Iron treatment and human intestinal Caco-2 cells

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The regulation of iron absorption has been the focus of many research projects over the past 30 y, but limited new insights have been made in the past decade. Indeed, if one were to read the descriptions of iron absorption and the regulation of transepithelial iron movement in the classic 1979 book *Iron Metabolism in Man*, by Bothwell et al (1), and compare it with what has been cited in recent reviews (2–4), one would find little to cheer about regarding our overall understanding of iron absorption regulation. Although great progress has been made regarding the cellular regulation of iron metabolism in cells via the now well-described iron response element binding protein (IRE-BP) system (2), we still have a limited understanding of the regulation of the movement of iron into human enterocytes and the regulation of the movement of iron across these cells. However, new findings in the past 5 y suggest a pathway to understanding this regulation.

Iron transport proteins that move iron from endosomal vesicles to the cytoplasm have been described and have been named divalent metal transporter 1 (DMT-1) and stimulator of iron transport (SFT) (5, 6). Although the former has specificity for divalent metals, it also appears to be located, at times, strategically on the apical membrane of enterocytes. Proposed mechanisms of regulation of iron involve not only these 2 iron transporters but others as well (7). Thus, the advent of cloning technology has allowed a rapid advance in identification of proteins that may be involved in iron movement into and across the human enterocyte. The question remains: Do these newly described proteins work in a coordinated fashion, in vivo, to control the transepithelial movement of iron?

The importance of the regulation of iron absorption has increased in the past decade with our understanding of the genetic alterations that occur in hereditary hemochromatosis. Studies by Feder (8) and others characterized the major histocompatibility complex class 1–like protein HFE as a fundamental regulator of iron absorption whose mutation is associated with iron overload disease. Those investigations laid the groundwork for studies into the interaction among iron loading, cellular iron status, and the regulation of HFE, SFT, and DMT1 gene expression.

The study by Tallkvist et al (9) published in this issue of the Journal was a targeted, in vitro study of these questions. The investigators used Caco-2 cells to explore the responses of DMT-1, SFT, and HFE to iron-status manipulations. In addition, they wanted to determine whether the movement of other divalent metals—manganese and zinc—were affected by exposing these human enterocyte cell cultures to iron loading. The key outcome variables measured were mineral uptake and transepithelial movement. Iron treatment of cells with 200 μmol Fe/L caused a decreased uptake of all 3 divalent metals and a decreased flux of iron and manganese, but not zinc, across these cells. This effect occurred between 24 and 72 h, which implies a modification in gene expression. The researchers attempted to understand potential mechanisms of these effects by measuring the mRNA concentrations of DMT-1, SFT, and HFE in the cell model; protein concentrations were not measured, however, which leads to some potential pitfalls in interpretation. Interestingly, if serum was not present in the media, DMT-1 mRNA concentrations decreased by about the same amount as did iron uptake and transepithelial transport, whereas this effect was not observed if serum was present. HFE and SFT mRNA were unaffected by iron loading of cells or by the presence of serum in the media. Measurements of TIR mRNA indicated little about the interaction of the regulation of these iron transport proteins with the Tf-TIR cycle for iron movement into cells because the amount of mRNA was low. The authors clearly established a fundamental response of DMT1 to iron loading. In addition, this article provides some important new information that iron and manganese movement across these human cell systems likely involves the regulation of amount of DMT-1. The final important finding was that high iron intakes had little effect on zinc transcellular movement, thus further clarifying a confusing body of literature about the interaction of these 2 minerals.

However, significant experiments still need to be conducted before any conclusions are made about mechanisms of regulation of iron absorption. These are especially critical with respect to our understanding of the in vivo regulation of iron absorption in hereditary hemochromatosis. The next steps need to include 1) experiments regarding more physiologically relevant forms of iron (iron-nitroloaceatic acid is not a form of iron that is normally present in the human gut; iron ascorbate, citrate, or gluconate would provide far more relevant data) and 2) the actual measurements of DMT-1, HFE, and SFT protein concentrations themselves within the context of both iron loading and iron deprivation. The experiments of Han et al (10) showed that both iron-deprived and iron-loaded Caco-2 cells could down- and up-regulate HFE protein content; the real reason for the discrepancy between these 2 reports is unresolved, but the thought of a reciprocal regulation with DMT-1 protein has great appeal.

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In the larger view, we can be increasingly optimistic that these kinds of experiments will soon elucidate the mechanism of regulation of iron uptake and transcellular movement of iron (7). The identification of the signaling process whereby body iron status is communicated to the enterocyte is of fundamental importance, because we increasingly need to view iron biology from the perspective of iron both as a nutrient and as a toxicant. Iron deficiency is clearly a significant public health problem in the world today, and iron overload is a significant issue for persons with genetic mutations that modify the normal feedback regulation of iron absorption. Studies such as those reported by Tallkvist et al give us one more piece of important information regarding the development of effective strategies to combat both of these public health problems.

REFERENCES


