CHAPTER 108

GRAFT-VERSUS-HOST DISEASE AND GRAFT-VERSUS-LEUKEMIA RESPONSES

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The ability of allogeneic hematopoietic cell transplantation (HCT) to cure certain hematologic malignancies is widely recognized. An important therapeutic aspect of HCT in eradicating malignant cells is the graft-versus-leukemia (GVL) effect. The importance of the GVL effect in allogeneic HCT has been recognized since the earliest experiments in stem cell transplantation. Forty years ago, Barnes and colleagues noted that leukemic mice treated with a subtherapeutic dose of radiation and a syngeneic (identical twin) graft transplant were more likely to relapse than mice given an allogeneic stem cell transplant.[1,2] They hypothesized that the allogeneic graft contained cells with immune reactivity necessary for eradicating residual leukemia cells. They also noted that recipients of allogeneic grafts, though less likely to relapse, died of a "wasting syndrome" now recognized as graft-versus-host disease (GVHD). Thus in addition to describing GVL, these experiments highlighted for the first time the intricate relationship between GVL and GVHD. Since these early experiments, both GVHD and the GVL effect have been studied extensively.[3] This chapter reviews the pathophysiology, clinical features, and treatment of GVHD and summarizes current understanding of the relationships between GVHD and the GVL effect.

GRAFT-VERSUS-HOST DISEASE: CLINICAL AND PATHOLOGIC ASPECTS

Ten years after the work of Barnes and Loutit, Billingham formulated the requirements for the development of GVHD: the graft must contain immunologically competent cells, the recipient must express tissue antigens that are not present in the transplant donor, and the recipient must be incapable of mounting an effective response to destroy the transplanted cells.[4] According to these criteria, GVHD can develop in various clinical settings when tissues containing immunocompetent cells (blood products, bone marrow, and some solid organs) are transferred between persons. The most common setting for the development of GVHD is following allogeneic HCT; without prophylactic immunosuppression, most allogeneic HCTs will be complicated by GVHD. GVHD is induced by mismatches between histocompatibility antigens between the donor and recipient. Matching of the major histocompatibility complex (MHC) antigens hastens engraftment and reduces the severity of GVHD.[5] In humans, the MHC region lies on the short arm of chromosome 6 and is called the HLA (human leukocyte antigen) region.[6] The HLA region is divided into two classes, class I and class II, each containing numerous gene loci that encode a large number of polymorphic alleles. MHC class I molecules are involved in the presentation of peptides to $CD8^+$ T cells, and class II molecules present peptides to $CD4^+$ T cells.[6,7] The determination of HLA types has become much more accurate with molecular techniques that replace earlier serologic or cellular methods. In patients whose ancestry involves extensive interracial mixing, the chances of identifying an HLA identical donor are diminished.[8]

Despite HLA identity between a patient and donor, substantial numbers of patients still develop GVHD because of differences in minor histocompatibility antigens (MiHAs) that lie outside the HLA loci. Most minor antigens are expressed on the cell surface as degraded peptides bound to specific HLA molecules, but the precise elucidation of many human minor antigens is yet to be accomplished.[9] In the United States, the average patient has a 25% chance of having an HLA match within his or her immediate family.[8] Patients who lack an HLA-identical family member donor must seek unrelated donor volunteers or cord blood donations.

Acute Graft-Versus-Host Disease

Acute GVHD can occur within days (in recipients who are not HLA-matched with the donor or in patients not given any prophylaxis) or as late as 6 months after transplantation. The incidence ranges from less than 10% to more than 80%, depending on the degree of histoincompatibility between donor and recipient, the number of T cells in the graft, the patient's age, and the GVHD prophylactic regimen.[10] The principal target organs include the immune system, skin, liver, and intestine. GVHD occurs first and most commonly in the skin as a pruritic maculopapular rash, often involving the palms, soles, and ears; it can progress to total-body erythroderma, with bullae formation, rupture along the epidermal-dermal border, and desquamation in severe cases.[10] Gastrointestinal (GI) and liver manifestations often appear later and rarely represent the first and only findings. Intestinal symptoms include anorexia, nausea, diarrhea (sometimes bloody), abdominal pain, and paralytic ileus.[10] Liver dysfunction includes hyperbilirubinemia and increased serum alkaline phosphatase and aminotransferase values. Coagulation studies may become abnormal, and hepatic failure with ascites and encephalopathy may develop in severe cases.[10–12] Hepatic GVHD can be distinguished from hepatic venoocclusive disease by weight gain or pain in the right upper quadrant in the latter.[12] Acute GVHD also results in the delayed recovery of immunocompetence.[10] The clinical result is profound immunodeficiency and susceptibility to infections, often further accentuated by the immunosuppressive agents used to treat GVHD.[10]

Pathologically, the sine qua non of acute GVHD is selective epithelial damage of target organs.[13,14] The epidermis and hair follicles are damaged and sometimes destroyed. Small bile ducts are profoundly affected, with segmental disruption. The destruction of intestinal crypts results in mucosal ulcerations that may be either patchy or diffuse. Other epithelial surfaces, such as the conjunctivae, vagina, and esophagus, are less commonly involved. A peculiarity of GVHD histology is the early paucity of mononuclear cell infiltrates; however, as the disease progresses, the inflammatory component may be substantial. Studies that identified inflammatory cytokines as soluble mediators of GVHD have suggested that direct contact between target cells and lymphocytes is not always required (see following sections). GVHD lesions are not evenly distributed: in the skin, damage is prominent at the tip of rete ridges; in the intestine, at the base of the crypts; and in the liver, in the periductular epithelium. These areas all contain a high proportion of stem cells, giving rise to the idea that GVHD targets may be undifferentiated epithelial cells with primitive surface antigens.[15]

The histologic severity of GVHD is at best semiquantitative, and consequently pathologic scores are not used to grade GVHD. Because it is often difficult to obtain an adequate tissue biopsy, and because it can be very difficult to distinguish GVHD from other post-HCT complications such as drug eruptions or infectious complications, the physician is left to use clinical judgment.

An independent committee of a multicenter phase III trial that assessed the presence and severity of GVHD was unable to confirm a high incidence of GVHD[16,17] Standard grading systems generally include clinical changes in the skin, GI tract, liver, and performance status (Table 108.1).[18] Although the severity of GVHD is often difficult to quantify, the overall maximal grade correlates with disease outcome: mild GVHD (grade I or II) is associated with little mortality, whereas higher grades are associated with significantly decreased survival.[18,19] Recent advances in the use of biomarkers at the onset of disease may soon be sufficiently accurate to guide therapy.[19]

Clinical Features of Acute Graft-Versus-Host Disease

The clinical features, staging, and grading of acute GVHD are summarized in Tables 108.1 and 108.2. In a comprehensive review of patients receiving therapy for acute GVHD, Martin and colleagues[20] found that 81% had skin involvement, 54% had GI involvement, and 50% had liver involvement at the initiation of therapy. After high-intensity (myeloablative) conditioning, acute GVHD generally occurs within 14–35 days of stem cell infusion. The time of onset may depend on the degree of histocompatibility, the number of donor T cells infused, and the prophylactic regimen for GVHD. A rapid and severe form of GVHD may occur in patients with severe HLA mismatches and in patients who receive T-cell replete transplants without or with inadequate in vivo GVHD prophylaxis.[21] Although such GVHD is sometimes called "hyperacute," this term is misleading because it is pathophysiologically distinct from hyperacute rejection after solid organ allografting, which is caused by preformed antibodies. This form of GVHD, which is manifested by fever, generalized erythroderma and desquamation, and often edema, typically occurs about 1 week after stem cell infusion and may be rapidly fatal. In patients receiving standard (in vivo) GVHD prophylaxis such as a combination of cyclosporine and methotrexate, the median onset of GVHD is typically 21–25 days after transplantation; however, after in vitro T-cell depletion of the graft, the onset of GVHD symptoms may be much later.[21] Thus the findings of rash and diarrhea by 1 week after transplantation would very likely be because of ineffective prophylaxis and would be very unlikely with the use of calcineurin inhibitors or in vitro T-cell depletion of the stem cell inoculum. A less ominous syndrome of fever, rash, and fluid retention occurring in the first 1–2 weeks after stem cell infusion is the "engraftment syndrome." These manifestations may be seen with either allogeneic or autologous transplantation. Although this syndrome's pathophysiology is poorly understood, it is thought to be caused by a wave of cytokine production as the graft starts to recover. These symptoms are related to, but distinct from, the "cytokine storm"[22] of acute GVHD because there is no concomitant T-cell–mediated attack. This syndrome responds immediately to steroids in most patients, and it typically presents earlier than acute GVHD.[15]

Skin is the most commonly affected organ (Fig. 108.1). In patients receiving transplants after myeloablative conditioning, the skin is usually the first organ involved, and GVHD often coincides with engraftment. However, the presentation of GVHD is more varied following nonmyeloablative transplants or donor lymphocyte infusions.[23] The characteristic maculopapular rash can spread throughout

TABLE 108.1 Clinical Manifestations and Staging of Acute Graft-Versus-Host Disease

Organ	Clinical Manifestations	Staging
Skin	Erythematous, maculopapular rash involving palms and soles; may become confluent Severe disease: bullae	Stage 1: <25% rash Stage 2: 25%–50% rash Stage 3: generalized erythroderma Stage 4: bullae
Liver	Painless jaundice with conjugated hyperbilirubinemia and increased alkaline phosphatase	Stage 1: bili 2–3 mg/dL Stage 2: bili 3.1–6 mg/dL Stage 3: bili 6.1–15 mg/dL Stage 4: bili >15 mg/dL
Gastrointestinal tract	Upper: nausea, vomiting, anorexia Lower: diarrhea, abdominal cramps, distension, ileus, bleeding	Stage 1: diarrhea >500 mL/day Stage 2: diarrhea >1000 mL/day Stage 3: diarrhea >1500 mL/day Stage 4: ileus, bleeding

TABLE 108.2 Glucksberg Criteria for Staging of Acute Graft-Versus-Host Disease[a]

Overall Grade	Skin	Liver		Gut
I	1–2	0		0
II	1–3	1	and/or	1
III	2–3	2–4	and/or	2–3
IV	2–4	2–4	and/or	2–4

[a]See Table 108.1 for individual organ staging. Traditionally, individual organs are staged without regard to attribution. The overall grade of graft-versus-host disease, however, reflects the actual extent of graft-versus-host disease. To achieve each overall grade, skin disease, liver and/or gut involvement are required.

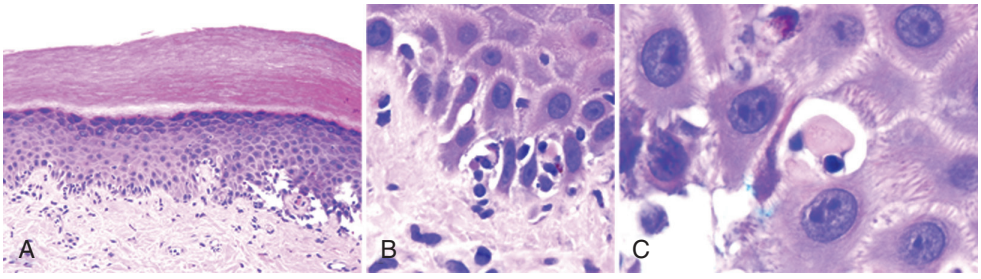

Fig. 108.1 GRAFT-VERSUS-HOST DISEASE, SKIN BIOPSY. This 40-year-old man with a history of relapsed Hodgkin lymphoma was status-postallogeneic stem cell transplant with donor lymphocyte infusion. He developed painful oral ulcers and a macular-papular rash on the arms, hand, and chest. The skin biopsy is from the palmar surface of the hand (A). It shows a scant lymphoid infiltrate in the dermis with a developing subepithelial blister *(right)*. There is basal vacuolar change with single lymphocytes in the epithelium, as well as apoptotic keratinocytes accompanied by lymphocytes (B, and detail, C). *(Courtesy Vesna Petronic-Rosic and Mark Racz, University of Chicago.)*

the rest of the body but usually spares the scalp; it is often described as feeling like a sunburn, tight or pruritic. In severe cases the skin may blister and ulcerate.[24] Histologic confirmation is critical to rule out drug reactions, viral infections, etc. Apoptosis at the base of dermal crypts is characteristic. Other features include dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes, and dermal perivascular lymphocytic infiltration.[25]

GI tract involvement of GVHD may present as nausea, vomiting, anorexia, diarrhea, and/or abdominal pain.[26] It is a panintestinal process, often with differences in severity between the upper and lower GI tracts. Gastric involvement gives rise to postprandial vomiting that is not always preceded by nausea. Although gastroparesis is seen after bone marrow transplant, it is usually not associated with GVHD. The diarrhea of GVHD is secretory; significant GI blood loss may occur as a result of mucosal ulceration and is associated with a poor prognosis.[27] In advanced disease, diffuse, severe abdominal pain, and distension is accompanied by voluminous diarrhea (>2 liters/day).[19,28]

Radiologic findings of the GI tract include luminal dilatation with thickening of the wall of the small bowel and air/fluid levels suggestive of an ileus on abdominal flat plates or small bowel series. Abdominal computed tomography may show the "ribbon" sign of diffuse thickening of the small bowel wall.[24] Little correlation exists between the extent of disease and the appearance of mucosa on endoscopy, but mucosal sloughing is pathognomonic for severe disease.[29] Nevertheless, some studies have shown that antral biopsies correlate well with the severity of GVHD in the duodenum and in the colon even when the presenting symptom is diarrhea.[29] Histologic analysis of tissue is imperative to establish the diagnosis. The histologic features of GI GVHD are the presence of apoptotic bodies in the base of crypts, crypt abscesses, crypt loss, loss of Paneth cells, and flattening of the surface epithelium.[28,30,31]

Liver function test abnormalities are common after bone marrow transplant and occur secondary to venoocclusive disease, drug toxicity, viral infection, sepsis, iron overload, and other causes of extrahepatic biliary obstruction.[12] The exact incidence of hepatic GVHD is unknown because many patients do not undergo liver biopsies. The development of jaundice or an increase in the alkaline phosphatase and bilirubin may be the initial features of acute GVHD of the liver. The histologic features of hepatic GVHD are endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis, and bile duct destruction and loss.[19,32]

Other Organs

Whether GVHD affects organs other than the classic triad of skin, liver, and gut has remained a matter of debate, although numerous reports suggest additional organ manifestations. The most likely candidate is the lung. Lung toxicity, including interstitial pneumonitis and diffuse alveolar hemorrhage, may occur in 20% to 60% of allogeneic transplant recipients but in fewer autologous transplant recipients. Causes of pulmonary damage other than GVHD include engraftment syndrome (see earlier), infection, radiation pneumonitis, and chemotherapy-related toxicity (e.g., methotrexate, busulfan).[21,33] One retrospective analysis failed to link severe pulmonary complications to clinical acute GVHD per se.[34] The mortality caused by pneumonia increases with the severity of GVHD, but this association may be related to increased immunosuppressive therapy.[21] A histopathologic signature of lymphocytic bronchitis has been associated with GVHD,[33] although not always.

Despite the ability of kidneys and hearts to serve as targets of transplant rejection, there is no convincing evidence for direct renal or cardiac damage from acute GVHD that is not secondary to drugs or infection. Similarly, neurologic complications are also common after transplantation but most can be attributed to drug toxicity, infection, or vascular insults.

Differential Diagnosis

Acute GVHD ought to be distinguished from any process that causes a constellation of fever, erythematous skin rash, and pulmonary edema that may occur during neutrophil recovery and has been termed engraftment or capillary leak syndrome.[35,36] In allogeneic transplant recipients distinction from acute GVHD is difficult. Engraftment syndrome is thought to reflect cellular and cytokine activities during early recovery of (donor-derived) blood cell counts and/or homeostatic proliferation of lymphocytes, but a precise delineation of the activated cells and mechanisms has not been demonstrated. Engraftment syndrome may be associated with increased mortality, primarily but not exclusively from pulmonary failure. Corticosteroid therapy may be effective particularly for the treatment of pulmonary manifestations.[37] Skin rashes may reflect delayed reactions to the conditioning regimen, antibiotics, or infections; furthermore, histopathologic skin changes consistent with acute GVHD can be mimicked by chemoradiotherapy and drug reactions.[21,38] Diarrhea can be a consequence of total-body irradiation (TBI), viral infection (especially with cytomegalovirus and other herpes viruses), parasitic infection, *Clostridium difficile* infection, nonspecific gastritis, narcotic withdrawal, and drug reactions: all of which mimic GVHD of the gut. Liver dysfunction can be caused by parenteral nutrition, venoocclusive disease, and viral or drug-induced hepatitis.

Genetic Basis of Graft-Versus-Host Disease

The graft-versus-host (GVH) reaction was first noted when irradiated mice were infused with allogeneic marrow and spleen cells.[39] Although mice recovered from radiation-induced injury and marrow aplasia, they subsequently died with "secondary disease,"[39] a phenomenon subsequently recognized as acute GVHD. Three requirements for the development of GVHD were formulated by Billingham.[4] First, the graft must contain immunologically competent cells, now recognized as mature T cells. In both experimental and clinical allogeneic HCT, the severity of GVHD correlates with the number of donor T cells transfused.[40,41] The precise nature of these cells and the mechanisms they use are now understood in greater detail (see later). Second, the recipient must be incapable of rejecting the transplanted cells (i.e., immunocompromised). After allogeneic HCT, the recipient is typically immunosuppressed by chemotherapy and/or radiotherapy before the hematopoietic cell infusion.[42] Third, the recipient must express tissue antigens that are not present in the transplant donor. Thus Billingham's third postulate stipulates that the GVH reaction occurs when donor immune cells recognize disparate host antigens.[4] These differences are governed by the genetic polymorphisms.[42]

HLA Matching

Recognition of alloantigens depends on the match with the presenting major histocompatibility molecule.[43–45] In humans, the MHC is governed by the HLA antigens that are encoded by the MHC gene complex on the short arm of chromosome 6 and can be categorized as class I, II, and III. Class I antigens (HLA-A, HLA-B, and HLA-C) are expressed on almost all cells of the body.[46] Class II antigens (DR, DQ, and DP) are primarily expressed on hematopoietic cells, although their expression can also be induced on other cell types following inflammation.[46] The incidence of acute GVHD is directly related to the degree of MHC mismatch.[42] The role of HLA mismatching of cord blood (CB) donors is more difficult to analyze compared with unrelated donor HCT, because allele typing of CB units for HLA-A, HLA-B, HLA-C, DRB1, and DQB1 is not routinely performed.[47] Nonetheless, the total number of HLA disparities between the recipient and the CB unit has been shown to correlate with risk for acute GVHD as the frequency of severe acute GVHD is lower in patients transplanted with HLA-matched (6/6) CB units.[47–49]

Minor Histocompatibility Antigens

In most clinical allogeneic transplants where MHC of donor and recipient are matched, donor T cells recognize MHC-bound peptides derived from the protein products of polymorphic genes (MiHAs) that are present in the host but not in the donor.[9,50–55] Substantial numbers (50%) of patients will develop acute GVHD despite receiving HLA-identical grafts as well as optimal

postgrafting immune suppression.[9,42,56] MiHAs are widely but variably expressed in different tissue,[51,56] which is one possible explanation for the unique target organ distribution in GVHD. Many MiHAs such as HA-1 and HA-2 are expressed on hematopoietic cells, which may be one reason for the host immune system to be a primary target for the GVH response, and helps explain the critical role of direct presentation by professional recipient antigen-presenting cells (APCs) in the GVH response.[57] By contrast, other MiHAs such as H-Y and HA-3 are expressed ubiquitously.[56] MiHAs do not all equally induce lethal GVHD but show hierarchic immunodominance.[58,59] Furthermore, the difference in a single immunodominant MiHA is insufficient to elicit GVHD in murine models, even though a single MiHA can elicit T-cell–mediated damage in a skin explant model.[60,61] However, the role of specific MiHAs that are able to induce clinical GVHD has not been systematically evaluated in large groups of patients.[62]

Other Non-HLA Genes

Genetic polymorphisms in several non-HLA genes such as in killer-cell immunoglobulin-like receptors (KIRs), cytokines, and nucleotide-binding oligomerization domain containing 2 (NOD2) genes have recently been shown to modulate the severity and incidence of GVHD.

KIRs on natural killer (NK) cells that bind to the HLA class I gene products are encoded on chromosome 19. Polymorphisms in the transmembrane and cytoplasmic domains of KIRs govern whether the receptor has inhibitory (such as KIR2DL1, 2DL2, 2DL3, and 3DL1) or activating potential. Two competing models have been proposed for HLA-KIR allorecognition by donor NK cells following allogeneic HCT: the "mismatched ligand" and the "missing ligand" models.[5,63–66] Both models are supported by several clinical observations, albeit in patients receiving very different transplant and immunosuppressive regimens (see Chapters 20 and 102).[64,67–69]

Proinflammatory cytokines involved in the classic cytokine storm of GVHD cause pathologic damage to target organs, such as the skin, liver, and GI tract (see later).[22] Several cytokine gene polymorphisms in both recipients and donors have been implicated. Specifically, tumor necrosis factor (TNF) polymorphisms (TNFd3/d3 in the recipient, TNF863 and TNF857 in donors and/or recipients and TNFd4, TNF-α-1031C, and tumor necrosis factor receptor (TNFR) II-196R in the donors) have been associated with an increased risk for acute GVHD and transplant-related mortality (TRM).[70,71] The three common haplotypes of the interleukin (IL)-10 gene promoter region in recipients, representing high, intermediate, and low production of IL-10, have been associated with severity of acute GVHD following HLA-matched sibling donor allogeneic HCT.[72] By contrast, smaller studies have found neither IL-10 nor TNF-α polymorphisms to be associated with GVHD following HLA-mismatched cord blood transplantation.[71,73] Interferon-gamma (IFN-γ) polymorphisms of the 2/2 genotype (high IFN-γ production) and 3/3 genotype (low IFN-γ production) have been associated with decreased or increased acute GVHD, respectively.[71,74]

NOD2/caspase-activating recruitment domain 15 (*CARD15*) gene polymorphisms in both the donors and recipients were recently shown to have a striking association between GI GVHD and overall mortality following related and unrelated donor allogeneic HCT.[75] Several of the associations with non-HLA polymorphisms will need to be confirmed in larger and more diverse populations. Furthermore, it is likely that the importance of non-HLA gene polymorphisms in GVHD will differ depending on the donor source (related versus unrelated), HLA disparity (matched versus mismatched), graft source (CB versus bone marrow [BM] versus peripheral blood stem cells), and the intensity of the conditioning.

PATHOPHYSIOLOGY OF ACUTE GRAFT-VERSUS-HOST DISEASE

It is helpful to remember two important principles when considering the pathophysiology of acute GVHD. First, acute GVHD represents exaggerated but normal inflammatory responses against foreign antigens (alloantigens) that are ubiquitously expressed in a setting where they are undesirable. The donor lymphocytes that have been infused into the recipient function appropriately, given the foreign environment they encounter. Second, donor lymphocytes encounter tissues in the recipient that have been often profoundly damaged. The effects of the underlying disease, prior infections, and the intensity of conditioning regimen all result in substantial changes not only in the immune cells but also in the endothelial and epithelial cells. Thus the allogeneic donor cells rapidly encounter not simply a foreign environment, but one that has been altered to promote the activation and proliferation of inflammatory cells. Therefore the pathophysiology of acute GVHD may be considered a distortion of the normal inflammatory cellular responses that, in addition to the absolute requirement of donor T cells, involves multiple other innate and adaptive cells and mediators.[76] The development and evolution of acute GVHD can be conceptualized in three sequential phases (Fig. 108.2) to provide a unified perspective on the complex cellular interactions and inflammatory cascades that lead to acute GVHD: (1) activation of the APCs; (2) donor T-cell activation, differentiation, and migration; and (3) effector phase.[76] It is important to note that this three-phase description permits a unified perspective on GVHD biology but it is not meant to suggest that all three phases are of equal importance or that GVHD occurs in a stepwise and sequential manner. The spatiotemporal relationships among these biologic processes, depending on the context, are likely to vary and their relevance to the induction, severity, and maintenance of GVHD may depend on the factors cited earlier.

Phase 1: Activation of Antigen-Presenting Cells

The earliest phase of acute GVHD is initiated by the profound damage caused by the underlying disease and infections and further exacerbated by bone marrow transplantation (BMT) conditioning regimens (which include TBI and chemotherapy) that are administered even before the infusion of donor cells.[77–81] This first step results in activation of the APCs.[7] Specifically, damaged host tissues respond with multiple changes, including the secretion of proinflammatory cytokines, such as TNF-α, IL-1 and IL-6 described as the cytokine storm.[79,80,82,83]

Such changes increase expression of adhesion molecules, costimulatory molecules, MHC antigens, and chemokine gradients that alert the residual host and the infused donor immune cells.[80] These "danger signals" activate host APCs.[84,85] Damage to the GI tract from the conditioning is particularly important in this process because it allows for systemic translocation of immunostimulatory microbial products such as lipopolysaccharide (LPS) that further enhance the activation of host APCs, and the secondary lymphoid tissue in the GI tract is likely the initial site of interaction between activated APCs and donor T cells.[80,86,87] This scenario accords with the observation that an increased risk for GVHD is associated with intensive conditioning regimens that cause extensive injury to epithelial and endothelial surfaces with a subsequent release of inflammatory cytokines and increases in expression of cell surface adhesion molecules.[80,81] The relationship among conditioning intensity, inflammatory cytokine, and GVHD severity has been supported by elegant murine studies.[82] Furthermore, the observations from these experimental studies have led to two recent clinical innovations to reduce clinical acute GVHD: (1) reduced intensity conditioning to decrease the damage to host tissues and thus limit activation of host APC and (2) KIR mismatches between donor and recipients to eliminate the host APCs by the alloreactive NK cells.[65,88]

Host-type APCs that are present and have been primed by conditioning are critical for the induction of this phase; recent evidence suggests that donor-type APCs exacerbate GVHD, but in certain experimental models, donor-type APC chimeras also induce GVHD.[85,89–91] In clinical situations, if donor-type APCs are present in sufficient quantity and have been appropriately primed, they too might play a role in the initiation and exacerbation of GVHD.[92–94] Among the cells with antigen-presenting capability, dendritic cells

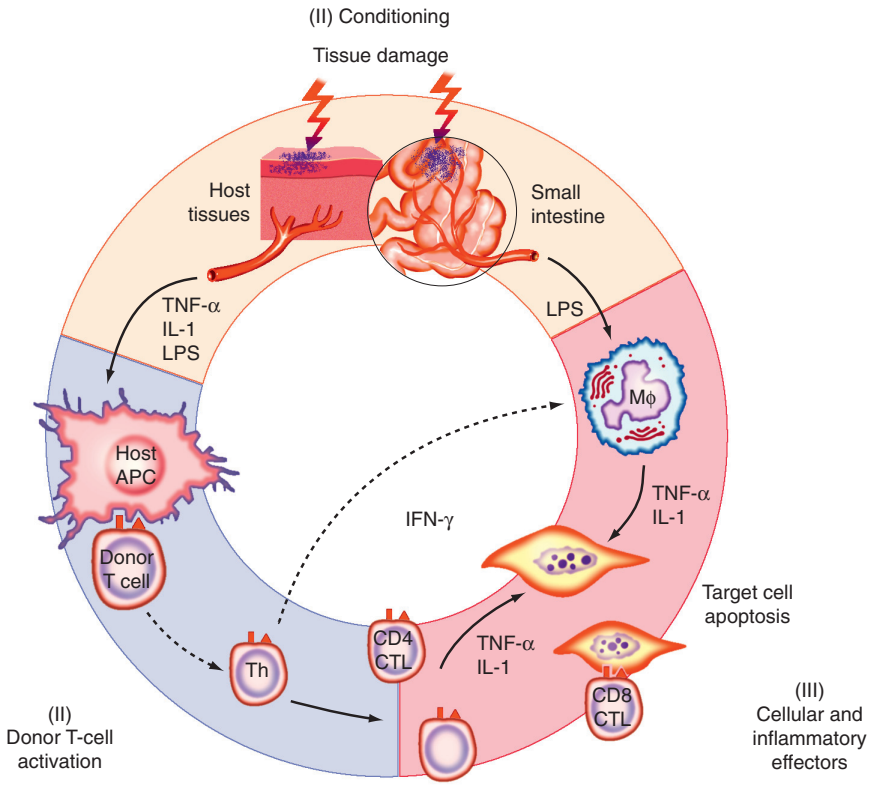

Fig. 108.2 PATHOPHYSIOLOGY OF GRAFT-VERSUS-HOST DISEASE. During step 1, irradiation and chemotherapy both damage and activate host tissues, including intestinal mucosa, liver, and the skin. Activated cell hosts then secrete inflammatory cytokines (e.g., TNF-α and IL-1), which can be measured in the systemic circulation. The cytokine release has important effects on APCs of the host, including increased expression of adhesion molecules (e.g., ICAM-1, VCAM-1) and of MHC class II antigens. These changes in the APCs enhance the recognition of host MHC and/or minor H antigens by mature donor T cells. During step 2, donor T-cell activation is characterized by proliferation of GVHD T cells and secretion of the Th1 cytokines IL-2 and IFN-γ. Both of these cytokines play central roles in clonal T-cell expansion, induction of CTL and NK cell responses, and the priming of mononuclear phagocytes. In step 3, mononuclear phagocytes primed by IFN-γ are triggered by a second signal such as endotoxin LPS to secrete cytopathic amounts of IL-I and TNF-α. LPS can leak through the intestinal mucosa damaged by the conditioning regimen to stimulate gut-associated lymphoid tissue or Kupffer cells in the liver; LPS that penetrates the epidermis may stimulate keratinocytes, dermal fibroblasts, and macrophages to produce similar cytokines in the skin. This mechanism results in the amplification of local tissue injury and further production of inflammatory effectors such as nitric oxide, which, together with CTL and NK effectors, leads to the observed target tissue destruction in the stem cell transplant host. CTL effectors use Fas/FasL, perforin/granzyme B, and membrane-bound cytokines to lyse target cells. *APC,* Antigen-presenting cell; *CTL,* cytotoxic T lymphocyte; *GVHD,* graft-versus-host disease; *ICAM,* intercellular adhesion molecule; *IFN,* interferon; *IL,* interleukin; *LPS,* lipopolysaccharide; *MHC,* major histocompatibility complex; *NK,* natural killer; *TNF,* tumor necrosis factor; *VCAM,* vascular cell adhesion molecule.

(DCs) are the most potent and play an important role in the induction of GVHD.[95] Experimental data suggest that GVHD can be regulated by qualitatively or quantitatively modulating distinct DC subsets.[96–101] Langerhans cells were also shown to be sufficient for the induction of GVHD when all other APCs were unable to prime donor T cells, although the role for Langerhans cells when all APCs are intact is dispensable.[102,103] Studies have yet to define roles for other DC subsets. In one clinical study persistence of host DC after day 100 correlated with the severity of acute GVHD, whereas elimination of host DCs was associated with reduced severity of acute GVHD.[93] The allostimulatory capacity of mature monocyte-derived DCs (mDCs) after reduced-intensity transplants was lower for up to 6 months compared with the mDCs from myeloablative transplant recipients, thus suggesting a role for host DCs and the reduction in danger signals secondary to less intense conditioning in acute GVHD.[104] Nonetheless, this concept of enhanced host APC activation explains a number of clinical observations such as increased risks for acute GVHD associated with advanced-stage malignancy, conditioning intensity, and histories of viral infections. However, recent data suggest that even in the absence of all host hematopoietic derived APCs, GVHD can still be initiated by host nonhematopoietic cells.[105] The exact nature of the host nonhematopoietic cells that can initiate GVHD and the context under which they may play a more dominant role remains to be understood. Moreover when all of host $CD11c^+$ DCs are eliminated, the severity of GVHD was found to be enhanced demonstrating a role for host DCs in mitigating GVHD severity.[106,107] Furthermore, a specific subset of host DCs, the $CD8^+$ DCs might mitigate GVHD severity.[108,109] By contrast donor-derived DCs, specifically, $CD103^+CD11b^-$ DCs migrate from the colon and markedly enhance alloantigen presentation within the mesenteric lymph nodes

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