Pharmacological Research 122 (2017) 90–95

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review

Gut microbiota and acute graft-versus-host disease

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ARTICLE INFO

Article history:
Received 26 January 2017
Received in revised form 19 April 2017
Accepted 29 May 2017
Available online 30 May 2017

Keywords:
Dysbiosis
Short chain fatty acids
Probiotics
Prebiotics
Postbiotics

ABSTRACT

Although allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment for various hematological diseases, acute graft-versus-host disease (GVHD) is a major cause of morbidity and mortality, and its management is clinically important. Advances in biological techniques have led to great progress in understanding the complex interactions between the host and the gut microbiota. The gut microbiota clearly modulates the immune response and is associated with the pathogenesis of various disorders. Also in allo-SCT, both preclinical and clinical results indicate that the gut microbiota is closely associated with the development of acute GVHD and transplant outcomes. These results led to the idea that improvement in quantitative and/or qualitative abnormalities of microbiota (dysbiosis) may be a new treatment strategy for acute GVHD. Evaluations of therapies targeting the gut microbiota such as probiotics or fecal microbiota transplantation have just begun. Furthermore, intervention in the gut microbiota with a nutritional approach including prebiotics, postbiotics, and antibiotics selection may also be another promising treatment option for acute GVHD.

Contents

1. Introduction

Although allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment for various hematological diseases, acute graft-versus-host disease (GVHD) is a major cause of morbidity and mortality [1]. Acute GVHD is driven by activated donor T cells that attack host tissues and primarily affects three organs: the skin, the gastrointestinal (GI) tract, and the liver, causing rash, diarrhea, and jaundice, respectively. The initial step in the development of acute GVHD is injury to the GI mucosa caused by conditioning (i.e., high-dose chemotherapy and irradiation). Damage to the mucosal barrier permits bacterial translocation across the mucosa. Translocated bacteria as well as damage-associated molecular patterns by damaged cells stimulate host- and/or donor-derived antigen presenting cells, which produce pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6, as well as prime donor T cells (Fig. 1) [2,3]. In this process, the gut microbiota plays a crucial role in the development of acute GVHD.

Because major components of the gut microbiota are anaerobic and difficult to culture [4,5], conventional cultivation methods cannot capture the entire picture of the gut microbiota. Molecular biological assessments using high-throughput sequencing technologies such as 16S rRNA gene sequencing and metagenomic analysis [6,7] have provided new insight into the complex interactions between the host and the gut microbiota. Not only the composition of the gut microbiota is associated with diseases; functional abnormalities are also linked to pathogenesis of various conditions, ranging from GI disorders (*e.g.*, inflammatory bowel disease, colon cancer) [8,9], liver disease [10], obesity, and cardiovascular disease [11], to allergic [12,13], metabolic [14], and even neurological disorders [15,16] and autism [17,18].

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http://dx.doi.org/10.1016/j.phrs.2017.05.028
1043-6618/

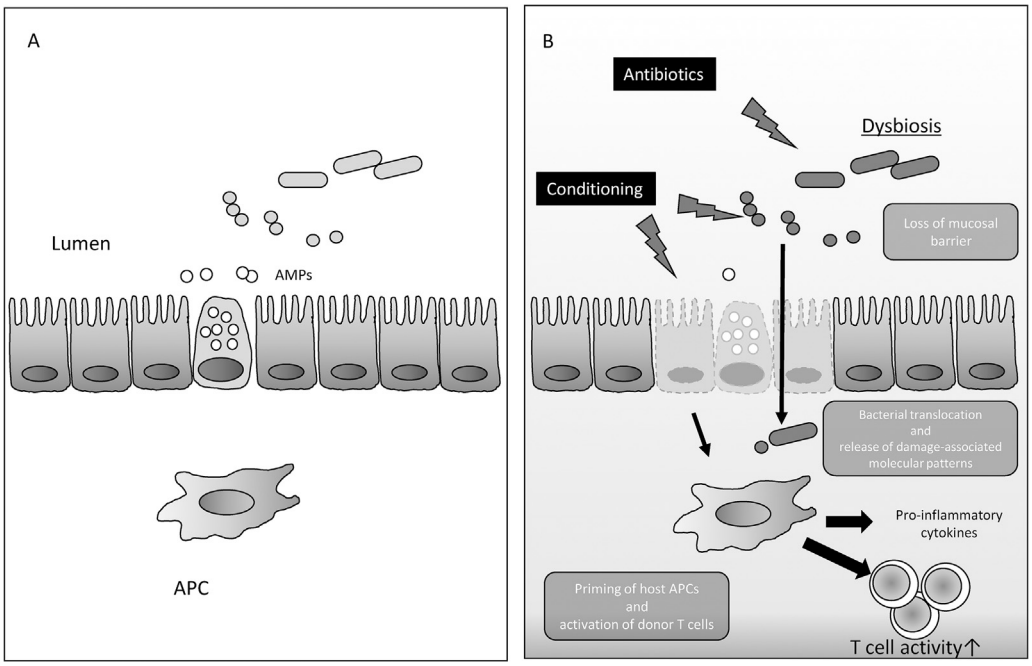

Fig. 1. Schematic overview of the development of acute GVHD.
A) Steady state. B) The initiation phase of acute GVHD. Injury to the gastrointestinal mucosa occurs following high-dose chemotherapy and/or irradiation. The loss of the mucosal barrier permits bacterial translocation. Translocated bacteria as well as damage-associated molecular patterns by damaged cells stimulate host- and/or donor-derived antigen presenting cells, which produce pro-inflammatory cytokines such as tumor necrosis factor-α, IL-1, and IL-6, and prime donor T cells. Abbreviations: AMPs, anti-microbial peptides; APC, antigen presenting cell.

The gut microbiota and its metabolites have been reported to play pivotal roles in both intestinal inflammation and the immune system [19–21]. Because allo-SCT recipients often receive antibiotics, imbalance of the gut microbiota ("dysbiosis") occurs in most patients and may promote pathological conditions involving bowel inflammation and the immune reaction, such as acute GVHD. Indeed, recent studies indicate that the gut microbiota is closely associated with the pathogenesis of acute GVHD [22–27].

In this review, we discuss the role of the gut microbiota in acute GVHD and its potential use for treatment of acute GVHD.

2. Gut microbiota and the development of acute GVHD

An association between the gut microbiota and the development of acute GVHD has long been suspected. In the 1970s, the use of murine allo-SCT models demonstrated that germ-free (bacteria-free) mice develop less severe acute GVHD than conventional mice and that eradication of the gut microbiota prevents the development of acute GVHD [28]. Then, several clinical trials were conducted to evaluate the prophylactic effect of the eradication of gut microbiota with oral non-absorbable antibiotics ("gut decontamination") against acute GVHD, but a clear benefit has not been demonstrated [29–32]. However, a more recent retrospective study showed that pediatric patients with successful total gut decontamination had a significantly lower rate of acute GVHD, although the overall incidence of acute GVHD was very low (8%) [33]. In this study, total gut decontamination was considered successful when stool cultures were negative for both fungi and bacteria in at least three of five samples obtained from day −10 to day +30 [33]. In a mouse model, loss of bacterial diversity is observed in GVHD mice after SCT [27]. On development of GVHD, mice treated with ampicillin before SCT (day −21 to −14) show a loss of *Blautia* and emergence of *Enterococcus*. However, when mice received *Lactobacillus johnsonii* (day −12 to −2) after ampicillin, they showed dominant *L. johnsonii*, no expansion of *Enterococcus* in their intestinal tract, and less severe GVHD compared to ampicillin-treated mice without *L. johnsonii* [27]. Another study using a GVHD mouse model also showed that administration of *Lactobacillus rhamnosus* GG (LGG) improves acute GVHD [34]. Gut decontamination or administration of probiotics (*Lactobacillus*) for amelioration of GVHD appears contradictory. However, the difference may be due to the method of preventing bacterial translocation, the killing of translocated bacteria by antibiotics, or protection from bacterial translocation by probiotics. Indeed, although not statistically significant, bacterial translocation is suppressed in mice treated with LGG or antibiotics compared to control mice [34].

In recent years, the association between the gut microbiota and acute GVHD and/or transplant outcomes has also been evaluated in humans (Table 1). Similar to the mouse model, loss of intestinal diversity is observed in patients with GVHD. Furthermore, an increase in *Lactobacillales* and a decrease in *Clostridiales* are also observed in GVHD patients, whereas these microbial changes are not observed in non-GVHD patients [27]. Holler et al. compared the microbial components pre- and post-transplantation. In transplant recipients, a shift in the gut microbiota with an increase in *Enterococci* and a complementary decrease in other *Firmicutes* and phyla was prominent in patients with gut GVHD [26]. Notably, the abundance of *Enterococci* in active gut GVHD was also seen in patients who did not receive antibiotics. In this study, they also showed that urinary 3 indoxyl sulfate, which originates from the degradation of tryptophan to indole by intestinal microbiota followed by microsomal oxidation to indoxyl and sulfonation in the liver, may be an indirect marker of bacterial disruption in allo-SCT patients. This group subsequently reported that low urinary 3 indoxyl sulfate levels within the first 10 days after allo-SCT are associated with higher transplant-related mortality (TRM: the probability of dying associated with transplantation) and lower overall survival (OS: the survival probability irrespective of disease status) [22]. Gut GVHD-related complications are the most common cause of transplant-related death [22]. Taur et al. evaluated the microbial diversity in allo-SCT patients at the time of engraftment. When allo-SCT patients were divided into three groups based on the inverse