Fine-tuning alloreactivity against HLA-DP to control leukemia with tolerable graft-*versus*-host disease

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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 for transplants from TCE-permissive donors over those from 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 donor 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 degrees 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 the study by Ruggeri *et al.* 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 who are associated with attenuated risks of GvHD and non-relapse mortality.[2-5] Their 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, there are strong data relating the HLA-DPB1 regulatory region variant rs9277534 with HLA-DPB1 expression,[2] increased GvHD,[2-3] and protection from relapse after allogeneic stem cell transplantation.[1,2] Furthermore, HLA class II downregulation has been associated with escape from immune control of leukemia 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 that 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 a narrower functional distance compared to that of the non-permissive disparities, and selection of a narrower immunopeptidome.[7-9]

A major limitation to the translation of this study's findings into a decrease in the risk of relapse after transplantation is that only 46% of patients express high levels of HLA-DPB1 based on the polymorphism of the regulatory region variant rs9277534 (see *Online Supplementary Figure S1A* in the paper by Ruggeri *et al.*)[1] Nevertheless, it is conceivable that, in the future, approaches can be devised 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 could be improved to 80% by additional donor DPB1 typing.[10]

While a study of the combined models (HLA-DPB1 expression and TCE-permissiveness) is highly innovative and important, we note that the findings require valida-

tion in independent study populations, and that analyses will need to account for a potential interaction between HLA-DPB1 expression and TCE-permissiveness for survival and relapse outcomes. Furthermore, application of these findings to unrelated donor search and selection strategies in current practice 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 practice, 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.

Disclosures

No conflicts of interest to disclose.

Contributions

JP and CA both wrote and edited the editorial.

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