laser injury, suggesting that P2X1-dependent activation of neutrophils plays an important role in the formation of the fibrin clot. This is a newly appreciated mechanism for ATP in the regulation of fibrin formation, as P2X7 expression on myeloid cells was previously shown to be required for the decryption of TF and release of TFβ microparticles leading to thrombin generation. Conversely, injection of WT neutrophils into injured P2X1−/− mice was not sufficient to reconstitute platelet accumulation into the growing thrombus; rather, P2X1 expression on both platelets and neutrophils is required for full platelet- and fibrin-rich hemostatic plug formation.

Although release of circulating nucleotides ATP and adenosine 5′-diphosphate (ADP; an important platelet agonist) positively regulates generation of the hemostatic plug close to the site of injury, an extra level of regulation is achieved by the metabolism of these extracellular nucleotides with increasing distance from the injured site. Endothelial and plasma ectonucleotidases, chiefly CD39 and CD73, hydrolyze ATP and ADP sequentially to adenosine 5′-monophosphate (AMP) and adenosine, respectively. In contrast to the neutrophil-activating properties of ATP, this study demonstrates that a selective agonist for the A2A adenosine receptor on neutrophils inhibits both neutrophil accumulation at the site of injury and elastase release from the activated neutrophils. This suggests that complete hydrolysis of ATP and ADP through AMP to adenosine may constrain fibrin deposition close to the site of injury by activating neutrophil A2A receptors as concentrations of adenosine (relative to ATP) rise further from the injury site, thereby inhibiting neutrophil elastase release and consequent inhibition of TFPI. Whether in vivo levels of adenosine are consistent with this model is at present unclear; nevertheless, such a mechanism would be consistent with studies that have shown enhanced fibrin deposition in CD39−/− mice.

In summary, this study demonstrates a novel role for the ionotropic ATP receptor P2X1 on neutrophils in the generation of fibrin at sites of vascular injury through the release of neutrophil elastase (to inactivate TFPI) and confirms a requirement for neutrophil P2X1 to work together with P2X1 on platelets to generate the hemostatic plug (see figure). Because nucleotide: nucleoside ratios are important for regulating both thrombotic and inflammatory events, P2X1 may be an attractive target for the development of antagonists to limit thrombo-inflammatory disease.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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*** TRANSPLANTATION ***

Comment on Pidala et al, page 2596

HLA-DP1 matching: are we there yet?

Aron Nagler SHEBA MEDICAL CENTER TEL HASHOMER

In this issue of Blood, Pidala et al report that nonpermissive DPB1 allele mismatch is associated with increased transplant-related mortality (TRM) and should be avoided to secure optimal unrelated donor hematopoietic stem cell transplantsations (HSCTs). Further, in the unrelated cord blood transplant setting, it was recently shown that allele level HLA-A, -B, -C, and -DRB1 locus matching between unrelated cord blood units and the recipients improves the engraftment and reduces TRM, thus improving the outcome after umbilical cord blood transplantation.

The DP locus of the HLA class II system was first described in 1978 as a target of alloreactive ‘T’-cell responses identified in secondary mixed lymphocyte cultures. With the advent of molecular biology techniques, the full degree of the HLA-DP polymorphism was described with 20 and 106 HLA-DPA1 and -DPB1 alleles, respectively. The overall clinical significance of HLA-DPB1 mismatches for the clinical outcome of HSCT is less clear, because the likelihood of patient-donor matching for this locus is still a matter of debate. The majority

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of unrelated donor HSCTs (80%) are performed across HLA-DP mismatches. Initial retrospective studies failed to demonstrate a significant impact of HLA-DPB1 mismatches on the incidence of acute graft-versus-host disease (aGVHD). More recent reports showed that the incidence of severe aGVHD was increased in HLA-DPB1-mismatched transplantation. None of these studies demonstrated a correlation between HLA-DPB1 mismatching and TRM. In contrast, several other studies have demonstrated that HLA-DPB1–mismatched HSCT is associated with a decreased risk of disease relapse. Moreover, HLA-DP–specific CD4+ T cells from HLA-DPB1–mismatched donor lymphocyte infusion (DLI) was shown to induce a graft vs leukemia reactivity in both the presence and absence of GVHD. DPB1-specific CD4+ T cells can target nonhematopoietic tissues mediating GVHD after DPB1–mismatched CD4+ DLI, which is further potentiated by cytomegalovirus reactivation upregulating HLA class II expression on nonhematopoietic tissues.

Theoretically, the risk after unrelated HSCT can be decreased by selection of unrelated donors who also match for HLA-DPB1; however, such donors are difficult to find. The identification of permissive and nonpermissive HLA mismatches has therefore become a main challenge for modern HSCT biology. Classifications of HLA-DPB1 mismatches based on T-cell epitope groups could identify mismatches that might be tolerated (permissive) and those that would increase risks (nonpermissive) after transplantation. A retrospective evaluation of 118 transplantations by the San Raffaele group showed that the presence of nonpermissive HLA-DPB1 mismatches correlates with significantly increased hazards for aGVHD and TRM but not for relapse compared with the permissive group. There was also a marked but statistically insignificant increase in the hazards of overall mortality. More recently, the International Histocompatibility Working Group in hematopoietic stem transplantation analyzed the results of 8539 HSCTs from unrelated donors; of them, 1719 (20%) were HLA-DPB1 matches, 2670 (31%) were nonpermissive HLA-DPB1 mismatches, and 4150 (49%) were permissive HLA-DPB1 mismatches. Nonpermissive mismatches were associated with a significant increase in the risks for overall mortality, nonrelapse mortality, and severe aGVHD, but not for relapse, compared with permissive mismatches. In addition, there were significant differences between permissive HLA-DPB1 mismatches and HLA-DPB1 matches in terms of nonrelapse mortality and relapse but not for overall mortality or aGVHD. The authors conclude that avoidance of an unrelated donor with a nonpermissive T-cell–epitope mismatch at HLA-DPB1 might provide a practical clinical strategy for lowering the risk of mortality after unrelated donor HSCT.

The current study by Pidala et al validates the same findings for a population receiving mostly non–total body irradiation–based myeloablative conditioning and mobilized peripheral blood rather than bone marrow grafts. The authors reported that among 8/8 matched cases, HLA-DPB1 and -DQB1 mismatches resulted in increased aGVHD, and -DPB1 mismatches decreased relapse. Nonpermissive DPB1 allele mismatch was associated with higher TRM compared with permissive DPB1 match or DPB1 match and increased overall mortality compared with permissive DPB1 mismatch in 8/8 and 10/10 matched cases. However, among 7/8 matched cases, no significant effects of DPB1 mismatches were observed. Interestingly, both permissive and nonpermissive HLA-DPB1 allele mismatches were associated with a significant decrease in relapse risk compared with HLA-DPB1 allele matched cases, with no difference in relapse observed between permissive and nonpermissive cases.

How should we use this information for improving the outcome of unrelated HSCT HLA-DP1 matching: are we there yet? The selection criteria for a volunteer donor for a modern unrelated HSCT should include a full matching of HLA-A, -B, -C, and -DRB1 and lack of nonpermissive -DPB1 mismatches. Obviously, adding high-resolution HLA-DPB1 typing and incorporation of HLA-DPB1 typing into the routine daily practice search algorithm will have implications not just on the time and cost incurred, but also on the chance of finding suitable unrelated donors for patients in urgent need of a transplant.

The issue of the effect of nonpermissible HLA-DPB1 mismatch on the relapse rate is still controversial but may be of importance for AML patients who receive transplants when not in remission. Finally, the role of HLA-DPB1 mismatches in reduced-intensity and reduced-toxicity transplants should be further studied.

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