Comment on Pak et al, page 3730

It’s hepcidin again, but is it the only master?

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In this issue, Pak and colleagues report that hepcidin production in mice is suppressed after phlebotomy or erythropoietin administration but that the suppression is reversed by inhibitors of erythropoiesis.

Iron is a precious metal for the organism because of its unsurpassed versatility as a biologic catalyst. It is involved in essential biologic functions such as oxygen transport, electron transfer, and DNA synthesis. However, when not appropriately shielded, iron plays a key role in the formation of extremely toxic oxygen radicals that can damage biologic molecules, cells, tissues, and entire organisms. All life forms have thus evolved exquisite regulatory mechanisms that, under normal conditions, delicately control iron metabolism at both cellular and organismal levels. In mammals, the amount of total body iron is regulated at the level of absorption in the proximal duodenum but, normally, iron absorption represents approximately only 1/30 of the plasma iron turnover. The major fraction (~80%) of plasma iron turnover is represented by this metal’s fluxes into the bone marrow for hemoglobin synthesis in developing red blood cells and the movement of iron from macrophages, which very efficiently recycle hemoglobin iron back to plasma transferrin. Total plasma iron (~3 mg) exchanges 10-fold every day and, until recently, we have been totally ignorant about the mechanisms that govern this tightly controlled pool.

The discovery of hepcidin2,3 has partially rectified our ignorance of this important regulatory mechanism. Now regarded as the principal iron regulatory hormone, hepcidin synthesis is stimulated by high organismal iron levels. Hepcidin blocks both intestinal absorption and iron release from stores (mainly macrophages) by inducing the internalization and degradation of ferroportin (cellular iron exporter). The opposite scenario develops when iron levels are low and, hence, hepcidin is a negative feedback controller in organismal iron homeostasis. Additionally, hepcidin production and levels negatively correlate with erythropoietic activity, but signals involved in this regulation are unknown.

Pak and colleagues investigated the link between erythropoiesis and hepcidin synthesis. At the core of their report is an experiment in which the authors confirm that anemia4 (following phlebotomy) causes a dramatic decrease in hepcidin mRNA levels. Strikingly, hepcidin mRNA levels did not respond to phlebotomy when inhibitors of erythropoiesis or antierythropoietin antibodies were administered prior to phlebotomy. This experiment provides clear evidence that erythropoietic activity is necessary for anemia-mediated suppression of hepcidin production. In additional control experiments, the authors excluded the possibilities that the inhibitors of erythropoiesis increased hepcidin expression via (1) inflammatory stimulation or (2) interference with tissue hypoxia. Moreover, the authors showed that hepcidin is not directly regulated by erythropoietin. This study considerably enhances our understanding of mechanisms involved in supplying appropriate amounts of iron from stores to plasma for erythropoiesis. Of interest, Necas’ laboratory independently reported that a decrease in hepcidin mRNA levels in hepatocytes from phenylhydrazine-treated mice was abrogated by ablation of bone marrow by irradiation.

The article by Pak et al contains one important finding that, however, was not commented upon by the authors. As shown in the figure, conditions of erythropoietin administration, combined with erythropoiesis inhibitors, led to an unexpected dyad of elevated plasma iron with increased hepcidin synthesis, suggesting that decreasing hepcidin levels is not physiology’s only mode of promoting iron release from stores. Additional evidence telling us that the regulation of iron release from stores is fairly complex comes from “classical” experiments revealing that upon increased demand, hemoglobin-derived iron is much more available for erythropoiesis than storage iron in the reticuloendothelial system. This implies that the so-called erythroid regulator, which presumably links iron release from stores to erythropoietic demand, involves more than “just hepcidin.” There is no doubt, based on current experimental evidence, that hepcidin, in response to elevated iron levels or inflammation, inhibits iron release from iron “donor” cells. However, there may be an alternative pathway by which the metal is highly efficiently released from hemoglobin-recycling macrophages when there is an exceptionally high demand for this metal.

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Refining therapy for AL amyloidosis

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In this issue, Seldin and colleagues report that the benefits of high-dose melphalan chemotherapy and autologous peripheral blood stem cell transplantation (SCT) can be safely extended to selected patients 65 years or older with immunoglobulin light-chain (AL) amyloidosis. This finding from the Boston Group, who pioneered this treatment in AL amyloidosis, indicates that older patients should not be excluded from consideration for SCT.

The data reported by Seldin and colleagues show that age plays an important role in both a patient’s eligibility for autologous peripheral blood stem cell transplantation (SCT) and in melphalan dose adjustments. Among the older patients, 34.3% were eligible for SCT, compared with 68.4% of younger patients (P < .001), and only 19% of older patients were eligible for full-dose melphalan (200 mg/m²) compared with 65% of younger patients (P < .001). The response rate in older patients, who received a lower dose of melphalan, was less than in younger patients (32% versus 43.5%, respectively), although the difference was not significant. This is consistent with data from large series of immunoglobulin light-chain (AL) amyloidosis patients treated with SCT showing that lower melphalan doses are associated with significant reductions of response rate.1,2 Despite increasing experience with SCT in AL amyloidosis and appropriate melphalan dosage adjustment,2 treatment-related mortality (TRM) remains substantial—it is consistently higher in multicenter trials (usually more than 20%) than in experienced single-center studies (approximately 10%).

Two large studies from the Boston Group1 and the Mayo Clinic2 showed that melphalan 200 mg/m² followed by SCT produced an unsurpassed high rate of hematologic responses (76%2 with 40% complete responses 1 year after SCT)1 that translated into extended survival (approaching 8 years).1 However, the outcome of SCT using lower doses of melphalan conditioning (100–140 mg/m²)2 with regard to hematologic response (53%2 with 33% complete responses 1 year after SCT)1 and survival (2.9 years)1 appears close to that achievable with less intensive and less toxic chemotherapy regimens. For instance, the association of oral melphalan and dexamethasone (M-Dex) in 46 AL amyloidosis patients ineligible for SCT produced hematologic responses in 67% (33% complete responses) and a median overall survival of 5.1 years (see figure) without significant toxicity.3 The efficacy and tolerability of M-Dex was confirmed by a French randomized multicenter trial comparing M-Dex and SCT. Sixty-five percent of patients treated with M-Dex achieved a hematologic response (32% complete responses), with TRM of 2%.4 No significant difference in hematologic response rate and survival was observed between the 2 treatments. However, in this multicenter study, the TRM of SCT was 24%, and only 29 patients undergoing transplantation were evaluable for response. Collectively, these findings indicate that M-Dex may be a viable alternative to SCT, particularly for patients requiring a reduction of the dose of melphalan conditioning. A phase 3 study comparing these 2 treatments in larger numbers of patients is warranted.

The therapy of AL amyloidosis is improving, but the quest for the best treatment continues. The effectiveness and tolerability of other regimens, such as the combination of cyclophosphamide, thalidomide, and dexamethasone,4 and of novel agents, such as lenalidomide5,6 and bortezomib, should also be tested in controlled, large trials. International collaboration is thus required in order to define the optimal therapy for AL amyloidosis.

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