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Review

Regulators of Iron Homeostasis: New Players in Metabolism, Cell Death, and Disease

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Iron is necessary for life, but can also cause cell death. Accordingly, cells evolved a robust, tightly regulated suite of genes for maintaining iron homeostasis. Previous mechanistic studies on iron homeostasis have granted insight into the role of iron in human health and disease. We highlight new regulators of iron metabolism, including iron-trafficking proteins [solute carrier family 39, SLC39, also known as ZRT/IRT-like protein, ZIP; and poly-(rC)-binding protein, PCBP] and a cargo receptor (NCOA4) that is crucial for release of ferritin-bound iron. We also discuss emerging roles of iron in apoptosis and a novel iron-dependent cell death pathway termed 'ferroptosis', the dysregulation of iron metabolism in human pathologies, and the use of iron chelators in cancer therapy.

Trends

Dysregulation of iron metabolism contributes to various human pathologies, including iron overload diseases and cancer.

Several new proteins have been identified as crucial iron traffickers and chaperones with important connections to human health.

Ferroptosis is a unique cell death pathway that is iron-dependent, non-apoptotic, non-necroptotic, and non-autophagic.

Dysregulation of the ferroportin/hepcidin regulatory axis contributes to tumor progression and is predictive of patient outcomes.

New iron chelators utilize more specific mechanisms to elicit anticancer activity.

Iron Homeostasis Is a Complex, Highly Regulated Process

Iron is required in a variety of important biological processes including oxygen transport (as heme in hemoglobin), DNA biosynthesis (as a cofactor of ribonucleotide reductase), and ATP generation (as a cofactor for many proteins in the citric acid cycle and electron transport chain); therefore, cells must maintain a sufficient amount of iron. However, iron is redox-active and can generate reactive oxygen species (ROS), leading to oxidative stress and initiation of signaling pathways crucial for cell survival and cell death [1]. To maintain adequate and safe amounts of iron, cells require the coordination of a wide variety of genes, which tightly control both intracellular (reviewed in [2,3]) and systemic (reviewed in [4]) iron metabolism. Extensive research by many groups has revealed key mechanisms in iron homeostasis (Box 1), as well as links between aberrations in iron homeostasis and human disease. The study of iron metabolism continues to be a dynamic field, with many breakthroughs and novel insights in the past several years. In this review we discuss recent advances in the function and regulation of key iron metabolism genes, including: ferritin (*FTH1* and *FTL)*, a protein complex that safely concentrates intracellular iron in a mineralized, redox-inactive form for later use; transferrin (*TF*), an iron-binding serum protein; transferrin receptor 1 (TfR1, *TFRC*), a plasma membrane protein that allows cellular uptake of iron-loaded transferrin; divalent metal transporter 1 (DMT1, *SLC11A2*), a metal transporter that is important for TfR1-mediated iron uptake and dietary iron absorption; ferroportin (Fpn, *SLC40A1*), the only known cellular iron efflux pump; and hepcidin (*HAMP)*, a circulating peptide hormone that regulates serum iron levels by causing ferroportin degradation. We also examine newly identified regulators in iron metabolism, including new membrane iron transporters and cytosolic iron trafficking proteins. In addition, we review new roles for iron in cell death pathways, as well as the importance of aberrant iron metabolism in human diseases such as cancer.

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Box 1. Control of Mammalian Iron Metabolism Occurs through Two Distinct, but Connected, Regulatory Systems

Intracellular iron metabolism is primarily controlled through coordinated post-transcriptional regulation of various iron metabolism genes (reviewed in [2,3]). Many mRNAs involved in iron metabolism contain iron-responsive elements (IREs): stem-loop structures located in 5′- or 3′-untranslated regions (UTRs) flanking the coding sequence (CDS) [76]. IREs bind two functionally similar iron regulatory proteins, IRP1 and IRP2. Depending upon whether the IRE is located within the 5′-UTR or in the 3′-UTR, the IRE–IRP interaction has opposite effects on target gene expression. In low iron conditions, 5′-UTR IREs are translationally repressed as a result of IRP blocking ribosome recruitment, whereas 3′-UTR IREs mediate enhanced mRNA stability, ultimately increasing protein levels (Figure IA, Low iron). High iron removes the IRPs, facilitating translational activation of 5′-UTR IRE mRNAs or degradation of 3′-UTR IRE mRNAs via endonuclease attack (Figure IA, High iron). 5′-UTR IREs are usually found in genes that lower the amount of cellular labile iron (i.e., iron that is unbound and redox active) such as ferritin and ferroportin, whereas 3′-UTR IREs are found in genes that facilitate iron uptake such as transferrin receptor 1 and divalent metal transporter 1 (Figure IA) Classically, it was believed that iron affected the IRE–IRP interaction entirely through effects on the IRPs. However, the ability of Fe^{2+} (and other metal ions) to directly bind to the IRE stem-loop was recently observed [77]. Fe^{2+} binding to 5′-UTR IREs induces a conformational change in the stem-loop, which decreases its affinity for IRPs [78] and increases its affinity for a ribosome recruitment factor eIF4F [79], showing that the IRE structure itself contributes to post-transcriptional control of gene expression.

In mammals, systemic iron homeostasis is controlled by the hepatocyte-secreted hormone hepcidin (reviewed in [4]). Hepcidin circulates in the serum and binds to the cellular iron exporter ferroportin (Fpn), stimulating Fpn degradation and leading to cellular retention of iron (Figure IB). Hepcidin expression is directly correlated with both cellular and serum iron statuses and is controlled through a complex iron-sensing signaling pathway (reviewed in [4]). Elevated serum hepcidin downregulates Fpn in duodenal enterocytes (which are responsible for dietary iron absorption), macrophages (which contain large amounts of iron from erythrocyte recycling), and hepatocytes (which act as an iron reservoir and export iron as needed). This leads to an overall reduction in serum iron (Figure IB). Some overlap exists between the IRE–IRP system and the hepcidin–Fpn axis (reviewed in [3]) because Fpn is regulated by IRPs though its 5′ -UTR IRE.

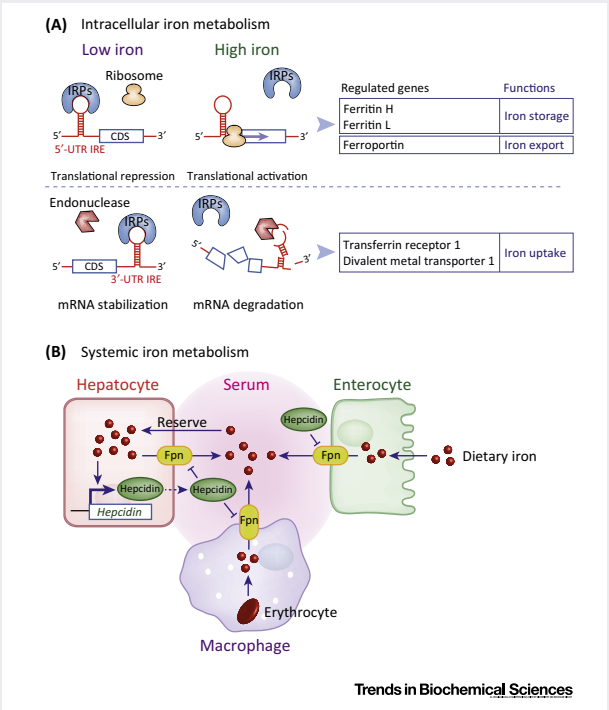

Figure I. Mechanisms of Intracellular and Systemic Iron Homeostasis. (A) Intracellular iron homeostasis is predominantly controlled by the post-transcriptional control of iron metabolism genes via the iron responsive element–iron regulatory protein (IRE–IRP) system. The iron-sensitive IRE–IRP interaction regulates the translation rate or mRNA stability of mRNAs depending upon the location of the IRE in the 5′- or 3′-untranslated region (UTR). (B) Systemic iron homeostasis is regulated by the circulating peptide hormone hepcidin, which binds to ferroportin (Fpn) on the plasma membrane and induces Fpn internalization and degradation on various cell types.