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Commentary

Muscle specific iron deficiency has systemic consequences

Jerry Kaplan *, Diane M. Ward

Department of Pathology, School of Medicine University of Utah, Salt Lake City, Utah,

Iron is an essential element for most prokaryotes and all eukaryotes. Iron is required for heme synthesis, iron–sulfur cluster synthesis and as a co-factor for a wide variety of enzymes. Most of the iron in vertebrates is found in hemoglobin in red blood cells and iron deficiency anemia is a significant medical problem. Iron, however, is found in all cells and iron deficiency is the most common nutritional deficiency in the world reportedly affecting two billion people (Camaschella 2015), particularly affecting young children and women (Pasricha et al. 2013). While the consequences of iron deficiency can be readily seen in cultured cells, the consequences of iron deficiency on specific tissues have been harder to define, largely due to the overwhelming systemic defects of iron-limited erythropoiesis. The ability to generate cell-specific genetic deletions in mice has permitted the analysis of iron-limitation on specific cell types in the absence of systemic iron deficiency. In vertebrates elemental iron enters cells through different transport systems. Iron exported through the absorptive intestinal cells is bound in plasma to transferrin (Tf) where it is delivered to cells that require it as shown by the expression of transferrin receptor 1 (Tfr1) on those cells. Cell types with the highest expression of Tfr1 include erythroid precursors and dividing cells. When the iron binding sites on Tf are occupied or when Tf is absent iron introduced into plasma can enter cells through other transport systems (Hentze et al. 2010).

It is clear that the Tf–Tfr1 interaction is the high affinity iron acquisition system. In order to identify the role of Tfr1 and iron deficiency on specific cell types, Andrews and colleagues generated tissue-specific deletions of the gene encoding Tfr1 (*Tfrc*). Several years ago the authors showed that a systemic loss of Tfr1 resulted in embryonic lethality but that many tissues can form in the absence of Tfr1 (Levy et al. 1999), suggesting that Tfr1–Tf system is not essential for all cell types. In this issue of *EBioMedicine*, Barrientos et al. (2015) describe the effects of deleting *Tfrc* in mouse skeletal muscle. Muscle tissue might be expected to be a high consumer of iron because of the presence of heme-containing myoglobin and for the need to generate ATP for contraction. Barrientos et al., demonstrated that loss of Tfr1-mediated iron delivery was critical for skeletal muscle metabolism, and that iron deficiency in muscle led to dramatic systemic changes. *Tfrc* deletion in skeletal muscle, mediated by the skeletal muscle specific actin promoter driving the Cre recombinase expression, did not affect embryonic viability. Mice were born but showed decreased growth and a loss of viability within two weeks of birth. Muscles were small but there was no decrease in the number of muscle fibers and no obvious signs of degeneration. Mitochondrial respiration was impaired and there were significant changes in both metabolites and transcripts, which suggested wholesale metabolic changes consistent with hypoxia and mitochondrial dysfunction. While some of these changes might be predicted as a consequence of iron deficiency and the requirement of iron for respiration, what was unexpected was were effects in tissues other than muscles. The authors describe significant changes in adipose tissue and liver. There was a striking time-dependent loss of adipocyte fat content and an increase in liver fat content. The loss of adipocyte fat stores was suggested to reflect increased fatty acid mobilization. Changes in muscle and liver metabolism were consistent with changes in energy metabolism leading to defective fatty acid catabolism and decreased glucose neogenesis. These effects were thought to result from decreased mitochondrial heme and iron-sulfur cluster synthesis affecting respiratory activity, and through loss of heme sensitive transcription. All metabolic and morphological changes could all be suppressed when systemic iron levels were increased by injections of iron-dextran, confirming that iron deficiency was casual to the defect. In other cell types, as recently shown by the Andrews group (Chen et al. 2015) and others (Senyilmaz et al. 2015), Tfr1 might have functions independent of iron acquisition.

The metabolite or hormone that triggered the effects on fat and liver remains to be elucidated. The changes in liver metabolism also appeared to be a response to altered muscle iron metabolism. The liver showed decreased iron content, which might be a consequence of increased iron export, as liver transcripts for the iron-regulatory hormone hepcidin were markedly decreased. Barrientos et al., results showed metabolic changes in muscle and subsequent dramatic changes in tissues that were not deleted for *Tfrc* offer a cautionary tale to the analysis of targeted deletions; one can't look just at the targeted organ. Changes in mitochondrial respiration due to loss of heme and iron–sulfur-cluster containing activities may explain much of the changes in metabolism. Of particular note is that Barrientos et al., showed that one of the effects of muscle cell *Tfrc* deletion was a decrease in aspartic acid synthesis, which requires mitochondrial respiration. Recent papers show that decreased mitochondrial respiration affects cell proliferation. Decreased proliferation was not due to changes in ATP levels but rather due to

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* Corresponding author.
E-mail address: jerry.kaplan@path.utah.edu (J. Kaplan).

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the mitochondrial production of aspartic acid, which is required for the synthesis of proteins, purines and pyrimidines (Sullivan et al. 2015; Birsoy et al. 2015). The finding that decreased muscle Tfr1-mediated iron acquisition can affect mitochondrial activity not only in muscle but also in liver has far reaching implications for the effects of iron deprivation. That muscle iron deficiency has "unappreciated" systemic effects may go beyond energy metabolism and affect both development and cognition. This is of particular importance in children and in pregnancy, in which the consequences of iron deficiency may last longer than the episode. Attention must be given to the first signs of anemia or iron deficiency to prevent such sequela.

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