterial metabolite unique to gut bacteria, because incubation of tacrolimus with hepatic microsomes did not produce M1, and M1 production can be detected in fecal specimens obtained from kidney transplant recipients (21). The group further investigated the pharmacokinetics of M1 and parent tacrolimus after oral administration of tacrolimus in ten kidney transplant recipients and found detectable but variable levels of M1 in the blood of all patients (22). Along with their previous finding of M1 production in the stool of kidney transplant recipients (21), the detection of M1 in the blood suggests that *in vivo* gut metabolism of tacrolimus is present. The relationship between the gut microbiota and tacrolimus is likely generalizable, because a recent study of 24 heart transplant

patients also showed an association between gut microbiota diversity and tacrolimus dosing requirements (23).

The metabolism of mycophenolate mofetil, another commonly used immunosuppressive drug in the kidney transplant population, may also be influenced by the gut microbiota. Enterohepatic recirculation of mycophenolic acid, the active form of mycophenolic mofetil, has been described (24) but the mechanism has not been explored in detail. Recent work by Taylor *et al.* investigated the role of bacterial beta-glucuronidase, an enzyme that can convert glucuronidated mycophenolic acid back to the active mycophenolic acid (25). The group reported that vancomycin eliminated bacteria with beta-glucuronidase activity, thereby decreasing side effects of mycophenolate mofetil, such as weight loss and colonic inflammation (26). Further studies are needed to better understand the extent of the gut microbiota's effect on mycophenolate mofetil's metabolism and toxicity.

Conclusions

The gut microbiota is increasingly recognized as influencing a variety of complications associated with kidney transplant recipients. Its role in post-transplant infections has been recently suggested, but further studies are needed to better understand how commensal organisms function as a community to combat infectious complications. Further characterization of these microbial consortia may allow the development of defined microbiota-based treatments for the prevention of infections. In addition, some bacterial subsets have protective properties from an infection standpoint and may also directly metabolize immunosuppressive medications essential for preserving graft function in kidney transplant recipients. Further research on the dynamics between the gut microbiota and immunosuppressive drug metabolism has the potential to personalize immunosuppressive therapies for kidney transplant recipients, and thereby reduce the post-transplant complications of infection and graft loss.

Disclosures

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Author Contributions

J. Huang and J.R. Lee wrote the original draft; and all authors conceptualized the study and reviewed and edited the manuscript.

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