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T cell Migration and Graft Versus Host Disease

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Abstract

Graft-Versus-Host Disease (GVHD) remains the major obstacle to a more favorable therapeutic outcome of allogeneic hematopoietic stem cell transplantation (HSCT). GVHD is mediated by immunocompetent donor T cells. The mature allo-reactive T cells, either $CD4^+$ T cells or $CD8^+$ T cells, within the "graft", can mediate GVHD. In this review article, we also describe the GVHD pathophysiologic events after bone marrow transplantation, including GVHD target recipient organs with the distribution of donor T cells, and distribution kinetics of donor T cells with accompanying cytokine expression.

Keywords: Graft-Versus-Host-Disease (GVHD); T cell migration

Introduction

Allogeneic Bone Marrow Transplantation (Allo-BMT) is a curative therapy for leukemia, aplastic anemia and immune deficiencies. The alloreactive donor T-cells that induce graft-versus-leukemia (GVL) effect may also initiate graft-versus-host disease (GVHD). GVHD is a serious problem that limits the use of allogeneic BMT. GVHD is mediated by immunocompetent donor T cells, which migrate to lymphoid tissues soon after infusion, recognize host alloantigens, and become activated upon interaction with host antigen presenting cells (APCs). Although the pathophysiologic mechanisms of GVHD still remains unclear now, it has been reported that GVHD develops in develops in three consecutive stages: (1) Pre-transplant conditioning results in inflammation coupled with a cytokine storm; (2) Activation of donor T-cells; (3) Finally, the activated donor T-cells assault certain tissues, such as Intestine, skin, liver, and lungs [1]. The occurrence and severity of GVHD depend on several factors, including the intensity of conditioning, the presence and number of donor T-cells in the graft, and the antigenic disparity between donor and recipient [2,3]. This review addresses the distribution, dynamic of activation and migration pattern of donor T cells in GVHD.

Either $CD4^+$ T cells or $CD8^+$ T cells can Initiate Lethal GVHD

In Allogeneic transplantations, in most cases, are performed between HLA-matched sibling's donors. The alloresponse is directed to minor histocompatibility antigens (miHA) expressed on host tissues [4-6]. The miHA are processed self-protein degradation products that can be presented in association with either major histocompatibility complex (MHC) class I or class II molecules on host parenchymal and antigen-presenting cells (APC), resulting in stimulation of donor $CD4^+$ and $CD8^+$ T cells, respectively [7-9]. Studies have shown that either the recipient's or donor's DCs can present allo-antigens to donor T-cells [10,11]. Allogeneic donor T cells with the same MHC molecules can thus recognize miHA that is not expressed by themselves. During the process of GVHD, activated donor T-cells migrate to target tissue and induce GVHD via either direct cell contactor (cytotoxic T-cells) or cytokine mediated toxicity (T-helper cells) [12]. Our group found that either CD4+ T cells or CD8+ T cells could initiate lethal GVHD independently in Allo-BMT mouse model. Friedman et al. [13] analyzed the T-cell responses after transplantation by CDR3-size spectratyping in B6 --> BALB/C Allo-BMT model. They revealed clonal or oligoclonal expansions of the Vβ 2, 4, and 6 to 14 families for the $CD4^+$ response and of the Vβ 4, 6, 8 to 11, and 14 families for the B6 CD8+ response. Appropriate positive selection of these T-cell receptor Vβ-skewed $CD4^+$ and $CD8^+$ T-cell subsets and their subsequent transfer into lethally irradiated BALB.B recipients resulted in fatal GVHD induction. In contrast, BALB B mice transplanted with non-skewed Vβ T cells survived, with minimal symptoms of GVHD. This indicates that there is special T cell subsets- T cell receptor Vβ-skewed T cells, in $CD4^+$T cells or $CD8^+$T cells, which involve in GVHD. It should be the special T cell subsets, T cell receptor Vβ-skewed T cells in both $CD4^+$ T cells and $CD8^+$ T cells, initiate lethal GVHD in the Allo-BMT mouse model.

T cell Migration in GVHD

Panoskaltsis-Mortari et al. [14] tracked the migration of eGFP transgenic donor cells post-transplant in a fully MHC-mismatched murine allo-BMT model. Within 2～3 days after transplantation, allogeneic T cells expanded in lymphoid tissues. Between 3 and 7 days post-transplant, allogeneic T cell numbers increased in GVHD target organs including the gastro-intestinal (GI) tract, liver, lungs, skin, central nervous system, gingiva, and nasal mucosal. In our study, donor T cells infiltrated the liver, spleen, skin, lungs, intestine, tongue, and small amounts eGFP+ cells were noted in the kidney and brain; but no eGFP+ cells were seen in the cardiac muscle or skeletal muscle [15]. These indicated that GVHD attacked not only liver, intestines and skin, but also lungs, tongue, and even kidneys or brain. For example, lungs were possibly the important GVHD target organ, which has been reported [16]. It has been found in clinic that GVHD was closely related to interstitial pneumonia. Perhaps, interstitial pneumonia post Allo-BMT was resulted from the secondary infection on the basis of GVHD immunologic injury of lungs [17]. GVHD involvement of the central nervous system and the brain has also been previously described in mice [18] and humans [19].

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Data demonstrated, in early post-transplant, donor T cells presented in lymphoid organ, such as spleen, but not in non-lymphoid organs such as liver and skin [20,21]. The sphingosine-1-phosphate receptor inhibitor FTY720, which prevents lymphocyte egress from lymphoid organs, inhibited target organ infiltration and GVHD lethality in a murine mode, suggesting that these donor T cells migrated after previous activation in lymphoid tissues [22,23].

IL-2 and CD25 Expression during T cell Migration

IL-2 is an important cytokine in immunologic responses. Secretion begins at 45 minutes after T-cell activation. CD25, the α-chain of the IL-2 receptor, is expressed at 2 hours after T-cell activation, combining to build a trimer with the β and γ-chains on the cellular membrane. Then, IL-2 combines to the receptor transmitting and signal for activation, proliferation, and differentiation [24]. As second signal of pCTL, the precursor cell of cytotoxic T lymphocytes, IL-2 combines with membrane CD25 on pCTL for activation, leading to antigenic-specific amplification, as antigenic specific CTL. Where T cells became effectors, the population showing with high CD25 expression and high IL-2 secretion disappears. Possible mechanisms of the process include down-regulation of IL-2 or CD25 expression and or activation-induced cell death after completing the immunologic response. Using mouse GVHD modal, Via et al. [25] established a mouse GVHD modal, and found the peak expression IL-2 on day 2～3 post transplantation, and decreased afterward. This short period of IL-2 expression on early stage of BMT also was confirmed by detecting of IL-2 mRNA by RT-PCR [26,27]. It was possible that the high expression of IL-2 and CD25 in the early stage of transplantation play a role in T cell activation.

Our group found recently the highest level of T cell population in spleen at day+4 was synchronized with the peak expression of CD25 by the donor T cells, and the highest serum levels of IL-2 [28]. Thus, it was highly possible that these T cells were activated in spleen and migrated to GVHD target organs, such as liver, GI tract, lungs, skin and so on, inducing tissue damage and the appearance of clinical manifestations. In fact, we noted that from days 2 to 16 donor T cells decreased in the spleen and increased in the liver [28].

These data support the donor T-cell migration hypothesis: During the development of GVHD, donor T cells migrate to lymphoid organs, such as the spleen, where they are activated. Thereafter they migrate to GVHD target organs to induce damage.

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