

## MAJOR-HISTOCOMPATIBILITY-COMPLEX CLASS I ALLELES AND ANTIGENS IN HEMATOPOIETIC-CELL TRANSPLANTATION

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### ABSTRACT

**Background** Successful engraftment of hematopoietic stem cells from unrelated donors is influenced by disparities between the donor and recipient for HLA-A, B, and C alleles. Disparities between HLA sequence polymorphisms that are serologically detectable are termed antigen mismatches, whereas those that can be identified only by DNA-based typing methods are termed allele mismatches. Whether both kinds of polymorphisms are important in transplantation is not known. We tested the hypothesis that allele mismatches that are detectable only at the DNA level are less immunogenic than those that are serologically detectable and thereby are associated with a lower risk of graft failure after hematopoietic-cell transplantation.

**Methods** We used DNA sequencing to define the HLA-A, B, and C alleles in 471 patients who received bone marrow from unrelated donors for the treatment of chronic myeloid leukemia after myeloablative conditioning therapy. The odds ratios for graft failure were determined for recipients of transplants from donors with a single class I allele mismatch, a single class I antigen mismatch, or two or more class I mismatches, as compared with those with no mismatch.

**Results** A single HLA allele mismatch did not increase the risk of graft failure, whereas a single antigen mismatch significantly increased the risk. The risk was also increased if the recipient was HLA homozygous at the mismatched class I locus or if the donor had two or more class I mismatches.

**Conclusions** HLA class I antigen mismatches that are serologically detectable confer an enhanced risk of graft failure after hematopoietic-cell transplantation. Transplants from donors with a single class I allele mismatch that is not serologically detectable may be used without an increased risk of graft failure. (N Engl J Med 2001;345:1794-800.)

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**M**AJOR-histocompatibility-complex alleles determine the tissue compatibility that is necessary for the acceptance of transplanted tissues.<sup>1</sup> Graft survival after kidney and heart transplantation is influenced by the extent of the HLA compatibility between the donor and the recipient.<sup>2,3</sup> Early studies showed that HLA mismatching between the donor and the recipient increases the risk of graft failure after bone marrow transplantation.<sup>4-7</sup> This risk is increased when the donor is heterozygous and the patient is homozygous at the same HLA locus.<sup>8</sup> More recent studies

showed that disparity between the donor and the recipient at the HLA-A, B, and C loci is a risk factor for graft failure after marrow transplantation from unrelated donors in patients with chronic myeloid leukemia.<sup>9</sup> The risk of graft failure is related to the number of mismatches of HLA-A, B, and C alleles.

A hallmark of HLA alleles is their extraordinary diversity.<sup>10</sup> Alleles encoding HLA molecules that are recognized by alloantibodies induced by pregnancy or transfusions have been identified as HLA antigens. Any given HLA antigen may be encoded by a family of HLA alleles with similar nucleotide sequences. Different alleles encoding the same antigen can be distinguished only by DNA-based typing methods. Transplant donor and recipient pairs with different HLA antigens always have different alleles (and are referred to as “antigen mismatched”) (Table 1), and pairs with the same allele always have the same antigen (“matched”). Some donors and recipients with the same HLA antigen have different alleles (“allele mismatched”). With few exceptions, HLA allele mismatches are characterized by amino acid substitutions in the regions of the HLA molecule that bind peptides for presentation to T cells, whereas HLA antigen mismatches are characterized by amino acid substitutions relevant to both peptide binding and contact with T cells.<sup>11-14</sup>

We tested the hypothesis that mismatches for the HLA-A, B, and C alleles are less immunogenic than antigen mismatches and are thereby associated with a lower risk of graft failure after transplantation of marrow from unrelated donors.

### METHODS

#### Study Population

A total of 548 patients who were prepared for transplantation with cyclophosphamide and total-body irradiation, underwent transplantation of bone marrow from unrelated donors for treatment of chronic myeloid leukemia, and survived beyond day 28 after transplantation were eligible for the study. Methotrexate and cyclosporine were administered for the prevention of graft-versus-host disease, and T cells were not removed from the donor marrow. A total of 471 donor-recipient pairs for which DNA or lymphoblastoid cell lines were available for retrospective class I and DPB1 sequencing were included in the analysis. Transplantations were performed between May 1985 and October 2000. The study

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**TABLE 1.** TERMINOLOGY FOR DONOR MATCHING OF HLA CLASS I ALLELES AND ANTIGENS.

TERM	MATCHING STATUS	EXAMPLES*	
		DONOR	RECIPIENT
Matched	Antigen matched	HLA-A2	HLA-A2
	Allele matched	HLA-A*0201	HLA-A*0201
Allele mismatched†	Antigen matched	HLA-A2	HLA-A2
	Allele mismatched	HLA-A*0201	HLA-A*0205
Antigen mismatched‡	Antigen mismatched	HLA-A2	HLA-A1
	Allele mismatched	HLA-A*0201	HLA-A*0101

\*HLA alleles and antigens are designated according to the World Health Organization nomenclature for factors of the HLA system.<sup>10</sup> The specific amino acid substitutions encoded by each allele are noted in Supplementary Appendix 1 (available with the full text of this article at <http://www.nejm.org>).

†Alleles are defined by DNA sequencing.

‡Antigens are defined by serologic analysis.

was approved by the institutional review board, and written informed consent was obtained from all patients.

#### Histocompatibility Testing and Criteria for Selection of Donors

Before transplantation, HLA-A and HLA-B antigens of the donor and the recipient were typed by the standard National Institutes of Health two-stage complement-dependent microcytotoxicity test, and HLA-DR and DQ antigens were typed with the use of purified B cells in a microcytotoxicity assay.<sup>15,16</sup> Before 1991, donor selection was based on matching for HLA-A, B, DR, and Dw.<sup>17</sup> After 1991, HLA-DRB1 allele typing was begun, and a single DRB1 allele mismatch was allowed for patients less than 36 years of age if a matched donor could not be identified.<sup>18</sup> In 1992, we began to use DQB1 allele typing and matching<sup>19</sup> for selection of donors and allowed a single DRB1 or DQB1 mismatch when a matched donor was not available. HLA-C serologic typing was used to select HLA-C-matched donors beginning in 1996, and matches were given priority over mismatches.<sup>7</sup> All donors had a negative lymphocytotoxic crossmatch before transplantation.

For this study, we sequenced HLA-A, B, C, and DPB1 alleles.<sup>9,20</sup> HLA-A, B, and C mismatches were defined as the presence of donor antigens or alleles not shared by the recipient. Antigen mismatches were detectable by serologic methods, whereas allele mismatches were detectable only by sequencing methods.<sup>10,21</sup> Recipient homozygosity at a mismatched locus was defined as the presence of a single allele.

#### Transplantation Procedure

All recipients were prepared for transplantation with intravenous cyclophosphamide (60 mg per kilogram of body weight), administered on each of two successive days, followed by total-body irradiation (1200 to 1575 cGy in 6 to 14 fractions). All protocols were reviewed and approved by the institutional review board at the center. Patients were assessed for engraftment if they survived beyond 28 days after infusion of bone marrow from an unrelated donor. Graft failure was defined as failure of the absolute neutrophil count to surpass 500 per cubic millimeter before relapse, second transplantation, or death (primary graft failure); a decrease in the absolute neutrophil count to less than 100 per cubic millimeter on at least three consecutive determinations at least one day apart after the initial engraftment without recovery before relapse, second transplantation, or death (secondary graft failure); or the absence of donor T cells as determined by testing for chimerism

with the use of variable-number tandem-repeat polymorphisms or in situ hybridization.<sup>7</sup>

#### Statistical Analysis

The primary end point of this study was graft failure, and survival was a secondary end point. Odds ratios for the probability of graft failure among class I mismatch categories were estimated with the use of conditional maximum-likelihood estimates from exact logistic regression, and P values were derived from Fisher's exact test. Survival percentages were estimated by the Kaplan–Meier method.<sup>22</sup> Comparisons of survival in each of the mismatched groups with survival in the matched group were based on the log-rank test. Variables previously shown to be associated with graft failure and other patient characteristics<sup>7,9,23</sup> were evaluated in each of the class I mismatch categories and compared with the use of the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables.

## RESULTS

#### Characteristics of the Study Population

Of the 471 donor–recipient pairs, 280 were matched for all six class I alleles, 49 had a mismatch for a single class I allele (16 HLA-A, 17 HLA-B, and 16 HLA-C), 56 had a single mismatch for a class I antigen (23 HLA-A, 4 HLA-B, and 29 HLA-C), and 86 had two or more mismatches for class I alleles or antigens in any combination (Table 2). Of the 105 pairs with a single class I mismatch, 86 (82 percent) were mismatched at HLA-DRB1, DQB1, or DPB1 as revealed by DNA typing. Primary graft failure was diagnosed in 26 patients, and secondary graft failure in 2 patients. In two patients, graft failure was diagnosed by the absence of donor T cells and granulocytes on routine follow-up examination one year after transplantation.

#### Effect of Recipient Homozygosity on the Risk of Graft Failure

Two graft failures occurred among the 280 transplants matched for HLA-A, B, and C (0.7 percent).

TABLE 2. CHARACTERISTICS OF THE STUDY POPULATION.\*

CHARACTERISTIC	MATCHED FOR HLA-A, B, AND C (N=280)	MISMATCHED FOR ONE HLA-A, B, OR C ALLELE (N=49)	MISMATCHED FOR ONE HLA-A, B, OR C ANTIGEN (N=56)	MULTIPLE MISMATCHES† (N=86)
Phase of disease (no.)				
Chronic phase	202	38	38	53
Accelerated phase	55	9	11	25
Blast crisis	11	1	5	2
Remission after blast crisis	12	1	2	6
Months between diagnosis and transplantation				
Median	13.7	14.0	17.2	21.1
Range	0.8–212.0	0–66.3	5.8–129.0	5.6–328.0
Matching status for HLA-DRB1, DQB1, and DPB1 (no.)				
Matched	66	10	9	16
One mismatch	108	15	22	26
Two or more mismatches	106	24	25	44
Recipient's age (yr)				
Median	37.0	36.1	36.9	33.5
Range	6.0–55.1	1.8–54.6	8.2–53.6	5.9–51.2
Dose of marrow cells ( $\times 10^{-8}$ /kg of body weight)				
Median	3.1	3.5	3.5	3.3
Range	0.4–30.0	1.1–18.9	0.9–14.3	1.4–18.4
Treated with more than 1200 cGy of total-body radiation (no.)	93	14	36	62

\*All patients received cyclophosphamide and total-body irradiation as a conditioning regimen and methotrexate and cyclosporine for immunosuppression after transplantation.

†Multiple mismatches were defined as any combination of two or more mismatches of antigens, alleles, or both at HLA-A, B, or C.

Among the 105 pairs mismatched for one class I allele or antigen, 7 recipients were homozygous and 98 were heterozygous at the mismatched locus (Table 3). Among pairs mismatched for a single allele, graft failure occurred in 1 of 2 homozygous recipients and in none of 47 heterozygous recipients ( $P=0.04$ ). Among pairs mismatched for a single antigen, graft failure occurred in 4 of 5 homozygous recipients and in 7 of 51 heterozygous recipients ( $P=0.004$ ). Recipient homozygosity for alleles or antigens was significantly associated with graft failure among patients with a single class I mismatch ( $P<0.001$ ).

The effect of recipient homozygosity was also evaluated in the 86 transplants with multiple class I allele and antigen mismatches in any combination. Among recipients who were homozygous at any HLA class I locus mismatched for two or three alleles, the proportions of graft failures were one of six and two of four, respectively. Among recipients who were heterozygous at all HLA class I loci mismatched for two, three, four, or five alleles, the proportions of graft failures were 8 of 47, 4 of 22, 1 of 4, and 0 of 3, respectively.

#### Effects of Allele and Antigen Mismatches on the Risk of Graft Failure

The risk of graft failure conferred by mismatches for HLA-A, B, and C alleles or antigens was measured in heterozygous recipients with a single mismatch (Table 4). Graft failure occurred in none of 47 recipients with donors who were mismatched for a single allele and in 7 of 51 recipients with donors mismatched for a single antigen (14 percent,  $P=0.01$ ). Among the 76 heterozygous pairs with multiple class I mismatches, 9 donors were mismatched for two or more alleles but no antigens and 67 were mismatched for at least one antigen. Graft failure occurred in 2 of 9 pairs with no antigen mismatching (22 percent) and in 11 of 67 pairs with antigen mismatching (16 percent).

In univariate logistic-regression analysis, the odds ratio for graft failure was influenced by the nature and number of mismatches at HLA-A, B, and C (Table 4). Mismatching involving a single HLA-A, B, or C allele was not associated with graft failure. Mismatching involving a single HLA-A, B, or C antigen, multiple HLA class I alleles, or multiple alleles

**TABLE 3.** EFFECT OF RECIPIENT HOMOZYGOSITY ON THE RISK OF GRAFT FAILURE IN TRANSPLANTS WITH SINGLE CLASS I MISMATCHES.

MISMATCH	PROPORTION WITH GRAFT FAILURE	
	HOMOZYGOUS RECIPIENTS	HETEROZYGOUS RECIPIENTS
	no. of failures/ no. of transplantations (%)	
Single allele*		
HLA-A	0/0	0/16
HLA-B	0/0	0/17
HLA-C	1/2 (50)	0/14
Single antigen†		
HLA-A	2/2 (100)	3/21 (14)
HLA-B	1/1 (100)	0/3
HLA-C	1/2 (50)	4/27 (15)
Total‡	5/7 (71)	7/98 (7)

\*P=0.04 for the comparison between groups (1/2 vs. 0/47).

†P=0.004 for the comparison between groups (4/5 vs. 7/51).

‡P<0.001.

and antigens was associated with an increased risk of graft failure (Table 4).

Previous studies have identified a low dose of marrow cells to be a risk factor for graft failure.<sup>7,9,23</sup> There was a suggestive difference in the dose of marrow cells among the groups categorized in Table 2 (P=0.07). The group with the lowest cell dose, however, consisted of patients matched for all six class I

alleles (lowest risk of graft failure). Other factors potentially associated with the risk of graft failure include the number of mismatched HLA class II alleles, the stage of disease at the time of transplantation, and the dose of total-body radiation. The distribution of mismatched class II alleles was not significantly different among the groups with mismatches categorized in Table 2 (P=0.32), nor was the distribution of disease stage (P=0.28). By protocol design, patients with class I mismatches were more likely to have received a higher dose of radiation. The odds ratio for the association between class I mismatching and graft failure was not significantly altered by the presence of HLA-DRB1, DQB1, or DPB1 disparity, the dose of total-body radiation, the dose of marrow cells, or the phase of disease.

Survival at five years for heterozygous recipients with matched donors, donors mismatched for a single class I allele, donors mismatched for a single class I antigen, and donors with multiple class I mismatches and for homozygous recipients with donors mismatched for a single class I allele or antigen was 62 percent, 49 percent, 53 percent, 44 percent, and 43 percent, respectively. Comparison of survival in each of the groups with mismatching with survival in the group with matching of alleles yielded P=0.17 for single allele mismatches, P=0.33 for single antigen mismatches, P=0.002 for multiple mismatches, and P=0.34 for homozygous recipients. Of the 30 patients with graft failure, 6 had recovery of autologous hematopoiesis and are alive. Two patients received reinfusion of cryopreserved autologous stem cells, and both are alive. Nine patients died before a second transplantation could be attempted. Thirteen

**TABLE 4.** PROPORTION OF HETEROZYGOUS RECIPIENTS WITH GRAFT FAILURES.\*

MATCHING STATUS	PROPORTION WITH GRAFT FAILURE	ODDS RATIO (95% CI)	P VALUE
	no. of failures/no. of transplantations (%)		
Matched	2/280 (0.7)	1.0	—
One class I mismatch			
HLA-A, B, or C allele	0/47	0 (-∞ to 31.9)	1.0
HLA-A, B, or C antigen	7/51 (14)	21.8 (4.0 to 221.2)	<0.001
Multiple class I mismatches			
Alleles†	2/9 (22)	37.4 (2.4 to 585.9)	0.005
Alleles and antigens‡	11/67 (16)	26.9 (5.7 to 256.5)	<0.001

\*The matched group is used for the comparison with each of the mismatched groups. CI denotes confidence interval.

†The two recipients with graft failure had two HLA-A mismatches with one HLA-C mismatch and two HLA-B mismatches, respectively.

‡The 11 recipients with graft failure had combinations of allele and antigen mismatches at HLA-A, B, and C.

patients received a second allogeneic transplantation, and seven of them are alive.

#### Comparison of Amino Acid Substitutions in Patients with Allele or Antigen Mismatches

Figure 1 illustrates the number and position of amino acid substitutions among the heterozygous patients mismatched for a single allele or a single antigen. The single allele mismatches were characterized by 0 to 8 nonsynonymous substitutions in the  $\alpha_1$  domain and by 0 to 9 substitutions in the  $\alpha_2$  domain (total range, 1 to 14; median, 2). The single antigen mismatches encoded 0 to 13 substitutions in the  $\alpha_1$  domain and 0 to 16 in the  $\alpha_2$  domain (total range, 1 to 27; median, 13). The allele and antigen mismatches differed not only in the number of nonsynonymous substitutions but also in the location of the mismatches in the two domains (Fig. 1 and Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>).

#### DISCUSSION

Graft failure remains a dangerous complication after transplantation of hematopoietic cells from unrelated donors.<sup>9,24-26</sup> Our analysis demonstrates that both qualitative and quantitative characteristics of disparity for HLA class I alleles and antigens can be used to categorize the risk of graft failure after transplantation of stem cells from unrelated donors for treatment of chronic myeloid leukemia with myeloablative preconditioning. Furthermore, homozygosity of the recipient was identified as a risk factor for graft failure.

Serologic reagents for the HLA-C locus have been difficult to obtain, possibly because the expression of HLA-C on the cell surface is low as compared with the expression of HLA-A and B antigens.<sup>27,28</sup> In this study, we used DNA sequencing to define HLA-C alleles, and this information was then mapped to standardized, serologically defined antigens.<sup>21</sup> The relation between HLA-C antigen and allele mismatches and the risk of graft failure followed the pattern observed with HLA-A and B antigen and allele mismatches. These observations indicate that identical criteria can be used to distinguish functionally important epitopes encoded by all three class I genes.

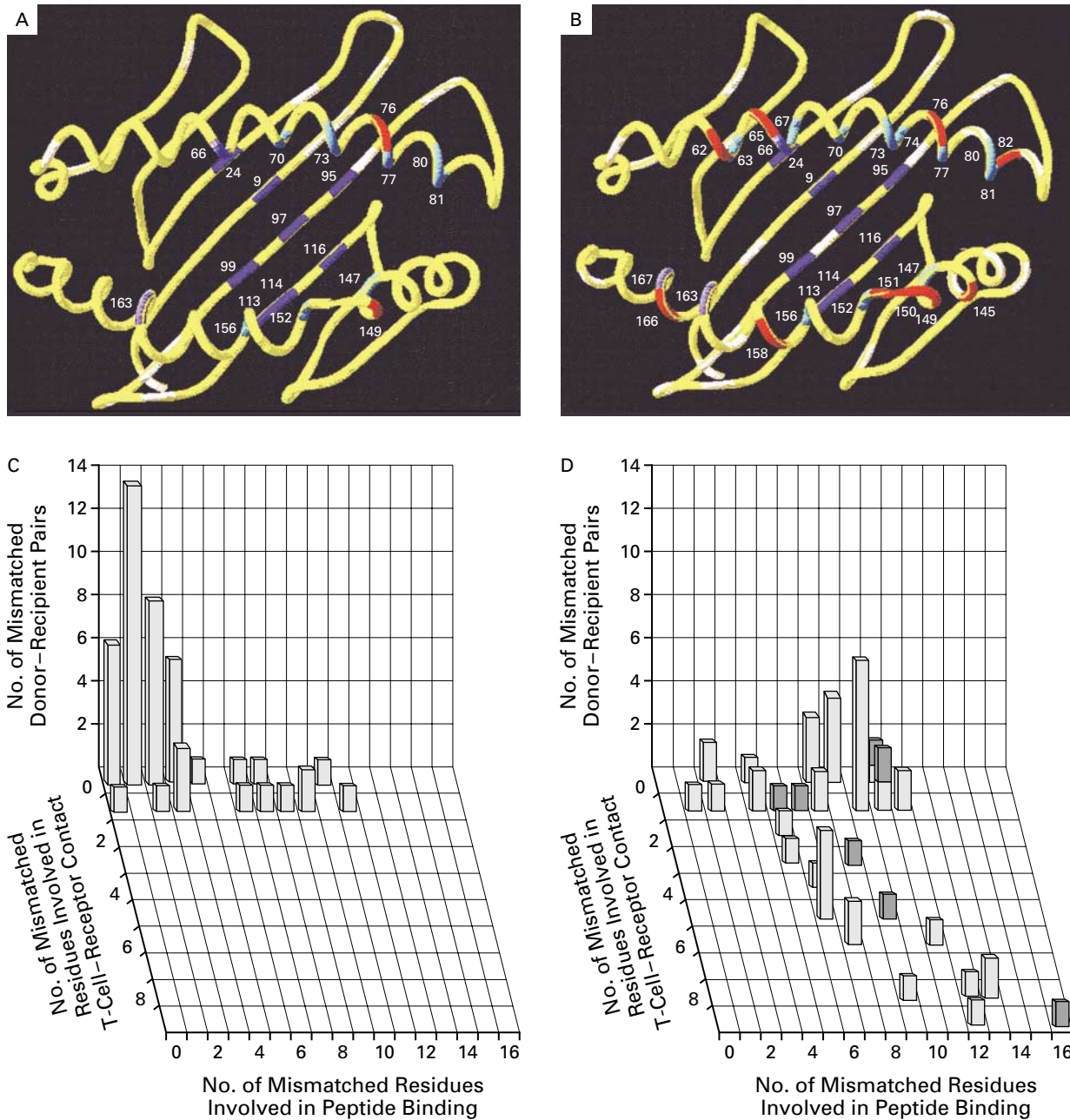
The identification of recipient homozygosity for HLA alleles or antigens as a risk factor for graft failure confirms and extends previous experience with haploidentical grafts from related donors.<sup>29</sup> Recipient class I disparity might induce an antirecipient T-cell cytotoxic response in the donor's cells, thereby eliminating any recipient cells that could cause graft failure. From a practical standpoint, if donor mismatches cannot be avoided, then the preferred HLA-A, B, or C allele or antigen mismatch should be at a locus for which the recipient is heterozygous, thereby ensuring a concomitant recipient mismatch to counterbalance the donor mismatch.

The T cells of the recipient cause graft rejection when they are activated by the class I alloantigens of the donor. Natural killer cells in the recipient can cause graft rejection when inhibition of their activation by class I molecules on donor cells is absent.<sup>30</sup> Among pairs mismatched at a single locus in our study, nine recipients had homozygous donors, and all had engraftment. These results do not support the hypothesis that the recipient's natural killer cells caused graft failure under the conditions we used for transplantation. Similarly, the high risk of graft failure among homozygous recipients with heterozygous donors indicates that the donor's natural killer cells could not prevent graft failure.

The distribution of substitutions in the coding sequences of HLA-A, B, and C alleles is not random.<sup>31</sup> Nearly all substitutions involve a change in the amino acid residues that influence binding of peptides in the internal groove or contact of the T-cell receptor with the external  $\alpha$  helix of the class I molecule.<sup>11-14,32</sup> The donor-recipient pairs that were mismatched for a single allele had 0 to 11 substitutions in the residues involved in peptide binding (median, 2) and 0 to 1 substitutions in residues involved in contact with the T-cell receptor (median, 0). The group with a single antigen mismatch had 0 to 16 substitutions in the residues involved in peptide binding (median, 8) and 0 to 9 substitutions in residues involved in contact with the T-cell receptor (median, 1). The allele-mismatch and antigen-mismatch groups differ significantly with respect to the median number of mismatches both for residues involved in peptide binding and for residues involved in T-cell-receptor contact ( $P < 0.001$ ) (Fig. 1 and Supplementary Appendix 1).

The seven grafts with single antigen mismatches that failed were mismatched for 5 to 16 residues implicated in peptide binding and for 0 to 9 residues involved in T-cell-receptor contact (Fig. 1D). These data demonstrate that T cells are sensitive to qualitative differences between donor and recipient class I molecules, which are defined by the substituted amino acids and their location, and to quantitative differences in the total number of mismatches. These differences together define permissible and nonpermissible HLA disparities in transplantation. The data further suggest that multiple nonsynonymous substitutions affecting peptide binding and T-cell-receptor contact were instrumental in augmenting the strength and breadth of T-cell responses that caused graft failure.<sup>33</sup> We hypothesize that multiple allele mismatches may provide the threshold of disparity needed to activate a similarly strong and broad T-cell response leading to graft failure, an effect that is limiting in single allele mismatches.

The function of an HLA molecule is an extension of its structure. The results of this study demonstrate that class I epitopes capable of generating a humoral response are also involved in the T-cell-mediated cy-



**Figure 1.** Number and Location of Mismatched Residues Encoded by Single Allele and Single Antigen Mismatches in the Study Population.

Panels A and B show the three-dimensional structure of the HLA class I molecule, depicting mismatched residues among the donor–recipient pairs who were mismatched for a single allele (Panel A) and a single antigen (Panel B). Residues are numbered according to their sequence in the protein. Residues involved in peptide binding are shown in dark blue for disparities in the  $\beta$ -pleated sheet and light blue for disparities in  $\alpha$  helices. Residues implicated in contact with the T-cell receptor are red. Mismatched residues that are not implicated in either peptide binding or T-cell–receptor contact are white; residues involved in both peptide binding and T-cell–receptor contact are gray. Panels C and D show the number of mismatched residues involved in peptide binding and T-cell–receptor contact in each donor–recipient pair mismatched for a single allele (Panel C) and in each pair mismatched for a single antigen (Panel D). Recipients who had graft failure are indicated in dark gray in Panel D. Data for one transplant recipient who did not have graft failure are not included in Panel D because insufficient DNA precluded sequencing of the mismatched HLA-B38 and B39 alleles.

totoxic responses that cause graft failure. A new definition of acceptable HLA mismatches that is based on functional epitopes may broaden the application of transplantation and provide a means for improving the overall success of transplantation as a curative procedure for hematologic cancers.

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