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Review

Mammalian target of rapamycin coordinates iron metabolism with iron-sulfur cluster assembly enzyme and tristetraprolin

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ABSTRACT

Both iron deficiency and excess are relatively common health concerns. Maintaining the body's levels of iron within precise boundaries is critical for cell functions. However, the difference between iron deficiency and overload is often a question of a scant few milligrams of iron. The mammalian target of rapamycin (mTOR), an atypical Ser/Thr protein kinase, is attracting significant amounts of interest due to its recently described role in iron homeostasis. Despite extensive study, a complete understanding of mTOR function has remained elusive. mTOR can form two multiprotein complexes that consist of mTOR complex 1 (mTORC1) and mTOR complex 2. Recent advances clearly demonstrate that mTORC1 can phosphorylate iron-sulfur cluster assembly enzyme ISCU and affect iron-sulfur clusters assembly. Moreover, mTOR is reported to control iron metabolism through modulation of tristetraprolin expression. It is now well appreciated that the hormonal hepcidin-ferroportin system and the cellular iron-responsive element/iron-regulatory protein regulatory network play important regulatory roles for systemic iron metabolism. Sustained ISCU protein levels enhanced by mTORC1 can inhibit iron-responsive element and iron-regulatory protein binding activities. In this study, hepcidin gene and protein expression in the livers of tristetraprolin knockout mice were dramatically reduced. Here, we highlight and summarize the current understanding of how mTOR pathways serve to modulate iron metabolism and homeostasis as the third iron-regulatory system.

Introduction

Iron is an essential cofactor in diverse biological processes such as oxygen transport, cellular respiration, and DNA synthesis. The average adult human body contains 2 to 4 g of iron. Iron deficiency can cause cellular growth arrest and death. However, iron is extremely toxic when present in excess: Ferrous iron reacts with hydrogen peroxides or lipid peroxides to generate hydroxyl or lipid radicals, respectively. So the levels of iron must be tightly controlled inside individual organelles, cells, and tissues. However, the molecular circuits that achieve iron balance under most conditions have only recently begun to be characterized. The iron content of the body is tightly regulated by at least two mechanisms, iron-regulatory proteins (IRPs) and RNA stem-loop iron-responsive elements (IREs) [1] and the transcriptional regulation of hepcidin [2].

IRPs are central regulators of cellular iron homeostasis due to their regulation of specific mRNAs encoding proteins of iron uptake, export, storage, and utilization. IRP1 can assume two different functions in the cell, depending on conditions [3] (Fig. 1). During iron deficiency, IRP1 binds to IREs to modulate the translation of iron metabolism genes. In iron-rich conditions, IRP1 binds an iron-sulfur cluster (ISC) to function as a cytosolic aconitase. IRP2 has ~60% sequence identity to IRP1, but IRP2 does not display aconitase activity [4]. In the case of IRP2, iron controls its RNA-binding activity by stimulating its ubiquitination and rapid proteasomal degradation [5]. IRP2 exhibits a different pattern of affinities to the IRE family than IRP1, having in general weaker binding to the non-ferritin types [6]. IRPs function to restore iron levels through stabilization of transferrin receptor 1 (TfR1) messenger RNA (mRNA) and increased iron uptake, mobilization of cellular iron stores, and reduction in cellular iron export through the suppression of ferroportin [7].

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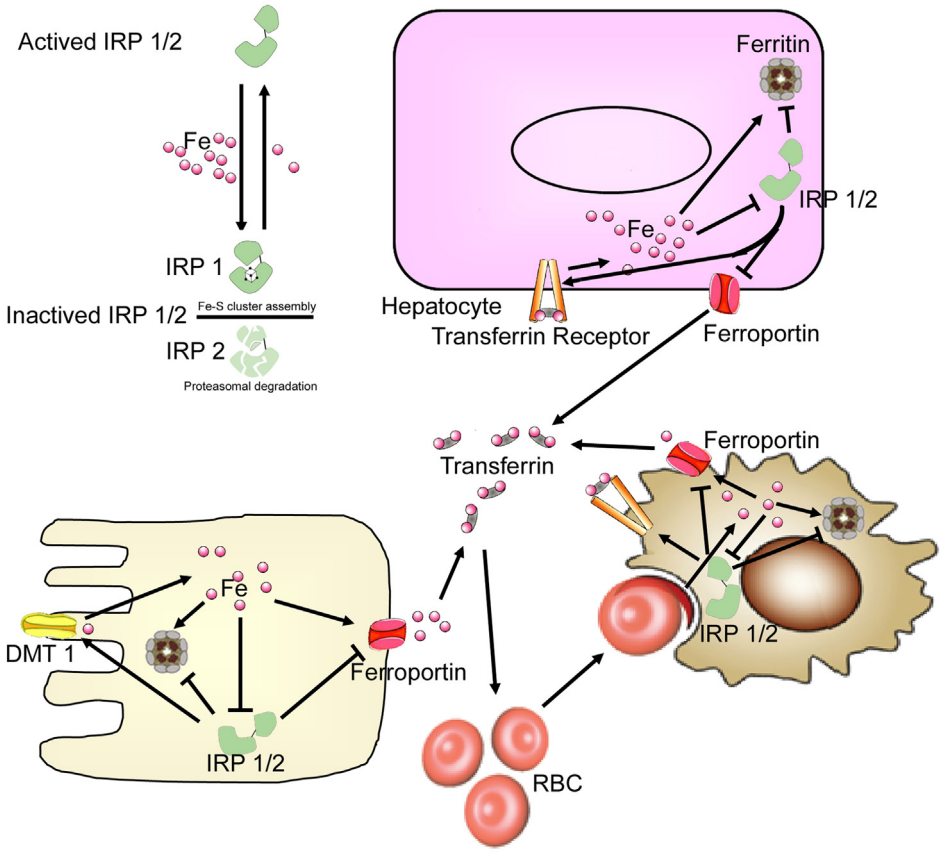

Fig. 1. Regulation of iron homeostasis by IRP/IRE in mammals. Cellular iron loading switches IRP1 from its IRE-binding form to an Fe-S cluster containing cytoplasmic aconitase and triggers proteasomal degradation of IRP2. Low iron levels promote accumulation of active IRP1 in its apo form and stabilize IRP2. IRP1 and IRP2 interact with IREs to coordinate the expression of proteins involved in iron uptake, export, and storage. DMT, divalent metal transporter; Fe, iron; IRE, iron-responsive element; IRP, iron-regulatory protein; RBC, red blood cell.

Hepcidin binds to the iron-transport protein ferroportin, resulting in its destruction and thereby inhibiting absorption of iron from the gastrointestinal tract and release of iron for macrophages [8] (Fig. 2). Additionally, an iron-conservation response has been recently described [9]. The study found that tandem zinc finger protein tristetraprolin (TTP) causes destabilization of mRNAs of nonessential iron-containing proteins and liberation of iron for use in vital processes by modulating TfR1 stability and altering cellular iron flux. TTP has already been demonstrated as the downstream target of mammalian target of rapamycin (mTOR) [9]. mTOR is a phosphatidylinositol 3-kinase (PI3 K)-like serine/threonine protein kinase that is evolutionarily conserved in all eukaryotes. The past several years have seen an explosion of interest in the mTOR signaling pathway, spurred in large part by the finding that inhibition of mTORC1 signaling can significantly increase life span and protect from age-related diseases in mouse models [10]. mTOR can form two separate protein complexes (mTORCs). mTOR complex 1 (mTORC1), which is acutely sensitive to rapamycin, regulates processes such as ribosomal biogenesis, cap-dependent translation, lysosomal biogenesis, and autophagy via substrates that include S6 kinase (S6 K), 4 E-binding protein 1 (4 E-BP1), TFEB1, and Ulk1. mTOR complex 2 (mTORC2), which is resistant to acute rapamycin treatment but can be disrupted by chronic rapamycin treatment in tissue culture as well as in vivo, is sensitive to growth factor signaling and regulates targets downstream of the insulin/insulin-like growth factor 1 (IGF-1) receptor via substrates that include Akt, serum/glucocorticoid-regulated kinase (SGK), and protein kinase C α (PKC α) [11]. It is clear that mTOR signaling regulates iron homeostasis, as treatment of mouse embryonic fibroblasts (MEFs) or H9 C2 cardiomyocyte with rapamycin leads to coordinated reduction in the expression of TfR1 and ferroportin 1, resulting in a net accumulation of cellular iron, whereas mTOR activation has the opposite effect [9]. Induction of TTP by rapamycin is unaltered in MEFs with defective IRP 1/2 signaling, suggesting that IRP/IRE is not involved in mTOR-dependent regulation of TTP [9]. However, silencing of ISCU not only inappropriately activated the IRP1 but also resulted in marked activation of the IRE-binding activity of IRP2 [12], suggesting that mTOR act as a "brake" on the IRP1/2 system. In addition to its effects on IRP1/2 system, mTOR inhibition leads to coordinated reduction in the expression of ferroportin, whereas mTOR inhibition by rapamycin in mouse liver has no effect on the expression of systemic iron-regulatory hormone hepcidin and two of its upstream regulators, bone morphogenic protein 6 and hemojuvel in [9]. Moreover, hepcidin and its upstream activator bone morphogenic protein 6 gene expression in TTP-deficient mouse livers were dramatically reduced. Thus, the function of mTOR/TTP/TfR in regulation of hepcidin appears to be complex and more research is needed. This review focuses on the molecular control of cellular iron homeostasis by mTOR, which is a parallel iron regulatory network.