Will MICA Glitter for Recipients of Kidney Transplants?

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Renal transplantation as the treatment of choice for end-stage renal failure is associated with excellent short-term results. The 1-year patient-survival rate is 96%, and the 1-year allograft-survival rate is more than 90%. Although the 5-year patient-survival rate after renal transplantation remains at about 90%, there is a steady attrition of allografts because of long-term rejection, which limits the 5-year allograft-survival rate to about 80%.1

In the more than half century since the first clinical renal transplantations in the early 1950s, the procedure has become standard practice. There has been steady progress in allograft survival since the development of proper HLA matching and sufficient immunosuppressive therapy.2 One or more mismatches in HLA-A, HLA-B, and HLA-DR antigens still reduce allograft survival significantly.

A variety of “minor antigens,” a term that lumps together several diverse antigens besides the HLA antigens, also play a role in allograft failure, independent of HLA. Among such antigens, the ABO blood-group antigens are the most important, and generally the antigens in the transplanted kidney should match those in the recipient, as in red-cell transfusion3; this has led to longer waiting lists for prospective recipients of blood group O. ABO antigens are expressed on most cell membranes and in kidney tissue. These antigens occur in soluble form in plasma. The urea transporter expressing the Kidd blood-group antigens is another potential minor antigen.4 Since it was cloned in 1994,5 the protein expressing the major-histocompatibility-complex (MHC) class I–related chain A (MICA) antigens, which is structurally similar to MHC class I proteins, has become implicated in the slow process of long-term allograft failure.6,7 In this issue of the Journal, Zou and colleagues8 report the results of a retrospective study of MICA antigens in 1910 recipients of kidney transplants from deceased donors.

MICA is a stress-inducible antigen expressed on the cell surface of epithelial and endothelial cells, fibroblasts, and monocytes. It is a ligand of the activating NKG2D receptor on natural killer cells, on γ/δ subgroups of T lymphocytes, and on α/β subgroups of CD8+ T lymphocytes. The diversity of protein variants encoded by the MICA gene9 may account for the fact that MICA, and not the closely related MHC class I–related chain B (MICB), is a good antigen to induce the humoral response. At the genetic level, MICA and MICB belong to the HLA class I gene complex, and they are located close to the HLA-B and HLA-A genes (Fig. 1).

Anti-MICA antibodies were present in the pretransplantation serum samples of about 11% of the patients in the study by Zou et al. The mean (±SE) graft-survival rate at 1 year was poorer among patients with such antibodies (88.3±2.2%) as compared with the rate among patients without such antibodies (93.0±0.6%). This difference was still evident 5 years after transplantation. The risk associated with anti-MICA antibodies appeared to be highest among patients with well-matched kidneys, which may hint that anti-MICA antibodies have an influence independent of HLA, and among patients with first renal transplants. HLA and clinical conditions other than immunization against MICA are more important than the presence of these antibodies, because no possible MICA effect was apparent in patients with HLA mismatches, retransplantation, or both.

The results of the study by Zou et al. do not...
point to an effect of multiple transfusions, although the incidence of such anti-MICA antibodies is reminiscent of that seen with anti-HLA antibodies. However, the technique of preparing the units of blood that the patients received was almost certainly heterogeneous, given the time frame and international scope of the Collaborative Transplant Study from which these data were derived. Thus, it is not possible to exclude sensitization after red-cell transfusions as a cause of the immunization against MICA.

Membrane-bound MICA proteins are constantly shed, and small quantities of these antigens can be found in the plasma of healthy persons. Roughly 10 ml of plasma is present even in a unit of packed red cells. Hence, plasma and blood products that are not subjected to leukoreduction are clear sources of MICA antigens. At present, there are many efforts to refine the production and preparation of blood and blood products, and the qualities of these preparations may be evaluated in prospective studies to assess their beneficial effects on outcomes. Molecular testing of blood donors is permitting us to detect and specifically define weak signals, such as weak D antigens and weak HLA antigens, that hitherto have not been detected by means of serologic testing. Some of these new signals should prove useful and may be clinically relevant.

The study by Zou and colleagues presents MICA as a classic antigen with effects mediated by antibodies that bind to it specifically. This mechanism is, in part, distinct from that of the related HLA proteins, which convey peptides to T lymphocytes and may mediate graft loss independent of anti-HLA antibodies. Thus, these diverse immune mechanisms are orchestrated by two highly related proteins, the genes for which are located in adjacent regions on one chromosome (Fig. 1). Anti-MICA antibodies might also be surrogate markers for a more fundamental effector mechanism. Natural killer cell alloreactivity, elicited by MICA binding to its ligand, may be another mechanism that might be operative in solid-organ transplantation. After all, the MHC gene locus is cluttered with genes regulating the

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**Figure 1. Localization of the MICA and HLA-B Genes within the HLA Complex on the Short Arm of Chromosome 6.**

The HLA complex is divided into three regions: class I, class II, and class III. Each class comprises a host of genes, and examples of genes are shown. The borders of the class I and class II regions with the class III region are delimited by the MHC class I–related chain B (MICB) and HLA-DRA genes, respectively. The MHC class I–related chain A (MICA) gene (arrow) is located close to HLA-B. The genes are separated by only about 50,000 base pairs at the DNA level. Physical distance is shown in millions of base pairs. Data are from the National Center for Biotechnology Information.
immune response that lie in close proximity to MICA. These genes are generally inherited en bloc along with MICA, a feature called linkage disequilibrium. Probing the actual mechanism of the MICA effect may lead to an even better understanding of this complex gene locus.

Although HLA remains the cornerstone of transplantation immunology, the exploration of MICA antigens and their corresponding antibodies may be seen as a new tool set for understanding the rejection of kidney transplants. As with the mineral mica, this MICA adds glitter to granite. How much clinical benefit an understanding of MICA will provide must be gauged in prospective clinical studies. Such studies may suggest whether anti-MICA antibody screening and cross-matching should be recommended or how the development of antibodies against MICA can be prevented in patients on waiting lists for kidney transplantation. An understanding of anti-MICA antibodies may provide information that extends beyond the role of MICA antigens and may ultimately benefit patient care, even before the pathogenesis of anti-MICA antibodies is fully known.

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