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The influence of the microbiota on the immune response to transplantation

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Abstract

Purpose of review—In the past decade, appreciation of the important effects of commensal microbes on immunity has grown exponentially. The effect of the microbiota on transplantation has only recently begun to be explored; however, our understanding of the mechanistic details of host-microbe interactions is still lacking.

Recent findings—It has become clear that transplantation is associated with changes in the microbiota in many different settings although what clinical events and therapeutic interventions contribute to these changes remains to be parsed out. Research groups have begun to identify associations between specific communities of organisms and transplant outcomes but it remains to be established whether microbial changes precede or follow transplant rejection episodes. Finally, results from continuing exploration of basic mechanisms by which microbial communities affect innate and adaptive immunity in various animal models of disease continues to inform research on the microbiota's effects on immune responses against transplanted organs.

Summary—Commensal microbes may alter immune responses to organ transplantation, but direct experiments are only beginning in the field to identify species and immune pathways responsible for these putative effects.

Keywords

microbiota; acute rejection; transplantation; tolerance

Introduction

The immune system is constantly in contact with commensal microbes, globally termed the microbiota. The majority of lymphocytes exist in barrier sites harboring commensal communities, including the intestine, lung, and skin. These tissues also feature a full

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Conflicts of interest

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complement of resident innate immune cells. Beyond such mucosal-resident cells, distal immune cells can also be affected by commensal microbes or their products that enter the circulation. It has become clear in recent years that interactions between immune cells and commensals are not neutral for the immune system; rather, the immune system is primed and shaped by commensals and it, in turn, can influence the composition of resident microbial communities. Hence, the behavior of the immune system when challenged by pathogens or in disease states is determined in part by the history of exposure to commensals (1–3).

Evidence is beginning to mount that the immunological challenge of organ transplantation may be one of the processes influenced by commensal microbes (4). However, understanding of the interaction between transplant immunity and commensals is in its infancy. Thus far, numerous patient studies have identified changes to the microbiota after transplantation. Excitingly, some studies have uncovered associations between specific shifts in commensals and graft outcomes after transplantation. The next challenge for the field, which clinical and basic research groups are beginning to address, is to elucidate the mechanisms underlying these associations. Such an understanding may allow rational manipulation of commensal communities in a pre- or peri-transplant manner to improve clinical outcomes. We will first summarize the field's understanding of the interaction between the microbiota and the immune system, with an emphasis on recent discoveries; subsequently, we will describe the growing number of studies addressing the role of commensals in transplantation.

Influence of the microbiota on the immune system

The microbiota is now known to exert direct and/or indirect effects on many cell types, including innate and adaptive immune cells (Figure 1).

Innate immune system

A number of studies have suggested that commensal products modify the effector activity of innate immune cells. Such effects have been observed both in mucosal tissues as well as in distal sites. Macrophages and dendritic cells (DCs) must be “primed” by microbial exposure in order to reach full functionality. This priming may act via an epigenetic mechanism that helps activate transcription of proinflammatory genes (5), or by directing cells to specific locations where they are needed to carry particular functions, as supported by the demonstration that DC homing to lymph nodes was compromised in the absence of microbiota (6). In these studies, alteration in commensals compromised the myeloid cells' ability to induce a protective T cell response to viral infections. Therefore, innate signaling downstream of the microbiota can alter the quality of both early and late responses to pathogens.

Such priming of innate cells can also increase the response to sterile immune challenge. For example, response to cancer therapy was shown to be reduced in antibiotic treated mice due to a defect in the ability of tumor-resident myeloid cells to produce inflammatory molecules (7). This finding suggests that in the context of transplantation, sensing of commensal molecules could contribute to an exuberant anti-graft response. Conversely, intranasal

introduction of a probiotic organism led to a reduced immune response to a viral pathogen (8). Though this model does not precisely mimic steady state sensing of the microbiota, it suggests that priming by microbiota can also exert immune inhibitory effects. In the case of transplantation, therefore, one could hypothesize that there may be pro-rejection and pro-regulatory commensals and it may ultimately be important to assess the microbial communities of both the donor and the host, as both donor and host myeloid cells can help prime alloreactive T cells (9,10).

Beyond mucosal tissues, commensal products appear able to influence the phenotype of cells in the bone marrow niche. This observation suggests that commensals may affect the development of all types of immune cells. For example, Clarke et al. showed that the neutrophils of antibiotic-treated mice were less able to kill bacterial pathogens (11). In this system, cell wall molecules from commensals entered the circulation and influenced neutrophils or their precursors in the bone marrow. Intriguingly, it appears that the microbiota contributes to the generation of myeloid cells as well as influences their phenotype. Similarly, germ-free and antibiotic-treated mice are deficient in myeloid precursors in the bone marrow, leading to increased susceptibility to systemic *Listeria monocytogenes* infection (12). Therefore, acute responses to organ transplantation could be influenced by the microbiota either at the level of alloantigen presentation by innate immune cells to T cells, or at the level of the effector innate immune cells that can be recruited to the graft after alloreactive T cell differentiation, such as macrophage-rich rejection after Th1 differentiation or neutrophil-rich rejection after Th17 differentiation (13). More generally, the inflammatory tone of the immune system may be set as cells develop in the bone marrow under the influence of the microbiota.

The commensal molecules (and the host sensors) that either confer full functionality to innate immune cells or establish a tolerogenic phenotype await full characterization. Identifying such interactions might allow acute neutralization of proinflammatory molecules and receptors prior to transplantation, or conversely administration of protolerogenic molecules. Many of these studies in fact imply that proinflammatory priming by the microbiota is reversible, suggesting that such approaches could indeed be therapeutically beneficial (7,14). Molecules implicated thus far in priming innate immune cells include TLR ligands (6), peptidoglycan sensed through the NLR pathway (11), as well as bacterial metabolites such as short chain fatty acids (15). Further study of which species of commensals play a dominant role in generating the sensed molecules, as well a more thorough understanding of the mechanism of such priming, will aid in our ability to manipulate commensals in a rational manner.

Adaptive immune system

Recent studies have shed light on the influence of the microbiota both on the quality and the specificity of lymphocyte responses. One active area of research has been on the ability of commensals to help polarize T-helper responses. Colonization of the gut by certain commensals induces regulatory T cells (T_{regs}) in the intestine. For example, the Honda group identified a specific community of *Clostridia* that can induce T_{regs} in the colon (16). The human commensal *Faecalibacterium prausnitzii*, which was identified in IBD patients,

also appears to possess regulatory properties (17). However, the implication of these studies that only a few species of bacteria possesses T_{reg} -inducing potential has recently been called into question. The Gordon group showed that the majority of human commensals they introduced into germ-free mice could induce intestinal T_{regs} (18). Indeed, an earlier study showed that a stereotypical model commensal community also was able to induce T_{regs} (19). Therefore, perhaps the presence of one key species of bacteria is less important in establishing regulatory T cells than the molecules the community produces.

Several studies have addressed the question of which specific bacterial molecules can induce T_{regs} . A series of mechanistic studies showed that polysaccharide A of *B. fragilis* can induce both T_H1 and T_{reg} cells (20–22). T_{regs} are also induced by short chain fatty acid metabolites produced by commensals (23,24). These metabolites are suggested to potentiate T_{reg} activity and formation via an epigenetic mechanism. Potentially such molecules could be used to promote a tolerogenic environment in the context of transplantation; however, most of the above studies suggest that the effect of intestinal commensals on T_{reg} formation is largely limited to the intestine and may not influence distal responses, such that it may not be useful for modulating immune responses to non-intestinal allografts.

Commensals are also important for inducing inflammatory subsets of T cells. Most notably, the T_H17 subset in mice appears to be largely dependent on a single commensal species, segmented filamentous bacteria (SFB) (25–27). SFB is required for T_H17 responses in the intestine and is also pivotal for immune responses in other tissues in the context of autoimmunity, including type I diabetes, rheumatoid arthritis and experimental autoimmune encephalomyelitis (22,28,29). Though most studies of the effect of commensals on adaptive immunity have focused on intestinal commensals, commensals from other barrier surfaces may also play important roles in local responses. For example, the Belkaid group showed that colonization of the skin by a human commensal can induce IFN- γ - and IL-17-producing T cells (30). In addition to the ability of commensals to induce inflammatory T cell differentiation, the architecture of lymphoid tissue itself is influenced by these microbes. Bouskra *et al.* showed that the formation of tertiary lymphoid structures is microbiota-dependent (31). Therefore, commensals could influence the response to grafts both by the localization of effector T cells in lymphoid organs and by T cell polarization.

In addition to commensals acting as T_H polarizing adjuvants, they appear to be the cognate target of mucosal T cell responses, as uncovered by a number of elegant studies of T cell specificity. At least some T_{regs} in the intestine appear to be specific for commensal species (32,33). Surprisingly, it also appears that most intestinal T_H17 cells induced by SFB are SFB-specific (27,34). It still remains unclear how this observation can be resolved with the fact that SFB influences responses to different antigens, as in certain autoimmune models (22,29). One possible explanation is that commensal-specific T cells can cross-react to other antigens. In fact, it has been shown that commensal-specific T cells in the peripheral blood of humans can cross-react to viral pathogens in hosts who have never been exposed to those pathogens (35). Thus, the shaping of the T cell repertoire by commensals could potentially influence transplant responses via cross-reactivity and determine the precursor frequency and memory status of T cells that cross-react with alloantigens. In most cases it appears that commensal-specific responses are contained to the gut. However, in the case of

inflammation, injury or innate immune defect, there can be systemic commensal-specific responses that are pro-inflammatory (36,37). Whether the immune suppressive regimen taken by transplant recipients could drive this type of defect, thus paradoxically causing commensal-specific responses that could potentially damage distal grafts, remains to be investigated.

In addition to modifying T cell responses, there seems to be a reciprocal relationship between commensals and antibodies. Influence of commensals on immunoglobulin responses is inferred from the identification of commensal-specific IgA. Flavell and colleagues recently showed that commensals bound by IgA in the intestine tend to be proinflammatory, especially in mice with colitis (38). This suggests that commensal-specific adaptive responses may not be equally directed to all commensals, but confined to those in contact with the mucosa or causing damage to the host. This is in agreement with studies showing that the mucus layer of the gut, and antimicrobial peptides within this layer, prevent the majority of bacteria from contacting the intestinal epithelium (39). IgA in turn can both alter the gene expression of commensals and block commensals from reaching the mucosa, therefore suggesting a feedback loop from the commensals to the immune system and vice versa (40).

There is some evidence that even systemic antibody responses are influenced by the microbiota, which could have implications for alloantibody-mediated transplant rejection. A recent study showed that sensing of the intestinal microbiota was required for a full antibody response to influenza vaccination (41). Another study suggested that a dysbiotic intestinal microbiota can induce commensal-specific IgG (42), which potentially might display cross-reactivity to other antigens, and possibly alloantigens.

In summary, immunological studies have shown that commensal communities can shape both inflammatory and regulatory adaptive responses. These effects are predominantly local, but especially in inflammatory and immune suppressed contexts, effects may be observed throughout the organism. Therefore, adaptive responses to the microbiota may influence the outcome of transplantation of both mucosal and non-mucosal tissues.

Microbiota in transplantation

Studies on the effect of the microbiota in transplantation, both in animal models and in patients, are still relatively rare. However, this area of inquiry is gaining traction due to our increased understanding of the basic mechanisms of immune-commensal crosstalk. Most of the studies to date examining the microbiota in conjunction with transplantation simply identify overall changes in the microbiota following transplantation. Certain associations have been identified between transplant outcome and specific shifts in microbial communities. In many cases, however, it is not clear whether the change is the cause or the effect of the observed transplant outcome. It is noteworthy that microbiota alterations have been observed in many transplant settings including transplantation of small bowel, lung, liver, and also organs such as kidney not directly in contact with commensals (43–46).

Several studies have suggested that a reduction in diversity of the microbiota is associated with poor clinical outcome after transplantation. For example, one group showed that a

reduction in diversity in patient fecal microbial communities after liver transplantation was associated with post-transplant diarrhea (45), while a second group observed that a decrease in fecal microbiota diversity after liver transplantation was associated with postoperative infection (47). Another group suggested that a reduction of the microbial diversity in rats may predict acute rejection of liver grafts, though differences were modest (48). While the liver is not directly in contact with the gut microbial community, it is subject to the influence of bacterial ligands circulating from the intestine, which have been shown to impact hepatic immune status (49,50). Therefore these basic studies suggest an association between changes in intestinal microbial communities and the immune response to liver transplants.

Studies of hematopoietic stem cell transplantation (HSCT) have also suggested that low diversity in intestinal microbiota communities leads to bacteremia and mortality (51,52). Potentially, a loss of diversity after transplantation could indicate the outgrowth of “pathobiont” species, which are immunologically neutral unless they expand to form a dominant, disease-causing part of the gut microbial community (53,54). However, loss of diversity appears not to be pathogenic in all cases. The Pamer and Van den Brink groups observed outgrowth of *Lactobacillus* species in patients after HSCT, but these bacteria appeared to be beneficial in a mouse model of graft-versus-host disease (GVHD) (55). Therefore, overall diversity level is not sufficient to predict pathology; future studies should try to address the effects on immunity of the species that dominate post-transplant microbiota in these varying contexts.

Transplant patients experience inflammation due to the transplantation procedure and the ischemia and reperfusion of the allograft but also immune suppression, which could in turn influence the microbiota community. Several studies in mice and non-human primates have observed that defects in immunity, especially in the intestine, can lead to an increase in systemic inflammation (37,50,56). A similar effect was observed in a study in non-human primates in which the immunosuppressive therapy alemtuzumab (Campath-1), in the absence of a transplant, led to a change in intestinal microbiota (57), including expansion of phyla recently identified as colitogenic (38). These observations suggest that immunosuppression during transplantation may lead to a more proinflammatory microbiota, which could potentially contribute to graft inflammation at both mucosal and/or distal sites. This hypothesis should be tested in animal models of transplantation so that causality can be clearly demonstrated. Moreover, analysis of patients on different immunosuppressive regimens could be undertaken to examine whether specific drugs are associated with specific types of microbiota alteration.

Though most studies have focused on intestinal microbes and transplantation, other mucosal communities can also contribute to rejection. For example, presence of the fungus *Aspergillus* was found to be associated with bronchiolitis obliterans syndrome (BOS) after lung transplantation (58). In another study, a shift in the balance between two *Pseudomonas* species in the lung was associated with BOS (44). However, a different study suggested that reestablishment of pre-transplant lung microbial composition was associated with lower BOS incidence, irrespective of this community’s *Pseudomonas* ratio (59). The strength of this study was that patients were followed longitudinally after transplantation, unlike studies in which only a single time point after transplantation was available. In general, inter-

personal variations in the microbiota are much greater than variation over time within individuals, so longitudinal analyses may be key to appreciating the causal effects of observed changes in microbiota (18,46,60). Moreover, the microbiota of different communities of people with different diet and environment can vary dramatically, such that multi-center studies may be important to define the causal effects of changes in the microbiota of transplant recipients (61,62).

All of the studies mentioned above address the microbiota of the transplant recipient. Does the microbiota of the donor matter? In theory donor organs might add to the new commensal community, such as in the case of a lung or small bowel transplant, or influence the phenotype of the graft-resident immune cells. However, one study addressing this question in a mouse model reported that donor microbiota did not influence the intensity of GVHD (63). Animal studies in the context of other disease models have also suggested that the effect of the microbiota may be reversible (5,6,14), and therefore the donor microbiota might not exert long-term effects.

While studies continue to ascribe potentially pathogenic changes to the microbiota following transplantation, the field may begin to seek interventions to reverse these changes. Interventions such as probiotics and antibiotics could be potentially helpful in certain contexts of transplantation, although the benefits of these approaches may depend on the initial state of the microbial community. One study has already demonstrated the potential benefit of such a probiotic approach in mice following HSCT (55). Recently, fecal transplants have been extremely successful in transferring a “healthy” intestinal microbiota and curbing dysbiosis in patients infected by *Clostridium difficile* (64). In the case of transplantation, unlike cases of unplanned infectious diseases, a transplant recipient’s microbiota in the form of broncho-alveolar lavage or fecal material could theoretically be frozen and then an “autograft” could be performed post-transplantation. Before such interventions are undertaken in patients, the field will need a more thorough understanding of the dynamics and effects of commensal communities following transplantation.

Conclusion

In recent years, our understanding of the interplay between the immune response and the microbiota has grown exponentially, as has our appreciation for the importance of immune-commensal crosstalk. Studies attempting to understand mechanistic details of these interactions face many challenges, not least of which is the emerging concept that there can be complex feedback from the immune response on the microbial community, as well as effects of the microbiota on the immune response. Moreover, different species can in some circumstances exert context-dependent effects. In the case of transplantation responses in particular, more mechanistic studies are needed to thoroughly understand the influence of commensals on both local as well as distal anti-graft responses. Recent studies have suggested that a loss of diversity in both lung and intestinal microbiota is associated with poor transplant outcomes. The results of more mechanistic studies, along with more longitudinal studies of patients, and the development of more targeted therapeutics to modify commensal communities, will contribute to our ability to target this potential modulator of transplant responses for therapeutic purposes.

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Key points

- Commensal microbes have major effects on local and distal innate and adaptive immune responses
- The diversity and composition of the microbiota change after transplantation
- Longitudinal studies in transplant recipients are necessary to establish a link between specific changes in microbiota composition and graft outcome
- Animal studies are needed to help clarify causality of changes in microbiota on post-transplant pathology, as well as underlying mechanisms

Figure 1. Model of commensal microbial effects on immune cells

Microbial communities exist in the intestine, lung and skin. Studies in animal models and patients have shown that alteration in microbial communities can modify immune cell numbers and function in a number of organs, both mucosal and distal from microbes. Cell types affected by commensals include T cells, B cells, bone marrow precursors, neutrophils, macrophages, and dendritic cells.