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DOI 10.1182/blood-2017-11-813899

TRANSFUSION MEDICINE

Comment on Saris et al, page 144

The delectability of platelets to a phagocyte

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In this issue of *Blood*, Saris et al show that some HLA antigens, namely, B8, B12, and B35, vary in expression on the platelets of some individuals and that this is a constant variant in these people.[1]

In this study, a unique opsonification assay is used to support the authors' hypothesis of antigen density as an important predictor of phagocytosis and measure of whether platelet transfusion refractoriness may occur. These laboratory studies were prompted by careful platelet transfusion studies done several decades ago where alloimmunized recipients to these antigens had good transfusion outcomes.[2,3]

An opsonin (from the Greek *opsōneîn*, "to prepare for eating and improving delectability") is any molecule that enhances phagocytosis by marking an antigen on a cell for an immune response (ie, causes the phagocyte to "relish" the marked cell). Classic immunohematology methodology shows that the determinants of the opsonification process and subsequent antigen clearance include antigen density, qualitative and quantitative features of the antibody, Fc receptor features, and activity of the effector cell, as well as most likely physical determinants such as surface tension and contact area.[4] Immunohematologists have taken advantage of these factors in both alloimmune and autoimmune destruction of cells to develop strategies to circumvent these pathologic processes.

The importance of HLA antigen density is, first, that these platelets with low antigen expression can be transfused into individuals and not be destroyed by alloantibodies with these HLA specificities and, secondly, the antigens may be less immunogenic if repeatedly transfused if there is no antigen presentation process that occurs. The advantage to the patient and to blood resource management would be increasing the number of potential platelet donors for all alloimmunized patients, who would ordinarily be excluded if one just relied on HLA typing results. To support their hypothesis, they first typed donors and determined the relative expression of these antigens. Those that showed little to no expression by monoclonal antibody typing of the platelets were used to test their delectability to phagocytic monocytes after opsonification with HLA antibody. Indeed, they showed that compared with opsonized controls, internalization of platelets obtained from donors with high HLA class I expression antigen density was significantly increased, in contrast to no observed internalization obtained from donors with low class I expression. Furthermore, they showed that the expression of HLA class I B locus antigens paralleled the expression on white cells and was a constant feature of these donors, which did not seem to vary with possible environmental conditions such as inflammation.

These studies support earlier transfusion outcome studies, where HLA-B12 mismatched platelets to refractory, alloimmunized patients with satisfactory increments in 69% of transfusions.[2] In this study, no immunohematologic studies were done; measure of antigen density was done to account for the failed transfusions. In many populations, HLA-B7, -B8, -B12, and -B35 are the most frequently expressed. Identifying donors with natural low expression of these frequent class I antigens could improve the availability of HLA matched donors. Clearly, before adopting such an approach to transfusions in patient populations, we will need to determine the efficacy of this approach. Further consideration of other factors may need to be given such as antibody titer, avidity, and isotype. It is possible that the threshold for expression and clearance may vary with specific patients. It is also possible that although a limited number of transfusion exposures of the donor may not provoke an immune response, eventually the patient will become immunized and refractory to the HLA type.

The strategies to provide platelet transfusions to alloimmunized patients include (1) HLA matching of donor recipient HLA class I A, B antigens, with or without identification of HLA antibody specificities,[5,6] and (2) cross matching platelets.[7,8] Of course, the HLA matching of donor and recipients is operationally complicated and expensive because the matching requires the availability of several thousand typed donors to provide the number of transfusions that may be necessary for a patient. The use of donors with acceptable antigen mismatches has

helped decrease the complexity of finding donors, along with screening the patient's sera and identifying HLA specificity and then using HLA types that lack these specificities.[9] Saris et al suggest that further characterization of the donor may be the determination of antigen density for donors and maintaining a registry that allows for their selection. Technically, this is feasible with relatively simple immunologic testing. Future studies should explore clinical effectiveness of such a "low HLA expressed mismatch" strategy and determine which expression levels result in satisfactory increments in refractory patients because of alloimmunization, and whether repetitive exposure to the same donor in a patient leads to a change in the immune effectors promoting opsonification. Overall, I think that Saris et al present a path to improving our approach in managing platelet alloimmunization and underscore how clinical observations serve to improve our understanding of biological processes.

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

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DOI 10.1182/blood-2017-11-815498