inside blood

## i to I and the eye

Asians with the adult i syndrome have cataracts; Europeans do not. What can be the explanation?

Different cells have different metabolic needs; sometimes an enzyme that functions admirably in one cell type might perform optimally in another cell type if its properties were altered. In such instances evolution has often avoided the "one size fits all" approach but has instead tailor-made an enzyme for each tissue. Sometimes entirely different genes are turned on in different tissues. For example, there are 2 distinct pyruvate kinase genes: *M* for muscle (also found in white blood cells) and *L* for liver (in modified form, also in red cells). In other cases a more thrifty and elegant mechanism has evolved, namely, differences in the transcription and/or splicing of the same gene in different tissues. An extreme example is the UDP-glucuronosyltransferase gene; this gene has no less than 12 separate first exons. Thus, depending upon which promoter is active, the *N*-terminal end of the transferase varies and, with it, its properties such as substrate specificity. Gilbert disease, well known to hematologists, is usually due to a polymorphism of the promoter of the most 3′ exon 1.

Predictably, such complexity in the steps leading to the formation of an mRNA results in complexity of disease phenotypes ostensibly the result of a deficiency of the same enzyme. Yu and colleagues (page 2081) have now solved the mystery of why Asian patients with the adult i phenotype have congenital cataracts while this clinical feature is not found in patients with other ethnic origins. They have discovered that the i-branching 1-6-*N*-acetylglucosaminyltransferase that converts i to I is one of those genes that offers each tissue a choice of different exons, 3 to be exact. Yu et al found that when the mutation was in the third exon, common to all 3 forms of the enzyme, cataracts represented a part of the clinical picture. In contrast, when one of the alternative first exons contains the mutation, only 1 of the 3 transcripts was affected, and cataracts were not present.

The complex solutions that evolution has utilized to optimize the functioning of cells have resulted in complexities of disease phenotypes that require considerable ingenuity to unravel.

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## UCB allogeneic transplantation for hemoglobinopathies

β-thalassemia and sickle cell disease reduce lifespan and quality of life for children and young adults, and the only cure for these disorders is allogeneic stem cell transplantation. The decision-making processes in recommending allogeneic transplantation for patients with thalassemia and sickle cell disease differ, due to the clinical heterogeneity of sickle cell disease, and transplantation is recommended only in patients with severe disease, particularly sickle-related neurologic problems. The potential risk of disabling chronic graft-versus-host disease (GVHD) raises concerns on the part of pediatric hematologists in the wide application of allogeneic transplantation for patients with hemoglobinopathies. Currently, the event-free survival rate after allogeneic HLA-matched sibling transplantation for thalassemia and sickle cell disease ranges from 82% to 86%. Nevertheless, short-term and long-term transplantation-related complications remain, particularly in older patients with lifelong complications of sickle cell disease. Novel conditioning regimens that minimize transplantation-associated toxicity have been developed. Moreover, alternative stem cell sources are currently being explored to increase the availability and efficacy of allogeneic transplantation for patients with β-thalassemia and sickle cell disease.

Although allogeneic stem cell transplantation can cure patients with hematologic disorders, limiting factors such as lack of suitable donors and GVHD toxicity have led to the exploration of umbilical cord blood (UCB) as an alternative source of hematopoietic stem cells. In this issue, Locatelli and members of the Eurocord Transplant Group (page 2137) report their retrospective analyses of 44 children with either thalassemia (n = 33) or sickle cell disease (n = 11) treated with fully ablative conditioning and allogeneic-related cord blood transplantation. No patient died, and the 2-year event-free and overall survival rates in these children are 79% and 90%, respectively. Further observations outlined in this issue parallel those reported on other series, which indicate that use of related cord blood has been associated with a very low incidence of acute and chronic GVHD. Locatelli et al observed grade II acute GVHD to occur in only 4 of 38 evaluable children (Kaplan-Meier estimate, 11%), with 2 of these children having received HLA disparate grafts, and only 2 of 36 children developed limited chronic GVHD (Kaplan-Meier estimate, 6%). The majority of these patients received cyclosporine alone as prophylaxis. This low incidence of GVHD compares favorably with the 15%-25% incidence of grade II-IV acute GVHD and the 25%-30% incidence of chronic GVHD observed in children receiving HLA-matched sibling allogeneic bone marrow grafts.

β-thalassemia and sickle cell disease are among the most common genetic disorders, affecting several million children and young adults worldwide. Proposed gene therapy–based strategies for these patients require complex, regulated, lineage-specific expression of the β-globin gene at relatively high levels. Although the recent discovery of the β-globin locus control region (LCR) has renewed interest in gene therapy, difficulties in attaining high-titer vectors, along with a tendency toward rearrangement when segments of the LCR are incorporated into retroviral vectors, have impeded further progress. As outlined by Locatelli and colleagues' study,