Hepcidin is the primary regulator of iron homeostasis: hepcidin modulates iron availability by promoting the internalization and degradation of ferroportin, a key iron transporter and so far the only identified mammalian iron exporter, which is essential for both iron absorption in the duodenum and recycling of iron/iron efflux by macrophages. Hepcidin is a negative regulator of iron absorption and mobilization; high hepcidin levels turn off both duodenal iron absorption and release of iron from macrophages while low hepcidin levels promote iron absorption and release of iron from macrophages. Thus, hepcidin levels are expected to be high in iron overload states and diminished in iron deficient states. Hepcidin production can be induced by inflammation, which explains the reduced availability of iron in the anemia of chronic disease, whereas anemia and hypoxia have been shown to increase iron absorption and mobilization by decreasing hepcidin production.\(^1\)

Previous work on assessing urinary levels of hepcidin was carried out using methods that required mass spectrometry detection and thus are of limited availability.\(^2,3\) Low levels of serum hepcidin have been reported using mass spectrometry detection in blood donors donating at least 13 whole blood units in a 2-year time span.\(^4\) Measurements of prohepcidin, the precursors of the biologically active 25 aa hepcidin, have been generally disappointing because they seem to be poorly correlated with hepcidin and unresponsive to known hepcidin regulators.\(^5\)

The work by Ganz et al validates an immunosassay for human hepcidin levels in serum, which has a lower limit of detection of 5 ng/mL and yields a normal range for serum hepcidin of 29 to 254 ng/mL in men and 16 to 288 ng/mL in women. The assay has enough sensitivity to detect changes in serum hepcidin due to diurnal variation and in response to oral iron.

The next challenge will be to demonstrate what is the additional value of these measurements compared with the traditional diagnostic repertoire for iron metabolism disorders. In particular, what will this assay add to the information presently conveyed by serum ferritin? Since both ferritin and hepcidin are similarly affected by changes in iron availability and inflammation, careful studies will be required to demonstrate the unique additional value of measuring serum hepcidin. The authors correctly point out in their work that hepcidin can change on a time scale much shorter than that of ferritin, and several iron overload conditions, including beta thalassemia, exhibit elevated serum ferritin in conjunction with an abnormally low serum hepcidin. Inappropriately high levels of serum hepcidin are also seen in familial forms of iron-refractory iron deficiency anemia due to mutation in TMPRSS6, a negative regulator of hepcidin transcription.\(^5,7\) Perhaps the greatest promise for the clinical applicability of this new assay for serum hepcidin resides with the diagnosis of iron deficiency at infancy. An abnormally low serum hepcidin could identify infants at the earliest phase of development of iron deficiency before changes in either ferritin or reticulocyte/red cell parameters take place. If such an assay were to be made available and validated for urine samples, it could simplify the screening for iron deficiency of infants. An abnormally low serum or urinary hepcidin could also be of value for identifying adult women who require iron supplementation therapy without using any other laboratory tests. It remains to be seen if the serum hepcidin assay could also help in better identifying patients with anemia of chronic disease and concomitant iron deficiency or patients with anemia of chronic renal failure, both of which are nonresponsive to erythropoietic-stimulating therapies. Finally, in patients with iron deficiency anemia and low ferritin, will an abnormally high hepcidin be of help in identifying patients who are unresponsive to oral iron therapy and require intravenous iron supplements? The availability of this assay opens the way to a variety of exciting studies on iron metabolism in human diseases.

**REFERENCES**


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**SNPs linking TNF with anemia**

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Anemia is highly prevalent in children in malaria-endemic areas. However, it is difficult to distinguish between IDA and ACD in affected populations. In this issue of Blood, Atkinson and colleagues identify SNPs in the TNFα gene that are associated with an increased risk of developing IDA during the malaria season.

Single nucleotide polymorphisms (SNPs) in the TNF gene locus (lying within the Major Histocompatibility Complex class III region on chromosome 6) have been identified as potential risk factors in the etiology of a number of diseases, including malaria. TNF promoter polymorphisms are associated with increased TNF gene transcription, and previous work has provided strong evidence that plasma tumor necrosis factor alpha (TNFα) levels are significantly elevated following malarial infection.\(^1\) TNFα is known to be a modifier of body iron status and, in their study, Atkinson et al investigated whether functional SNPs and haplotypes across the TNF gene locus were associated with anemia during the malaria season. A cohort of 780 children was recruited from rural villages in the malaria-endemic West Kiang region of The Gambia.

Blood samples were collected from each child at the start (baseline measurement) and end of the malaria season. The samples were used to assess iron status and inflammation as well as to provide...
The data revealed a significant increase in the prevalence of iron deficiency and iron deficiency anemia (IDA), together with a marginal rise in plasma TNF-α levels (they did not measure circulating TNF-α levels in this study). Previous work has shown that TNF-α is a powerful inhibitor of iron absorption by the intestinal epithelium, and thereby diminish the effects of TNF-α on intestinal iron absorption and macrophage iron recycling. The possible involvement of the LTA locus in controlling iron homeostasis is unclear at present.

Despite being portrayed in many studies as a disease risk–associated region, Atkinson et al speculate that there might in fact be potential benefits in carrying SNPs in the TNF gene locus. They suggest that the association between TNF promoter polymorphisms, malaria, and nutritional iron deficiency and IDA may have developed as an evolutionary adaptation to limit iron availability for microorganisms and thereby offer protection against the development of infectious diseases.

REFERENCES
6. Roodman GD, Bird A, Hutzler D, et al. Tumor necrosis factor B-like (IxBα) and lymphocyte alpha (LTA) genes, which lie immediately upstream of TNF-α, were more likely to be iron replete at the end of the malaria season. Other members of the IkB family of proteins inhibit the actions of the transcription factor Nuclear Factor-kappa B (NF-κB), which is required for the transcriptional activation of the TNF-α gene. The authors speculate that IxBα might also inhibit NF-κB and thereby diminish the effects of TNF-α on intestinal iron absorption and macrophage iron recycling. The possible involvement of the LTA SNP in controlling iron homeostasis is unclear at present.

Comment on Benimetyska et al, page 4343

SOS! Defibrotide to the rescue

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Hepatic SOS, formerly referred to as veno-occlusive disease, develops in up to 10% of patients undergoing stem cell transplantation, a substantial percentage of whom succumb to this disorder. A number of therapeutic approaches have failed to significantly alter the relentless course of SOS, though recent evidence suggests that defibrotide ameliorates SOS and may improve survival. In this issue of Blood, Benimetyska and colleagues characterize the interactions of defibrotide with endothelial cells, providing new insight into potential mechanisms underlying its efficacy in SOS.
SNPs linking *TNF* with anemia

Paul Sharp