For well over 30 y, it has been known that at the absorptive and metabolic levels, minerals, both macro and trace, interact with one another. With the knowledge gained in the same time span, greater insight has been established as to how the stores of a particular mineral may regulate the absorption of that same mineral. Additionally, we have a greater understanding of how the concentrations of one mineral in the diet may negatively influence the absorption of another mineral. In earlier days, many of these interactions were reduced to an oversimplistic view that the valence of a mineral was a determining factor where one mineral could interfere with the absorption of another mineral that was in dietary excess. Essentially, there was a notion that some minerals could share a common carrier based on valence state. Using this reasoning, it was expected, for instance, that ferrous and cupric forms of iron and copper, respectively, could affect the absorption of the other. There are cases in which minerals do share a common carrier [divalent metal transporter 1 (DMT1)], but the competitive inhibition of one mineral by another appears to be overly simplistic. Our understanding of how dietary zinc and copper interact with one another in terms of the amount absorbed when one was in molar excess of the other changed with the discovery that the protein metallothionein had a significant impact on the absorption of these 2 minerals. Enterocytes have the capacity to regulate the amount of minerals absorbed into the portal blood supply through novel means. Increased dietary zinc stimulated transcription of the gene encoding for metallothionein, but this protein had a greater affinity for copper than for zinc (1). In practical terms, this means that copper will be tightly bound to metallothionein and would be unavailable for absorption by the portal blood supply. The copper would be lost to the fecal compartment as enterocytes are sloughed off every 24 to 48 h (1). This finding was seminal in that it demonstrated that nutrients could function not only at the metabolic level but also at the gene level. This discovery changed how many of us studied nutrition issues, particularly those dealing with trace minerals. We now know that selenium, copper, zinc, iron, chromium, and others exert their influence at the molecular level and do not function merely as cofactors or structural components of enzymes of other cell structures.

Thirty years or so later, we are still unraveling the nature of how changes in the concentrations of one trace mineral affect the absorption and utilization of another. Today, we have the advantages of using more sophisticated approaches given to us by the gifts of molecular biology discoveries and the techniques required for these discoveries. The work of Gulec and Collins (2) reported in this issue of *The Journal of Nutrition* provides us with a greater understanding of the molecular biology aspects of copper and iron absorption and how the absorption of one impacts the other. We have been aware that excess dietary iron can decrease copper absorption, and the reverse is true in that excess dietary copper may impair iron absorption. Although it has largely been known how both iron and copper per se are absorbed, new information reveals that iron may be absorbed by what has historically been thought to be only a copper transport protein. The Collins laboratory has studied the role that the Menkes copper-transporting ATPase (*Atp7a*) gene, responsible for copper transport, has upon iron absorption. This gene is referred to as the Menkes gene. In individuals with mutations in this gene, there is an inability to absorb copper, leading to acute copper deficiency. It would appear from this latest study that the absorption of trace minerals is like an orchestra that has a seasoned conductor making sure that all the players perform at the right time and with their best performance. On the other hand, are there multiple conductors each regulating a separate mineral?

In iron deficiency, *Atp7a* is upregulated, resulting in increased uptake of copper by the portal blood supply because this protein is a known copper exporter (3). The gene is controlled by hypoxia inducible factor 2a (HIF2a), which is induced during states of iron deficiency. HIF2a is transcription factors that are sensors of low tissue oxygen or hypoxic states, which may exist when iron deficiency is present. When low oxygen is present in tissues such as in enterocytes of the small intestine, HIF2a is upregulated and produced to regulate those genes involved with iron homeostasis (4–6). For instance, HIF2a is upregulated and binds to the promoter of the genes encoding DMT1, ferroportin 1, and Ferric reductase of enterocytes that converts ferric to ferrous iron, which is absorbed (4–6). These actions collectively increase the uptake of iron by the small intestine. Furthermore, HIF2a will decrease expression of hepcidin by the liver, thereby allowing a greater absorption of iron into the blood supply. In addition to its impact upon iron metabolism, HIF2a has an impact on copper metabolism indirectly because it will also, in turn, transcriptionally upregulate *Atp7a* and the intracellular copper binding proteins metallothionein I/II (7,8). In the study reported by Gulec and Collins (2), silencing the expression of *Atp7a* using knockdown technology in rat intestinal epithelial (IEC-6) cells resulted in increased ferric reductase expression and ferroportin 1 transcriptional activation; both of which enhance iron absorption. The transcriptional activation of ferroportin 1 in the intestinal epithelium by mechanisms other than hypoxia has not been reported according to the study’s authors. The key finding here, however, is that *Atp7a*, a known copper transport protein, may be the missing link as to how copper may affect iron absorption. On the other hand, if copper flux is altered with *Atp7a*, is it lack of the protein per se or the change in copper concentrations from the knockdown of *Atp7a* that has an impact upon iron metabolism and its regulatory proteins? This question is left unanswered.

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* Commentary

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unanswered. More important, however, is the recognition that, in the grand scheme of things, the entire interorgan messaging of iron and copper metabolism is elegant, from the role of hepcidin in the liver to its communication with ferroportin in the duodenum to block iron entry into the portal circulation.

Knowing the molecular aspects of interorgan control of mineral homeostasis is also essential as opposed to studying a cell system in isolation. The entire organism must be considered in terms of how trace mineral status has an impact upon absorption in this delicate balance and orchestration of events. A question that could be posed is what is the consequence of mutations in Atp7a, such as what occurs with Menkes disease, upon overall iron metabolism? A search of the literature reveals little to answer this question. However, a recent article by the authors (9) of the current study used brindled (MoBr/Br) mice, which have a 6-bp deletion in the Atp7a gene, as a model of Menkes disease. The results suggested that these animals were able to adequately regulate iron absorption through compensatory mechanisms. Thus, whereas ATP7a does play a role in iron absorption, it remains to be resolved how important the function of ATP7a is for iron metabolism overall in cases of perturbed ATP7a function, and its overall role in health and disease. The nature of how copper and iron are absorbed and their interaction with one another appears to be made clearer, on the one hand, but deepens it further, on the other hand, as new questions emerge.

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Literature Cited