through inhibition of elastase-induced cleavage and release of HS from the extracellular matrix in host tissues.

These observations have significant implications for our understanding of the biology of GVHD and also toward potential development of novel therapeutic strategies. They add to the growing body of evidence demonstrating the impact of DAMPs in regulating alloreactivity and indicate that targeting specific DAMPs might regulate GVHD.[6] This work echoes the recent observations on the anti-inflammatory effects of AAT.[7-9] The study suggests, but does not directly demonstrate, that AAT "dampens" GVHD through the reduction of the DAMP, HS. While clarifying, like all interesting observations, the study raises additional questions. The critical role for TLR4-MyD88 pathways in aggravating GVHD is in contrast to recent findings by Li et al.[10] This could represent a potential strain dependency of the observations made by Brennan et al. It should remind us that insights from animal models, especially when they conflict, must be extrapolated to humans with caution. The increased levels of HS observed at the onset of GVHD in humans nonetheless add depth to Brennan and colleagues' observations. These observations will ideally have to be confirmed prospectively in a larger and more uniform cohort of patients. However, intriguingly, AAT mitigated GVHD in multiple models. Along with previous observations, this study further underscores the potent effects of AAT in modulating inflammation and immunity.[7-9] Brennan et al's observations and those by another study[8] suggest that in some GVHD models, the immunologic effects of AAT might be directly mediated by its antiprotease activity. However, this notion remains to be tested directly and definitively in these models. Indeed, whether the basic tenet that all functions of AAT are directly attributable to its ability to target elasatse remains to be rigorously tested.[9] The key cellular targets and the critical molecular mechanisms of AAT-mediated immune regulation are thus unknown. Nonetheless, in light of the clinical availability of AAT and its long track record of safety in humans, the observations of Brennan and colleagues along with those of others[7-9] suggest that administration of AAT may be considered as an adjunct to standard therapy, in carefully designed clinical trials to mitigate GVHD.

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REFERENCES

1. Johnson GB, Brunn GJ, Kodaira Y, Platt JL. Receptor-mediated monitoring of tissue well-being via detection of soluble heparan sulfate by Toll-like receptor 4. *J Immunol.* 2002;168(10):5233-5239.
2. Brennan TV, Lin L, Huang X, et al. Heparan sulfate, an endogenous TLR4 agonist, promotes acute GVHD after allogeneic stem cell transplantation. *Blood.* 2012;120(14):2899-2908.
3. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science.* 2010;327(5963):291-295.
4. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol.* 2012;12(6):443-458.
5. Paczesny S, Hanauer D, Sun Y, Reddy P. New perspectives on the biology of acute GVHD. *Bone Marrow Transplant.* 2010;45(1):1-11.
6. Zeiser R, Penack O, Holler E, Idzko M. Danger signals activating innate immunity in graft-versus-host disease. *J Mol Med (Berl).* 2011;89(9):833-845.
7. Tawara I, Sun Y, Lewis EC, et al. Alpha-1-antitrypsin monotherapy reduces graft-versus-host disease after experimental allogeneic bone marrow transplantation. *Proc Natl Acad Sci U S A.* 2012;109(2):564-569.
8. Marcondes AM, Li X, Tabellini L, et al. Inhibition of IL-32 activation by {alpha}-1 antitrypsin suppresses alloreactivity and increases survival in an allogeneic murine marrow transplantation model. *Blood.* 2011;118(18):5031-5039.
9. Lewis EC. Expanding the clinical indications for alpha-1-antitrypsin therapy [published online ahead of print May 16, 2012]. *Mol Med.* doi:10.2119/molmed.2011.00196.
10. Li H, Matte-Martone C, Tan HS, et al. Graft-versus-host disease is independent of innate signaling pathways triggered by pathogens in host hematopoietic cells. *J Immunol.* 2011;186(1):230-241.

TRANSPLANTATION

Comment on Horan et al, page 2918

HLA factors in transplantation for nonmalignant hematologic disorders

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In this issue of *Blood*, a study by Horan and colleagues shows that differences in the HLA alleles of patients and unrelated donors in hematopoietic stem cell transplantation (HSCT) for nonmalignant diseases result in increased risk for adverse treatment outcome.[1] This is the largest dataset examined so far for the evaluation of HLA mismatches in HSCT for nonmalignant diseases. It includes predominantly pediatric patients diagnosed with 39 diseases. Many patients received nonmyeloablative conditioning; a significant proportion of the infused grafts were depleted of T-lymphocytes; 6 diseases account for 77% of the cases.

Currently, the criteria used for selection of unrelated donors for nonmalignant diseases derive from studies performed in HSCT for patients with malignant diseases[2]; in the latter it was found that the HLA mismatches associated with patient mortality. The study by Horan et al shows that HLA mismatches in HLA-A, -B, -C, and DRB1 loci also have a significant impact in outcome of HSCT for nonmalignant diseases. This study provides useful insights that can be applied to the definition of unrelated donor selection criteria for nonmalignant diseases. The nonmalignant disease cohort[1] differs significantly from those examining HSCT for hematologic malignancies[2] in age, conditioning regimens, and graft composition. In the nonmalignant disease study the incidence of graft failure was at least 2 to 3 times higher than in the cohorts of malignant diseases. In nonmalignant disease transplantation, many patient deaths (29.8%) were associated with graft failure. The multivariate analyses showed that the occurrence of a single or a double mismatch in HLA-A, -B, -C, or DRB1 loci associated with graft failure; 2 HLA mismatches were also associated with mortality. The single HLA mismatch associated with patient death only in the univariate analysis. Interestingly, in nonmalignant disease HSCT, the mismatched HLA loci did not associate with any type or grade of graft-versus-host disease (GVHD). Horan and colleagues noted that the absence of an association between HLA mismatch and acute GVHD was likely because most of the patients received a lymphocyte-depleting antibody and/or received an ex vivo T cell–depleted graft. These findings contrast with those made in HSCT for malignant diseases; in the latter, the HLA mismatches associate risks for acute

GVHD, nonrelapse mortality, or treatment-related mortality. Therefore, the causes of death in HSCT for malignant and nonmalignant diseases appear to differ significantly. The increased incidence of graft failure in nonmalignant disease transplantation may be caused by preserved or enhanced patient immune competence as they have not received chemotherapy prior to the preparative regimen.

This study was limited in sample size and a more detailed analysis of the impact in individual HLA loci or of the type of mismatch was not possible. Horan et al indicate that differences at either of the classically matched HLA loci (A, B, C, DRB1) at either allele or antigen level mismatches appear to have an equivalent impact in outcome. In nonmalignant disease study the mismatches in HLA-DQ and DP loci were not associated with poor outcomes. However, an adverse effect of mismatches in these loci cannot be fully excluded because the group of patients presenting mismatches in HLA-A, -B, -C, or DRB1 loci had more mismatches in HLA-DQ and/or DP loci.

In the study by Horan et al the impact of preformed allo-antibodies in the patients' serum that could react with the mismatched donor antigens (DSAs) was not evaluated. Other studies of HSCT in malignant diseases showed an association between DSA and primary graft failure (PGF).[3,4] Typically, many nonmalignant disease patients have preserved or enhanced immune function and often receive blood transfusions; it is likely that in nonmalignant diseases the incidence of humoral HLA allo-immunization may be even higher than in patients with hematologic malignancies. Therefore, in the nonmalignant disease HSCT setting, the presence of anti-HLA donor antigens may be more significant in outcome by increasing the risk of PGF. Future nonmalignant disease studies should be performed to directly investigate the impact of DSA on outcome. It is suggested that the evaluation of anti-HLA antibodies reactive with donor antigens should now be performed prospectively in HSCT for nonmalignant diseases for the selection of unrelated donors.

Although humoral sensitization plays a significant role in graft rejection, the patient's T-cell HLA allo-reactivity may also cause graft failure. In HSCT for malignant diseases, 30% to 40% of PGFs present anti-HLA antibodies reactive with the mismatched donor antigens[3,4]; it can be argued that a significant proportion of the remaining PGF cases may have resulted from rejection mediated by patients' T-cell lymphocytes. In the nonmalignant disease HSCT study,[1] HLA mismatches associate with graft failure at both allele and antigen levels. It can be argued that because most of the HLA allele level mismatches are not recognized by allo-antibodies, the negative impact of these mismatches may result from T-cell allo-recognition.

The present study sets grounds for further investigation of HLA matching in nonmalignant diseases, specifically in factors determining risk for graft failure. Investigations in this area may allow expanding HSC sources from either unrelated cord blood units or from donors presenting a mismatch in 1 HLA haplotype. These graft sources are easily and rapidly available for children with nonmalignant diseases; however, due to higher risk of graft failure they are not always preferred. Therefore, further insight into histcompatibility factors may allow the development of strategies for identifying patient/donor pairs with low risk for graft rejection; the resulting criteria may allow finding allogeneic HSC sources for almost all patients.

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REFERENCES

1. Horan J, Wang T, Haagenson M, et al. Evaluation of HLA matching in unrelated hematopoietic stem cell transplantation for nonmalignant disorders. *Blood.* 2012;120(14):2918-2924.

2. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood.* 2007;110(13):4576-4583.

3. Spellman S, Bray R, Rosen-Bronson S, et al. The detection of donordirected, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. *Blood.* 2010;115(13):2704-2708.

4. Ciurea SO, Thall PF, Wang X, et al. Donor-specific anti-HLA Abs and graft failure in matched unrelated donor hematopoietic stem cell transplantation. *Blood.* 2011;118(22):5957-5964.