Int J Hematol (2015) 101:428–437
DOI 10.1007/s12185-015-1781-5

Intestinal microbiota-related effects on graft-versus-host disease

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Received: 10 March 2015 / Accepted: 16 March 2015 / Published online: 27 March 2015

Abstract Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an increasingly important treatment for conditions including hematopoietic malignancies and inherited hematopoietic disorders, and is considered to be the most effective form of tumor immunotherapy available to date. However, graft-versus-host disease (GVHD) remains a major source of morbidity and mortality following allo-HSCT, and understanding the mechanisms of GVHD has been highlighted as a key research priority. During development of GVHD, activation of various immune cells, especially donor T cells, leads to damage of target organs including skin, liver, hematopoietic system, and of particular clinical importance, gut. In addition to histocompatibility complex differences between the donor and recipient, pretransplant conditioning with chemotherapy and irradiation also contributes to GVHD by damaging the gut, resulting in systemic exposure to microbial products normally confined to the intestinal lumen. The intestinal microbiota is a modulator of gastrointestinal immune homeostasis. It also promotes the maintenance of epithelial cells. Recent reports provide growing evidence of the impact of intestinal microbiota on GVHD pathophysiology. This review summarizes current knowledge of changes and effects of intestinal microbiota in the setting of allo-HSCT. We will also discuss potential future strategies of intestinal microbiota manipulation that might be advantageous in decreasing allo-HSCT-related morbidity and mortality.

Keywords Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) · Graft-versus-host disease (GVHD) · Gut microbiota · *Lactobacillales* · *Enterobacteriales* · *Clostridiales* · Dysbiosis · Antimicrobial peptide · 16S rRNA · Deep-sequencing technology · IL-22 · Paneth cell · Regenerating islet-derived III alpha/gamma · Antibiotics · T cell

Introduction

Allo-HSCT has been utilized to treat a variety of disorders; however, its efficacy is limited by the occurrence of GVHD [1]. A relationship between the microbiota and GVHD has long been suspected and is recently being extensively investigated by researchers.

The human gastrointestinal (GI) tract harbors an estimated ~10^{14} individual bacteria belonging to about 1000 species in any single individual, and ~15,000 species of bacteria have been identified from human GI samples [2–4]. Less than 30 % of these bacteria are amenable to conventional culture techniques, which makes their identification and functional analysis difficult. In recent years, deep-sequencing technology has made it possible to characterize the composition of intestinal microbial contents free of the selective biases of culture-based methods. Sequencing of bacterial 16S rRNA gene was developed in the 1970s [5], and in combination with subsequent genetic methodologies, including in situ hybridization and polymerase chain reaction (PCR), this method allows rapid identification of bacterial isolates from clinical samples [6]. Recently, high-throughput sequencing technologies,

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so-called deep-sequencing methods allow investigators to characterize the composition of mixed bacterial samples. This has led to a surge of interest investigating how bacteria can contribute to outcomes ranging from obesity [7, 8], atherosclerosis [9], and cancer [10–12], to allergies and asthma [13], and even to autism [14]. Deep-sequencing of 16S rRNA has yet to be utilized routinely in the clinical setting due to practical barriers for implementation including time, cost, and complexity, and the lack, thus far, of clinically actionable findings. More recently, rapid next-generation technologies are being developed [15] that are expected to lower the threshold to clinical translation.

Since the early 1970s, researchers have known that the commensal bacteria residing in our intestines, collectively termed the intestinal microbiota, are important mediators of the biology of allo-HSCT [16, 17]. Early studies in mice and humans suggested a link between an individual's intestinal microbial flora and his/her propensity for GVHD. Clinical strategies to suppress the intestinal microbiota in an attempt to prevent GVHD initially showed considerable promise [18, 19]; however, these strategies failed to demonstrate consistent benefit [20–22]. Thus, the best means of preventing GVHD by modulating intestinal microbiota have remained unclear. In the current era of rapidly developing new technologies for deep-sequencing of 16S rRNA, the microbiota has been now been re-examined in relation to a variety of clinical outcomes including several that are related to allo-HSCT. Several groups have recently discovered important relationships between the microbiota and outcomes in allo-HSCT recipients [23–25]. In the current review, we provide an update focusing on the biology of intestinal homeostasis in relation to the microbiota in the setting of allo-HSCT and its impact on GVHD.

Intestinal immune homeostasis and the key players

Among trillions of bacteria, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* dominate in human adult intestine [26] and only a very small number of these bacteria are known to be pathogenic. The interactions between the host and commensal microbiota as a whole can have an impact on various aspects of the host immunogenic biology [27–29].

Hematopoietic cells in intestinal homeostasis

Various populations of hematopoietic cells participate in intestinal homeostasis. Myeloid cells including macrophages and dendritic cells (DCs) mediate immune tolerance and protection. CX3CR1-expressing nonmigratory macrophages keep close contact with intestinal epithelial cells (IECs) to mediate clearance of enteropathogens and commensal bacteria that invade the epithelial barriers [30]. In response to commensal bacteria, IECs produce cytokines in response to signals mediated via pathogen recognition receptors (PRRs). These cytokines promote the development of tolerogenic DCs and macrophages [31], including TGF-β-producing $CD103^{+}CD11b^{+}$ DCs within the GI tract, which in turn induce expansion of FoxP3-expressing regulatory T cells (Treg) [32]. DCs carry antigenic material and live bacteria to secondary lymphoid organs including mesenteric lymph nodes (MLNs) and Peyer's patches where their cargo is presented to adaptive immune cells [30]. This induces the differentiation and recruitment of Tregs as well as gut-homing effector T cells to the site of antigen encounter in the intestinal lamina propria (LP) [33]. One potential molecular mechanism linking the microbiota to T cell function involves indoleamine 2,3-dioxygenase (IDO), an enzyme expressed by DCs and macrophages that catalyzes the initial rate-limiting step in tryptophan degradation. Inflammatory cytokines, such as IFN-γ, induce IDO, and this inhibits T cell activation through the consumption of tryptophan and expands Tregs, inducing immune tolerance [34]. Germ-free mice have been reported to exhibit decreased levels of IDO, suggesting a role of microbiota in the regulation of IDO [35].

B cells are also involved in the regulation of the immune system within intestinal tissues. Commensal organisms have recently been shown to influence early B cell lineage development in the gut LP [36]. B cell class switching to IgA is mediated by cytokines secreted by IECs in both T cell-dependent and T cell-independent manners. IgA is transported by IECs across the epithelial barrier into the intestinal lumen to serve as another important line of defense barrier against microbes [31].

Moreover, T cells play important roles in intestinal immunity. An important function of the microbiota is to metabolize materials ingested by the host. This results in the production of short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate. Thus, the intestinal "metabolome" consists of products from discrete host metabolism, microbial metabolism, and mammalian microbial co-metabolism [37]. These SCFAs have been shown to induce Tregs through upregulation of gut-homing molecules [38] and FoxP3 [39] in the colon. A subset of bacteria from the order *Clostridiales* has been identified as important for induction of colonic Tregs [40, 41], potentially by upregulating TGF-β to support FoxP3 induction. In contrast, pathogen-associated stimuli cause inflammatory responses via IL-1 and IL-6 induction, resulting in Th1 and Th17 activation [42]. Tregs also play a critical role in GI homeostasis via the anti-inflammatory cytokine IL-10 with a direct impact on macrophages [43–45]. Another report demonstrated de novo generation of colonic Tregs by utilizing a cocktail of altered flora [46].

The recently recognized population of lymphocytes known as innate lymphoid cells (ILCs) [47, 48] also plays an important role in intestinal immune homeostasis. They are classified into three distinct subpopulations termed group 1 through 3 on the basis of the expression of specific transcriptional factors, cell surface markers, as well as the ability to secrete particular cytokines. Group 3 ILCs expressing RORγt in the intestine have been found to regulate commensal bacteria by inhibiting local and systemic inflammation. In response to IL-23 signals emanating from myeloid cells, these group 3 ILCs produce IL-22, which is a potent regenerative factor for epithelial cells [49]. We speculate that this is one of several cellular mechanisms that serve to protect intestinal epithelium during inflammation by restoring immune tolerance at the epithelial interface. For example, ILCs have also been recently reported to produce colony-stimulating factor 2 (Csf2, also known as GM-CSF) in response to macrophage-derived IL-1b, which stimulates DCs to produce retinoic acid, which to promote Treg recruitment [50]. Manipulation of these cytokine-mediated epithelial protection pathways might potentially be exploited in the treatment of patients with intestinal inflammatory diseases such as GVHD, radiation enteritis, or inflammatory bowel disease.

Intestinal epithelium in intestinal homeostasis

IECs assemble the intestinal epithelium which maintains a physical and biochemical barrier to separate intestinal tissues from luminal organisms [51]. Intestinal epithelial stem cells can give rise to all subsets of differentiated IECs, including goblet cells, enteroendocrine cells, enterocytes, and Paneth cells. These stem cells reside at the base of intestinal crypts and are dependent on Wnt signaling. [52]. The mucins secreted by goblet cells into the intestinal lumen form a mucus layer that acts as a first line of defense against microbes [53]. Paneth cells reside within the crypts and secrete various antimicrobial peptides (AMPs) that inhibit the growth of and kill bacteria by compromising the integrity of microbial cell membranes [31]. AMPs include defensins, cathelicidins, and calprotectins. In addition to neutralizing pathogenic bacteria, defensins also amplify adaptive immune responses resulting in both Th1- and Th2-dependent responses by activation of immature DCs [54]. Cathelicidin is mainly produced in the neutrophils; however, it is also an inducible product of ECs [55]. Another recently described AMP, a C-type lectin regenerating islet-derived protein III gamma (RegIIIγ; RegIIIα in humans), is secreted by Paneth cells in a myeloid differentiation primary response protein 88 (MYD88)-dependent manner and plays an important role in separating luminal bacteria from the intestinal epithelial surface [56, 57].

The intestinal mucosa functions to immunologically survey the intestinal lumen, monitoring harmless commensal bacteria as well as potential harmful pathogens [58]. IECs recognize a variety of microbial products in both antigen-dependent and antigen-independent manners to participate in coordinated immune tolerance, or alternatively immune response [31]. Microbiota-associated molecular patterns are directly recognized by pathogen recognition receptors (PRRs) expressed on IECs. PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs), and mediate recognition of microbial ligands or endogenous signals associated with pathogenesis to modulate cellular responses [59, 60]. One highly specialized subpopulation of IECs called microfold cell function to sample antigens and microorganisms for presentation to the mucosal immune system [61]. Moreover, subepithelial macrophages sample luminal contents through their interactions with transepithelial DCs [62]. It is well known that dysregulation of the surveillance mechanisms utilized by the intestinal mucosa can lead to the development of inflammatory bowel disease and other disorders [63].

An observation that speaks to the intimate and codependent relationship of the host with its microbiota is that many aspects of intestinal immune homeostasis fail to develop in the absence of the intestinal microbiota. Germ-free mice show defective development of gut-associated lymphoid tissues and antibody production [64]. IECs in germ-free mice have altered patterns of microvilli formation and decreased rates of cell turnover compared to conventionally housed mice, leading to defective expansion of defensins and other AMPs. In coordination with various types of immune cells, IECs have a significant impact on both the microbiota and homeostasis of the host tissue.

Interactions among components of the microbiota

Interactions among components of the microbiota present another line of defense against potential pathogens. A recent report indicates that commensal bacteria themselves function to prevent the overgrowth of potential pathogens [65]. Host and environmental factors can modulate microbiota composition, resulting in fluctuations in intestinal microbial diversity. These factors include age [66], antimicrobial use [67], disease [68], inflammation [69], metabolites [70], stress [71], and diet [72], particularly malnourishment [73, 74].

Effects of allo-HSCT and GVHD on intestinal homeostasis and microbiota

Allo-HSCT and GVHD cause disruption of intestinal barrier/homeostasis

Pretransplantation conditioning regimens, which often include combinations of chemotherapy and total body

irradiation (TBI), are critical for the success of transplants because they allow engraftment of allogeneic hematopoietic cells and often also treat the underlying malignancy. However, conditioning also disrupts the delicate interplay between host and microbiota by way of mucositis, other organ dysfunction, and increased susceptibility to infection. Bacterial lipopolysaccharide (LPS) is released from the injured gut during conditioning, inducing TLRs and leading to a cytokine storm that enhances the development of GVHD. In murine models, TBI dose correlated inversely with gut barrier function as measured by translocated LPS in the serum [75]. This phenomenon has been confirmed in a clinical study [76] in which the translocation of an orally administered radiolabeled tracer was found to be higher after conventional myeloablative conditioning than reduced intensity conditioning. GVHD itself further deteriorates intestinal barrier function, suggesting that conditioning and GVHD can cause synergistic damage to the epithelium [77, 78].

Cell death in the intestinal epithelium, especially the compartment of the rapidly proliferating crypt cells, leads to impaired replenishment of the villus epithelium and drives loss of intestinal barrier function. Patients manifest nausea, diarrhea, and abdominal discomfort with mild loss of barrier function from intestinal inflammation and treatment options are limited to supportive care [79]. Several efforts are ongoing to develop approaches to protect epithelial cells from damage in the setting of GVHD. Strategies in murine models of GVHD to support epithelial cell recovery have shown promise by utilizing Wnt agonist R-spondin1 [80] and IL-22 [77]. Recovery of the intestinal epithelium from injury appears to be dependent on repopulation of intestinal stem cells that were compromised by GVHD. IL-22 producing ILCs have been found to be extremely diminished in the intestines of mice suffering from GVHD, possibly contributing to the loss of intestinal epithelial cells [77]. Furthermore, Paneth cells are markedly reduced in the setting of GVHD in both mice [25, 81] and humans [82]. Patients with reduced number of Paneth cells at onset of GI GVHD were at higher risk for nonrelapse mortality [82]. These reports indicate the importance of regeneration of intestinal stem cells and warrant development of interventions to protect them after transplantation.

Both mouse and clinical studies have demonstrated impaired humoral immunity in recipients of allo-HSCT [83–85]. Reduced IgA concentration intestinal lumen was observed in mice after transplantation [25]. In patients, the serum levels of IgA generally recovers by 6 months after allo-HSCT; however, recovery is impaired in those who develop acute or chronic GVHD [86].

There is mounting evidence that the effects of GVHD on intestine-derived antimicrobial molecules seem to be molecule-specific. Paneth cells express both α-defensins and the antimicrobial lectin RegIIIγ at steady state [87]; the levels of α-defensins are significantly reduced during GVHD, while expression of RegIIIγ is profoundly increased [23]. RegIIIα, a human homolog of mouse RegIIIγ, is found to be similarly upregulated in the serum samples of patients with intestinal GVHD [88].

Allo-HSCT and GVHD cause changes in intestinal microbiota

The impact of GVHD on the intestinal microbiota is receiving increased attention and has been explored by several groups. While mice transplanted in the absence of GVHD exhibit only mild changes in microbiota composition, murine GVHD is associated with many specific changes in the intestinal flora, including a loss of microbial diversity, dysbiosis (imbalance of intestinal flora), and the expansion of the bacterial orders *Lactobacillales* (including *Lactobacillus*, *Enterococcus*, and *Streptococcus* species) or *Enterobacteriales* (including *Escherichia*, *Klebsiella*, and *Enterobacter* species), the latter of which may adversely impact on GVHD. This is also accompanied by a corresponding loss of obligately anaerobic bacteria from the phylum *Firmicutes*, including members of the order *Clostridiales* [25, 81, 89].

In contrast to these findings in mice, in humans allo-HSCT uncomplicated by GVHD is associated with major changes in microbiota composition [90]. This species difference may be explained by the frequent administrations of antibiotics in patients after allo-HSCT, whereas antibiotics are not commonly used in murine models of allo-HSCT experiments. Allo-HSCT is associated with a loss of flora diversity and expansion of certain bacterial species. *Enterococcus*, *Streptococcus*, and various *Enterobacteriales* are commonly expanded after allo-HSCT, and their increased abundance can precede bloodstream infection by the same organism [91]. Exposure to metronidazole during allo-HSCT increases the risk for developing enterococcal expansion. These findings may suggest that reduction of obligately anaerobic commensals leads to impaired suppression of *Enterococcus*.

Separate from antibiotics, how might GVHD itself affect the intestinal microbiota? Recent reports indicate that the abundance of certain bacteria that play important homeostatic roles, especially *Clostridiales*, could be affected during GVHD. In concert with observations made in mice, patients who develop GVHD display microbiota shifts away from dominance of *Clostridiales* species to dominance by *Lactobacillales* or *Enterobacteriales* [24, 25, 92]. Interestingly, changes in nutritional intake, especially the malnutrition that plagues transplant patients, might be an explanation for these shifts in intestinal flora composition, as a pattern of loss of *Clostridiales* can be observed in

volunteers given high-protein and low-carbohydrate diets [93] or diets derived entirely from animal products [94]. The findings of bacterial shift from *Clostridiales* observed during GVHD may reflect maladaptation of these bacteria, given the fact that many of the *Clostridiales* perform the bulk of fermentation of consumed nondigestible carbohydrates. Their metabolites are thought to produce health benefits [94], and in the setting of GVHD, changes in diet nutrition in the patients can affect metabolic functions of the bacteria. Another important finding that Clostridial species prevent inflammation by upregulating Tregs in the intestines [40] invites speculation that GVHD may deplete anti-inflammatory cell populations by reducing the abundance of *Clostridiales*. Consistent with this notion, we have observed that re-introduction of a mixture of 17 *Clostridial* isolates derived from human stool prolongs the survival of mice with GVHD (unpublished results).

Effects of microbiota changes on GVHD outcomes

Studies from as early as the 1970s in mice and in patients suggested a link between microbes and GVHD. These were followed by clinical trials that reported less GVHD when allo-HSCT was performed in an isolated, protective environment with laminar airflow and gut decontamination [18, 19, 95]. Subsequent studies, however, could not confirm a clear benefit of these protective environments [20–22], and the practice of laminar airflow isolation was abandoned in the early 1990s [96]. The reasons behind these inconsistent results remain unclear but could be due to variable success in total decontamination in the gut.

In the early studies, mice transplanted in germ-free conditions [16] or treated with gut-decontaminating antibiotics [17] developed significantly less GVHD, which demonstrated that the microbiota contributes to the development of GVHD-related lethality. Reports from Germany [97] and the Netherlands [98] showed that prophylactic complete gut decontamination prevented acute GVHD. Another study of the prophylactic use of the broad-spectrum antibiotic meropenem during episodes of neutropenia or fever reported a favorable effect on the morbidity of allo-HSCT [99]. Gut decontamination continues to be practiced at many centers, but there is no consensus regarding ideal choice of antibiotic coverage and its benefits remain controversial. Careful studies focusing on effects of different-spectrum antibiotics on bacterial commensals and transplant-related outcomes are needed. Hopefully, such trials could be done in both mice and patients and would include analysis of commensal metabolites.

Our group has recently reported a detailed analysis of patient fecal samples early after allo-HSCT [100]. We enrolled eighty recipients who provided fecal samples at the time of neutrophil recovery. We found microbial diversity, as quantified by the Simpson index, was predictive of overall survival (OS). Mortality was especially increased in patients with the lowest intestinal diversity, with OS at 3 years of 36 % in the low-diversity group, compared to 60 and 67 % in the intermediate- and high-intestinal-diversity groups, respectively. The increase in mortality in the low-diversity group could be largely attributed to increased death due to GVHD or infection, rather than relapse or disease progression.

Recent studies have sought to elucidate mechanisms by which the microbiota can modulate GVHD-mediated inflammation. It has been established that LPS initiates the process of GVHD by signaling through TLR4 [75]. A role for TLR9 and its downstream signaling adaptor MYD88 was observed in an intestinal GVHD model [89]. The biology of TLRs and MYD88/TRIF signaling has been investigated by several groups, but remains controversial, with disparate results observed in different model systems and tissues. [101–103]. One report [104] described an important role for neutrophils recruited into intestinal tissue following bacterial translocation that had been induced by TBI. In this study, neutrophilic infiltration mediated localized tissue damage by production of reactive oxygen species, resulting in exacerbated GVHD. Interestingly, severe neutropenia following reduced intensity conditioning is related to increased GVHD and nonrelapse mortality [105]. However, it remains unclear whether neutropenia directly contributes to GVHD severity, or alternatively whether neutropenia is associated with frequent use of antibiotics that then lead to GVHD. An additional pathway that mediates inflammatory responses to microbiota during GVHD includes the Nlrp3 inflammasome via IL-1β production [106]. In addition, our group and others found that NOD2, which serves to recognize bacterial peptidoglycan, appears to mediate protective effects against GVHD in both mice [107] and humans [108].

The development of strategies to manipulate gut flora to suppress development of GHVD would be a welcome addition to the armamentarium of the care of the transplant patient. It would be very encouraging if strategies to manipulate gut flora could be developed to produce favorable conditions that could minimize GVHD. Studies in murine models found that certain intestinal Lactobacilli can reduce experimental GVHD [25] and indeed, decreased severity of GVHD as well as improved survival of recipients was observed following the administration of probiotic bacteria [109]. Thus, replenishing the microbiota through probiotic therapy may potentially offer a novel approach to attenuate GVHD and its associated risk for bloodstream infections (Fig. 1). Members of *Enterobacteriales* and *Enterococcus* may be potential contributors to worse GVHD in both mice [25, 81] and humans [24, 92], though causation and potential mechanisms remain to be elucidated.

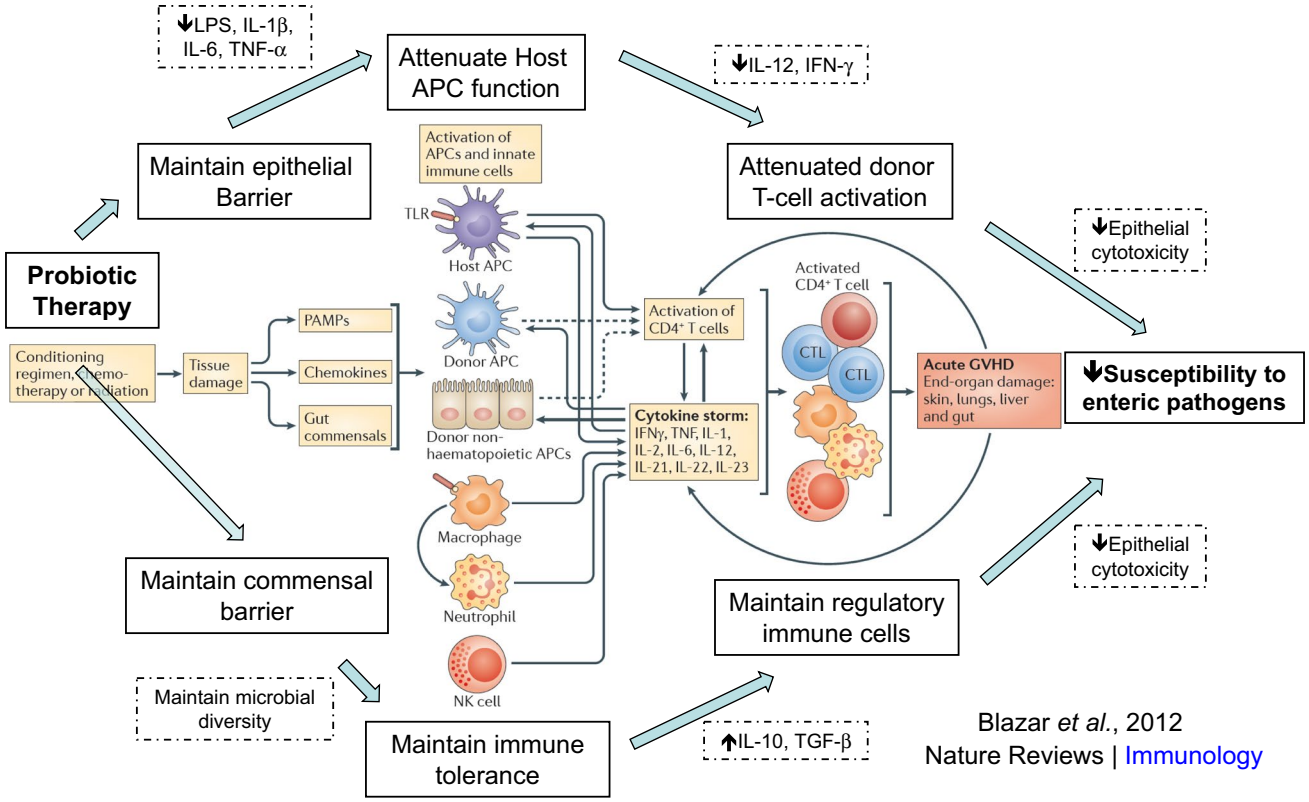

Fig. 1 Roles of probiotic therapy in preventing acute GVHD. Probiotic therapy reduces susceptibility to harmful enteric pathogens by maintaining epithelial and commensal barriers

Table 1 Factors altering microbiota homeostasis during allo-HSCT and proposed therapies targeting restoration in intestinal microbial diversity

Dysbiosis (-> Inflammation/epithelial damage)	Eubiosis (-> Immune regulation/epithelial restoration)
GVHD	Growth factors (KGF)
Conditioning chemotherapy/irradiation	Probiotics (Lactobacillus)
Antimicrobial therapy	Cellular therapy (ISC, MSC)
Alloreactivity	Cytokines (IL-22)
Supplemental nutrition (intralipids)	SCFA (butyrate/acetate)
Mucositis	Polysaccharide A/vitamin A
Infection (viral/bacterial)	Antimicrobial peptides (REGIIIα)
	Reduced intensity conditioning
	Narrow-spectrum antimicrobials

We have focused on the microbiota in the setting of HSCT. Could the microbiota of the donor have effects on the outcomes after allo-HSCT? This question is not yet fully answered. A recent study of hematopoietic grafts derived from mice raised in germ-free conditions indicated that the presence or absence of donor microbiota does not dramatically impact on GVHD severity [110].

There have not been enough published reports to draw conclusions about the impact of microbiota on graft-versus-tumor (GVT) activities in the setting of allo-HSCT. Recent reports suggest that microbiota could bolster the effects of chemotherapy [11, 111].Whether changes in the composition of microbiota can modulate GVT activities remains an open question.

Summary and future directions

There is growing evidence that the microbiota could impact on GVHD, and GVHD could also lead to dysbiosis of the microbiota [29, 112]. The complex interactions between microbiota and GVHD including the differential roles of

donor vs. host microbiota, and pathways of microbiota-associated molecular patterns and PRRs remain to be further examined. Additional studies are needed to better characterize the bacterial mediators of increased or reduced risk for GVHD, bacterial ligands and metabolites that modulate host tissues, and the cellular components that carry out microbiota effects (Table 1). The ultimate goal would be to establish novel strategies to modulate the microbiota in a rational way to mitigate GVHD while maintaining host immune functions that mediate favorable anti-tumor activities to prevent relapse after allo-HSCT, contributing to better outcomes in patients.

Acknowledgments Y. Shono is supported by Lymphoma Research Foundation and American Society for Blood and Marrow Transplantation (New Investigator Award).

Conflict of interest Authors have no conflict of interest.

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