single-center reporting, high- versus low-resolution MICA typing, HLA disparity in the patient cohorts (matched vs potentially mismatched), and differing experimental approaches. As called for by Parmar et al, confirmation of the role of MICA in GI aGVHD in a larger cohort of patients is necessary, particularly using high-resolution typing methods.

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Response:

MHC class I chain–related gene A (MICA) in unrelated donor transplantation

We thank Anderson et al for their questions regarding our report.[1] In brief, they failed to observe an association of major histocompatibility complex (MHC) class I chain–related gene A (MICA) mismatches and graft-versus-host disease (GVHD). The studies, however, have differences in design. Anderson and coworkers performed MICA typing in 38 donor-recipient pairs selected on the basis of complete matching in alleles of 12 human leukocyte antigen (HLA) loci (HLA-A, B, C, DRB1, DQB1, and DPB1), whereas in our study (n = 236) typing was performed without any bias on the basis of match grade with a subsequent outcome analysis. They had only one case of MICA mismatch, and that case did not develop GVHD.[2] In our cohort MICA mismatch frequency was 8.6%; the incidence of grade II-IV acute GVHD was significantly higher in MICA-mismatched patients after multivariate analysis.

The observed differences may be related to the discrepancy in sample sizes. Both series show the low frequency of MICA mismatches in HLA-A/B/C/DRB1/DQB1–matched subjects, which results from tight linkage disequilibrium between HLA-B and MICA, as demonstrated in our dataset. Furthermore, because we used high-resolution MICA typing as previously described,[2] resolution level should not explain differences in outcomes between the studies. The 38 pairs described by Anderson were matched in all HLA loci including DPB1, whereas in our study only 16% percent of the pairs (26 of 167) that were fully matched in HLA-A/B/C/DRB1/DQB1 in both graft-versus-host (GVH) and host-versus-graft (HVG) directions were also fully matched in HLA-DPB1. The low frequency of mismatch in MICA (2.6%) in their analysis is likely the result of inclusion of patients carrying conserved HLA haplotypes. In contrast, in our set of patients matched in 10/10 alleles in the GVH direction (n = 172), there were 8 examples of mismatches in MICA (4.7%) in the GVH vector. It is important to note that HLA-DPB1 mismatches[3] were proportionally distributed in the MICA-matched and -mismatched pairs in our cohort (74% vs 63%; *P* = not significant), and the association of MICA mismatch with acute GVHD was independent of mismatches in HLA-DPB1.

The strength of the 2-locus linkage disequilibrium may differ in different HLA alleles and haplotypes; it is possible that some HLA-B alleles or haplotypes including specific HLA-B alleles show weaker linkage disequilibrium with MICA than others. We found that one or more of the alleles B*1801, B*3501, or B*3801 were present in 8 of 9 donor/recipient pairs matched in 10/10 alleles of HLA-A, B, C, DRB1 and DQB1 loci and presented one mismatch in MICA; in contrast, those HLA-B alleles were present in 28% (35 of 158) of the pairs fully matched in MICA and HLA-A/B/C/DRB1/DQB1 loci. The different distribution of HLA-B*1801, B*3501, and B*3801 in MICA matched and mismatched pairs was highly significant ($P < .001$), suggesting that haplotypes or haplotype fragments bearing these alleles show higher grades of diversity, which, in turn, result in MICA mismatches in pairs otherwise matched in other HLA alleles.

Anderson et al extended the analysis to a larger cohort of HLA 8/8 matched pairs (n = 1676), in which MICA allele assignment was made putatively on the basis of the most common HLA-B/MICA associations, not on actual typing. D′ is a measurement of linkage disequilibrium. The tightest link has a value of 1.0, and a value close to 0 indicates random association. The D′ between HLA-B and MICA ranges in 0.87 to 0.95 in randomly selected persons with either African American or white ancestry.[4] These values are lower than the estimations of D′ made by Anderson analyzing patients with a 12/12 allele-matched donor. The predictions of MICA alleles in these patients may be less accurate than those made for patients matching in DQ and DP in addition to the 8/8 alleles. In addition, their analysis identified only statistically nonsignificant trends for the association of MICA polymorphisms and gastrointestinal GVHD. Similarly, our study failed to identify an association between presence of MICA*008 and outcomes. Therefore, the polymorphism in MICA molecules by themselves may play a small if any role in determining susceptibility/resistance to acute GVHD and other outcomes in allogeneic hematopoietic stem cell transplantation.

In summary, MICA mismatches are uncommon in 10/10 or 12/12 allele-matched pairs. However, our study indicates that MICA may be a transplantation locus, a finding that deserves evaluation in larger cohorts. Studies investigating mismatches in MICA paired with mismatches in other loci that may lead to increased risk of GVHD[5] are also warranted.

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