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Fine-tuning alloreactivity against HLA-DP to control leukemia with tolerable GVHD

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In this issue of Haematologica, Ruggeri et al report that for patients with high expression of HLA-DPB1, hematopoietic stem cell transplantation from unrelated donors who have a mismatch at HLA-DPB1 that is permissive for T cell epitopes (TCE) improves relapse-free survival over non-TCE permissive mismatched or even HLA-DPB1 matched donors. Overall survival is also improved over non-TCE permissive mismatched but not over HLA-DPB1 matched donors.[1]

The development of large worldwide registries of HLA typed volunteers has allowed transplantation of compatible unrelated donors cells for most patients in need. However, because of the poor linkage disequilibrium between HLA-DP and the rest of the HLA haplotype, most donors have not been selected based on HLA-DPB1, so that about 80% of unrelated transplants have been mismatched at HLA-DPB1. Alloreactivity to isolated HLA-DPB1 mismatch has been associated with a decreased risk of leukemia relapse but also an increased risk of acute graft-versus-host disease (GVHD) and non-relapse mortality, with no net advantage for disease-free or overall survival.

Distinct HLA-DPB1 disparities are associated with varying degree of alloreactivity, and multiple models have attempted to identify beneficial disparities associated with improved control of leukemia and less dangerous disparities associated with less serious GVHD. The two models addressed in this manuscript are the level of HLA-DPB1 expression in the recipient that is directly associated with greater protection from leukemia relapse but also more GVHD, and the selection of TCE-permissive, HLA-DPB1 mismatched donors that are associated with attenuated risks of GVHD and non-

relapse mortality.[2-5] The paper reports a significant interaction between high HLA-DPB1 expression in the host and donor HLA-DPB1 TCE-permissiveness in opposing directions, with lower mortality associated with donor TCE-permissiveness in the high-expression recipient group despite increased GVHD and decreased leukemia relapse.[1]

Mechanistically, data are strong relating the HLA-DPB1 regulatory region variant rs9277534 with HLA-DPB1 expression,[2] increased GVHD,[2-3] and protection from relapse after allogenic stem cell transplantation.[1,2] Furthermore, escape from immune control of leukemia has been associated with HLA class II downregulation after allogeneic stem cell transplantation.[6] Additional studies, however, should formally demonstrate that the HLA-DPB1 regulatory region variant rs9277534 is associated with HLA-DPB1 expression in leukemia, and lower levels of HLA-DPB1 in leukemia increase the risk of relapse after allogeneic stem cell transplantation.

Functional studies have clustered HLA-DPB1 mismatched pairs into relatively well defined TCE groups, and clinical association studies have found lower risk of GVHD and mortality within these functionally defined TCE permissive disparities.[4-5] Thus, it is not surprising that TCE-defined permissive HLA-DPB1 disparate donors protect recipients with high HLA-DPB1 expression from excess GVHD and mortality.[1] The mechanisms by which TCE permissive HLA-DPB1 mismatches protect from excess alloreactivity and GVHD-dependent mortality have been related to the more narrow functional distance compared to the non-permissive disparities, and selection of a more narrow immunopeptidome.[7-9]

A major limitation in the translation of this study's findings to decrease the risk of relapse after transplantation is that only 46% of the patients express high levels of HLA-DPB1 based on the polymorphism of the regulatory region variant rs9277534 (Supplemental Figure S1A).[1] It is conceivable, however, that approaches can be devised at some point in time to upregulate expression of HLA-DPB1 in leukemia. The baseline DPB1 TCE-permissive match rate among recipients with high expression of HLA-DPB1 was 49% in this study, but it should improve to 80% after additional donor DPB1 typing.[10]

While study of the combined models (HLA-DPB1 expression and TCE-permissiveness) is highly innovative and important, we note that these findings require validation in independent study populations, and that analyses will need to account for potential interaction between HLA-DPB1 expression and TCE-permissiveness for survival and relapse outcomes. As well, application of these findings to unrelated donor search and selection strategy under current practices may be limited: In 65% of the cases studied, classification by the two models was convergent, such that high expression converged with TCE non-permissive status and low expression converged with TCE permissive status. We anticipate that under current practices TCE-permissive donors would be preferentially selected when available. Possible future application of this combined model approach would require routine assessment of HLA-DPB1 expression, and preferential use of TCE-permissive donors among those with high expression.

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