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Perspective

Intracellular Storage and Regulation of Cellular Iron Homeostasis

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DESCRIPTION

Iron homeostasis in cells is dependent on the regulation of iron genes post-transcription, which is accomplished through the interaction of IRP with IRE in the mRNA un-translated segments of these genes. IRP1 and IRP2 promote iron intake in iron-deficient situations by stabilizing TFR1 mRNA and reducing iron storage and export by inhibiting ferritin and ferroportin translation, respectively. IRP1 is transformed into cytosolic aconitase by Fe/S clusters in iron-replete cells, but IRP2 is degraded by iron-dependent proteasomes. The IRP1/aconitase inter-conversion shows that iron acceleration by its own availability through Fe/S clusters and, its effect, relates iron to tricarboxylic acid and cell metabolism. IRP1 functions in hypoxic tissues like the duodenum and kidneys, where IRP2 binds IRE at normal tissue oxygen levels. When there is an iron deficiency, cells may reabsorb iron through a process called ferritinophagy, which is mediated by the multifunctional protein NCOA4. This protein, which was initially identified as an androgen nuclear receptor transcriptional co-activator, is iron-regulated post-translational. The E3 ubiquitin ligase HERC2 binds to NCOA4 in cells depleted in iron, where NCOA4 is then digested by the proteasome. In cells lacking in iron, NCOA4 binds to ferritin and causes its breakdown. Because NCOA4 regulates the origins of DNA duplication and the availability of iron, its deletion *in vitro* makes cells more susceptible to replication stress and ageing. Mice lacking NCOA4 show increased vulnerability to iron deficiency anemia, decreased iron recycling, and liver and spleen ferritin accumulation. A function for ferritinophagy in hemoglobinization in-vitro, and it was suggested by the high NCOA4 expression in erythroblasts. However, iron storing macrophages' contribution to systemic equilibrium where the process has the greatest impact.

Storage of iron in homeostasis

The "ferritin nano-cage," a cytosolic heteropolymer made up of 24 subunits of heavy (FTH1) and light (FTL1) ferritin chains, is a cytosolic heteropolymer that stores iron from the LIP that is not required for metabolic processes. For a short time, multi-subunit caged ferritin can resist extreme temperatures and a wide variety of pH values, which is required to stop free Fe^{2+} iron from producing excessive ROS. The ferritin nanocage keeps iron accessible by converting it to its soluble form (Fe^{2+}) when needed while storing it in cells in an insoluble, non-toxic state (Fe^{3+}). Due to the ferroxidase activity of FTH1, the iron in the core cavity is kept as tiny crystalline particles in its ferric Fe^{3+} form. Moreover, the mitochondrial form of ferritin that may both defend mitochondria against iron-mediated toxicity and serve as a rapid and effective source of iron in this organelle. The ferritin-sequestered iron can become accessible through ferritin breakdown when intracellular iron levels are low. Low levels of iron cause the ferritin complex to be targeted for auto lysosome breakdown, or "ferritinophagy," *via* Nuclear Receptor Co-activator 4 (NCOA4). Because NCOA4-null animals are unable to undergo ferritinophagy, the higher retention of iron within ferritin complexes leads to a decrease in the amount of iron exported from cells, which ultimately causes iron deficient anemia. On the other hand, iron loaded cells dramatically increase the turnover of NCOA4 to prevent ferritin breakdown and hence boost iron storage.

Regulation of iron

When a cell is iron deficient, cellular iron homeostasis is closely controlled to increase the iron supply, and when a cell is iron replete, to reduce the supply and encourage storage. The iron-dependent binding of Iron Regulatory Proteins (IRPs) IRP1 and IRP2 to stem-loop structures [Iron-Responsive Elements (IREs)] in the Untranslated Regions (UTRs) of messenger RNAs (mRNAs) encoding various iron-related proteins is the most well-understood mechanism for this regulation, though it can take place at various levels. The IRPs are in their mRNA-binding conformations when the quantity of iron in the cell is low. A small amount of ferritin is synthesized when iron storage is not needed because translation is blocked by the binding of IRPs to the 5′ UTR of the ferritin mRNA. A greater amount of TfR1 can be produced on the cell membrane as a result of the IRPs' simultaneous binding to IREs in the 3′ UTR of the TfR1 mRNA, which prevents the message from being processed. The cell can then enhance its iron intake as a result of this effect. IRPs do not bind to IREs in cells with high levels of iron,

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allowing translation of the ferritin mRNA to occur and exposing the TfR1 mRNA to destruction. These circumstances encourage storage of iron and restrict its uptake by cells. Other mRNAs with IREs include those for the enzymes DMT1, FPN1, 5-aminolevulinic acid synthase 2, and hypoxia inducible factor 2. Overall, these modifications ensure that the cells mount a suitable physiological response to changes in intracellular iron concentrations.

CONCLUSION

The fact that ferritin and TfR1 concentrations change depending on iron status has significant diagnostic implications. It was previously mentioned that minute amounts of ferritin aresecreted from storage sites, and as a result, the serum ferritin concentration represents the quantity of stored iron. Because the extracellular domain of the protein can be cleaved by proteolytic cleavage at the plasma membrane, trace levels of TfR1 can also be found in the serum. Because TfR1 concentrations increase when iron concentrations are low, the resulting soluble TfR is a helpful indicator of Iron Deficiency (ID) and is proportional to the body's complement of cell surface TfR1. Many iron-related genes are known to be regulated at the transcriptional level by elements like hypoxia, cytokines, and hormones. Many iron-related genes will be regulated even by iron itself to some extent.