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PROGRESS IN HEMATOLOGY

Iron metabolism and the related diseases

Iron metabolism and related diseases: an overview

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Iron is an essential metal not only for oxygen delivery but also for cellular processes, including ATP production and DNA biosynthesis. Iron is utilized by the semi-closed system and is not actively excreted from the body. This system is advantageous, because it prevents the shortage of this important metal and is not influenced by the environmental status. In this system, the iron supply depends on a narrow gate at the duodenum, and iron accumulates in the organ once it is overloaded. These specificities of iron metabolism lead to the high frequency of iron deficiency anemia (IDA) among young females and secondary hemochromatosis due to blood transfusion.

Despite being an indispensable metal for maintaining life, iron is a very toxic metal producing reactive oxygen species (ROS), Hence, the level of iron is strictly regulated in the body and its cells. The key factor regulating the amount of iron in the body is hepcidin [1]. Hepcidin inhibits the release of iron from enterocytes and macrophages by degrading ferroportin, which is a unique exporter of iron. The level of hepcidin is regulated by several factors, including transferrin saturation, erythropoiesis, and oxygen level. Moreover, infection also changes the level of hepcidin, thereby altering the dynamics of iron in the body for protecting the hosts against pathogens, which require iron for survival and proliferation.

The amount of cellular iron is regulated by the iron-responsive element (IRE) and iron-regulatory protein (IRP) system. IRP binds to IRE, and regulates the translation of iron-related genes, which have IRE in 5′- or 3′-UTR. The activity of both IRP1 and 2 depend on the concentration of cellular iron, and balance the iron uptake and utilization [2].

A breakdown of the iron maintenance system leads to iron-related diseases, which are primarily classified into two groups: iron-overload disease and iron-deficient disease (Fig. 1). In this review series, five iron-related diseases, which are representative of an iron-overload or iron-deficient disease, are reviewed by experts. Congenital and secondary hemochromatoses are diseases characterized by systemic iron accumulation in various organs, such as the liver, heart, and endocrine glands, which finally result in organ failures. Congenital hemochromatosis is caused by germline mutations of genes involved in iron metabolism, whereas secondary hemochromatosis is primarily caused by repeated blood transfusion for congenital anemia or acquired bone marrow failure syndrome, including myelodysplastic syndrome. Sideroblastic anemia is characterized by the emergence of ring sideroblasts, in which overloaded iron accumulates in the mitochondria. IDA is the most common anemia worldwide, and 10–20% of young females in Japan suffer from this disease. Although treatment options for IDA are limited, novel intravenous and oral iron supplements are being developed. Regarding iron storage in the body, anemia caused by infection/inflammation is neither due to iron overload nor deficiency, but is caused by changes in the iron distribution in the body, thereby leading to a deficiency of available iron for use. This change in iron dynamics is a physiological response against pathogens such as bacteria.

Iron is not a simple oxygen-delivering molecule, but an important molecule involved in cancer, infection, inflammation, and cell death. Thus, understanding the properties and function of iron leads to recognizing its importance in fundamental homeostasis and pathological conditions.

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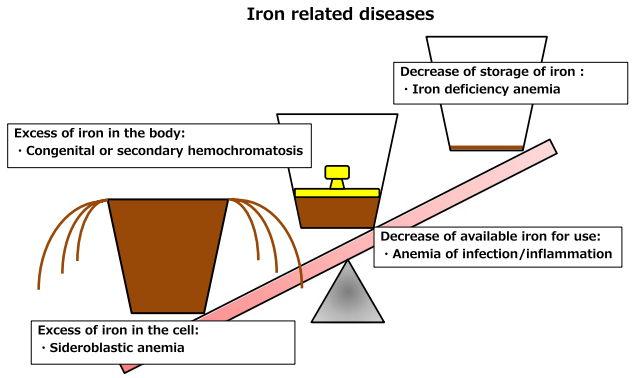

Fig. 1 Iron-related diseases. Hemochromatosis is an iron related disease caused by a systemic iron overload, and sideroblastic anemia is an iron related disease caused by a mitochondrial iron overload. Iron deficiency anemia is an iron related disease caused by a shortage of iron storage. Anemia of infection/inflammation is neither iron overload nor iron deficient disease, but it is an iron related disease caused by a shortage of available iron.

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