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Editorial

Introduction to a review series on iron metabolism and its disorders

Iron is one of the most abundant elements, and although hematologists associate iron with hemoglobin production, it is also absolutely essential in a myriad of biochemical reactions in microorganisms, plants, and animals.[1] This is certainly true in humans as well. The effects of occult iron deficiency in the absence of anemia are now well documented in terms of cognitive function in children and the elderly. In fact, as is discussed in this review series, 15% to 20% of the world's population is affected by iron deficiency anemia. The number of individuals affected by occult iron deficiency without anemia is unknown but likely much higher.

The recognition of iron deficiency anemia as a worldwide health problem led early medical pioneers to try to understand the mechanisms of iron deficiency. Iron balance in humans is tightly regulated. Humans have no way to excrete iron and lose only ~2 mg per day from desquamation of epithelial surfaces. Several studies in the 1950s and 1960s revealed that iron absorption was the primary mechanism of regulation of iron homeostasis and that anemia and erythropoietic activity in the marrow played an important role, predicting discoveries that were to come.[2,3] The important concepts of effective and ineffective erythropoiesis were worked out in early investigations based on iron balance studies in patients with various types of anemia.[4,5]

From an evolutionary standpoint, it seems that changes from hunter-gatherer culture with high iron intake to an agricultural society may have been responsible for the appearance of genes that increase iron uptake.[6] The description of iron overload by Trousseau in 1865, subsequent recognition of kindreds with hemochromatosis in the 1930s, and discovery of the HFE gene made it clear that genetics plays an important role in the regulation of iron balance and that iron is toxic, producing endocrine dysfunction and liver cancer. In the 1950s and 1960s, chronic transfusion became standard for thalassemia major, extending survival past early childhood; however, such patients usually died by age 15 years as a result of iron-induced cardiac disease. From these disorders, it became clear that the cellular distribution of iron in patients who developed iron overload from too much absorption was not the same as that in those with transfusional overload. The degree of toxicity depended not only on the amount of iron in the body but on organ distribution, and this in turn was related in part to bone marrow activity. Patients with ineffective erythropoiesis or no erythropoiesis experience much more toxicity that those with effective erythropoiesis.

Since the 1970s, our understanding of iron metabolism, transport, and toxicity has progressed exponentially. Our understanding of receptor-mediated iron transport via 2 different transferrin receptors was rapidly followed by the idea of nontransferrin-bound iron (NTBI).[7] The role of the reactive Fe^{++} subspecies of NTBI that can enter cells through calcium and zinc transporters began to shed light on loading of the heart and endocrine organs as well as organ toxicity. The discovery of the major iron regulator hepcidin in 2001 seemed to supercharge the field, leading to our understanding of the interaction between hepcidin and ferroportin to regulate cellular iron export and the whole machinery, comprising transferrin receptor 2 (TFR2) as the iron sensor as well as HFE and other proteins, behind the regulation of hepcidin itself. This was coincident with the rapid development of the molecular biology methodology that accelerated research and led not only to the discovery of new iron regulation pathways but also to the description of hundreds of mutations in these pathways that are associated with human disease, including TMPRSS6, which decreases iron transport, causing iron deficiency.[8]

Therefore, we are happy to present this review series on iron metabolism and its disorders:

- Chia-Yu Wang and Jodie L. Babitt, "Liver iron sensing and body iron homeostasis"
- Clara Camaschella, "Iron deficiency"
- Guenter Weiss, Tomas Ganz, and Lawrence T. Goodnough, "Anemia of inflammation"
- Stefano Rivella, "Iron metabolism under conditions of ineffective erythropoiesis in β-thalassemia"
- Sarah Ducamp and Mark D. Fleming, "The molecular genetics of sideroblastic anemia"

Wang and Babitt discuss liver iron sensing and body iron homeostasis. The liver senses iron balance in part through TFR2 and regulates production of hepcidin. The key role of this system in iron homeostasis and the relation to genetic disorders in the components of the iron sensing system are discussed.

Camaschella discusses iron deficiency from an epidemiological standpoint as well as an integrated approach that highlights our current understanding of the regulation of iron homeostasis. She

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examines how this understanding influences the diagnosis and management of this common disorder.

Weiss et al review anemia of inflammation. The complex interactions of genes that control hepcidin and erythropoietin to create relative iron maldistribution as well as the complexities of diagnosing and managing combined iron deficiency and anemia of inflammation are discussed. Some exciting new approaches to the clinical modulation of hepcidin may be helpful in this disorder.

Rivella examines iron metabolism modulated by ineffective erythropoiesis in β-thalassemia. Ineffective erythropoiesis is the hallmark of marrow activity in thalassemia and leads to significant abnormalities in iron homeostasis. New understanding of these mechanisms has already led to new treatments, and there are several approaches under investigation that show promise.

Ducamp and Fleming discuss the molecular genetics of sideroblastic anemia. Trafficking of iron between the cytosol and mitochondria represents an entirely new microcosm where iron is both essential and detrimental. These acquired and genetic disorders cause significant dysfunction in the marrow as well as in other organ systems.

In 2018, we can clinically directly and noninvasively measure the nonreactive form of iron (Fe^{+3}) in specific organs by magnetic resonance imaging; we have excellent chelators to remove toxic labile iron and normalize iron stores, new drugs and small molecules are in trials to modulate iron transport, phase 3 clinical trials of a new drug that blocks ineffective erythropoiesis in thalassemia and myelodysplastic syndromes have just been successfully completed, and survival of transfusion-dependent thalassemia patients is much improved. With these clinical and molecular tools, we anticipate that our ability to understand and help patients with iron-related disorders will continue to rapidly increase. We also trust that this review series will be of value to those interested and involved in research on iron metabolism and the clinical management of patients with these disorders.

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