Comment on Hankins et al, page 2269

Hydroxyurea therapy in SS children

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Children with sickle cell anemia treated with hydroxyurea at 2 years of age maintain Hb F levels above 20% for 4 to 6 years with little hematologic toxicity and no increased risks of infection. Its ability to prevent subclinical organ damage, however, is yet to be proven.

More than 10 years ago the Multicenter Study of Hydroxyurea (MSH) showed reduction in painful crises, acute chest syndromes, and hospitalizations in adults with sickle cell anemia (SS) treated with hydroxyurea (HU).[1] Hankins and colleagues now report an update of a phase 2 trial (Hydroxyurea Safety and Organ Toxicity [HUSOFT]) of hydroxyurea in children with SS started on HU before 2 years of age. The study demonstrates that oral HU maintains mean hemoglobin F (Hb F) levels higher than 20% for 4 to 6 years with little hematologic toxicity and without significant increased risks of infection. Using almost 20-year-old historic controls from the Comprehensive Study of Sickle Cell Disease (CSSCD),[2] Hankins et al demonstrate a reduction in the rate of acute chest syndrome and improved growth rates. Reduction in rates of painful crises could not be assessed since no adequate historic or contemporary controls were available.

Clinically silent organ damage in the brain, spleen, lungs, and kidneys begins early in childhood in SS and often leads to significant disability and organ failure. Thus, it is important to determine whether HU can prevent occult and acute organ damage in children with SS. What is clear in this study is that HU treatment started before the age of 2 years and continued for 4 to 6 years does not uniformly prevent early signs of end organ disease in the spleen and brain. Among 14 children with measurements of baseline splenic function, only 3 had normal splenic function after 4 years of HU therapy. Perhaps HU treatment slows the progression of splenic deterioration; 6 (43%) of 14 were functionally asplenic after 4 years of therapy compared with a 94% incidence of asplenia in age-matched CSSCD historic controls. Three of 14 subjects had abnormal magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) central nervous system (CNS) studies after 4 years of therapy. It was not clear whether these lesions existed prior to HU treatment. One subject developed a silent CNS infarct between 4 and 6 years of therapy. Two children who were functionally asplenic before therapy regained normal splenic function, and 1 child resolved a mild CNS arterial stenosis on HU therapy.

Although children compared with adults seem to respond more uniformly to HU with higher Hb F levels, both children and adult subjects with SS demonstrate marked heterogeneity of clinical response to therapy so far. There is early evidence in adults that HU therapy is not uniformly accessible or beneficial.[3,4] Reasons for lack of effectiveness of HU in adults with SS are not known but may include genetic variation in pretherapy Hb F and white blood count (WBC) levels, failure to push HU doses to optimal therapeutic levels, noncompliance, a perceived lack of response after short-term trials, and patient or physician concern for as-yet-undetermined long-term side effects of HU. Ten years from now do we want to say HU is efficacious in children but not effective? Further trials of HU in adults or children should incorporate means to determine what is responsible for this heterogeneous response in clinical outcomes and whether the drug will be both efficacious and effective. ■

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Comment on Braun et al, page 2375, and comment on Potula et al, page 2382

IDO production, adaptive immunity, and CTL killing

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Indoleamine 2,3-dioxygenase, an enzyme induced in antigen-presenting cells by specific proinflammatory mediators such as prostaglandin E_2 (PGE_2) or viral infection, can inactivate specific T-cell functions.

Dendritic cells (DCs) are key regulators of immune responses capable of promoting and suppressing T-cell activation. This functional plasticity is the net result of DCs integrating a plethora of signals in their local microenvironment. Most DC studies examine signals required for inducing protective immunity rather than tolerance. An interesting candidate for the latter is indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme in tryptophan catabolism, which is expressed by antigen-presenting cells (APCs) such as macrophages and DC populations.

IDO production can suppress adaptive immunity and has a complex role in immunoregulation, such as T-cell tolerance to cancer and allografts, protection of the allogeneic fetus, resistance to autoimmune diabetes,[1] and regulation of fungal pathogenicity.[2] Tolerance induction by IDO appears, at least in part, to

be attributed to depletion of the amino acid tryptophan, and resultant increase in metabolites (eg, kynurenine). Interferon-γ (IFN-γ) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)/B7 engagement induce IDO in APCs.[1] In this issue of *Blood*, 2 groups report novel insights that further elucidate the regulatory role and potential pharmacologic intervention of IDO activity in immunity.

Braun and colleagues describe a 2-step induction of IDO in human monocyte-derived DCs (MoDCs), a widely used in vitro model for studying DC function. Affymetrix gene array analysis indicated that DCs matured with tumor necrosis factor-α (TNF-α) and prostaglandin E_2 (PGE_2), expressed 100-fold higher IDO mRNA. Interestingly, although PGE_2 was responsible for IDO transcriptional up-regulation, other stimuli (such as TNF-α or Toll-like receptor [TLR] ligands) were required for its functional activation. Finally, PGE_2 mediated IDO induction via the E prostanoid-2 (EP2) receptor and cyclic adenosine monophosphate (cAMP) signaling.

These findings shed new light on IDO regulation by inflammatory mediators and explain why mRNA expression did not strictly correlate with IDO activity in previous reports. They also highlight a novel role of PGE_2 (and perhaps other cAMP agonists such as adenosine triphosphate [ATP]) in modulating DC functional capacity via IDO induction. PGE_2 (and ATP) can induce DC migration towards lymph node–directing chemokines,[3-5] attenuate interleukin-12p70 (IL-12p70) and IL-27 production and induce IL-23 production for memory T-cell activation.[6] PGE_2 is frequently used in maturing MoDCs used for cancer immunotherapy, and so PGE_2 induction of IDO has implications for this strategy. However, do these findings indicate that PGE_2–matured DCs are immunosuppressive or rather that they attenuate the magnitude of responses to avoid excessive tissue damage? Although the functional consequences of DC-derived IDO on T cells was not addressed by this group, previous reports by Terness and colleagues[7] demonstrate that inhibition of T-cell activation by IDO^+ DCs may not be a preponderant effect but may depend on the activation context.

What are the consequences of APCs producing IDO? A second paper appearing in this edition may shed light on this question. Potula and colleagues report that HIV-1 infection induces IDO^+ macrophages that are subsequently protected from cytotoxic T lymphocyte (CTL) killing. Their persistence in the brain likely causes HIV-encephalitis (HIVE). Furthermore, pharmacologic inhibition of IDO enhanced CTL function and clearance of virally infected brain macrophages, highlighting that virally induced IDO in APCs may represent a unique viral escape mechanism. It is unclear whether IDO inhibits CTL development per se, since increased CTL numbers were found with IDO^+ macrophages in HIVE brains. Munn et al recently showed that IDO^+ plasmacytoid DCs directly suppress T-cell function via activation of the general control kinase 2 (GCN2) kinase pathway.[8] Thus, IDO^+ APCs may inactivate CTL function and escape CTL lysis.

Although APC resistance to CTL lysis appears deleterious in HIVE, it may be beneficial in certain contexts such as protecting antigen (Ag)–loaded, migratory DCs (activated via PGE_2) from CTL attack en route to lymph nodes. It is unclear from current studies whether IDO production is continuous or transient upon stimulus withdrawl. Closer examination of IDO^+ APC and CTL interactions are required to more fully understand the implications. However, these 2 studies indicate that therapeutic inhibition of IDO may prove promising for enhancing (antiviral and tumor) or attenuating (autoimmune and transplantation) immune responses in a context-dependent manner. A better understanding of the regulation of IDO expression within the immune system may open new avenues for manipulating immunity in health and disease. ■

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HEMOSTASIS

Comment on Freson et al, page 2356

β1-tubulin in human platelets: not simply a structural cell frame

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Freson and colleagues present a novel polymorphism of platelet β1-tubulin that is frequent in the healthy population and may protect men against arterial thrombosis.

Microtubules represent one of the major components of the cytoskeletons of eukaryotic cells and play an essential function in the maintainance of cell shape, but participate also in cell division, ciliar and flagellar motility, and intracellular transport.[1] Eukaryotic organisms express multiple isotypes of α- and β-tubulin, the basic building block of the microtubule.[1]

Among the β-tubulin isoforms, β1-tubulin is specifically expressed in platelets and mature megakaryocytes,[2] and accounts for about 90% of the β-tubulin present in the platelet marginal band, a single peripheral microtubule strand that maintains the discoid shape.

Platelets play a critical role in hemostasis, but also in arterial thrombosis. At rest, they circulate in blood as small anucleated discs which, following blood-vessel injury, interact with exposed elements of the underlying connective tissue, rapidly changing their shape to spheres, the latter