

## Review

# Pathogenesis of Acute Graft-Versus-Host Disease: Cytokines and Cellular Effectors

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### ABSTRACT

The pathogenesis of acute graft versus host disease (GVHD) is multistep process. This review considers acute GVHD in three sequential steps: conditioning regimen, donor T cell activation, and effector mechanisms. In step one, the conditioning regimen simultaneously damages and activates host tissues, amplifying antigen presentation to allogeneic donor T cells. In step two, donor T cells, activated by host alloantigens, proliferate and secrete a variety of cytokines. Type 1 cytokines (interleukin-2 and interferon- $\gamma$ ) are critical for acute GVHD, but several regulatory mechanisms of tissue damage include inflammatory cytokines and cytolytic cellular effectors. The gastrointestinal (GI) tract is a principal target organ because damage to the GI mucosa can release inflammatory mediators such as endotoxin that amplify systemic disease. The inflammatory processes of acute GVHD can be considered as a distortion of the cellular responses to viral and bacterial infections. Cell-mediated toxicity is critical to other GVHD target organs, particularly the liver, where Fas-mediated injury predominates. The cytolytic pathways (e.g., perforin) clearly intensify acute GVHD, although they are not necessary for systemic disease in several model systems. Many of these insights come from animal models using mutant mouse strains that can clarify the role of individual proteins or cell types in the disease process. These insights should allow the testing of new classes of drugs and inhibitors in clinical bone marrow transplantation.

### INTRODUCTION

OUR UNDERSTANDING OF THE PATHOPHYSIOLOGY of graft-versus-host disease (GVHD) has improved greatly with recent advances in our understanding of the cellular and humoral interactions that are intrinsic to all inflammatory processes. In allogeneic bone marrow transplantation (BMT), donor lymphocytes are infused into a host that has been profoundly damaged. The pathophysiology of acute GVHD may be considered to be a distortion of the cellular response to viral and Gram-negative

bacterial infections. The principal target organs of GVHD support suggest a close relationship between infection and GVHD. The skin, gut, and liver all share an extensive exposure to endotoxin and other bacterial products that can trigger and amplify local inflammation. This exposure distinguishes them from organs like the heart and kidneys that are not GVHD targets. Because of their situation as primary barriers to infection, these target organs have large populations of professional antigen-presenting cells (APCs) such as macrophages and dendritic cells that may enhance the graft-versus-host (GVH) reaction.

## PHASE ONE: HOST TISSUE DAMAGE FROM CHEMORADIOTHERAPY

Recent findings implicate the excessive production of cytokines, which are the central regulatory molecules of the immune system, as well as cellular effectors in the induction and maintenance of experimental and clinical GVHD (1–3). The pathophysiology of acute GVHD can be considered in a framework of three sequential phases (1,3). The first phase is not strictly part of GVHD because it starts before the donor cells are infused. The transplant conditioning regimen damages and activates host tissues, including the intestinal mucosa, liver, and other tissues. Activated host cells secrete inflammatory cytokines, such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1 (4), and growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) (5–7). The presence of inflammatory cytokines during this phase may upregulate adhesion molecules (8) and major histocompatibility complex (MHC) antigens (9–13), thereby enhancing the recognition of host MHC or minor histocompatibility antigens by mature donor T cells after the cellular component of the graft is infused. Increased expression of cell-surface adhesion molecules may also occur (14–16). The relationship between conditioning intensity, inflammatory cytokines, and GVHD severity was recently further supported in animal models (17). Moreover, the risk of inducing severe acute GVHD appears to be less if the lymphocytes are infused well after the primary tissue injury has resolved (18,19).

## PHASE TWO: DONOR T-CELL RESPONSE TO HOST ANTIGENS

The second phase of acute GVHD includes presentation of host antigens to donor T cells and the subsequent proliferation and differentiation of these activated T cells. When a CD4<sup>+</sup> cell enters the recipient bloodstream, it will generally interact with the MHC class II molecules of the APCs, whereas a CD8<sup>+</sup> cell will interact with MHC class I antigens. Data suggest that host APCs are particularly important to the activation of donor T cells (20).

T cell activation requires two signals. The first signal is provided by the TCR–peptide–MHC interaction (21,22). The second, or costimulatory signal, requires contact with APCs (23,24). The second signal determines the outcome of the activation sequence, leading to either complete activation, partial activation or to a long-lasting state of antigen-specific unresponsiveness, termed anergy. Several ligands can provide costimulation for resting T cells; the best-characterized costimulatory molecules are the B7 antigens, which bind to two T cell surface receptors, CD28, and CTLA-4 (25,26).

T cells that secrete IL-2 and interferon- $\gamma$  (IFN- $\gamma$ ) (Type 1 cytokines) are critical mediators of acute GVHD. The importance of GVHD has been demonstrated in both experimental and clinical BMT. First, IL-2 is secreted by donor CD4<sup>+</sup> T cells in the first days after experimental allogeneic BMT (27). Second, the blockade of IL-2 with antibodies to IL-2 or its receptor can inhibit the development of experimental disease (27). Clinically, the precursor frequency of host-specific, IL-2-producing T cells (precursor frequency of helper T cells) is predictive for the risk of acute GVHD (28,29). In addition, soluble IL-2 receptor levels may be a sensitive indicator of impending GVHD onset, and they correlate with disease severity (30).

Increased serum levels of IFN- $\gamma$  are associated with acute GVHD, and lymphocytes from animals with GVHD secrete significantly greater amounts of IFN- $\gamma$  than lymphocytes from non-GVHD controls (31–35). Additional evidence of a role for IFN- $\gamma$  in experimental acute GVHD includes: priming of macrophages by IFN- $\gamma$  during acute GVHD to produce inflammatory cytokines (36); induction of pathology in skin tissues and the gastrointestinal tract by IFN- $\gamma$  (37,38); suppression of T lymphocyte function characteristic of acute GVHD by IFN- $\gamma$  (39,40); prevention of acute GVHD when CD8<sup>+</sup> cells are incapable of IFN- $\gamma$  production (41); and inhibition of acute GVHD by direct or indirect blockade of IFN- $\gamma$  (37,42–44).

The preincubation of donor T cells in the presence of the Th2 cytokine IL-4 can polarize these T cells toward a Th2 cytokine phenotype (43). Transplantation of polarized Th2 T cell populations failed to induce acute GVHD to MHC class I or class II antigens. These experiments strongly supported the concept that the balance in Th1 and Th2 cytokines is critical for the development (or prevention) of acute GVHD. Further data show that Th2 cells maintain some anti-leukemic efficacy, and can support lymphohematopoietic engraftment (44,45). Peripheral blood hematopoietic cells collected after mobilization with granulocyte colony-stimulating factor (G-CSF) suggest that Th1  $\rightarrow$  Th2 polarization may occur, albeit indirectly, resulting in less GVHD compared to saline-treated controls (46–48). This effect also changes the production of other inflammatory cytokines such as TNF- $\alpha$  (49,50).

Regulatory cells may also help determine the ultimate response of donor T cells to host antigens. CD4-CD8 double-negative T cells (usually NK1.1<sup>+</sup>) can suppress a T cell response in a mixed lymphocyte reaction (MLR) and can prevent GVHD in vivo. Presumably these regulatory cells develop to control the intensity of the overall response to a specific antigen. The balance between reactive T cells and suppressor T cells could thus control the intensity of GVHD. Other potential avenues for tolerance

induction may occur at the cellular level. Groux et al. demonstrated that CD4<sup>+</sup> T cells, grown *ex vivo* in the prolonged presence of IL-10, suppressed inflammatory bowel disease that was induced by pathogenic T cells (51). These cells were termed “Tr1.” Moreover, Tr1 cells have been isolated from the peripheral blood of severe combined immunodeficiency (SCID) patients after allogeneic stem cell transplantation, in which high levels of IL-10 *in vivo* are associated with donor/host tolerance (52). These results suggest that prolonged exposure of naive CD4<sup>+</sup> T cells to IL-10 may result in a population of Tr1 cells that can regulate immune responses and modulate GVHD.

### PHASE THREE: INFLAMMATORY EFFECTORS

The third phase of acute GVHD is complex, and the precise relationship between cytokines induced during the second phase and mediators of tissue damage during this phase is an area of active investigation. Mononuclear phagocytes, which have been primed with Th1 cytokines during phase two, receive a second, triggering signal to increase the secretion of the inflammatory cytokines TNF- $\alpha$  and IL-1. This stimulus may be provided by lipopolysaccharide (endotoxin, LPS), which can leak through the intestinal mucosa damaged by the conditioning regimen. LPS subsequently may stimulate gut-associated lymphocytes and macrophages (36). LPS reaching skin tissues may also stimulate keratinocytes, dermal fibroblasts, and macrophages to produce similar cytokines in the dermis and epidermis (5–7). TNF- $\alpha$  can cause direct tissue damage by inducing necrosis of target cells, or it may induce tissue destruction during GVHD through apoptosis, or programmed cell death. The induction of apoptosis commonly occurs after activation of the TNF- $\alpha$ -Fas antigen pathway (53). Apoptosis is probably critical to GVHD in the large intestine (54), skin (55,56), and possibly in endothelial cells (57). In addition to these proinflammatory cytokines, excess nitric oxide (NO) produced by activated macrophages may contribute to the deleterious effects on GVHD target tissues, particularly immunosuppression (40,58,59). Thus, the induction of inflammatory cytokines may synergize with the cellular damage caused by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells (60,61), resulting in the amplification of local tissue injury and further promotion of an inflammatory response.

The gastrointestinal (GI) tract plays a critical role in the amplification of experimental acute GVHD. Damage to the intestinal mucosa in phase 1 and by cytolytic effectors activated in phase 2 allows translocation of LPS from the intestinal lumen into the circulation. LPS sub-

sequently stimulates additional cytokine production by gut-associated lymphocytes and macrophages in the GI tract and by keratinocytes, dermal fibroblasts, and macrophages within the skin. This mechanism may amplify local tissue injury and further promote an inflammatory response which, together with the CTL and NK component, leads to target tissue destruction in the BMT host. Damage to the GI tract in phase 3 increases LPS release, which stimulates further cytokine production causing additional GI tract damage. Thus, the GI tract is critical to propagating the “cytokine storm,” which is characteristic of acute GVHD.

The histological features of GVHD of the GI tract in clinical GVHD and experimental GVHD following myeloablative conditioning are characterized by villus blunting, lamina propria inflammation, crypt destruction (with crypt stem cell loss), and mucosal atrophy. These features can be induced in animals by the administration of exogenous cytokines, including TNF- $\alpha$  (62) and IL-1 (63). Furthermore, the inhibition of IFN- $\gamma$  (37), TNF- $\alpha$  (64), IL-1 (63), or NO (65) can reduce GI tract histopathology in animals with GVHD. In contrast, CTL effectors do not appear to play a dominant role in experimental GVHD of the GI tract (17,66–70), despite the ability of intraepithelial lymphocytes to induce Fas-mediated apoptosis of host-type tumor cells (71).

The role of LPS and inflammatory cytokines in GVHD explain a number of unique and seemingly unrelated aspects of GVHD. For example, a number of analyses of clinical transplants noted increased risks of GVHD associated with advanced-stage leukemia, certain intensive conditioning regimens, and viral infections (14–16). Similarly, the reduction in GVHD seen in gnotobiotic mice (72,73) and in patients with aplastic anemia undergoing transplantation in laminar airflow environments with gut decontamination (74) may be explained by the reduction of bacterial LPS on the skin and gut. The beneficial effect of protective environments may be less apparent in patients receiving transplants for malignancies, because prior therapy and associated infections may have resulted in an environment that facilitates GVHD.

An alternative approach to prevent GI tract damage during allogeneic BMT may permit the exploitation of intensive conditioning as an antileukemic modality without requiring T cell depletion. One possible approach involves strengthening the GI mucosal barrier before BMT conditioning to prevent entry of immunostimulatory molecules from the GI tract lumen into the circulation. Because direct shielding of the GI tract from total body irradiation (TBI) is not feasible, this effort relies on pharmacological agents that provide a “cytokine shield” to reduce mucosal sensitivity to radiation and/or chemotherapy. This approach is attractive because it blocks inflammatory cytokine dysregulation before the

initiation of the cascade. In addition, by acting as indirect cytokine antagonists, these shields would not impede the physiological functions of cytokines in cellular differentiation (as might be the case with complete neutralization of TNF- $\alpha$  and IL-1). Two growth factors, IL-11 and keratinocyte growth factor (17,75–77) have recently shown particular promise as cytokine shields.

### PHASE THREE: CYTOLYTIC EFFECTORS

Although cytokines clearly play important roles in the morbidity and mortality of systemic GVHD, they may be less important as mediators of damage in individual GVHD target organs. The unusual cluster of GVHD target organs (skin, gut, and liver) is not adequately explained by the systemic release of cytokines. Furthermore, the absence of GVHD toxicity in other visceral organs, such as the kidneys, argues against circulating cytokines as the sole causation of tissue-specific damage.

Cell-mediated cytotoxicity is thought to contribute to the destruction of GVHD target tissues. T cells can effect cytolysis by either direct contact or the release of soluble mediators such as TNF- $\alpha$ . Contact-dependent cell-mediated cytotoxicity can be effected through a secretory pathway involving granule release or by effector cell membrane ligand interaction with death receptors on the membrane of the target cell (78,79). Following secretion of granules by the effector cell, the polymerization of perforin upon binding to the target membrane is crucial to optimize penetration of granule contents, including granzymes A and B, into the targeted cells. Apoptosis of target cells is then rapidly induced by granzyme B activation of the caspase cascade. A common pathway appears to operate in signaling through so-called death receptors (DR). A number of ligands have been identified on T cells that possess the capability to trimerize TNFR (TNF + receptor)-like DR molecules. In addition to the well-characterized FasL (CD95L)–Fas(CD95) DR ligand-receptor pair, additional molecules, including TWEAK (DR3 ligand) and TRAIL (DR4,5 ligand), have recently been identified as capable of activating the caspase system and subsequent apoptosis (80–83). Although the physiological function(s) of DR3,4, and 5 are not presently known, the expression of TRAIL and TWEAK on T cells may be important contributors to this process.

During the past several years, a number of experimental allogeneic BMT studies have used donor inocula that are unable to mediate either perforin/granzyme or FasL-Fas dependent killing (66,84–88). Transplantation of perforin-deficient T cells results in a marked delay in the onset of weight loss and mortality from GVHD to MHC and minor H antigens (66,84). However, these studies also revealed that although greater numbers of per-

forin-deficient T cells were required to induce GVHD with comparable kinetics to that caused by normal T cells, weight loss and mortality could be induced in the absence of perforin-dependent killing. Moreover, the clinical signs of GVHD including kyphosis, alopecia, skin lesions, and diarrhea, as well as histopathological changes in the skin, liver, and lymphohematopoietic compartment, were all eventually observed following transplant of perforin-deficient T cells (66,84). Thus, it is now clear that the perforin/granzyme pathway is not necessary to generate tissue damage.

Perforin-deficient T cells retain the capacity to mediate FasL-dependent killing. Accordingly, experiments have been performed to examine the consequences of transplanting donor cells unable to signal Fas-mediated apoptosis. These studies have utilized T cells from mice with a naturally occurring genetic mutation resulting in a FasL protein (*gld/gld*) that cannot trimerize Fas, and therefore fails to induce Fas signaling (89). Transplantation of donor T cells with functionally defective FasL into lethally irradiated MHC-matched allogeneic recipients resulted in the induction of weight loss and lethality (66). In contrast to the findings using perforin-deficient cells, transplantation of comparable numbers of FasL-defective T cells versus wild-type T cells resulted in only a modest delay in weight loss and a small increase in median survival time (66). Thus, the presence of perforin and other potential effector pathways in the *gld* T cells were capable of inducing cachexia and lethality of GVHD (66,87).

FasL-mediated cytotoxicity may be an important effector pathway in hepatic GVHD. First, hepatic GVHD has been found to be markedly diminished following transplant of FasL-defective T cells and normal marrow. In the absence of donor-mediated FasL-dependent cytotoxicity, minimal liver inflammation was observed in two minor histocompatibility antigens (MiHA) disparate BMT models (66). Compatible with this notion, a recent study reported that administration of anti-FasL (but not anti-TNF antibody) significantly blocked the hepatic in a model of GVHD to MHL antigens (69).

In summary, recent investigations have begun to define the contributions of cell-mediated cytotoxicity via both perforin/granzyme and FasL-dependent pathways to both systemic GVHD and to GVHD target organ damage. The newly emerging molecular pathways of death signals should provide more complete and precise definitions of requirements for GVHD-induced pathogenesis. Because CD4<sup>+</sup> and CD8<sup>+</sup> cells can mediate both GVHD and GVL activity, assessing the relative contributions of each of the cytotoxic pathways in individual subsets may help in the potential dissociation of GVHD from GVL. As our understanding of the relative contribution of each of these pathways to GVHD pathology in

individual GVHD target organs deepens, novel strategies to optimize prophylaxis and therapy for individual host tissues may emerge.

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