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A closer look at permissive HLA mismatch

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In this issue of Blood, Pidala et al add a missing piece of information on the impact of amino acid substitutions (AASs) at specific peptide positions of class I antigens.1

Identifying the optimal unrelated donor (UD) for hematopoietic stem cell transplantation has been a moving target over the last few decades.2-6 As shown in the figure, the side view from the paper of Pidala et al shows specific positions of the HLA class I molecule, at which AASs were studied. In multivariate analysis, they find that a mismatch at HLA-C position 116 predicts an increased risk of severe acute graft-versus-host disease (GVHD; hazard ratio [HR], 1.45) and mortality (HR, 1.20); a mismatch at HLA-C position 99 is associated with increased transplant-related mortality (TRM; HR, 1.37); and a mismatch at HLA-B position 9 is associated with increased chronic GVHD (HR, 2.28). No substitution at the HLA-A locus is significantly associated with outcome.6 The largest number of patients were in the C116 and C99 mismatched groups.

The issue has been evaluated in the past,4,7 and it is interesting that those reports also were leading in the same direction: some mismatches should be avoided, because they predict GVHD and/or mortality and should be classified as nonpermissive.

There are conceptual and clinical consequences that derive from the findings of Pidala and coworkers.1 Among the first is the biologic and functional role of AASs in key positions of the HLA class I molecule, which had been shown in the past to be crucial for peptide binding and allorecognition8: the increased risk of severe acute GVHD and/or death, when these mismatches are present, proves the correlation between allorecognition and T-cell activation in vivo. In addition, it is possible that different peptides, or a different peptide presentation, may be driving the acute or chronic variants of GVHD. The increased risk of GVHD was seen in univariate analysis and also after adjusting for patient, disease, and transplant variables including GVHD prophylaxis and T-cell depletion.

The most striking result is that 7/8 allele-matched UD grafts, when the single mismatch lacks AASs at position C116, C99, or B9, have outcomes very similar, if not identical, to 8/8 matched donors: the clinical consequence is obvious. This report expands our ability to select a suitable donor when only 7/8 matched, and this is very important. If one takes substitutions in position C116, the paper tells us that 453 patients (or 7% of the entire population) received a 7/8 mismatched UD graft, lacking the C116 substitution, and their risk of severe acute GVHD was the same as 5274 patients with 8/8 matched donors. The number of UD searches worldwide per year exceeds 40 000 (World Marrow Donor Association report 2011; www.wmda.org): the finding of Pidala and coworkers is thus relevant for >2500 patients/year, finding a 7/8 permissive mismatched donor. The paper also tells us that 9% of the patients had a C116 nonpermissive mismatch; accordingly, >3000 patients/year should decide and/or be counseled of whether to proceed with the transplant, despite a higher risk of complications, or continue the UD donor search to find a better match. This will be based on the clinical conditions of the patient, especially the phase of the disease.

Whatever the decision, we have come a step closer to the definition of a permissive mismatch, and we may now use these
Mast cells and GVHD: old cells with a new role

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In this issue of Blood, Leveson-Gower et al describe an immunomodulatory role of mast cells in graft-versus-host disease (GVHD).1

GVHD is the major obstacle to allogeneic stem cell transplantation, and its pathophysiology is being increasingly analyzed.2 There is little doubt that T cells are the effector cells, and histocompatibility antigens are the targets against which they are directed. However, how the damage is caused in the target organs, skin, gut, and liver is still under debate. It is not known why some patients still develop severe GVHD under immunosuppressive treatment and others do not. Neither histocompatibility differences nor composition of the graft allows a precise prognosis of GVHD. Mechanisms of modulation of the immune response have come into focus; innate immunity with release of cytokines, antigen presentation, stimulation and expansion of T cells, involvement of naive and memory T cells, effector T cells, and their effector mechanisms including recruitment of other cells such as B cells, macrophages, and others play important roles. Nevertheless, immune tolerance may be accomplished by the same mechanisms that prevent immune damage in situations other than transplants. This tolerance may be a “cease fire” by mechanisms mediated by programmed death 1/programmed death 1-ligand ligation, as well as B7/ cytotoxic T lymphocyte antigen 4 binding. Several forms of regulatory immune cells have been described.3 Regulatory T cells that have been characterized by Edinger et al4 and others as part of adaptive immunity, they have both modulatory and effector functions. It has become evident that they also play a role in the modulation of T-cell responses. Mast cells may stimulate T cells by secreting tumor necrosis factor α, and may also down-regulate T cells by secreting IL-10.5 Mice with a partial knockout of KitW-sh/Wsh are not anemic but are deficient in functional mast cells; these mice also have more GVHD as shown by the accumulation of luciferase-positive donor T cells of the FVB strain in the gut, the cervical lymph nodes, and the liver. More severe GVHD seen in C57BL/6-KitW-sh/Wsh mice was due to increased proliferation of donor T cells. However the addition of regulatory T cells improved the survival of the animals compared with that of animals given only conventional T cells. The injection of cultured bone marrow mast cells (BMCMCs) into the abdomen could improve survival. This improvement was not as evident in mice given IL-10–deficient BMCMCs. The paper raises important questions regarding the role of mast cells in GVHD. Previous papers on murine GVHD of the skin show a prominent role of CD8 T cells and mast cells, the mast cells being degranulated as early as 7 days after transplantation;6 CD4 T cells and natural killer cells follow these early events. Lu et al showed that mast cells are necessary7 for positive suppressor cells and veto cells also have immunomodulatory functions. Their suppressive activity may be direct by cell-cell contact or via dendritic cells modulating T cells. In this article, a new form of immunomodulation has been proposed: suppression of GVHD via the secretion of interleukin (IL)-10 by mast cells.1

Mast cells were first described by Ehrlich in his doctoral thesis; he suspected a nutritive role of the granula of the mast cells for other cells in bone marrow. In the mean time, we learned that mast cells contain many biologically active substances such as histamine, heparin, proteases, and cytokines. These have a beneficial role in the immune control of worm infestations; their role in allergies after binding IgE and immune complexes is less beneficial. Mast cells contain many different biologically active substances; various functions have been attributed to mast cells in different organs as the mucosa, the skin and the connective tissue. As part of innate immunity, they have a stimulatory role; as part of adaptive immunity, they have both modulatory and effector functions. It has become evident that they also play a role in the modulation of T-cell responses. Mast cells may stimulate T cells by secreting tumor necrosis factor α, and may also down-regulate T cells by secreting IL-10.5 Mice with a partial knockout of KitW-sh/Wsh are not anemic but are deficient in functional mast cells; these mice also have more GVHD as shown by the accumulation of luciferase-positive donor T cells of the FVB strain in the gut, the cervical lymph nodes, and the liver. More severe GVHD seen in C57BL/6-KitW-sh/Wsh mice was due to increased proliferation of donor T cells. However the addition of regulatory T cells improved the survival of the animals compared with that of animals given only conventional T cells. The injection of cultured bone marrow mast cells (BMCMCs) into the abdomen could improve survival. This improvement was not as evident in mice given IL-10–deficient BMCMCs. The paper raises important questions regarding the role of mast cells in GVHD. Previous papers on murine GVHD of the skin show a prominent role of CD8 T cells and mast cells, the mast cells being degranulated as early as 7 days after transplantation;6 CD4 T cells and natural killer cells follow these early events. Lu et al showed that mast cells are necessary7 for positive suppressor cells and veto cells also have immunomodulatory functions. Their suppressive activity may be direct by cell-cell contact or via dendritic cells modulating T cells. In this article, a new form of immunomodulation has been proposed: suppression of GVHD via the secretion of interleukin (IL)-10 by mast cells.1

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