To the editor:

Significantly higher frequencies of alloreactive CD4+ T cells responding to nonpermissive than to permissive HLA-DPB1 T-cell epitope disparities

Increasing evidence suggests that donor-recipient disparities for human leukocyte antigen (HLA)–DPB1 can be of clinical importance in unrelated hematopoietic stem cell transplantation (HSCT).1 Two overlapping algorithms for functional T-cell epitope (TCE) matching involving 3 (TCE3) or 4 (TCE4) groups of DPB1 alleles have previously been shown to be significantly predictive of survival after 10/10 and 9/10 matched unrelated HSCT.2,3 In both TCE3 and TCE4, nonpermissive mismatches are directed against 2 groups of immunogenic antigens encoded by DPB1*09:01, 10:01, 17:01 (TCE3/4 group 1) and DPB1*03:01, 14:01, 45:01 (TCE3/4 group 2), respectively.2,3 In TCE3, all other frequent DPB1 alleles including DPB1*02:01, 04:01, 04:02 and others are classified as poorly immunogenic TCE3 group 3, and DPB1 mismatches against these alleles are predicted to be permissive.2 In TCE4, TCE3 group 3 is further subdivided into 2 separate groups comprising DPB1*02 (TCE4 group 3) and the other alleles (TCE4 group 4), with intermediate and poor immunogenicity, respectively.3

Rutten and colleagues have recently shown that T-cell responses could be obtained against DP antigens from all 4 groups,4,5 thereby confirming the observations that led to the discovery of the DP locus by primed lymphocyte testing,6 as well as those obtained later in mixed lymphocyte reactions (MLRs).7,8 Interestingly, ex vivo evidence was previously reported by Rutten and colleagues4 who showed that in 2 patients after 10/10 matched HSCT, the number of T cells responding to mismatched DP alloantigens was highest for TCE3/4 group 2 (2.72%), lower for TCE3 group 4 (1.81% ± 2.82%), but higher than those against TCE4 group 4 (1.81% ± 2.82%), resulting in no significant net effect on the predictable value of TCE3 and TCE4.

Our data provide, for the first time, in vitro evidence for differential immunogenicity of DPB1 according to our algorithms. Interestingly, ex vivo evidence was previously reported by Rutten and colleagues4 who showed that in 2 patients after 10/10 matched HSCT, the number of T cells responding to mismatched DP alloantigens was highest for TCE3/4 group 2 (2.72%), lower for TCE3 group 4 (1.08%), and lowest for TCE4 group 4 (0.41%). Further work is needed to determine the molecular and cellular basis of our algorithms, including the role of the DPα chain.

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Figure 1. Quantification of alloreactive CD4+ T cells responding to permissive or nonpermissive DPB1 TCE3 or TCE4 disparities. Classical 1-way MLRs were set up between R-S pairs of unrelated volunteers selected for the same patient and matched between each other for 10/10 of the HLA-A, -B, -C, -DRB, and -DQB1 alleles, but mismatched for -DPB1. R cells consisted of peripheral blood mononuclear cells (PBMCs), while S cells in most cases were PBMCs depleted of CD3-T cells, with a mean of 44.75% CD4+ T cells, with a mean of 25.17% CD4+ T cells. Pairwise comparison of the results obtained in the different groups was performed by the Kruskal-Wallis test followed by the Dunn multiple comparison posttest. (Left panel) In the TCE3 permissive group (n = 15), the mismatched DPB1 allele expressed by S was encoded by DPB1*04:02 (n = 4), 02:02 (n = 1), 04:01 (n = 5), 04:02 (n = 3), 11:01 (n = 1), 13:01 (n = 1). In the TCE3 nonpermissive group (n = 9), the mismatched DPB1 allele expressed by S was encoded by DPB1*03:01 (n = 3), 09:01 (n = 2), 10:01 (n = 3) or 17:01 (n = 1). The frequency of CD4+ T cells specifically responding to TCE3 permissive mismatches was significantly lower compared with TCE3 nonpermissive mismatches (**P < .05) and compared with fully mismatched third-party alloantigens (***P < .001). (Right panel) In the TCE4 permissive group (n = 10), the mismatched DPB1 allele expressed by S was encoded by DPB1*04:01 (n = 5), 04:02 (n = 3), 11:01 (n = 1), 13:01 (n = 1). In the TCE4 nonpermissive group (n = 15), the mismatched DPB1 allele expressed by S was encoded by DPB1*02:01 (n = 4), 02:02 (n = 1), 03:01 (n = 3), 09:01 (n = 2), 10:01 (n = 3) or 17:01 (n = 1). The frequency of CD4+ T cells specifically responding to TCE4 permissive mismatches was significantly lower compared with TCE4 nonpermissive mismatches (**P < .05) and compared with fully mismatched third-party alloantigens (***P < .001).

The authors declare that approval was obtained from the San Raffaele Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

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