

Novel role for divalent metal-ion transporter-1 in the absorption of iron derived from heme

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Iron deficiency is the most prevalent micronutrient deficiency worldwide. Whereas dietary heme iron offers greater bioavailability than nonheme iron, relatively little is known about the mechanisms of heme-iron absorption. Heme (ferrous protoporphyrin IX) is thought to be taken up intact into the enterocyte via a receptor-mediated endocytosis. How ferrous iron (Fe^{2+}) is exported from the endosome (or lysosome) after its liberation from heme is not known. Divalent metal-ion transporter-1 (DMT1) is a widely expressed Fe^{2+} transporter that serves the uptake of nonheme iron at the intestinal brush border. We considered a role for DMT1 also in the endo-/lysosomal export of heme-derived iron, in analogy with its established role in endosomal transport of iron derived from transferrin. We tested a role for DMT1 in intestinal heme-iron absorption by examining intestinal handling of heme in a mouse model lacking intestinal DMT1 (i.e. $\text{DMT1}^{\text{int/int}}$). Generation of the $\text{DMT1}^{\text{int/int}}$ model, by crossing floxed DMT1 and villin-Cre transgenic lines, was described previously [Gunshin et al (2005) *J. Clin. Invest.* **115**, 1258–1266]. The $\text{DMT1}^{\text{int/int}}$ mouse exhibited a severe microcytic, hypochromic anemia—characterized by profound decreases in hematocrit (Hct, $\text{DMT1}^{\text{int/int}}$, $7\% \pm \text{SD } 2\%$ cf. wildtype, $44\% \pm 4\%$; $n = 7-9$), hemoglobin concentration, mean corpuscular volume, and serum iron—accompanied by cardiac hypertrophy, splenomegaly, and severely depleted nonheme iron stores (liver, spleen). Intraperitoneal iron injection (bypassing the intestinal lesion) corrected the iron-deficiency anemia phenotype of the $\text{DMT1}^{\text{int/int}}$ mouse. Feeding $\text{DMT1}^{\text{int/int}}$ mice red blood cells (washed, packed cells resuspended in an equal volume of saline) via intragastric gavage once per week for 6 weeks had no effect on hematological variables (e.g. Hct, $10\% \pm 3\%$; $n = 4$), blood-iron variables, or liver nonheme iron content. In contrast, feeding RBCs to wildtype mice increased their nonheme liver iron stores by over 130%, confirming a functional heme-absorptive pathway in wildtype animals. Our data reveal a novel role for DMT1 in heme-iron absorption. Future studies will be directed at measuring [^{59}Fe]heme absorption by direct methods and localizing DMT1 within the heme-absorptive pathway.