HLA immunogenetics in hematopoietic stem cell transplantation

Recent research has suggested that non-HLA immunogenetics, in particular cytokine gene polymorphisms, play an important role in the outcome of HLA-matched sibling transplantations including graft-versus-host disease (GVHD) and transplant-related mortality. More recently the gene polymorphisms for the mannose-binding lectin (Mullighan et al, Blood. 2002;99: 3524-3529) have been shown to be associated with infection in a heterogeneous cohort of allogeneic hematopoietic stem cell transplantation (SCT) patients. Bacterial and fungal infections, as well as GVHD, are the most life-threatening factors following SCT. Improved individual patient supportive care including modified prophylaxis and immunosuppression may be possible with the use of a genetic risk-factor analysis by identifying those patients at greatest risk of SCT complications due to either their own or their donor’s genotype. The polymorphisms of the gene under study often occur within the promoter regions of the gene giving rise, for example, to individual genotypically determined high or low levels of the cytokine or high or low levels of enzyme activity.

In a unique study, Rocha and colleagues (page 3908) have elegantly identified patient and donor inflammatory and host-defense genetic risk factors associated with neutrophil recovery and bacterial infections. Donor genetic risk factors influencing bacterial infections were identified by the study of myeloperoxidase gene (MPO) polymorphisms (−463A>G polymorphism). The cumulative incidence of at least one bacterial infection was assessed at day 180 after SCT. The cumulative incidence for MPO donor genotype AG was 38%, and for AA 50%, compared with 20% in the negative-risk donor genotype of GG. The MPO donor risk genotype (AG or AA) may reflect the decreased enzymatic activities of MPO present in engrafted neutrophils. The AA genotype was also associated with the risk of non-leukemic death.

The FcyRIIIB genotype of the donor was also associated with a delay in time to neutrophil recovery and risk of early death. Rocha et al further confirmed earlier studies of our own on the protective role of donor IL-1 receptor antagonist genotype in acute GVHD. Their study of a homogeneous population of transplantation patients using multifactorial analysis further strengthens the importance of non-HLA immunogenetics in allogeneic SCT. The results form the basis of further studies on the mechanism of activity of host defense against infection and, in addition to other genetic risk-factor analyses, may aid in both choice of donor and establishing new SCT prophylactic and therapeutic strategies.

—Anne M. Dickinson
University of Newcastle