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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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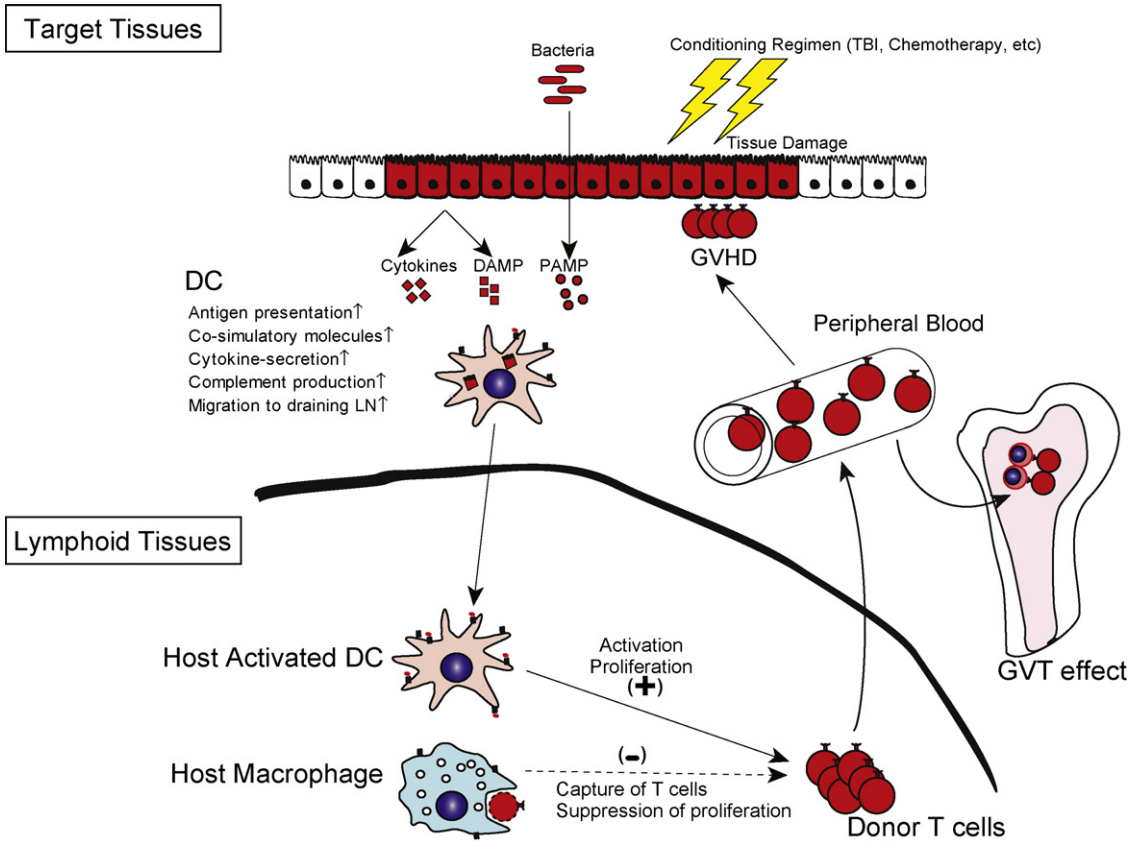

Fig. 1. Host DC control the induction of GVH reactions. Pre-transplant conditioning regimen leads to host tissue damage, release of inflammatory cytokines, increased complement production, and bacterial translocation due to loss of intestinal mucosal integrity and cell death. Host DC activation triggered 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,