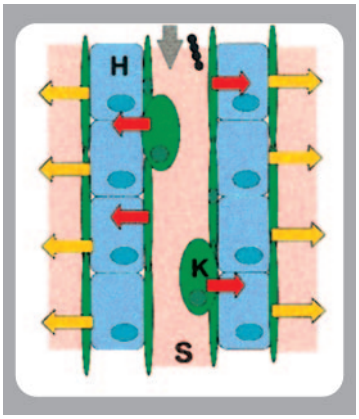
inside blood

Unlocking the mysteries of iron homeostasis and of the anemia of chronic disease: is hepcidin the key?

When the long and difficult search for the HLA-linked gene was finally brought to a conclusion by the cloning of *HFE,* it was generally thought that the discovery of this elusive molecule would provide us with true insight into how body iron is regulated. After all, mutation of this gene was known to cause iron overload—sometimes very severe iron overload. But the discovery of the *HFE* gene raised more questions than it answered and served as a powerful stimulus for the application of the methods of modern molecular biology to the problem of iron homeostasis. Thus, as a result of the use of database search, positional cloning, knockout mice, injection of pooled RNA, and subtraction cloning, new actors in the arena of iron homeostasis were discovered: transferrin receptor 2, DMT1, ferroportin, hephaestin, duodenal cytochrome b, and, probably most interesting of all, hepcidin.

In this issue (page 783) Tomas Ganz, the discoverer of hepcidin as a antimicrobial peptide, provides the reader with an incisive review of the complex structure and of the probable physiologic action and regulation of this small polypeptide. Not only does



hepcidin appear a key regulator of body iron content, but it may play an important role in defense against infection by depriving microorganisms of a ready source of iron. Thus, hepcidin may prove to be an important key to understanding of one of the most common anemias of all, the anemia of chronic disease. This is a fertile area for further research, and in the Ganz article there are ample provocative suggestions for additional studies.

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AML beyond the boundaries of daunomycin and cytarabine

Since the introduction of the anthracyclins and cytarabine some decades ago, there has been little progress in remission induction therapy of acute myeloid leukemia (AML). Genetic lesions in AML uncovered by molecular analysis provide opportunities for therapeutic targeting. AML cells express growth factor receptors that contain kinases or activate kinases downstream within the cell. These kinases offer potential targets for intervention as well. VEGFR-2 (vascular endothelial growth receptor type 2) and the hematopoietic growth factor receptors KIT (for stem cell factor) and FLT3 (FMS-like tyrosine kinase 3) are prototypes of receptors with intrinsic kinase activity expressed on AML blasts. These receptors have been implicated in autocrine and paracrine pathogenetic mechanisms of growth of AML. Activating mutations in the *FLT3* and *KIT* receptors may be acquired during the evolution of AML. *FLT3* and *KIT* mutations constitutively induce growth signals (in the absence of growth factor) and therefore define additional conditions suitable for therapeutic targeting. The most common form of *FLT3* mutations (FLT3 internal tandem duplications) occurs in 20%-30% of cases and defines an aggressive form of AML that has a high rate of recurrence (see, eg, Gilliland et al, Rev Curr Opin Hematol. 2002;9:274-281). Similarly, mutations in *KIT* confer negative prognostic impact in subsets of AML (Care et al, Br J Haematol. 2003;121:775-777).

SU5416 is an indoline compound that may abrogate the signaling of activated kinase receptors and lead the leukemic cells into apoptosis (see, eg, Levis et al, Blood. 2002;99:3885-3891; Yee et al, Blood. 2002; 100:2941-2949). SU5416 blocks not only kinase activity of VEGF-R2 but also KIT and FLT3 receptors, wild-type as well as mutant. In this issue, Giles and colleagues (page 795) report on a phase 2 study of SU5416. The investigators present the toxicity and pharmacokinetic profiles and report 4 responses among 56 patients with refractory and relapsed AML and MDS. Whether these responses classify SU5416 as a candidate of sufficient interest for further development is presently unclear. The investigators noted no complete responses, but their series comprised highly unfavorable AMLs, with several patients not completing the treatment plan. Further, in order to understand the efficacy of the inhibitor, one would like to correlate the clinical responses with the level of abrogated signaling and induced cell kill of the patients' primary cells by SU5416 in vitro. Also, one would like to know about the presence of genetic abnormalities (eg, *FLT3* mutations) in this series. This correlative documentation is not given. The study is exemplary of the laboratory and clinical orchestrated development of various kinase inhibitors that is currently in full swing at several research sites. One hopes these intense investigational activities will advance AML therapeutics toward new boundaries.

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