

T-Cell Alloreactivity in Hematopoietic Stem Cell Transplantation

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INTRODUCTION

Graft-versus-host disease (GVHD), lymphopenia, and immune deficiency are major complications of allogeneic hematopoietic stem cell transplantation and are causes of morbidity and mortality [1,2]. Immune suppression (IS) therapy administered for control of GVHD, injury to the thymus occurring during conditioning and GVHD, and decreased thymus-dependent lymphopoiesis in older patients are major contributors to delayed immune reconstitution. GVHD is initiated by donor T cells responding to alloantigen either minor histocompatibility antigens or major histocompatibility determinants in the case of HLA-mismatched transplants [3,4]. Clinical GVHD occurs when a sufficient number of host-reactive donor T cells are activated and achieve sustainable effector functions despite administration of prophylactic IS therapy. Standard GVHD prophylaxis usually consists of a calcineurin inhibitor together with methotrexate or mycophenolic acid. Despite the best empirical prophylaxis therapy, clinically significant GVHD requiring additional immune suppression therapy occurs in 40% to 80% of transplantations (HLA matched and mismatched). A recent analysis of Seattle data has documented that approximately 50% of HLA-matched transplant patients who receive combined prophylaxis therapy can be successfully withdrawn from all IS within 2 years; however, 20% of patients may remain IS dependent for 5 years or longer [5].

The incidence, severity, and time of onset of acute GVHD are determined by the degree of disparity, as well as the number and affinity of host-reactive donor T-cell receptors specific for host alloantigen. A kinetic model of GVHD predicts that clinical disease is probable when the frequency of host-reactive T cells reaches a critical threshold. Detailed quantitative un-

derstanding of the variables that affect alloreactivity and the clinical syndromes we recognize as acute and chronic GVHD remain subjects of active clinical research.

DONOR T-CELL ACTIVATION AND ALLOREACTIVITY AFTER TRANSPLANTATION

The expression of HLA-DR by peripheral blood T cells, as well as other markers such as CD25 and CD38, is evidence of T-cell activation. Early after transplantation, the frequency of DR⁺ T cells is greater in unrelated donor and HLA-mismatched transplants than matched sibling donor (MSD) transplants and is greater in patients who develop acute GVHD. DR⁺ T cells peak before the onset of acute GVHD. The numbers of T cells and DR⁺ T cells decrease dramatically after the administration of glucocorticosteroids for treatment of GVHD. Levels of DR⁺ T cells remain lower in patients who are free of clinical GVHD, but they can remain increased above normal levels for several months after transplantation.

ACTIVATION-INDUCED CELL DEATH

Programmed cell death, or apoptosis, plays an important role in lymphocyte homeostasis. Recent studies have demonstrated an increase in apoptotic T cells in peripheral blood and increased apoptosis during short-term in vitro culture [6]. At 18 to 21 days after transplantation, apoptosis occurs among 50% to 80% of CD3⁺ T cells during 24 hours of culture. Levels of apoptosis are higher in patients with acute GVHD and patients who receive transplants from HLA-mismatched donors. CD4⁺ cells are more susceptible to apoptosis than CD8⁺ cells, whereas

CD3⁺/CD56⁺ natural killer cells are resistant. HLA-DR⁺ and CD45RO⁺CD4⁺ cells are more likely to undergo apoptosis than HLA-DR⁺/CD25⁺ and HLA-DR⁺/CD45RA⁺ cells. The level of apoptosis early after hematopoietic stem cell transplantation correlates with lymphopenia and delayed recovery of CD4 counts. These results are consistent with the hypotheses that T cells activated by host alloantigen undergo clonal deletion and that a strong persistent alloreaction contributes to lymphopenia.

CHANGES IN T CELLS AFTER TREATMENT OF GVHD

Administration of glucocorticosteroids (steroids) for the treatment of GVHD induces lymphopenia and reduces the number of apoptotic T cells in the peripheral blood. The reduction in apoptotic cells is sustained in steroid responders, but DR⁺ apoptosis-prone T cells reappear in patients whose steroid treatment fails.

IN VITRO INDUCTION OF APOPTOSIS WITH GLUCOCORTICOSTEROID AND ANTI-CD3 MONOCLONAL ANTIBODY

T cells from patients with acute GVHD are more susceptible to dexamethasone-induced and CD3-induced apoptosis in vitro than T cells from patients without GVHD. Dexamethasone and anti-CD3 antibody induce apoptosis preferentially among DR⁺ or CD38⁺ activated T cells, whereas T cells that express CD25 are relatively resistant. Sensitivity to dexamethasone is lost in GVHD patients who become resistant to glucocorticosteroid therapy, but T cells from steroid-resistant patients remain sensitive to CD3-induced apoptosis. Sensitivity to CD3-induced apoptosis may have utility as a predictor of patients likely to experience treatment failure with steroid treatment or to become steroid resistant to GVHD. This approach to assessing alloreactivity and response to GVHD treatment may provide an objective indicator for early intervention with alternate GVHD treatment.

CHANGES IN HOST-REACTIVE T-CELL ACTIVITY

To understand the changes in host reactivity that occur after transplantation, we monitored host-reactive T-cell responses by using a limiting dilution assay in a longitudinal study. The frequency of both cytotoxic T cells and interleukin (IL)-2-secreting helper T cells was assayed in HLA MSD and matched unrelated donor (MURD) transplants. As expected, the pretransplantation donor-versus-recipient cytotoxic T-lymphocyte precursor (CTLp) frequency was significantly higher for MURD (32 CTLp/10⁶ CD3⁺ cells) than for HLA-identical sibling pairs (9 CTLp/

10⁶ CD3⁺ cells). Host-reactive T-cell frequencies uniformly increased during the first 90 days after transplantation. The magnitude of response was equivalent for MSD and MURD recipients (median CTLp at 3 months after transplantation, 54 and 53 CTLp/10⁶ CD3⁺ cells). However, at 1 year after transplantation, the median CTLp for MSD transplants (41/10⁶ CD3⁺ cells) was significantly lower ($P < .01$) than for MURD transplants (106/10⁶ CD3⁺ cells). At 1 year, significant decreases in CTLp were observed in 9 of 12 MSD transplants, but CTLp in MURD transplants continued to increase during the first year and then peaked after year 1. A significant decrease in MURD transplants occurred during the second year in 9 of 10 cases. A decrease in anti-host T-cell activity generally correlated with a reduction of immune suppression therapy, but CTLp levels above baseline were also observed in a few patients who remained GVHD free after withdrawal from all immune suppression.

ANALYSIS OF GENE EXPRESSION AFTER HEMATOPOIETIC CELL TRANSPLANTATION: NEW APPROACH TO MONITORING ALLOREACTIVITY

Serial blood samples were obtained from a cohort of 50 patients every 2 to 3 weeks after transplantation through day 100 and immediately before the administration of steroids for treatment of acute GVHD, and complementary DNA was prepared from freshly isolated RNA for gene array experiments. Patients treated for acute GVHD who survived at least 180 days were categorized according to steroid response: (1) complete response, (2) steroid dependence, and (3) treatment failure (ie, progressive GVHD).

Initial experiments were aimed at assessing global gene expression in blood leucocytes collected from patients early after transplantation with the Affymetrix 22000 gene chip [7]. Studies with samples obtained at day 21 demonstrated a massive alteration in gene expression. Significant changes were identified in 1176 genes among 15 patients compared with 10 normal controls. A relatively small number of genes from among the 1176 identified were predictive of acute GVHD in 8 of the 15 patients who developed acute GVHD within 1 week (day 21-28) compared with the other 7 patients, who remained free of GVHD for at least 90 days. Only 7 genes from the 1176 were associated with development of clinical GVHD (3 increased and 4 decreased expression). Subsequent experiments focused on longitudinal paired comparisons for individual patients comparing gene expression at 2 time points before the onset of GVHD. Eight patients were studied at 18 to 21 days and 28 days after transplantation. Four of these patients developed acute GVHD within the following week. Changes preceding the onset of GVHD were detected

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