

Role of dendritic cells and chemokines in acute graft-versus-host disease

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1. ABSTRACT

Graft-versus-host disease (GVHD) is a major complication of allogeneic bone marrow transplantation. GVHD is caused by donor T cells that recognize and react to recipient histocompatibility differences, resulting in significant morbidity and mortality. The pathophysiology of GVHD is complex, which occurs in three phases: induction phase, activation phase and effector phase. Numerous studies have demonstrated that GVHD involves multiple inflammatory cells and cytokines, in particular of antigen presenting cells, chemokines and T cell subsets. This review will discuss roles of a special antigen presenting cell: dendritic cell and chemokines in T cell-mediated acute GVHD.

2. INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many malignant and nonmalignant disorders (1). However, a major adverse reaction of allogeneic HSCT, graft-versus-host disease (GVHD), remains a lethal complication that limits its wider application (2). GVHD was first noted when irradiated mice were infused with allogeneic marrow and spleen cells (2). Although mice recovered from radiation injury and marrow aplasia, they subsequently died with 'secondary disease', a syndrome consisting of diarrhea, weight loss, skin changes, and liver abnormalities (2). This phenomenon was recognized as GVHD. GVHD occurs when transplanted donor T cells recognize and react

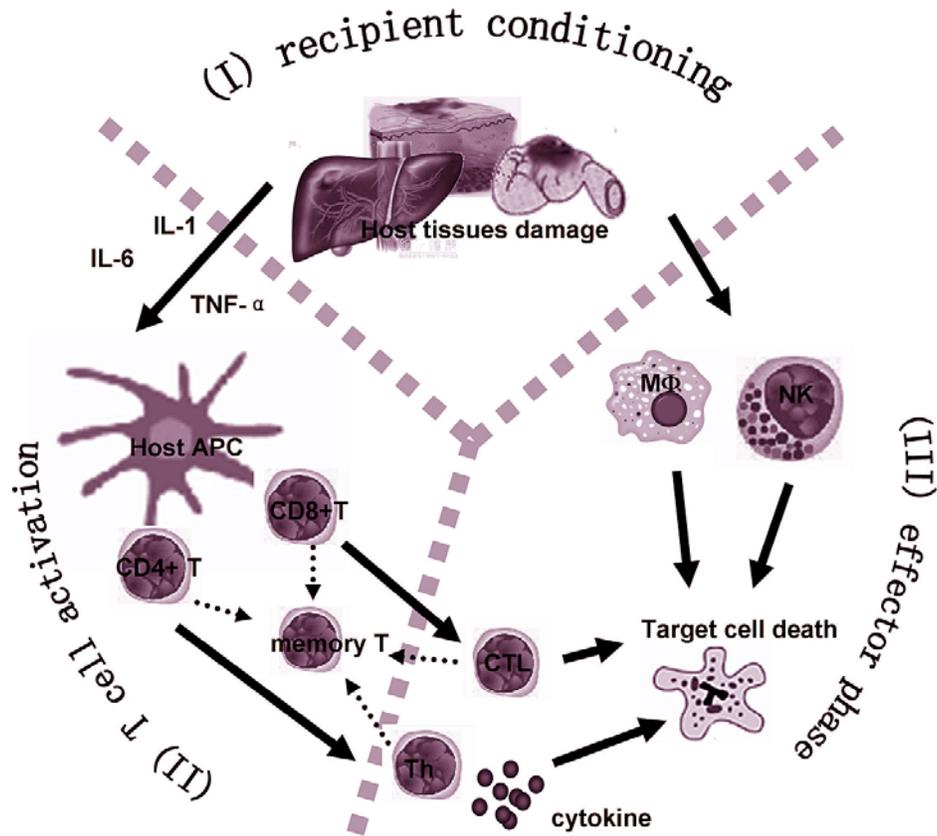


Figure 1. Acute GVHD pathophysiology. Pathologic mechanisms of acute GVHD as three sequential phases: I, recipient conditioning; II, T cell activation, differentiation, and migration; III, inflammatory effectors.

to recipient histocompatibility antigens and subsequently mediate host tissue injuries, resulting in significant morbidity and mortality (3). GVHD may occur within two to six weeks following allogeneic HSCT (i.e. acute GVHD), and primarily affects the skin, liver and the gastrointestinal tract. It has been a major obstacle to the clinical application of HSCT (4).

Three factors are required for the development of GVHD (5). First, the graft must contain a sufficient number of immunologically competent cells, which are now recognized as mature T cells. Second, the host should have important transplantation isoantigens lacking in the graft. Hence, the host appears foreign to the graft and is capable of stimulating donor cells antigenically. Third, the host immune system must be incapable of mounting an effective immune response against the graft, at least for a sufficient time for the latter to manifest its immunological competence. Acute GVHD can be conceptualized as a three-phase model that elucidates the three major processes that lead to GVHD (6). The first phase involves tissue damage related to the disease status and transplant conditioning regimens, leading to the production of inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha (6). During this phase, dendritic cells (DCs) that are the most potent specialized antigen presenting cells (APCs) are activated to initiate

alloreactive T cell responses. The second phase consists of donor T cell activation, proliferation and functional differentiation into effector T cells (6). Donor T cells recognize allogeneic antigens presented by host APCs and are further activated by cosignals expressed by APCs (7). At the final phase host-reactive effector T cells are recruited by chemokines into GVHD target organs, resulting in host tissue injury (6). Chemokines are small proteins, secreted by various cells, such as macrophages, DCs, activated T cells, and endothelial cells. Cells expressing chemokine receptors are attracted to the sites according to the concentration gradient of the chemokines. Influx of inflammatory cells with the ability to produce more chemokines attract more inflammatory cells such as macrophages, NK cells, granulocytes, and activated T cells, etc., which initiates the next cycle of inflammation mediating host tissue injury.

3. PHASE 1: CONDITIONING REGIMEN

The transplant conditioning regimen which includes total body irradiation and/or chemotherapy is important in the pathogenesis of acute GVHD because it can damage the host tissues, including the intestinal mucosa, liver, and other tissues (Figure 1) (8, 9). The transplant conditioning regimen is important in the pathogenesis of acute GVHD because it can damage the

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host tissues, including the intestinal mucosa, liver, and other tissues. Activated host cells respond with multiple changes, including the secretion of proinflammatory cytokines, such as IL-1 and TNF- α , which increase the expression of adhesion molecules, costimulatory molecules, major histocompatibility complex (MHC) antigens, and chemokines (10, 11). Such 'danger signals' expressed by injured host tissues are critical for the activation of host DCs and are necessary for the initiation of the alloreaction (12). In addition, conditioning leads to rapid and transient chemokine up-regulation in GVHD target tissues ahead of GVHD-associated T cell infiltration, which is influenced by the time since conditioning, conditioning intensity, and recipient strain (13). Therefore, injury to the host is important in the initiation of the clinical syndrome of acute GVHD.

3.1. Host DCs initiate acute GVHD

A seminal event in GVHD initiation is the activation of host APCs. Damage to the gastrointestinal tract from the conditioning allows for immunostimulatory microbial products such as lipopolysaccharide that further enhance activation of host APCs (10). Both host and cross-presenting donor APCs are involved in GVHD. Data from recent studies suggest that donor APCs can exacerbate GVHD, and in certain experimental models can also induce GVHD (14-16). In clinical situations, if donor APCs are present in sufficient quantity and have been appropriately primed, they also might play a role in the initiation and exacerbation of GVHD (17, 18). However, host APCs that are primed by preparative conditioning are particularly important in the induction of GVHD (19). Recipients with functionally defect APCs show significant low risk of developing CD4⁺ T cell- or CD8⁺ T cell-mediated GVHD than wild-type recipients, suggesting a predominant role of direct presentation over cross-presentation of antigens in GVHD (20). This implies that selective targeting of host DCs may be a promising strategy to prevent GVHD.

3.2. Elimination of host DCs

Depleting host DCs before the conditioning regimen can promote tolerance and reduce GVHD without the need for prolonged T cell-targeted immunosuppression (21). Such an approach, perhaps using toxin-conjugated or radiolabeled antibodies, could expand the range of diseases treated with allogeneic BMT. Evidence shows that high circulating DC levels significantly increase the risk for relapse and acute GVHD and predict death after allogeneic HSCT (22, 23). 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 (18). Anti-CD52 antibody administration depletes both host and donor T cells when used in preparative regimens for allogeneic transplantation. CD52 has also been reported to be expressed on DCs, and *in vivo* pretransplant Campath-1G (anti-CD52) caused a rapid depletion of host circulating DCs (24). Anti-CD52 abrogates GVHD not only by T cell depletion, but also by removing monocyte-derived DCs (moDCs) and their precursors (25). This would mitigate moDC phagocytosis and presentation of host antigens to donor T cells in the inflammatory pretransplantation

environment, thereby limiting GVHD. Later after transplantation, in a less inflammatory environment, it may allow all the DCs to exert a proactive role in graft-versus-tumor (GVT) reactions and immune reconstitution, thus providing a separation of the deleterious from the beneficial graft-host interactions at the level of antigen presentation, rather than solely at the level of T cells.

3.3. Immature DCs

The ability of DCs to induce immunity or tolerance appears to be related to their state of functional maturation. Like other nonproliferating cells, DCs are resistant to myeloablative regimens that target cycling cells, including total body irradiation. The cytokine storm associated with pretransplantation disease status and preparative conditioning irradiation can result in rapid activation and maturation of host DCs (26). In contrast to mature DCs (mDCs) that stimulate T cells through high expression of MHC II and costimulatory molecules, immature DCs (iDCs) can inhibit T cell responses (27, 28). The regulation of DC growth and maturation can be studied using *in vitro* culture techniques that facilitate efforts to maximize the tolerogenic potential of donor DCs, which may lead to improved strategies for the enhancement of allograft survival. It has been observed that using transforming growth factor (TGF)- β 1 in conjunction with granulocyte-macrophage colony stimulating factor inhibits DC maturation (29). TGF- β 1-treated DCs, deficient in surface costimulatory molecules, inhibit alloantigen-specific T cell responses thereby inducing graft hyporeactivity and prolonging graft survival through aspects of iDC including direct killing of T cells, induction of T cell anergy or stimulation of T regulatory (T_{reg}) cell generation. The proteasome inhibitor bortezomib, which has been used in the treatment of GVHD in animal models, inhibits the generation of mDCs by blunting inflammation-induced DC maturation (30, 31). As the maturation stages of DCs determine whether they prime or tolerize T cells, a potential role of bortezomib has been suggested in modulating immune responses through inhibition of DC maturation. Also it has been found that using anti-P-selectin lectin-EGF domain monoclonal antibody that blocks the adhesion of P-, E-, and L-selectin, can interfere functional maturation of iDCs (32).

3.4. Myeloid DCs and plasmacytoid DCs

There are two distinct subtypes of DC: the myeloid DC (MDC) and the plasmacytoid DC (PDC). MDCs, derived from myeloid bone marrow precursors, function primarily in uptake, processing and antigen presentation; while PDCs, derived from lymphoid precursors, are the main producers of type I interferons (33). Most work on peripheral tolerogenic properties of DC has been performed using 'classic' MDCs, for their immature forms can induce T cell tolerance. Moreover, evidences have accumulated indicating that PDCs also have the potential abilities (34, 35). Freshly isolated mouse PDC precursors have poor stimulatory capacity for naïve allogeneic antigen-specific T cells (36-38). PDC precursors isolated from human peripheral blood can induce antigen-specific anergy in CD4⁺ T cells. Moreover it has been demonstrated that immature mouse PDCs induce T_{reg} cells *ex vivo* (39-41). In human, PDCs activated by

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phosphorothioated CpG-oligodeoxynucleotides prime CD4⁺ T cells to produce a T_{reg} cell profile (42). In addition, human naïve CD8⁺ T cells primed *in vitro* with CD40L (CD154)-activated, allogeneic PDCs differentiate into IL-10^{hi}IFN-γ^{lo}-producing T_{reg} cells (43). In clinical observation, it is reported that use of granulocyte colony-stimulating factor could expand donor peripheral blood stem cells and induce *in vivo* mobilization of PDCs to decrease acute GVHD, which suggested that donor PDCs have a role in GVHD (17).

3.5. Regulatory DCs

Clinical applications of normal DCs may not be suitable for the treatment of immunopathogenic diseases, because they likely change into mDCs under inflammatory conditions (44). Sato *et al.* established an immunotherapeutic method involving DCs with potent immunoregulatory property (designated as regulatory DCs, rDCs) for acute GVHD in allogeneic BMT in murine models (45). Expressing high levels of MHC molecules and extremely low levels of costimulatory molecules, rDCs prevent acute GVHD through controlling the activity of alloreactive T cells. Thus a single injection of rDCs following allogeneic BMT controlled the ability of the transplanted T cells to induce acute GVHD, indicating rDCs may be useful for the treatment of acute GVHD (46-48).

4. PHASE 2: DONOR T CELL ACTIVATION, DIFFERENTIATION AND MIGRATION

The interaction between infused donor T cells and the primed APCs leads to initiation of the second phase of acute GVHD. This phase includes antigen recognition, activation, proliferation, differentiation and migration of these alloreactive donor T cells.

When a mature T cell is suddenly placed into the circulation of an allogeneic host, it will travel through the bloodstream in a fashion similar to its journey in the donor. Before antigen recognition and activation, a T cell must roll along the endothelial surfaces. If the T cell receptor (TCR) recognizes any particular antigen (CD4⁺ cell interacts with the MHC class II molecules, whereas CD8⁺ cell interacts with MHC class I antigens), that results in activation of the T cell. Adhesion molecules then firmly anchor the T cell and prevent any further rolling. The greater the disparity between donor and recipient MHC, the greater response of the T cells will there be. After allogeneic T cells enter the recipient blood circulation through high endothelial venules (HEVs), they home into the secondary lymphoid tissues where they become activated and proliferate. Some of them are even eliminated by the process of clonal deletion in an apparent effort to regulate the severity of the immune response. Activated alloreactive T cells then migrate from the secondary lymphoid tissue into the peripheral target organs to initiate the inflammatory process, and finally cause various clinical symptoms.

4.1. PDCs and MDCs trafficking to the secondary lymphoid tissues in different patterns

In vivo, MDC precursors exit the bone marrow, entering the blood and finally in every peripheral tissues.

There they uptake antigens and exit in a “semi-mature” state and traffic via afferent lymphatics to T cell areas of secondary lymphoid tissues, where they promote T cell tolerance or induce T cell activation and proliferation (49). PDCs seem to follow a different pattern. PDC precursors appear to exit the blood via HEVs for direct entrance into secondary lymphoid tissues (50). Currently, there is no evidence that PDC precursors migrate into peripheral tissues in response to the CC chemokines, which believed to recruit bone marrow- and blood-derived MDCs (49). Freshly isolated PDC precursors express CCR7, which will not become functional until PDC maturation. However, MDCs do not express this CC chemokine receptor until maturation (51). Inhibition of the CCR7 pathway may represent an approach to GVHD prevention (52). It is suggested that TGF-β1 can not only inhibit the expression of CCR7 in DCs and DC precursors derived from hematopoietic progenitor cells, but also inhibit the migration of these cells in response to macrophage inflammatory protein (MIP)-3 beta (one of the ligands for CCR7) (53). Compared with MDCs, the unique migratory pattern of PDCs appears to rely on the expression of CD62L (L-Selectin) by human PDC precursors and CXCR3 and CD62E (E-Selectin) by mouse PDC precursors (50, 54, 55).

4.2. Antigen presentation to T cells

Although it now seems intuitive that alloreactive donor T cells mediate GVHD, this was not proven until the late 1970s by Korngold and Sprent, who later demonstrated the need for antigen processing and presentation of host antigens to donor T cells (56, 57). T cell-DC interaction is important not only because DCs are critical to the initiation of T cell responses to both MHC and minor histocompatibility antigens (miHAs), but also because stable T cell-DC interactions may precede the development of both tolerance and immunity (58). After allogeneic HSCT, both host and donor DCs are present in secondary lymphoid organs. The TCR on donor T cells can recognize alloantigens either on host DCs by direct presentation or on donor DCs by indirect presentation (7, 59). In direct presentation, donor T cells recognize either the peptide bound to allogeneic MHC molecules or the allogeneic MHC molecules without peptide (Figure 2). During indirect presentation, donor T cells recognize miHAs, which are peptides derived from polymorphic genes unique to the host and are presented by shared MHC molecules in the setting of matched allotransplants. In humans, most cases of acute GVHD develop when both host DCs and donor DCs are present in the peripheral blood after allogeneic HSCT, though host DCs may play a critical role in inducing GVHD across the miHA mismatch (7). It has been suggested recently that presentation of distinct target antigens by host APCs and donor APCs might play a differential role in mediating target organ damage (60, 61).

4.3. Host APCs in the activation and effector phases

Host APCs are required for both the T cell activation and the effector phases of acute GVHD (14). Tissue-specific depletion of hepatic and splenic APCs by systemic administration of liposomal clodronate significantly reduces the recruitment of activated allogeneic

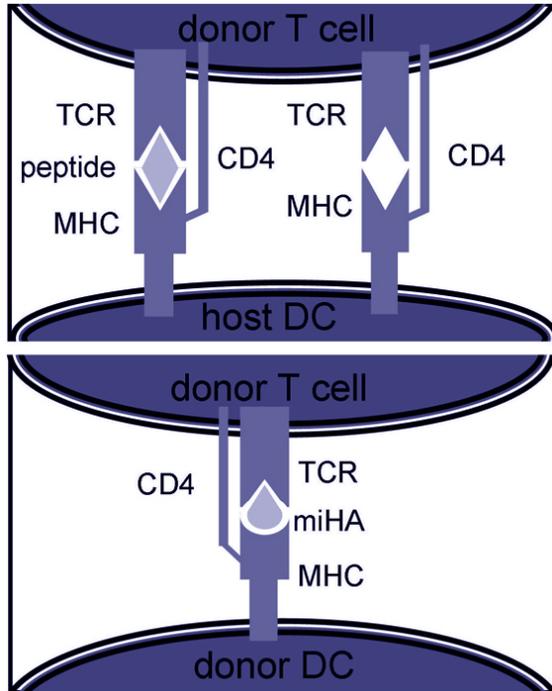


Figure 2. Antigen presentation to donor T cells. Diagram of donor T cells interacting with host and donor DCs: The TCR on donor T cells can recognize alloantigens either on host DCs by direct presentation or on donor DCs by indirect presentation. In direct presentation, donor T cells recognize either the peptide bound to allogeneic MHC molecules or the allogeneic MHC molecules without peptide. In indirect presentation, donor T cells recognize miHAs, which are peptides derived from polymorphic genes unique to the host and are recognized because they are presented by shared MHC molecules in the setting of matched allotransplants. In humans, host DCs play a critical role in inducing GVHD across the miHA mismatch.

CD8⁺ T cells into the livers of recipient mice (62). This selective APC depletion also results in the inhibition of acute GVHD, but this effect is largely confined to the liver, where resident APCs have been depleted. Partial APC depletion and GVHD amelioration result in partially improved survival of liposomal clodronate-treated mice. These results indicate that tissue-resident APCs play an important role in controlling the local recruitment of alloreactive donor T cells and the subsequent development of acute GVHD. However, it is not yet known which subsets of APCs play a dominant role in recruiting/retaining activated CD8⁺ T cells to GVHD target tissues, and by what molecular mechanisms this recruitment/retention process occurs. Further understanding the molecular basis by which host tissue APCs interact with allogeneic CD8⁺ T cells to mediate acute GVHD in the target tissues may identify promising targets for the development of novel strategies for GVHD therapy.

4.4. Chemokines and T cell migration

Donor T cells migrate to the secondary lymphoid tissues, recognize alloantigens on host/donor APCs, and

become activated. They then exit the secondary lymphoid tissues and traffic to the target organs and finally cause tissue damage (63). Migration of donor T cells into GVHD target organs plays a critical role in the development of GVHD and chemokines and their receptors are important molecules involved in this process (64). Several studies have demonstrated up-regulation of proinflammatory chemokines such as CCL2, CCL3, CCL4, CCL5 and CXCL9, CXCL10, and CXCL11 in lymphoid tissues within 3 days after transplantation, suggesting that after activation, alloreactive T cells may respond to proinflammatory chemokines to recirculate to these sites during GVHD (65). Expression of CXCL9, CXCL10, and CXCL11 preceded that of other chemokines (66). Expression of all chemokines increased earlier in spleen than in liver and lung, consistent with earlier expansion of donor cells at that site (67). The expression of CCR2 on donor derived CD8⁺ T cells is relevant for the control of CD8⁺ T cell migration and development of GVHD, since recipients of CCR2 deficient (CCR2^{Δ/Δ}) CD8⁺ T cells developed less gut and liver damage (68). Assessment of donor CD8⁺ T cell target organ infiltration revealed that CCR2^{Δ/Δ} CD8⁺ T cells had an intrinsic migratory defect to the gut and liver. Interestingly, the GVT effect mediated by CCR2^{Δ/Δ} CD8⁺ T cells was preserved, which suggests that interference with T cell migration by blockade of CCR2 signaling can separate GVHD from GVT activity. The coordinated expression of chemokines and receptors may be important in the directed migration of alloreactive T cells during GVHD. Transfer of CCR5 deficient (CCR5^{Δ/Δ}) donor cells can enhance or diminish T cell migration into specific GVHD target organs depending on whether the recipient has received conditioning therapy (65). Transfer of CCR5^{Δ/Δ} donor cells to nonconditioned haploidentical recipients resulted in reduced donor cell infiltration in hepatic and lymphoid tissues than to conditioned hosts. This suggests that targeting CCR5 will only be effective clinically in the absence of myeloablative conditioning therapy. Additionally, CCR5^{Δ/Δ} T cells have enhanced migration towards the CXCR3 ligand, CXCL10, demonstrating a novel role for CCR5. CCR6 seems to have a major role in GVHD development by facilitating recruitment of alloreactive effector/memory CD4⁺ T cells to target tissues and it has been identified as a potential therapeutic target for GVHD (66). Blockade of chemokine production or function may provide a new approach to the prevention or treatment of GVHD.

5. PHASE 3: INFLAMMATORY EFFECTORS

The effector phase that leads to target organ damage is a complex cascade of events mediated by multiple cellular effectors such as cytotoxic T lymphocytes (Tcs), T helper cells (Ths) and NK cells and inflammatory effectors such as TNF-alpha, IL-1 and nitric oxide. Chemokines expressed in inflamed tissues upon stimulation by proinflammatory effectors are specialized for the recruitment of effector cells, such as Tcs (69).

5.1. Chemokine gradients determine the target organs

Acute GVHD involves mainly the skin, liver and intestines. Other organs such as the heart, muscle and

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central nervous system are seldom affected, although their parenchymal cells also express alloantigens. This might be related to differential chemokine gradients in the target organs, since T cell migration is largely controlled by the expression of chemokine and chemokine receptors. It has been shown that spatiotemporal chemokine gradients might determine not only the severity but also the unusual cluster of GVHD target organs (70). Experimental data suggested that in the spleen and liver, MIP-1, MIP-2 and monokine induced by gamma-interferon (Mig) were the predominant chemokines expressed, and in the skin, MIP-1, MIP-2, monocyte chemoattractant protein (MCP)-1 and MCP-3 were all highly expressed; however, in the heart, the predominant chemokines expressed were MCP-1 and MCP-3 (67, 71, 72). This distinct pattern of chemokine expression associated with these organs may contribute to the preferential recruitment of inflammatory cells into the liver and skin, but not into the heart, during acute GVHD. MIP-2 was up-regulated in the target organs but peaked later than did MIP-1 and Mig, suggesting it might be responsible for recruiting inflammatory cells into the target organs at a later stage of acute GVHD. It was found that recruitment of CD8⁺ T cells to acute GVHD liver relied heavily on MIP-1, but less important for CD4⁺ T cells that expressed much lower CCR5 than CD8⁺ T cells (73, 74). These observations indicate that chemokines other than MIP-1 play a critical role in the recruitment of CD4⁺ T cells into the target organs. In support of this, it was reported that CXCR3 was up-regulated on CD4⁺ T cells during allogeneic activation (75). Hepatic infiltration of activated CD8⁺ T cells is a major feature of GVHD. CXCR6 is highly expressed by liver-infiltrating CD8⁺ T cells. Hepatic accumulation of donor CD8⁺, but not donor CD4⁺, lymphocytes was significantly reduced in GVHD induced by transfer of CXCR6 lymphocytes, indicating that CXCR6 helps mediate the recruitment of activated CD8⁺ T cells in GVHD-induced hepatitis and may be a useful target to treat pathological inflammation in the liver (76). Based on the difference of chemokine expression observed, it is possible to modulate acute GVHD by changing the micro-environmental chemokine repertoire in reducing the recruitment of alloreactive cells.

5.2. Chemokine modulation

Effector T cell migration into GVHD target tissues, which may not be required for certain GVT effects, can be modulated by tissue-specific chemokine expression so as to reduce GVHD while enhancing GVT effects. Such efforts are being facilitated by ongoing clinical development of small molecule inhibitors of chemokine pathways (77). Studies have shown that inhibition of CCL17 elaborated by cutaneous epithelial cells can prevent T cell migration to skin and therefore prevent skin GVHD (78). It has been suggested that inhibition of the CCR9 ligand, thymus-expressed chemokine, which is elaborated by gut epithelial cells, may prevent donor T cell migration to intestines, with resultant reduction in gut GVHD (79). In studies using CCR5-deficient donor T cells and neutralizing monoclonal antibody against the chemokine mucosal addressin cellular adhesion molecule, investigators demonstrated that inhibition of T cells migration to the gut prevented GVHD (80). Experimental data suggest that

chemokine CCL3 (MIP-1 alpha) produced by liver epithelial cells prevents hepatic migration of CCR5⁺ donor T cells, with resultant reduction in liver GVHD (81, 82). Modulation of chemokines may also impact on the balance of Th1/Tc1 and Th2/Tc2 cytokine-secreting subsets, and thereby influence GVHD (83-85).

5.3. Memory T cells

A small proportion of alloreactive T cells responsible for acute GVHD survived after the apoptotic death of host-reactive donor effector cells (86, 87). These alloreactive T cells (including both CD8⁺ and CD4⁺) expressed memory phenotype, persisted for the lifetime of mice with ongoing GVHD, and were able to respond to restimulation of host DCs more rapidly than donor naïve and effector T cells and caused persistent host tissue injury. The persistent stimulation of host mIHAs was critical for the generation of these alloreactive memory T cells. These data suggested that effective GVHD prevention and treatment can only be achieved by targeting both effector and memory T cell tissue injury (88).

5.4. Reconstitution of DCs

Reconstitution of DCs after HSCT is important for immune responses against alloantigens and pathogens. It has been demonstrated that the impairment of recovery of DC significantly increased the risk of relapse and acute GVHD and predicted death after allogeneic HSCT (22, 89). It is also found that high PDC recovery three months after HSCT predicted an improved overall survival, while low PDC was associated with acute GVHD and acute GVHD impaired PDC recovery one to three months after HSCT (22, 89-92). Steroids administration also impaired PDC recovery, and patients with lower numbers of PDC were more susceptible to viral infection (89, 91-93).

6. CONCLUSIONS AND PERSPECTIVES

GVHD remains the major toxicity of allogeneic BMT; it is a complex that is unlikely to be controlled by a single agent. Presently, therapy for GVHD is limited to immunosuppression directed largely against T cells. Mechanistic studies in experimental animal models provide a better understanding of the complex relationships and cascade of events mediated by cellular and inflammatory factors including DCs and chemokines. Thus, strategies for preventing GVHD could be developed that are based on modulating host APCs and chemokines. Such strategies could expand the safety and application of allogeneic BMT in treatment of common genetic and neoplastic diseases.

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Abbreviations: HSCT: Allogeneic hematopoietic stem cell transplantation; GVHD: Graft-versus-host disease; BMT: bone marrow transplantation; IL: interleukin; TNF: tumor necrosis factor; DC: Dendritic cell; APC: antigen presenting cell; MHC: major histocompatibility complex; moDC: monocyte-derived DC; GVT: graft-versus-tumor; mDC: mature DC; iDC: immature DC; TGF: transforming growth factor; T_{reg} cell: T regulatory cell; MDC: myeloid DC; PDC: plasmacytoid DC; rDC: regulatory DC; TCR: T cell receptor; HEV: high endothelial venule; MIP: macrophage inflammatory protein; miHA: minor histocompatibility antigen; Tc: cytotoxic T lymphocyte; Th: T helper cell; Mig: monokine induced by gamma-interferon; MCP: monocyte chemotactic protein

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