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Educational Reviews

Reprint of: Acute Graft-versus-Host Disease: Novel Biological Insights☆

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A B S T R A C T

Graft-versus-host disease (GVHD) continues to be a leading cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. Recent insights into intestinal homeostasis and uncovering of new pathways and targets have greatly reconciled our understanding of GVHD pathophysiology and will reshape contemporary GVHD prophylaxis and treatment. Gastrointestinal (GI) GVHD is the major cause of mortality. Emerging data indicate that intestinal stem cells (ISCs) and their niche Paneth cells are targeted, resulting in dysregulation of the intestinal homeostasis and microbial ecology. The microbiota and their metabolites shape the immune system and intestinal homeostasis, and they may alter host susceptibility to GVHD. Protection of the ISC niche system and modification of the intestinal microbiota and metabolome to restore intestinal homeostasis may, thus, represent a novel approach to modulate GVHD and infection. Damage to the intestine plays a central role in amplifying systemic GVHD by propagating a proinflammatory cytokine milieu. Molecular targeting to inhibit kinase signaling may be a promising approach to treat GVHD, ideally via targeting the redundant effect of multiple cytokines on immune cells and enterocytes. In this review, we discuss insights on the biology of GI GVHD, interaction of microflora and metabolome with the hosts, identification of potential new target organs, and identification and targeting of novel T cell–signaling pathways. Better understanding of GVHD biology will, thus, pave a way to develop novel treatment strategies with great clinical benefits.

INTRODUCTION

Acute graft-versus-host disease (GVHD) is an immunologically mediated process, involving donor T cell responses to host alloantigens and the dysregulation of inflammatory cytokine cascade after allogeneic hematopoietic stem cell transplantation (allo-SCT). Studies on GVHD pathophysiology have been primarily focusing on mechanisms of T cell activation in the induction phase of GVHD. Recent studies on the fundamental mechanisms of the target injury highlight complex interactions between different effector cell type and target cells in peripheral tissue. Particularly, gastrointestinal (GI) tract damage and subsequent alteration of the intestinal homeostasis play important roles in amplifying GVHD [1]. Emerging data suggest that alterations in the intestinal microbiota and metabolome also play crucial roles in modulating the severity of acute GVHD.

Current GVHD prophylaxis and treatment are only partially effective, with an increased risk for infections, disease relapse, and long-term adverse effects. Data suggest that use of T cell–directed immunosuppressants potentially inhibits tolerance induction, at least in part by suppressing regulatory T cell (Treg) homeostasis [2]. Cytokines and chemokines are the major players in GVHD and blockade of TNF-α, IL-6, and C-C chemokine receptor type 5 (CCR5) has been tested based on data from mouse models [3-7]. Recent progress in our understanding of signaling pathway and molecular targeting enables us to target the redundant effect of multiple cytokines. Thus, better understanding and a more targeted approach of signaling pathways in T cells with a newer class of immunomodulatory approaches could lead to more effective control of GVHD. In this review, we discuss newer experimental insights on the biology of GI-GVHD and the interaction of intestinal microbiota and metabolome with the host and novel strategies for T cell–signaling manipulation in the regulation of GVHD.

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EMERGING CONCEPTS ON TISSUE INJURY IN GVHD

Disruption of the Intestinal Homeostasis and Microbial Ecology in GI GVHD

Intestinal GVHD is characterized by severe villous atrophy and crypt degeneration, but the crypt cell degeneration has been suggested to be the initial lesions of intestinal GVHD [8-10]. Intestinal stem cells (ISCs) and their niche Paneth cells reside within the crypts and play a pivotal role in both physiologic tissue renewal and regeneration of the injured epithelium. We and others have tested the hypothesis that ISCs and their niche could be primary targets in GVHD in mice [11-13]. Irradiation induces apoptosis of ISCs within 24 hours while sparing Paneth cells, but ISCs rapidly recover and restore the normal architecture of the small intestine in the absence of GVHD [12,14]. However, once GVHD develops, both ISCs and Paneth cells do not recover, indicating that the ISC-niche system is the target in intestinal GVHD (Figure 1) [11-13].

Secretory cells, such as Paneth cells and goblet cells, play a critical role in maintaining intestinal microbial ecology and protecting hosts from pathogens. Paneth cells shape the microbial composition by secreting a range of antimicrobial peptides, such as α-defensins [15]. In GVHD, Paneth cell loss results in a reduced secretion of α-defensins, leading to intestinal dysbiosis [13,16-19]. Goblet cells shield the epithelium from luminal bacteria by secreting mucin [20]. Goblet cell injury in GVHD permits translocation and dissemination of dominant luminal pathogens, which further accelerates GVHD and creates a vicious cycle of GVHD and infections [21,22]. These mechanisms explain why GI GVHD is often prolonged and refractory to treatment and represents a risk factor for septicemia. These findings have been confirmed in human studies; loss of Paneth cells and dysbiosis are hallmarks of GI GVHD and associated with increased nonrelapse mortality [17,23-26]. The effects of innate cells, such as neutrophils, monocytes, and innate lymphoid cells, in target injury are also now becoming known [11,27,28].

The intestinal microbiota has been given a putative role in the pathogenesis of GVHD since the pioneering studies in the early 1970s [29,30]. Although the focus so far has been on bacteria and their metabolites, several clinical observations have also suggested a role for *Candida* in the pathogenesis of GVHD; *Candida* colonization in the gut is a risk of acute GVHD (aGVHD) and antifungal prophylaxis with fluconazole reduced aGVHD [31,32]. However, a mechanistic link between fungal infection and GVHD has never been demonstrated. A component of the *Candida* cell wall, α-mannan, is recognized by the C-type lectin receptor Dectin-2 and stimulates macrophages to produce cytokines, such as IL-6 and IL-23, which drive a Th17-skewed response [33]. A lung-specific chemokine/cytokine environment in GVHD leads to accumulation of Th17 cells in the lung [33,34]. α-Mannan or heat-killed *Candida albicans* exacerbate systemic aGVHD, particularly in the lung [33]. Thus, not only bacteria but also fungi residing on the mucosal surface play an important role in GVHD. Th1 and Th17 responses may differentially contribute to tissue-specific aGVHD. However, studies using an IL-17 fate-mapping reporter highlight the complex plasticity and heterogeneity in cytokine expression in effector T cell subsets involved in the development of GVHD [33-36], which will need further elucidation to guide rational development of preventive and therapeutic interventions.

Protection of the ISC Niche System as a Novel Approach to Restore Intestinal Homeostasis and Control GVHD

Attention has now begun to focus on protection of the ISC niche system to regulate GVHD. ISCs express IL-22 receptors

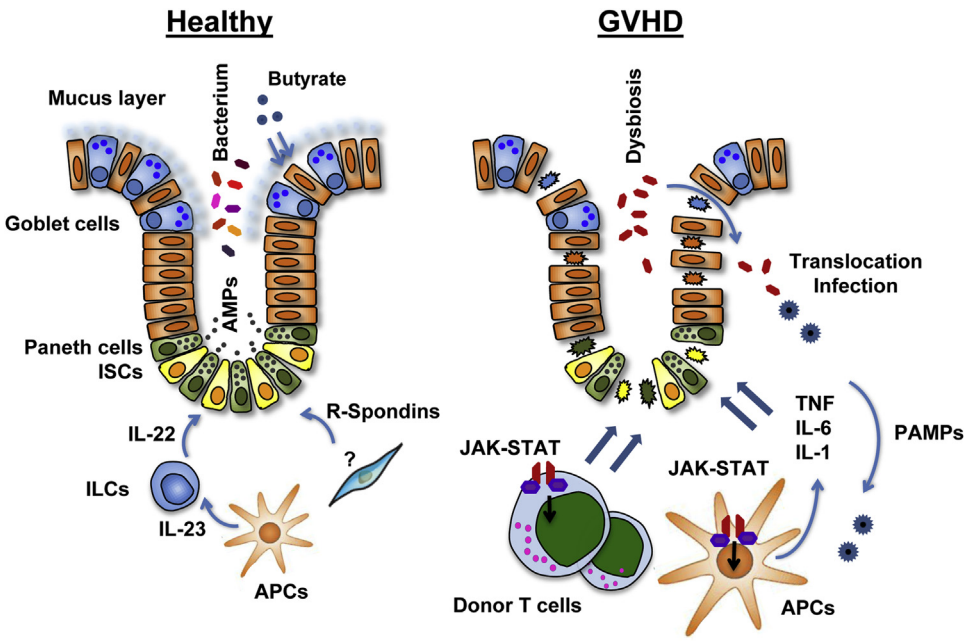

Figure 1. Homeostasis of self-renewing small intestinal epithelium results from ISCs, which locate at the base of the crypts and interspersed between their niche Paneth cells. IL-22 produced from innate lymphoid cells (ILCs) upon stimulation of IL-23 from antigen-presenting cells (APCs) and R-spondins play a role in self-renewal and differentiation of ISCs. Paneth cells maintain intestinal microbial ecology by secreting antimicrobial peptides (AMPs) into the lumen. Goblet cells shield the epithelium from luminal bacteria by secreting mucin. Intestinal homeostasis depends on proper interaction between the mucosal immune system and intestinal microbiota and its metabolites, such as butyrate. After allo-SCT, donor T cells and inflammatory cytokines, such as TNF, IL-6, and IL-1, damage the ISC-niche system. Paneth cell loss results in a reduced secretion of AMPs, leading to intestinal dysbiosis. Tissue injury permits translocation and dissemination of dominant luminal pathogens and pathogen-associated molecular patterns, which further accelerates GVHD by propagating a proinflammatory cytokine milieu. JAK-STAT pathways are required for responses to multiple cytokines and, thus, represent potential new targets in GVHD.