linking proteins, ankyrin and protein 4.1R, is responsible for the remarkable flexibility, mechanical stability, and cohesion of the normal red cell membrane. Various inherited red cell membrane disorders, such as hereditary elliptocytosis, ovalocytosis, and spherocytosis, result from either a misassembled skeletal network and/or defects in linkage of the network to the membrane. Over the past 3 decades, identification of mutations in genes encoding α- and β-spectrin, protein 4.1R, ankyrin, dematin, and band 3 in various red cell membrane disorders of both human and mouse, in conjunction with detailed biochemical and structural characterization of the various protein components, has greatly expanded our understanding of the molecular and structural basis of red cell membrane disorders.

Despite significant progress, several questions remain unanswered. Why and how is the actin filament length tightly regulated to be 37 nm in the red cell membrane skeleton? What are the contributions of tropomyosin, tropomodulin, dematin, and adducin in regulating actin filament length? Can deficiency of these proteins account for the 10% to 15% of cases of human hereditary spherocytosis and elliptocytosis in which the underlying molecular defect has yet to be defined? The study of Moyer and colleagues begins to provide some answers to these questions by showing that tropomodulin does play a role in regulating actin filament length and that absence of tropomodulin leads to assembly of a disordered membrane skeleton.

What are the implications of these findings? One is that tropomodulin—like other protein components of the red cell membrane skeleton that interact with actin such as adducin, dematin, and protein 4.1R—is a key regulator of red cell membrane stability. Hence, deficiency of tropomodulin in mouse red cells results in spherocytic elliptocytosis. These findings, along with similar findings from adducin- and dematin-deficient mouse red cells, raise the possibility that mutations in genes encoding the actin-capping proteins may account for the 10% to 15% of cases of human hereditary spherocytosis and elliptocytosis in which the underlying molecular defect has yet to be defined. But in the broader context, the reported findings could lead to obtaining new insights into the assembly during terminal erythropoietic differentiation of the unique and highly ordered spectrin-actin-based red cell membrane skeleton, which is critical to ensure the remarkable durability of the mature erythrocyte during its 120-day life span in circulation.

**REFERENCES**


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**Transplantation**

Comment on Cooley et al, page 2411

**Donor selection for AML: do the KIR**

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How to select the donor when there is a choice of several HLA-matched donors? In this issue of *Blood*, Cooley and colleagues describe that matched donors with a favorable KIR gene content confer a significantly reduced risk of posttransplantation relapse in patients with AML.

A logeneic hematopoietic stem cell transplantation (HSCT) was developed to cure otherwise incurable leukemia. Whereas HSCT was initially restricted to patients who had a human leukocyte antigen (HLA)—matched sibling donor, more and more patients with otherwise incurable leukemia benefit from HSCT by the expansion of the donor pool through the recruitment of matched unrelated volunteer donors. HLA matching for
HLA class I and II alleles is still the most important criterion for donor selection. Beyond the eradication of leukemic cells by the myeloablative regimen and the replacement of defective bone marrow by the allogeneic graft, the success of HSCT depends to a large extent, on the balance between the donors’ alloreactive T lymphocytes against the recipients’ tissues (graft-versus-host disease [GVHD]) and the favorable reaction of the donors’ T lymphocytes toward the leukemic cells (graft-versus-leukemia effect [GVL]). More recently, it has also been shown that the recipients’ innate donor immune system also contributes significantly to the eradication of residual leukemic cells. Natural killer (NK) cells, as key members of the innate immune system, seem to play an especially important role in leukemia control after HSCT.

Alloreactive NK cells were first described as GVL effectors in HLA-A–3–loci mismatched haploidentical transplantation using T cell-depleted grafts, with impressive GVL effects in patients with acute myeloid leukemia (AML) reported. NK cells express killer cell immunoglobulin-like receptors (KIR) that recognize polymorphic epitopes of HLA class I alleles, called KIR ligands, among them KIR receptors that can lead to activation or inhibition of the NK-cell activity upon binding to certain HLA class I alleles. If the inhibitory KIR does not bind to its KIR ligand, inhibition does not occur (lack of inhibition), and the NK cell is in activated status and can exert an NK-alloreactive GVL effect.

KIR genes are encoded by a set of 15 loci and 2 pseudogenes that are closely linked and inherited as a haplotype. KIR gene content can further be organized into KIR haplotype A and B. KIR A haplotypes have simple, fixed gene content, whereas B haplotypes have variable gene content. Based on this distinction, all individuals can be assigned to either A/A genotype (ie, homozygous for A haplotypes) or the B/x genotype (having 1 or 2 B haplotypes). In addition, KIR A and B haplotypes have distinctive centromeric (Cen) and telomeric (Tel) gene–content motifs. Because HLA and KIR segregate independently on different chromosomes, HLA-identical individuals can have completely different KIR genotypes. The influence of the donor KIR genotype has been reported previously and the relapse free survival of unrelated donor transplantation for AML was significantly improved if the donors had the B/x genotype compared to A/A donors, and similar effects have been reported in sibling donor settings.

In the current study, Cooley and colleagues further analyzed in detail the contribution of the centromeric and telomeric motifs to the clinical benefit conferred by B haplotype donors. They KIR genotyped donors from 1409 unrelated HLA-matched and mismatched T-replete transplants for AML (n = 1086) and acute lymphoblastic leukemia (ALL, n = 323) and calculated the KIR B content score for each donor (ie, the total number of centromeric and telomeric motifs containing B haplotype genes). As described previously, they confirmed that the KIR genotype exclusively influenced the outcome for AML, but not ALL. Donors’ B genes in the centromeric region of both KIR haplotypes (Cen-B/B genotype) had a strong effect and Cen-B/B homozygous donors conferred a striking antileukemic effect with a cumulative incidence of relapse of 15.4% compared with 36.5% for Cen-A/A donors (P < .0001).

Their analysis further revealed that, compared with A haplotype motifs, centromeric and telomeric B motifs both contributed to relapse protection and improved survival, and donors with a B content score of 2 or higher provided significant protection from relapse compared with donors with a KIR B content score of 0 or 1. Within the group whose KIR B content score 2 or higher, the reduction in relapse and the increase of disease-free survival was greater when the donor was homozygous for Cen-B (see figure).

The donor KIR genotype did not have any influence on rates of transplant-related mortality, grade II-IV or III-IV GVHD, or chronic GVHD. The effects of donor KIR B content score of 2 or higher on reduction in relapse and disease-free survival (DFS) and overall survival were similar for HLA-matched and partially matched transplants. Based on their analysis, the selection for transplant donors with a KIR B content score of 2 or higher has the potential to reduce the risk of relapse by 50% and the relative risk of relapse or death by 20% in patients with AML.

The present work confirms and extends previous findings and raises several important issues: Besides the classical HLA matching for class I and II, there is with the KIR gene family an independent second immunogenetic system that has a significant influence on the outcome of allogeneic HSCT. It is not clear why this effect is seen only in adult patients with AML but not with ALL. In pediatric patients with ALL, an influence of the donor KIR genotype or phenotype has been described in haploidentical transplantation with T cell-depleted grafts. There might be significant differences in the expression of various inhibitory or activatory KIR ligands on AML and ALL blasts in adults and children. Further research into the interaction of NK cells with AML and ALL targets might reveal such differences, and the antileukemic effects of the donor KIR genotype might also be harnessed in patients with ALL, for example by manipulating the HLA/KIR interactions.

Inexpensive methods for KIR genotyping are available and can be easily applied concomitantly to HLA genotyping. Based on the
already published data, the detailed analysis in this article, and the only positive but not negative effects of donor KIR genotypes on the transplantation outcome, the time has come to add KIR genotyping to the confirmatory HLA genotyping during the donor search for patients with AML and to select among different HLA-matched donors for a given patient the one donor predictive for the most effective relapse protection based on his KIR B gene content score as described by Cooley and colleagues.

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