inside blood

"Affenmensch" defect defined

Porphyria cutanea tarda (PCT) is the most common form of the porphyria and occurs both in inherited and acquired forms. Uroporphyrinogen decarboxylase (URO-D) deficiency is responsible for all PCT. Adult patients are often called "Affenmensch," and younger patients, "monkey children," because of the immense pigmentation and hypertrichosis due to porphyrin-induced photosensitivity that occur particularly on the face and extremities.

Phillips and colleagues (page 3179) report the first structural analysis of URO-D mutants in the familial form of PCT (fPCT) and define their functional consequences. They have studied 12 URO-D mutants by bacterial expression and have found some as insoluble, while most others as soluble, proteins. Three soluble mutant proteins were then subjected to X-ray crystallographic analysis. There are 3 important points that merit particular mention in their study. First, crystal structures of the 3 URO-D mutants demonstrated a common structural change, the disorder of a surface loop. Second, most of the mutations lie near the URO-D dimer interface, suggesting that disruption of the dimer interface may be critical for enzymatic activity. Third, none of the mutations were lethal; that is, they were "conservative" and had significant residual activity. These findings thus define the structural basis of the functional significance of URO-D mutations in fPCT and also permit prediction why 30 other URO-D mutants reported elsewhere may be associated with low enzyme activity.

fPCT is an intriguing genetic disease in that not only the URO-D defect but also various other factors may play a role in its pathogenesis, for example, alcohol, iron, and estrogen. Recent evidence also suggests that an inhibitor of hepatic URO-D may be generated and involved in clinical expression of PCT. Perhaps some day, structural analysis of the PCT defect might also uncover an influence of these accessory factors on the structure of URO-D.

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In search of the ideal allogeneic inoculum

For more than 30 years, physicians have transplanted allogeneic hematopoietic cells (HCs) harvested from the bone marrow cavity without any specific HC stimulation. During the past decade, blood HCs collected by apheresis after stimulation with granulocyte-colony stimulating factor (G-CSF) of the donor have been explored as an alternative source and it was demonstrated in a phase III trial that G-CSF–mobilized blood HCs are the preferred inoculum, compared with marrow HCs that had been harvested from "steady state" donors, at least for patients in advanced stages of their hematologic malignancy (Bensinger et al. N Engl J Med. 2001;344:175-181).

Last year, intriguing phase II data were reported from 3 independent groups (Couban et al, Biol Blood Marrow Transpl. 2000;6:422-427; Isola et al, Biol Blood Marrow Transpl. 2000;6:428-433; Serody et al, Biol Blood Marrow Transpl. 2000;6:434-440) indicating that G-CSF–treated donors provide marrow HCs that lead to rapid engraftment and a relatively low rate of graft-versus-host disease (GVHD). Here, Morton and colleagues (page 3186) report phase III trial results showing that G-CSF–mobilized HCs derived from marrow or blood have virtually equivalent engraftment kinetics for granulocytes and platelets but that marrow HCs are associated with significantly less steroid refractory acute GVHD and a lower incidence of chronic GVHD. One would like to see this important observation confirmed in a uniform patient population conditioned with a single preparatory regimen.

Existing preclinical data could explain the interesting observation described by Morton and colleagues. These studies in murine models indicate that bone marrow T cells induce less GVHD than equivalent amounts of blood T cells (189:1073-1081; Lan et al, Blood. 2001;97:3458-3465; Zeng et al, Blood. In press). Likewise, human T cells from marrow or blood not only differ quantitatively but also may have vastly different qualitative features and functions. In the days of microarray assays, such differences should soon become evident.

Progress toward optimizing the allogeneic graft continues to be made. Ultimately, ex vivo manipulation of allogeneic HCs, regardless of the source, will provide the patient with the best result: a graft that leads to rapid and durable engraftment with preserved graft-versus-tumor effects and without GVHD.

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Pumped on steroids

Steroid receptors play critical roles in myeloid development, functioning as transcriptional activators of the genes that guide the myeloid cell from progenitor to a mature granulocyte or monocyte. The 2 most important steroid receptors in myeloid development are the retinoic acid receptor and the related vitamin D_3 receptor. Since the observation more than 2 decades ago that retinoic acid or vitamin D_3 could stimulate myeloid leukemia cell lines to differentiate to mature granulocytes or monocytes, the mechanism of action of these steroid receptors has been under intense study. The finding that the retinoic acid receptor alpha *(RARα)* was translocated in almost all cases of acute promyelocyte leukemia (APL) lent further motivation to these studies.