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Review

Harnessing dendritic cells to improve allogeneic hematopoietic cell transplantation outcome

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ABSTRACT

In clinical practice, hematopoietic cell transplantation (HCT) is now recognized as a powerful means of delivering effective cellular immunotherapy for malignant and non-malignant diseases. In patients with severe hematological malignancies, the success of allogeneic HCT is largely based on immunologic graft-versus-tumor (GVT) effects mediated by allogeneic T lymphocytes present in the graft. Unfortunately, this beneficial effect is counterbalanced by the occurrence of graft versus host reactions directed against normal host tissues resulting in graft versus host disease (GVHD), a potentially life-threatening complication that limits the success of allogeneic HCT. Therefore, while preserving beneficial GVT effects, a major objective in allogeneic HCT is the prevention of GVHD. Studies in the last decade revealed the central role of dendritic cells and macrophages in modulating graft versus host immune reactions after allogeneic HCT. In this review, we summarize recent progress and potential new therapeutic avenues using dendritic cell-based strategies to improve allogeneic HCT outcome.

1. Introduction

Dendritic cells (DCs) are specialized, bone marrow-derived leukocytes critical to the onset of both innate and adaptive immunity against pathogens [1]. In the setting of allogeneic hematopoietic cell transplantation (HCT), major or minor histocompatibility antigens (miHA), rather than microbial products, are the antigenic stimuli [2]. Host histocompatibility antigens stimulate donor T cells against the recipient leading to graft versus host (GVH) reactions. GVH reactions eradicate the recipient hematopoiesis including the malignant clone and often damages peripheral tissues, causing graft versus host disease (GVHD). Host DC have a unique role in the transplant setting as they present major histocompatibility antigens or miHA to donor CD8+ T cells much more efficiently than donor-derived DC [3]. In addition to DC, we recently found that recipient macrophages also play a key role in the modulation of post-transplant immune responses. As DC and macrophages are bone marrow-derived, it has been assumed that hematopoietic cell transplantation leads to the replacement of host DC by donor DC in a similar kinetic in the blood, bone marrow and distant organs. However, it emerges that DC and macrophage homeostasis is more complex and depends on the site, nature of transplant, intensity of the conditioning regimen, dose of donor T cells, and age-related variables. Recent data also established that DC are formed of different subsets that are diverse in origin and function and revealed that specific DC populations play distinct roles in tissue immunity. Understanding the role of DC subsets and macrophages in patients undergoing allogeneic HCT is critical since the quantity and quality of the graft versus host response is one of the main factor that control the outcome of transplantation.

2. Allogeneic hematopoietic cell transplantation

Allogeneic HCT was initially developed to allow the delivery of myeloablative doses of radiation and/or chemotherapy and increase killing of tumor cells in patients with hematological malignancies. However, such high dose chemotherapy regimen also results in the permanent loss of the patient bone marrow function, requiring rescue with donor hematopoietic progenitors also called “the graft”, which are administered as an intravenous infusion. Engraftment of donor allogeneic hematopoietic cells is facilitated by myelo-suppressive and immuno-suppressive conditionings given just prior to the infusion of donor cells. Typically the donor hematopoietic graft is enriched in hematopoietic progenitors and donor allogeneic T cells but also contain DC precursors, mature

Abbreviations: DLI, donor lymphocyte infusion; GVHD, graft versus host disease; GVT, graft-versus-tumor; HCT, hematopoietic cell transplantation; miHA, minor histocompatibility antigen; LC, Langerhans cell; TAA, tumor associated antigen.

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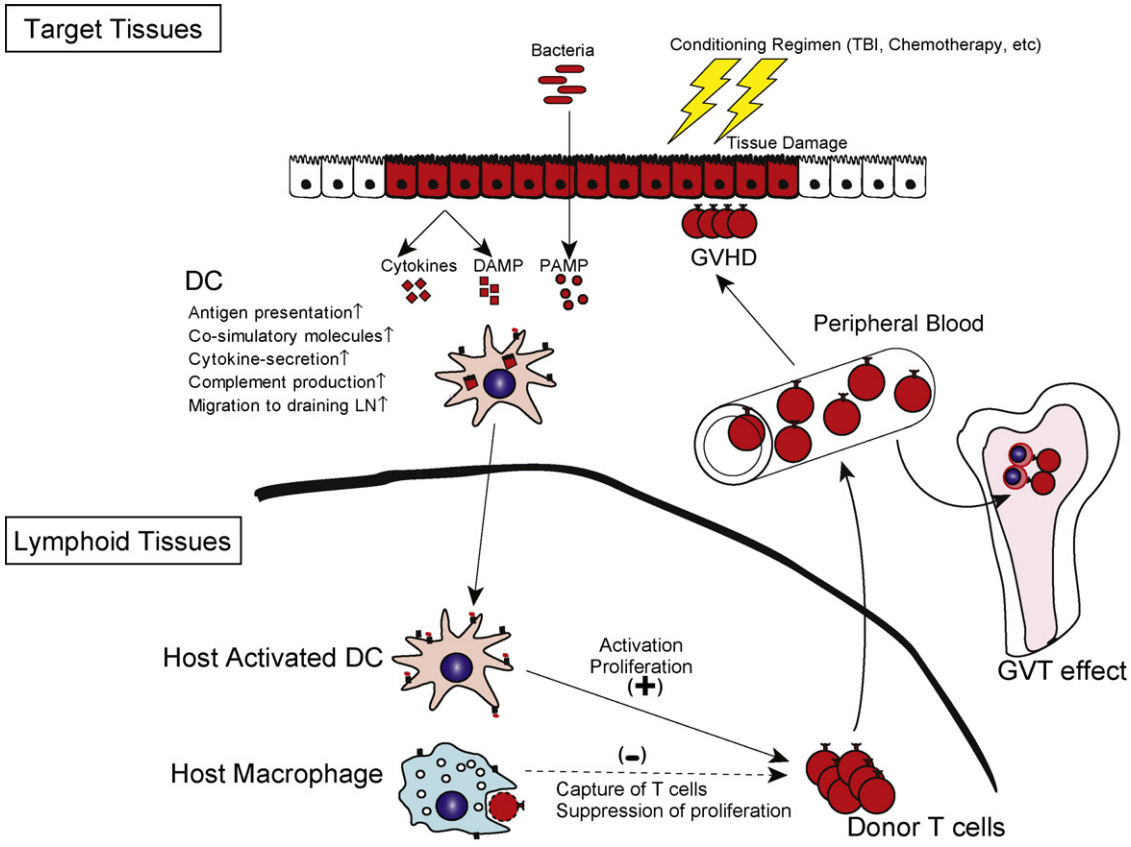

Fig. 1. Host DC control the induction of GVH reactions. Pre-transplant conditioning regimen leads to host tissue damage, release of inflammatory cytokines, increased complement production, and bacterial translocation due to loss of intestinal mucosal integrity and cell death. Host DC activation triggered by damage associated molecular pattern (DAMP), pathogen associated molecular pattern (PAMP), inflammatory cytokines or complement migrate to lymphoid organs and prime donor T ells against host miHA. Tissue inflammation facilitates the recruitment of T cells that recognize tissue specific miHA and promote the development of GVHD. CD8+ T cell that recognize miHA expressed on hematopoietic cells eradicate host hematopoiesis including the malignant clone leading to GVT.

DC and plasmacytoid DC. Allo-HCT outcome is largely dependent on the extent of immune reconstitution and the balance between beneficial immunological responses against hematological malignancies, graft-versus-tumor (GVT) effect, and detrimental GVHD. Many parameters, such as the intensity of the conditioning regimen and sources of hematopoietic cells, donor T-cell dose and degree of major histocompatibility antigens and miHA diversity modulate allogeneic HCT outcome (Fig. 1). The recent realization that donor T cells rather than high dose chemotherapy control the eradication of host malignant cells after allogeneic HCT has brought a proliferation of non-myeloablative and reduced intensity conditioning regimens that shift the burden of disease eradication from cytotoxic chemoradiation to GVT effects [4–6]. Although the use of lower dose conditioning regimens has reduced host tissue damage and allogeneic HCT related morbidity, GVHD incidence continue to remain the main limitation of reduced intensity allogeneic HCT procedures [5,7].

3. The graft versus host response: graft versus host and graft versus tumor response

3.1. Antigen specific immune recognition in allogeneic transplants (see Fig. 2)

In MHC-matched transplant, miHA derive from recipient's polymorphic proteins that differ from those of the donor. Most miHA represent allelic forms of normal proteins that arise due to single nucleotide polymorphisms (SNP) [8], although differential expression may also occur as a result of gene deletion [9]. Twenty autosomal encoded miHA and 10 Y-chromosome encoded miHA have been discovered to date and the list is rapidly expanding [10,11]. Because allogeneic HCT are performed mainly in the context of hematological malignancies many miHA that are present on hematopoietic cells are likely also expressed by the malignant cells. The frequency of a T cell reacting miHA has been estimated to be approximately 1 in 10^6. In the MHC-mismatch setting, MHC-molecules are recognized directly by donor T cells with variable contribution of MHC-bounded peptide and frequency of alloreactive T cells in this mode has been estimated to 1 in 10^2–10^3 which results in a much stronger primary T cell proliferation response [12].

In contrast to solid tumor associated antigens, all miHA expressed by the malignant hematopoietic clone should theoretically be able to elicit donor T cell responses since the donor immune system is not tolerant to these antigens. The clinical manifestations of immune responses against miHA are likely to be determined by the specific tissue expression of the proteins encoding these antigens. miHA constitutively expressed in many tissues are likely to be targets for a combined alloreactive immune response directed against the host tissue and the tumor, and lead to GVHD and GVT. Whereas, T cell responses directed against antigens that are restricted to the hematopoietic system including the malignant hematopoietic cell clone are likely to mediate GVT reactivity without severe GVHD [13–15].

3.2. Graft versus host disease (Fig. 1)

Acute GVHD is defined as a progressive, systemic disease characterized by immuno-suppression and inflammation of the skin,

liver and intestines. GVHD occurs in 10–50% of patients even with HLA-identical sibling donors [16] and leads to death in up to 25% of patients [17]. The complex pathophysiology involves host tissue damage, which results from the conditioning regimen, inflammatory cytokines (such as tumor-necrosis factor-α, interferon-γ, interleukin-1 (IL-1), IL-2 and IL-12, and effector cells that include cytotoxic T lymphocytes (CTLs), natural killer (NK) cells and macrophages [18]. In addition to acute GVHD, recipients of allogeneic HCT are at risk of developing chronic GVHD, a pleiotropic syndrome with similarities to autoimmune diseases [19,20]. Despite the complexity of these processes, T-cell depletion of the donor hematopoietic cell graft remains one of the most effective ways to prevent GVHD in animal models and patients illustrating the importance of allo-reactive donor T cells in the development of acute and chronic GVHD [21–23].

3.3. Graft-versus-tumor activity (Fig. 1)

A major conceptual advance in transplantation occurred with the recognition that immunological activity of donor T cells not only causes GVHD but is a critical factor in eradicating residual recipient hematopoiesis and malignancy [24–26]. Although donor T cell depletion reduces GVHD, it also leads to increased relapse risk [23]. The potential of donor T cells to secure remission is most dramatically demonstrated by the use of donor lymphocyte infusion (DLI) to treat post-transplant relapses [27–29]. Several miHA that drive GVH reactions have now been identified, allowing cellular responses to be monitored directly [13,14,30–32]. GVT is likely to be a manifestation of the GVH response in hematopoietic tissues and therefore dependent on the same cellular process of induction [33–35]. GVT appears to occur at a lower threshold than GVHD in studies of escalated DLI in mice and humans [36,37] suggesting that the hematopoietic tissue is the most sensitive target organ of donor immune responses. This suggests that it may be possible to take advantage of a therapeutic window in the GVH response to separate GVT from GVHD. Understanding the homeostasis of antigen presenting cells and how this controls the induction of donor immunity is vital to this aim.

4. Experimental models to study graft versus host response (for a complete review see Ref. [38])

Mouse models of allogeneic HCT have been critical for our understanding of the mechanisms that control allogeneic recognition. In contrast to humans, mice after a single dose of total body irradiation, is able to accommodate completely mismatched transplants without post-transplant immunosuppression. This may be due to lower minor antigenic diversity and decreased exposure to infection in mice compared to humans. Despite these differences, murine GVHD shows many parallels with human disease and may be scored by lethality, weight loss or changes in posture and fur texture. However, it is important to take into consideration key variables that include: (1) the cytotoxic regimen, (2) the type and number of donor immune cells infused, (3) the degree of MHC mismatch and (4) the strain combination.

5. Role of DC subsets in graft versus host reactions (Figs. 2 and 3)

In the artificial setting of transplantation, host and donor-derived DC coexist for several days in recipients after allogeneic HCT. Host DC are uniquely suited to present miHA or MHC molecules directly to CD8+ T cells, whereas donor DC initiate CD8+ T cell effector responses only though a process called cross-presentation in which host cell associated antigens are loaded and presented in the MHC class I compartment. Several lines of work suggest that direct presentation of host antigens plays a key role in initiating graft versus host responses after allogeneic HCT.

5.1. Host DC prime donor T cells to induce GVHD in lymphoid organs during the first few days following allogeneic HCT

Acute GVHD is primarily a cell-mediated disorder. The interaction between donor T cells present in the graft and hematopoietic cells in lymphoid organs was first demonstrated by the elegant experiments of Sprent and colleagues (reviewed in [3]). In these studies, recipient mice were infused with T cells, which were later collected from the efferent lymph by cannulation of the thoracic duct. Alloreactive T cells were initially trapped in the lymphoid organs for 24–48 h and then emerge primed to induce GVHD. The critical role of host APC in the induction of GVHD has been demonstrated in experiments showing that bone marrow chimeric mice, in which host hematopoietic cells are unable to prime donor T cells are protected from GVHD after allogeneic HCT [39–42], whereas alloantigen expression on host target epithelium is not essential for allo-reactive T cell attack of the skin, liver, and intestine of recipient animals [40]. Donor APC play a supplementary role and are able to augment acute GVHD through cross-presentation [41,43]. They are also equivalent to recipient APC in initiating CD4-mediated chronic GVHD [44]. Further work confirmed the importance of host DC compared with other APC and demonstrates that recipient DC 'add-back' is sufficient to induce GVHD in chimeric recipients in which host APCs were syngeneic to donors or were deficient in MHC [45,46]. While it is assumed that DC play a significant role, the role of plasmacytoid DC remains unclear and studies have suggested that host plasmacytoid DC aggravate [47] or improve GVHD [48].

5.2. Host DC control GVT

Immunological protection from relapse, or GVT effect, is likely to be a manifestation of the GVH response in hematopoietic tissue and therefore dependent on the same cellular process of induction [33,34]. Transient pancytopenia often accompanies donor lymphocyte infusion responses [49] and is the cardinal feature of transfusion-associated GVHD [50] indicating that BM is indeed a target organ of the engrafting immune system.

Animal models also established the key role of recipient, but not donor APC for GVT mediated by CD4+ and CD8+ cells [41,51]. For CD8 T cell-mediated GVT, alloantigens must be present on both recipient APC and tumor; tumor lines expressing co-stimulatory molecules are also unable to substitute for professional APC [51]. In contrast, donor APC, while not required for GVT, are able to mediate some CD8 T cell-dependent GVT activity at lower tumor burden while sparing the effect of GVHD [35,41,51]. GVT appears to occur at a lower threshold than GVHD in studies of escalated donor lymphocyte infusions in mice and humans, suggesting that access to a narrow therapeutic window between GVT and GVHD is possible [36,37]. In murine models, recipient lymphoid tissue DC are sufficient to prime robust GVT responses and are readily accessible by donor T cells in the hematopoietic compartment [35,51,52]. In contrast, recipient peripheral tissues are not infiltrated by alloreactive donor T cells in the absence of inflammation [53]. The interaction of donor T cells with lymphoid tissue, but not peripheral, DC populations may achieve a selective benefit in promoting GVT without GVHD [35,51–53].

5.3. Replacement of host DC by donor DC after allogeneic HCT

The replacement of host DC by donor DC is highly dependent on the type of conditioning regimen. In mice, 30% host DCs are

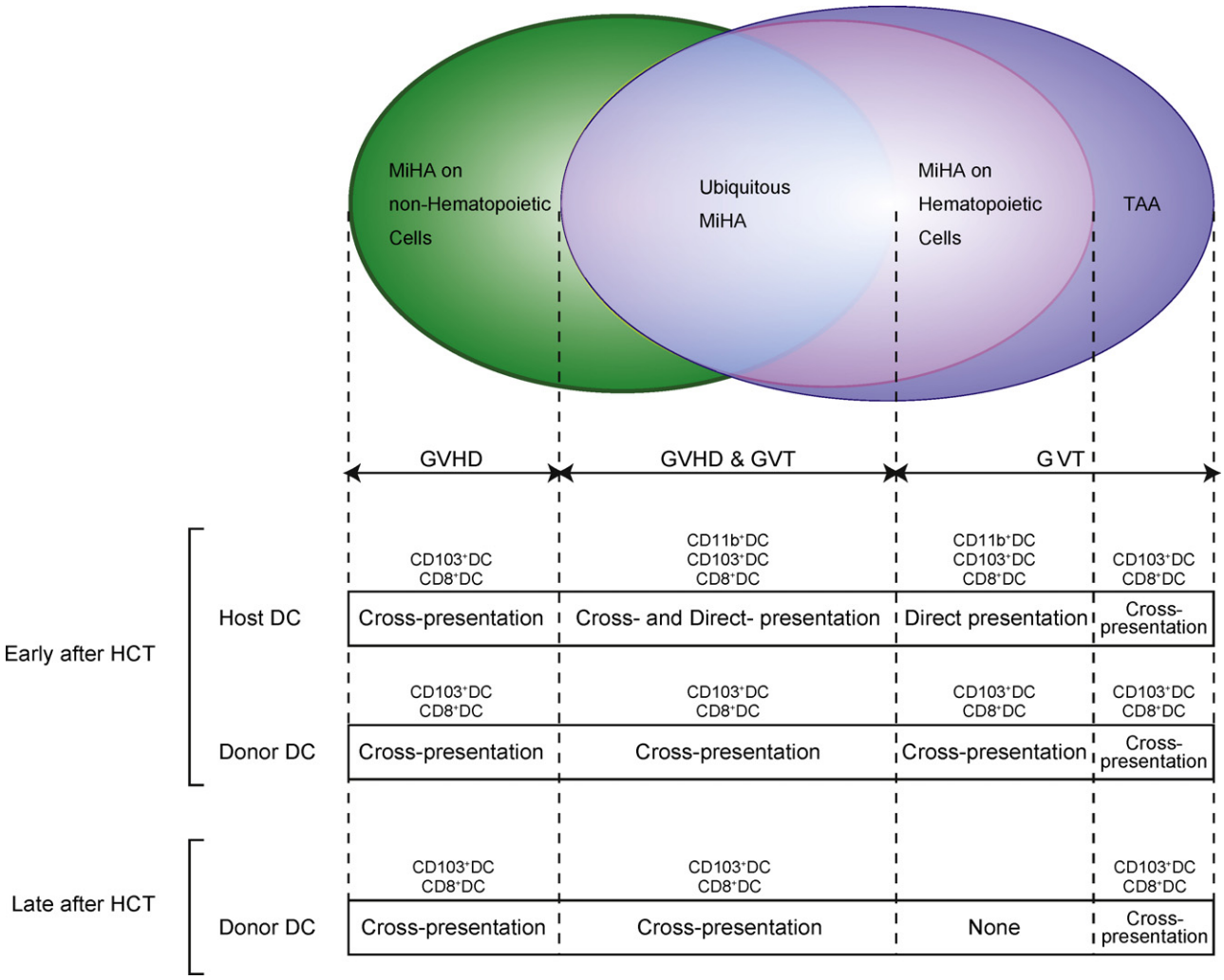

Fig. 2. Generation of miHA specific CD8 effector cells after allogeneic HCT. miHA constitutively expressed in many tissues are targets for a combined allo-reactive immune response directed against the host tissue and the tumor and lead to GVHD and GVT. Whereas, T cell responses directed against antigens that are restricted to the hematopoietic system including the malignant hematopoietic cell clone are likely to mediate GVT reactivity without severe GVHD. During the early days post-transplant, host DC are uniquely able to present hematopoietic cell specific-miHA through the direct presentation pathway but also cross-present tissue specific miHA playing a key role in the induction of GVHD and GVT. Later after transplantation, host hematopoietic cells including host DC are replaced by donor-derived cells. Donor DC are mainly able to cross-present non-hematopoietic tissue miHA, since host hematopoietic cells are eliminated at this point. This may explain why donor DC are less important for the induction of GVT against hematopoietic malignancies.

still present in the spleen, 24 h after lethal irradiation and less than 1% 48 h later ([39] and unpublished data). In the same model, donor allogeneic T cells are activated 6 h after transplantation and start to proliferate 72 h after transplant [39]. Due to accessibility issues, human DC turnover after transplant has been mainly studied in peripheral blood. In patients that receive myelo-ablative and non myelo-ablative regimens, the majority of circulating DCs are of donor origin even in the presence of mixed chimerism in other lineages ([54,55] and Mielcarek and Merad unpublished).

5.4. DC subsets have different ability to induce T cell effector responses (Figs. 2 and 3)

We and others have established that DC represent a heterogeneous population of cells with different origin and functions [56]. Non-lymphoid tissue CD103+ DC and lymphoid organ CD8+ DC are developmentally related and have a unique ability to cross-present cell associated antigens to CD8+ T cells [56]. Mice lacking the transcription factor Batf3, IRF8 and the inhibitor of DNA binding protein Id2 lack lymphoid tissue CD8+ DC and non lymphoid tissue CD103+ DC and are compromised in their ability to cross-present cell associated antigens and prime anti-tumor and antiviral immunity [57]. Tissue migratory DC instruct LN T cells to home to tissues in which DC originally reside [58–60]. Consistently, T cells activated by mesenteric LN DC leads to more severe gut GVHD compared to splenic, skin draining LN or liver DCs after allogeneic HCT [61].

5.5. The conditioning regimen differently affects tissue DC subsets

In contrast to circulating DC, much less is known about the turnover of tissue DC after allogeneic HCT. In mice and human non-lymphoid tissues, DC turnover is affected by the intensity of conditioning and status of GVHD [55,62,63]. In mice, DC that populate the epidermis also called Langerhans cells (LC) can resist high dose of irradiation [64] but are eliminated upon cutaneous GVHD lesions [65]. Host remaining LC are sufficient [65] but not required [66] to induce GVHD in MHC mismatch [65] and miHA mismatch [67] transplant recipient. Host DC can also persist for prolonged periods of time in the dermis of lethally irradiated animals [63]. In patients that receive allogeneic HCT, host epidermal LC remain in the skin for weeks after transplant [68] especially in patients that receive non myelo-ablative regimens ([62] and Mielcarek and

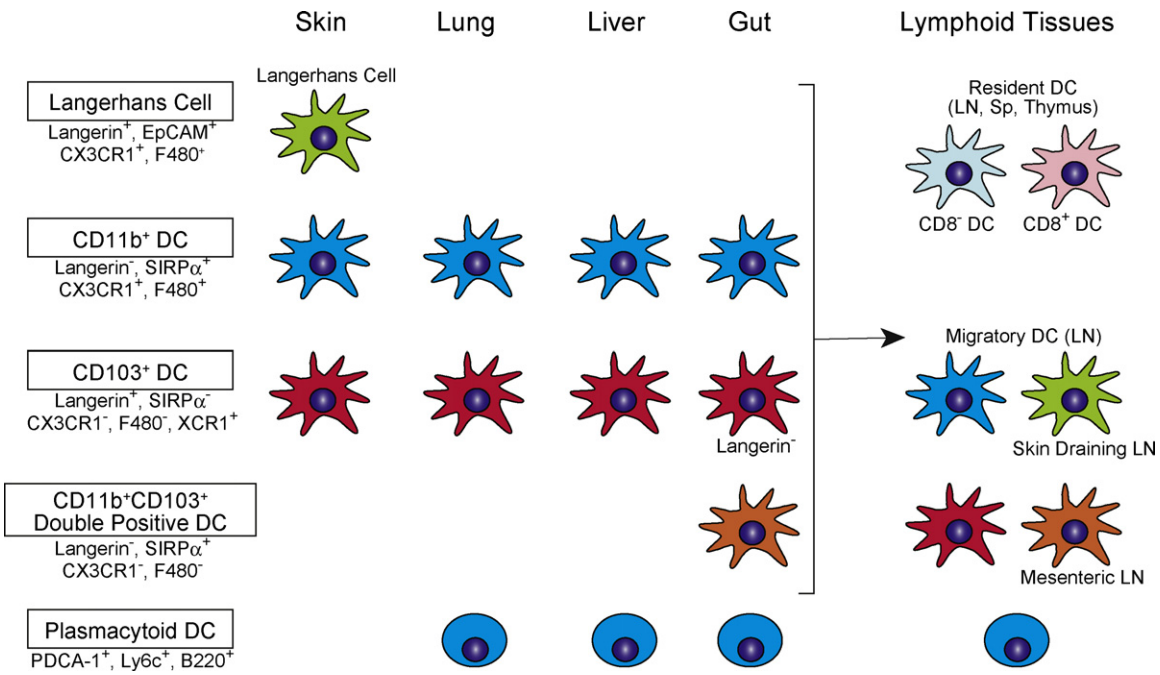

Fig. 3. APC populations that populate target tissues. This cartoon summarizes the phenotype of DC subsets that populate non-lymphoid and lymphoid tissues in mice. Non lymphoid tissue resident CD103+ DC and lymphoid tissue resident CD8+ DC are developmentally related and are uniquely equipped to cross-present cell associated antigens (for a complete review see Ref. [56]). TAA; tumor associated antigen.

Merad unpublished). The turnover of gut and liver DC after allogeneic HCT has been less explored.

5.6. DC sensors in GVHD (Fig. 1)

Similar to other foreign proteins, host DC expressing miHA drive efficient host specific donor T cell response and GVHD only if host DC/donor T cell interaction occur in an inflammatory context. Tissue damage induced by the conditioning regimen control DC priming potential. Primary DC sensors of tissue damage after allogeneic HCT remain unclear despite intense research efforts by several laboratories. Studies have shown that HMGB1 levels increase during GVHD and HMGB1 polymorphism correlates with allogeneic HCT outcome in patients [69,70]. Myd88$^{-/-}$ recipient mice develop GVHD [3] and TRIF and MyD88 deficient DC or plasmacytoid DC add-back to irradiated MHC-deficient mice can still be activated and lead to GVHD, suggesting that sensors other than TLR signals are sufficient to activate DC to initiate GVHD [47]. Randomized trial, using recombinant anti-human IL-1 receptor antagonist (Anikinra) failed to control GVHD [71] in patients suggesting that either inflammasome-mediated DC activation is not critical to the induction of GVHD or that Anikinra does not sufficiently inhibit IL-1 function after allogeneic HCT. Since bacterial translocation is common after HCT [72], several studies have explored the role of NOD2/CARD15, a molecule that recognizes muramyl dipeptide (MDP) produced by most bacteria [73] in HCT outcome. In murine GVHD model, NOD2 deficient DCs show enhanced ability to activate donor T cells, resulting in more severe GVHD compared to wild type recipient, which is consistent with NOD2 modulatory role observed in other intestinal inflammatory models [74–78]. Consistently, clinical studies also showed that NOD2 single nucleotide polymorphisms are associated with higher GVHD risk although these results remain controversial (reviewed in [79]). Allogeneic HCT also leads to local production of C3a and C5a anaphylatoxins by APC and T cells. Binding of anaphylatoxins to C3aR and C5aR expressed on T cells and APC leads to T cell proliferation and the release of innate cytokines (e.g. IL-12, IL-23) and upregulation of co-stimulatory molecules (e.g. CD80) expression by APC, which together amplify the effector T-cell response [80,81] and contribute to the clinical expression of GVHD (Kwan, Merad and Heeger unpublished)

6. Role of macrophages in graft versus host reactions

The current dogma suggests that similar to host DC, host macrophages contribute to the induction of GVHD after allogeneic HCT. This concept was based on experiments showing that the pre-transplant conditioning regimen leads to the release of inflammatory cytokines by host macrophages [82], and that the concomitant depletion of DC and macrophages improves GVHD [83]. By developing new means to target host macrophages while sparing host DC we have recently revisited the role of host macrophages in GVHD (Hashimoto and Merad unpublished data). Our data revealed that host DC and macrophages have opposite contribution to GVHD outcome. In contrast to DC, host remaining macrophages reduce the expansion of activated donor T cells through their ability to engulf allo-reactive T cells and modulate T cell proliferation, and consequently limit the severity of GVHD (Hashimoto and Merad unpublished data). The immunemodulatory role of macrophages has already been reported in several settings. In tumors, for example, macrophages modulate T cell function through several mechanisms that include but are not limited to the production of iNOS, arginase, and IDO [84,85]. These molecules have also been shown to modulate GVHD after allogeneic HCT [86–90].

7. Therapeutic implications

The prominent role of host APC in initiating GVH responses and the importance of GVT in eradicating human malignancy suggest that DC targeted therapy has the potential to improve the therapeutic benefit of GVT in relation to GVHD. Below we summarize potential DC-based strategies to improve allogeneic HCT outcome.

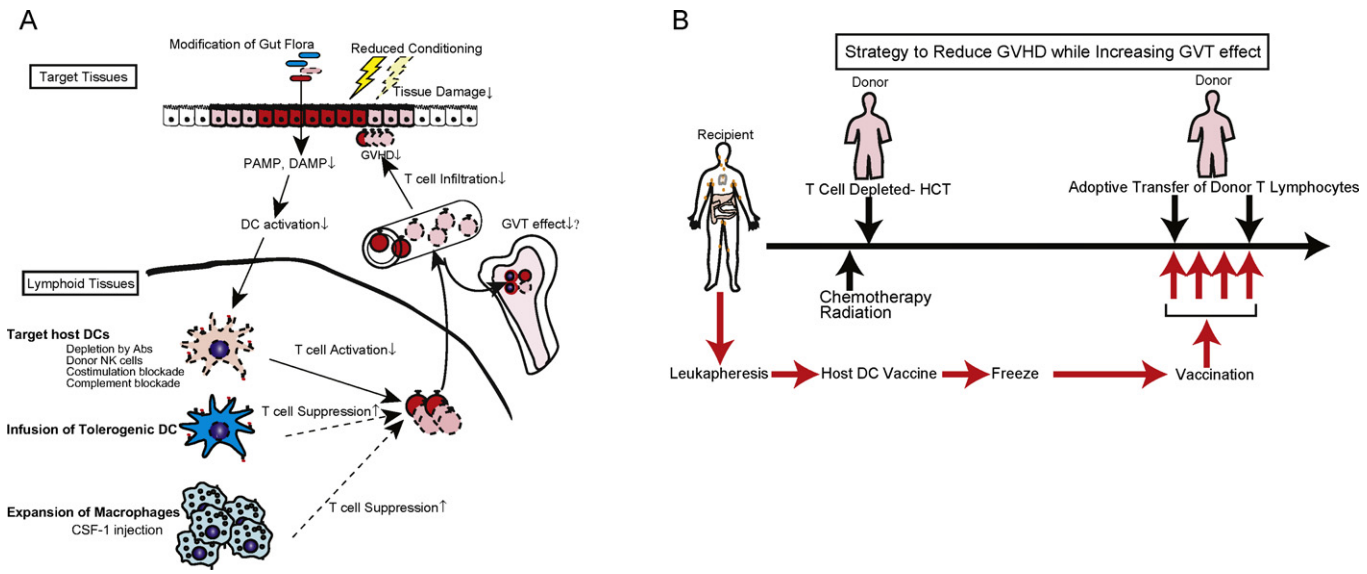

Fig. 4. DC-based strategies to improve allogeneic HCT outcome. (A) DC targeting to reduce graft versus host reactions. Reduced intensity conditioning regimen, reduction and modification of the gut flora, depletion of host DC using antibodies or donor NK cells and modulation of DC function reduce host DC ability to prime donor T cells to host miHA and induce GVH reactions. Injection of tolerogenic DC and expansion of host macrophages could also be used to modulate donor T cell expansion and induction of GVH responses. The main limitation of these strategies is that they also modulate GVT. (B) Strategy to reduce GVHD while preserving GVT. Donor T cell depletion from the graft strongly reduces GVHD and GVT. To circumvent the reduction of GVT while preserving GVHD, donor lymphocytes injection will be provided only once the tissue inflammation subsides. However since at later time-points most host hematopoietic cells are eliminated, one strategy to promote donor specific immunity to the malignant clone will be also to provide activated host DC. Host DC vaccines are generated from circulating monocytes isolated prior to transplant and activated with LPS or CD40 ligand and either left untreated or pulsed with tumor associated antigens (TAA) whenever possible. Co-injection of donor lymphocytes and host activated DC should promote the priming of donor T cells to host hematopoietic miHA, whereas injection of host activated DC pulsed with TAA may help expand TAA specific T cell response. Absence of tissue injury should limit donor T cell infiltration in peripheral tissues and the induction of GVHD.

7.1. Targeting APC to improve GVHD (Fig. 4)

As discussed above, host DC that remain in lymphoid tissues for several days after the conditioning regimen control the priming of donor T cells to host antigens and the induction of GVHD. Therefore depleting or modulating host DC function during the peri-transplant setting should interfere with donor T cell priming. Already conventional immuno-suppressive drugs such as calcineurin inhibitors, mycophenolate mofetil and glucocorticoids are now known to mediate some of their actions through DC modulation [91–93]. Blocking antibodies to CD83 a molecule expressed specifically on activated DC prevent acute GVHD in a human xenograft mouse transplant model without impairing anti-viral immunity [94]. NK cells ability to improve GVHD is also thought to be due to NK mediated depletion of host remaining APC [95], although more recent studies suggest that NK cells also deplete alloreactive donor T cells [96]. Flt3 signaling, in addition to its known function on progenitor cells, may have an additional role in maintaining mature DC populations [97]. The development of small molecule Flt3 inhibitors for treatment of leukemia [98] provides a timely opportunity to test the effects of Flt3 inhibition on GVHD; encouraging results have already been achieved in the amelioration of experimental autoimmune encephalomyelitis (EAE) [99].

In addition to modulating host DC function, injecting tolerogenic DC or expanding immunosuppressive macrophages could also help modulate GVHD. Adaptive transfer of tolerogenic DC generated in the presence of GM-CSF, IL-10, TGF-β1 and LPS [100,101], histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) [102] or vasoactive intestinal peptide (VIP) [103] have been shown to reduce GVHD when injected during the peri-transplant setting in mice. We have recently found that pre-transplant administration of CSF-1, a cytokine required for macrophage development, survival and proliferation *in vivo* [104] expand the host macrophage pool and dramatically improve GVHD morbidity after allo HCT (Hashimoto and Merad unpublished data)

7.2. Harnessing DC to induce GVT

In contrast to solid tumors, very little studies have analyzed the role of DC vaccines in GVT. DC vaccination at the time of transplant has many advantages. Most transplanted patients have no or low tumor burden, adoptively transferred donor T cells are not tolerant to host antigens, the conditioning regimen eliminates host T regulatory cells, lymphopenic-induced homeostatic proliferation of donor T cells decreases the priming threshold and expand relatively small population of tumor reactive cells [105–108]. However, immunosuppression often aggravated by the occurrence of GVHD could compromise vaccine efficacy [15,109], although recent results from a phase I clinical trial in which inactivated GM-CSF secreting tumor cells were administered early after allogeneic non-myeloablative HCT in the presence of a calcineurin inhibitor was able to induce to antigen specific priming without increasing GVHD [110].

The main risk of utilizing host DC vaccine to induce GVT is the reactivation of GVHD. Consistently, adoptive transfer of host DC after allogeneic HCT in mice increased GVT but also reactivated GVHD [46]. However, as discussed above the interaction of donor T cells with lymphoid, but not peripheral tissue DC populations may achieve a selective benefit in promoting GVT without GVHD. This argument underpins the logic of delayed T cell add back strategies [111] and pre-emptive delayed DLI [112] which allow the inflammatory insult of conditioning to subside prior to the infusion of donor T cells as discussed in the therapeutic section. Optimally pre-emptive DLI could also be administered together with host DC vaccines to promote the priming of an efficient donor T cells against host miHA (Fig. 4).

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