Therapeutic Strategies to Modulate Iron Absorption in Human Disorders

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NIH Office of Dietary Supplements
Seminar Series; Feb. 18, 2026

NIH National Institutes of Health
Office of Dietary Supplements

UF UNIVERSITY of FLORIDA

Objectives

- Outline the Basics of Iron Homeostasis
  - Focus: Intestinal iron absorption
    - Heme iron (HI) vs. nonheme iron (NHI)
- Discuss Iron-related Disorders in Humans
  - Iron-deficiency Anemia (IDA)
  - Hereditary Hemochromatosis (HH)
  - β-Thalassemia Intermedia (βTI)

  } Iron-loading Disorders
- List Novel Approaches to Modulate Iron Absorption
  - Enhance absorption in IDA
  - Block absorption in HH, βTI

Systemic Iron Homeostasis

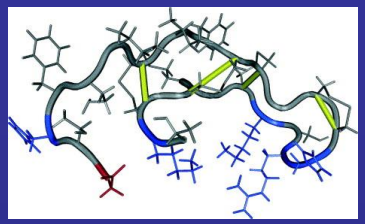
- Dietary iron does not meet physiologic needs
  - Iron is avidly conserved/recycled (25 mg/d)
- Scenescent RBCs undergo erythrophagocytosis
  - RE macrophages
  - Hemoglobin degraded, Fe stored or released to TF in blood
- Most iron for erythropoiesis (bone marrow)
- No active, regulated excretory mechanism
  - Daily losses minimal (1-2 mg/d), non-specific
- ***Intestinal iron absorption = homeostatic checkpoint***
- Excess iron deposited in tissues is TOXIC

Pathological Outcomes

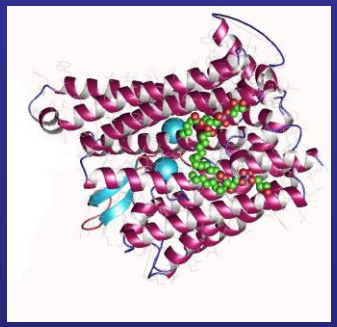
- Iron Deficiency Anemia (IDA)
  - Lethargy, anemia/hypoxia, pica, weakness, shortness of breath
  - Poor growth, cognitive deficits

- Iron Overload (HH, βTI)
- Iron accumulates in:
  - Liver, pancreas, gonads, joints, heart
  - Joint pain, diabetes, impotence, cardiomyopathy, liver fibrosis/cirrhosis/cancer

Molecular Regulation of Iron Homeostasis

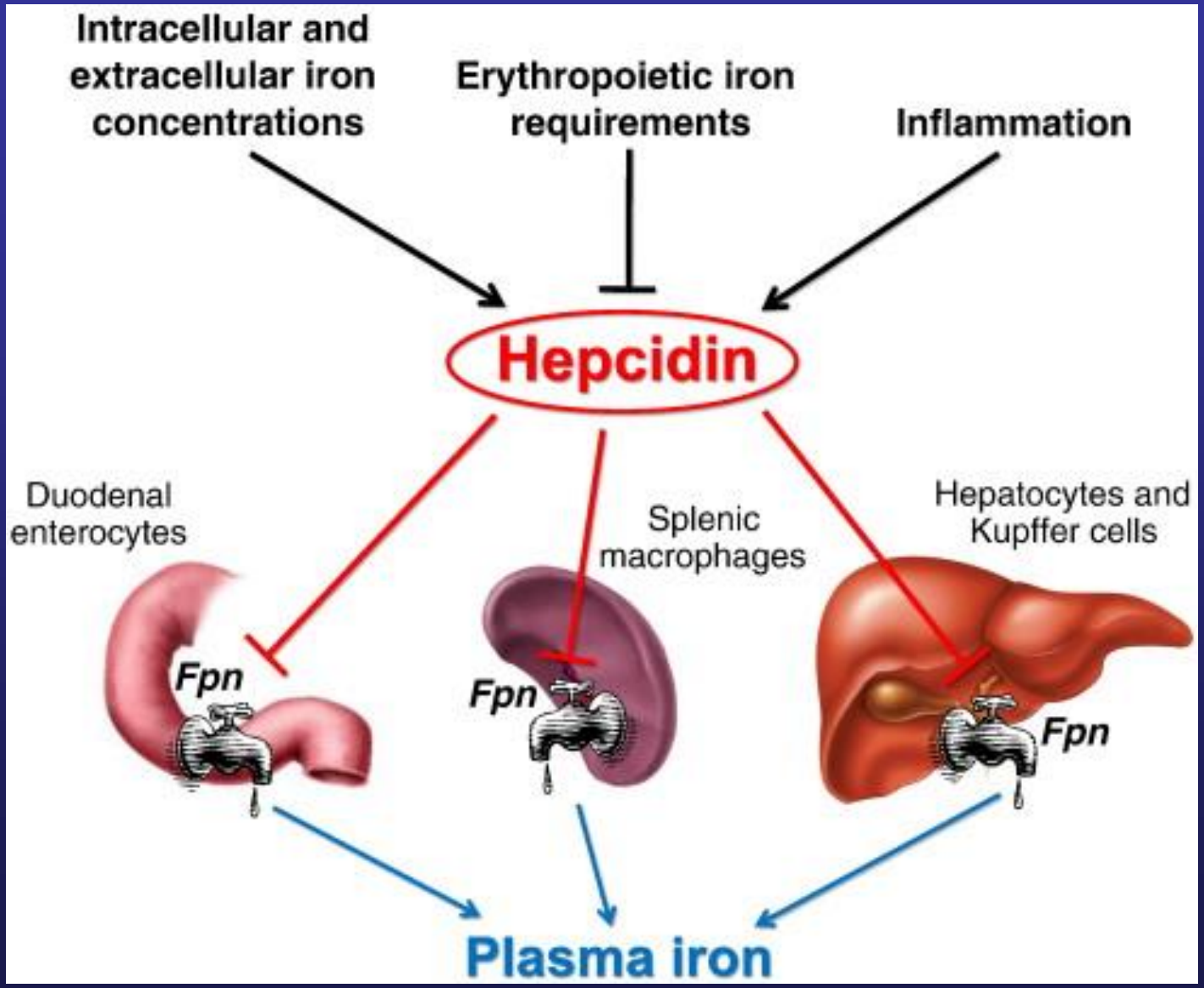


- Hepcidin: the iron-regulatory hormone
  - 25 amino acid peptide hormone produced in liver



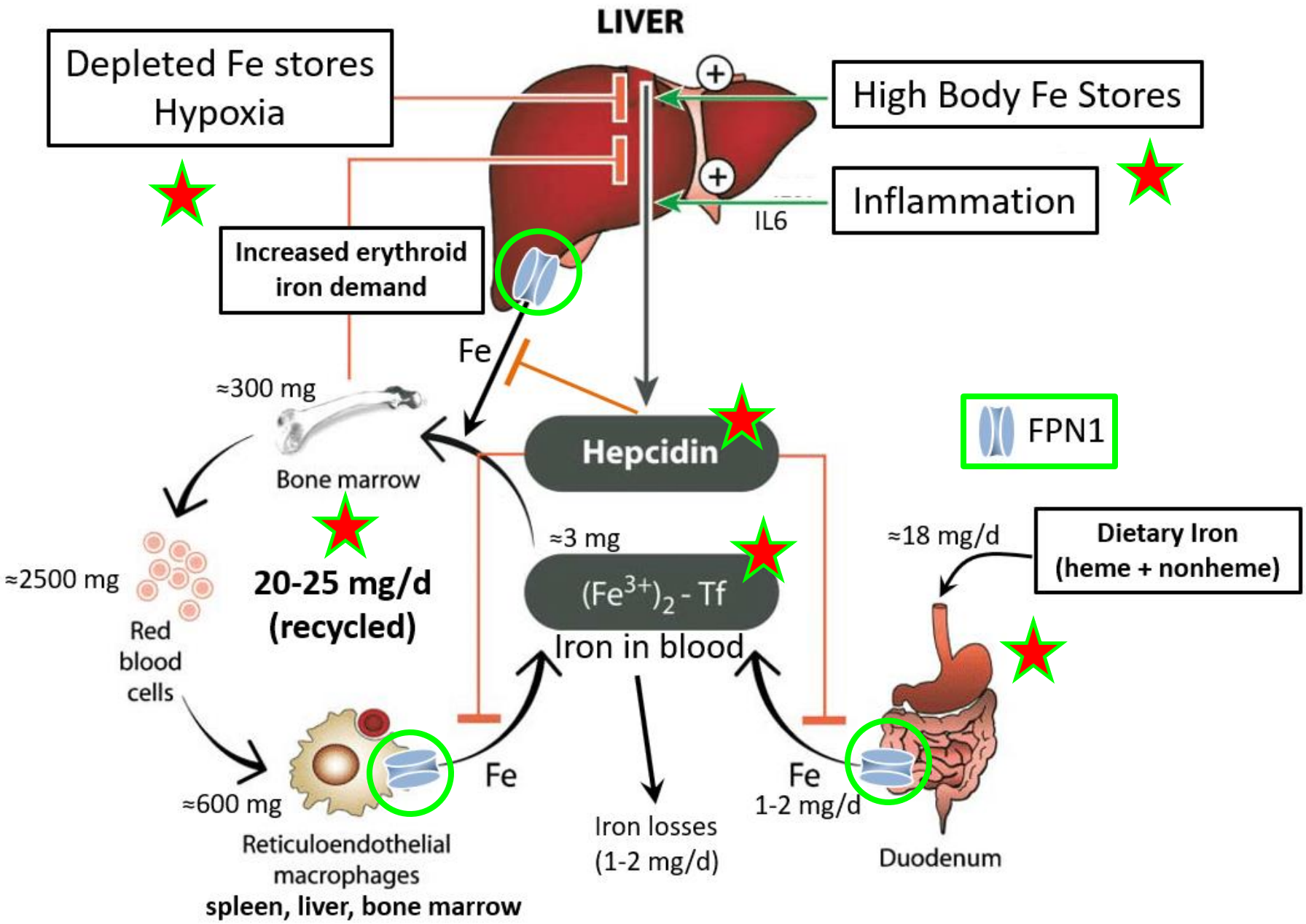
- Binds to FPN1- internalization and degradation
- Blocks iron release from cells that express FPN1
  - Duodenal enterocytes, RE macrophages, hepatocytes
  - Elevated iron stores, inflammation = Increased HEPC
  - ID / hypoxia, increased erythropoietic demand = Decreased HEPC
- KO = iron overload; Over-expression = IDA

Function of Hepcidin = Decrease Serum Iron

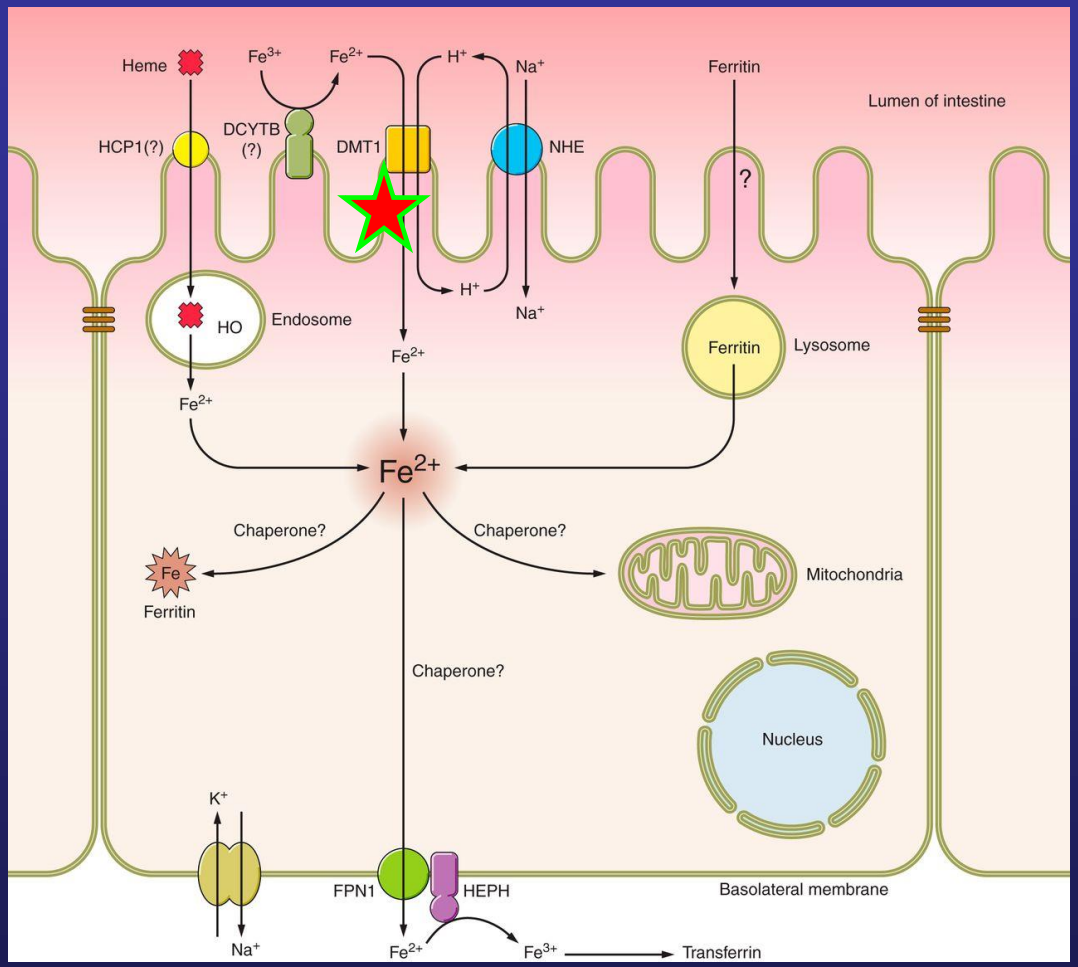


doi.org/10.1016/j.bbamcr.2012.01.014

Systematic Iron Homeostasis: Absorption, Storage and Recycling



Iron Transport Across Duodenal Enterocytes

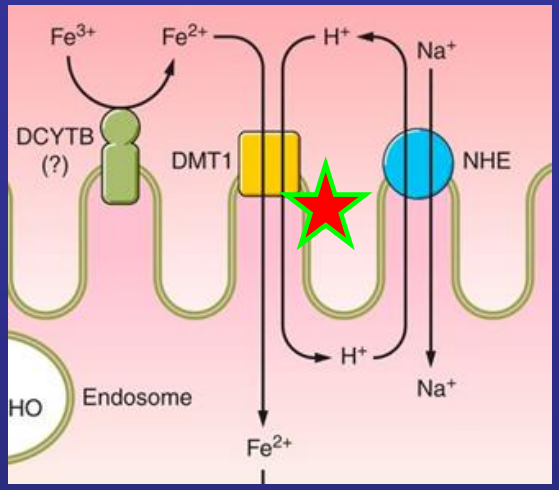


Am J Physiol Gastrointest Liver Physiol. 307(4):G397-409, 2014
DOI: 10.1152/ajpgi.00348.2013

- Duodenal cytochrome B (DCYTB)
  - Ferrireductase
- Divalent metal-ion transporter 1 (DMT1)
  - Ferrous iron importer
- Ferritin
  - Intracellular iron storage
- Ferroportin 1 (FPN1)
  - Ferrous iron export
  - Hepcidin target
- Hephaestin (HEPH)
  - Ferroxidase)
- Transferrin (TF)
  - Iron transport protein

Divalent Metal-Ion Transporter 1 (DMT1)

- Fe^{2+}-proton cotransporter
  - Belgrade (*b*) rat
  - Microcytic anemia (*mk*) mouse
  - Two functions:
    - Intestinal iron (NHI) absorption
    - Cellular iron acquisition- transferrin cycle
  - Induced by iron depletion / hypoxia

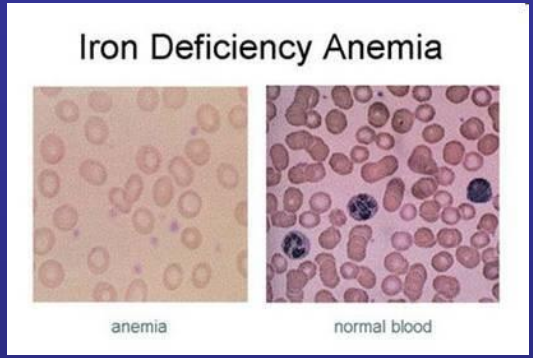


- Mutations in DMT1 cause severe IDA (humans and rodents)
- Intestine-specific Dmt1 KO mice, severe IDA
  - When fed diets with only NHI

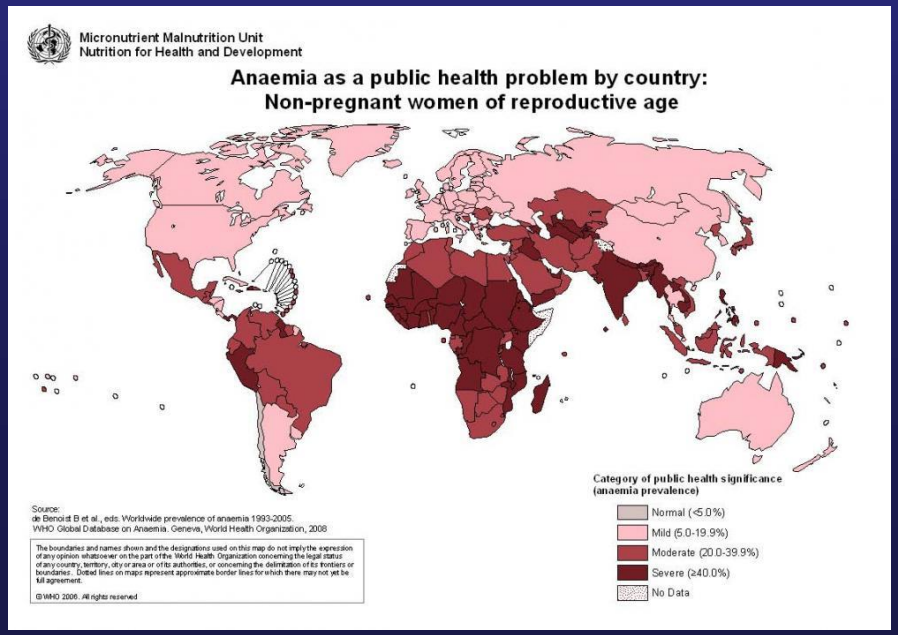
- DMT1 may be a target of intraluminal hepcidin
- DMT's role in intestinal heme-iron absorption unknown

Iron-deficiency Anemia

- **Stages of iron deficiency**
  I. Decreased stores
  II. Decreased transport
  III. Decreased hemoglobin synthesis
  IV. Anemia: hypochromic, microcytic



- Leading risk factor for disability and death worldwide
- 2 billion people affected
- **WHO estimates**
  - Developing countries
    - Children <5 (39%)
    - Children 5-14 (48%)
    - Women (42%)
    - Pregnant women (58%)

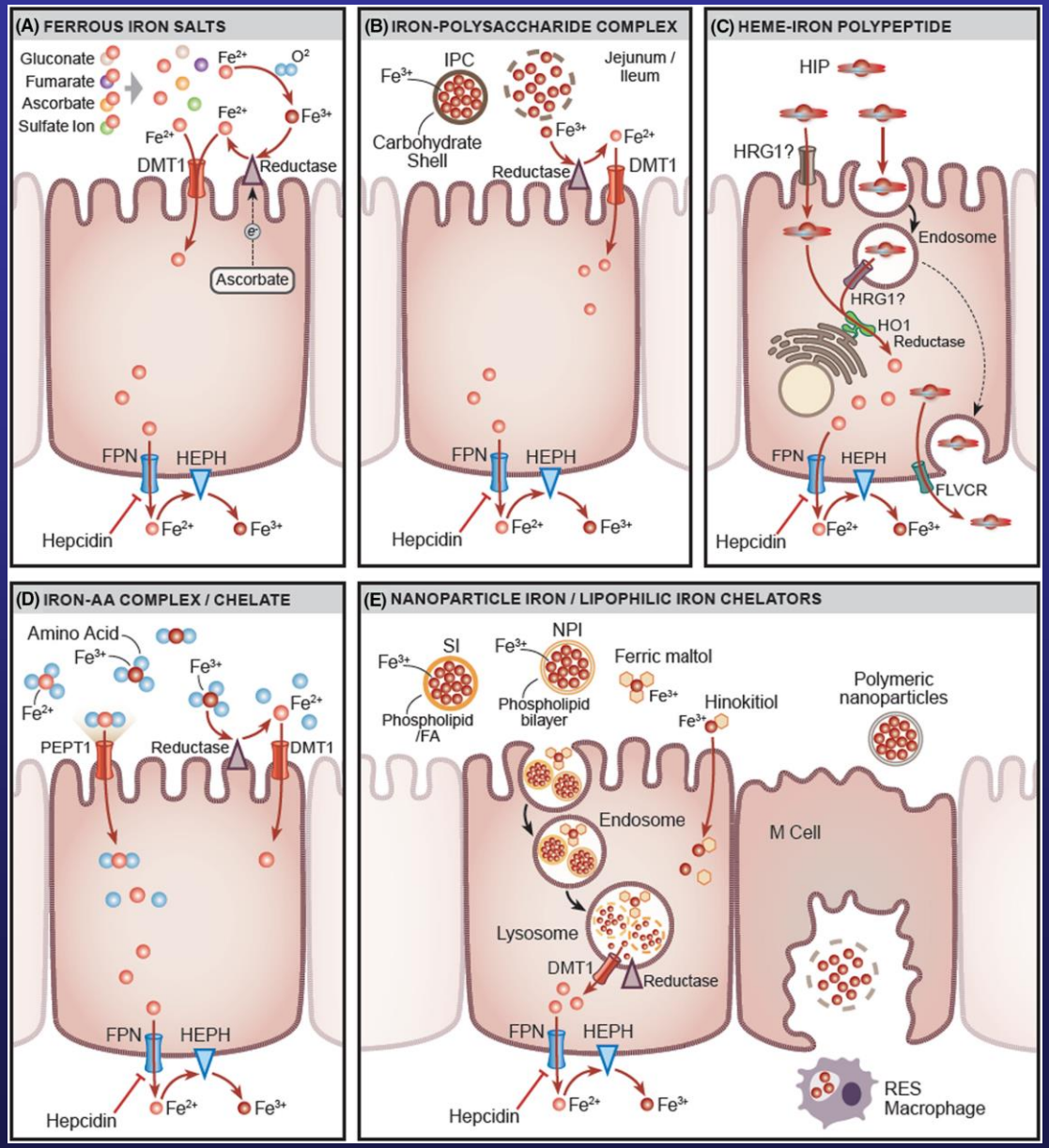


Oral Iron Supplementation

- **Most common txt for IDA (globally)**
- Iron salts (NHI) most common ($FeSO_4$)
  - Low bioavailability
  - Txt induces hepcidin (blocks absorption)
  - Supraphysiological doses required
    - GI side effects

- Ongoing research- identify better oral iron supplements
  - Higher bioavailability
  - Lower GI side effects
  - Not regulated by hepcidin

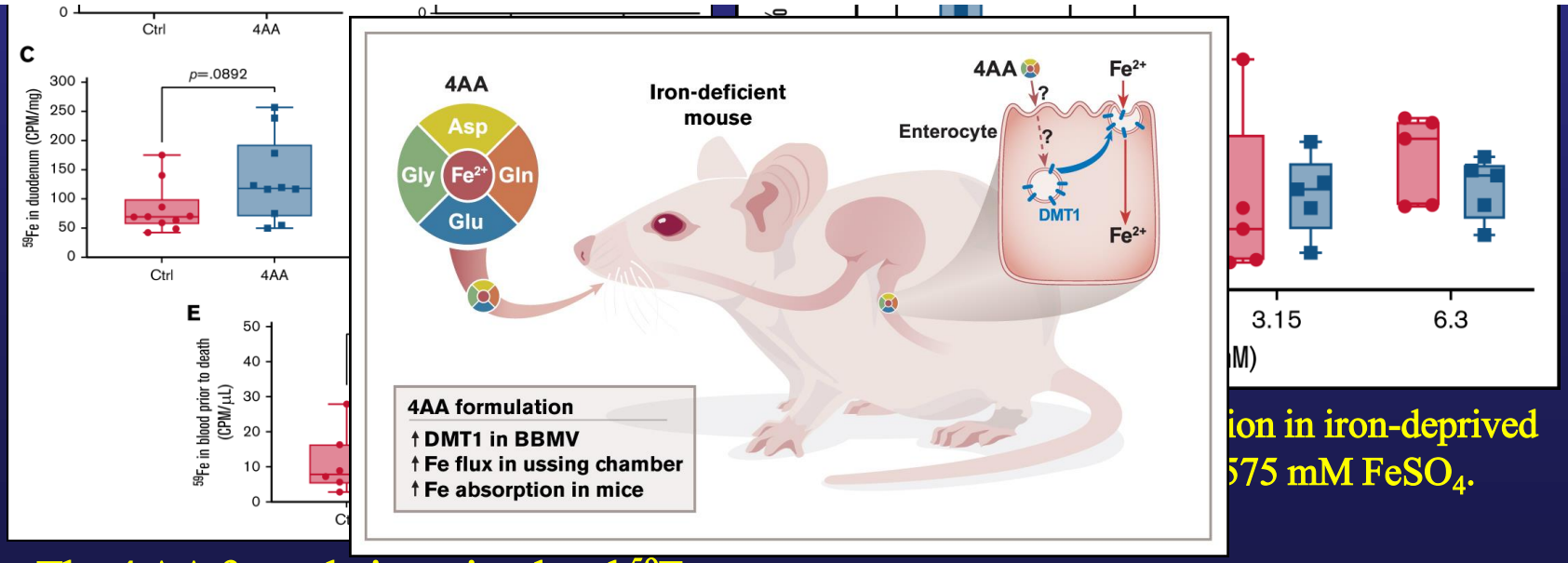
Oral iron supplements and pathways of absorption



Br J Haematol. . 2024 Mar;204(3):759-773. doi: 10.1111/bjh.19268

Four AAs increase DMT1 abundance in duodenal brush-border membrane vesicles and enhance iron absorption in iron-deprived mice

Select AAs thus enhance iron absorption by inducing DMT1 trafficking onto the apical membrane of duodenal enterocytes. We speculate that further refinement of this new 4 AA formulation will ultimately allow iron repletion at lower effective doses (thus mitigating negative side effects of excess enteral iron).



ion in iron-deprived
575 mM $FeSO_4$.

The 4 AA formulation stimulated ^{59}Fe absorption in iron-deficient mice.

Blood Adv (2022) 6 (10): 3011–3021.
https://doi.org/10.1182/bloodadvances.2021005111

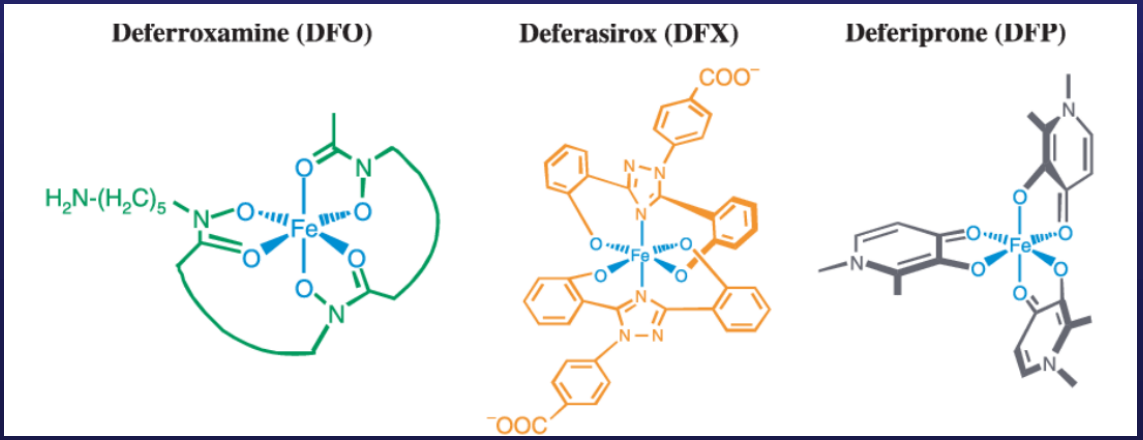
- **Genetic Iron-loading Disorders**
  - Hereditary Hemochromatosis (HH)
    - Mutant genes- *HFE, TFR2, HJV, HAMP*
      - Required for hepcidin production
      - Low hepcidin = high iron absorption = iron loading
  - β-thalassemia Intermedia (βTI)
    - *HBB* (hemoglobin subunit beta) mutations
    - Iron-loading anemia
    - Non-transfusion-dependent form of disease
      - Low hepcidin = high iron absorption = iron loading

Iron-Overload Disorders

- Elevated intestinal iron absorption
  - Inappropriately low hepcidin
- Plasma iron exceeds TF binding capacity
  - Non-transferrin bound iron (NTBI)
  - TF-independent iron uptake into cells
- Iron accumulates in parenchymal tissues
  - Oxidative stress, tissue damage
  - Organ dysfunction

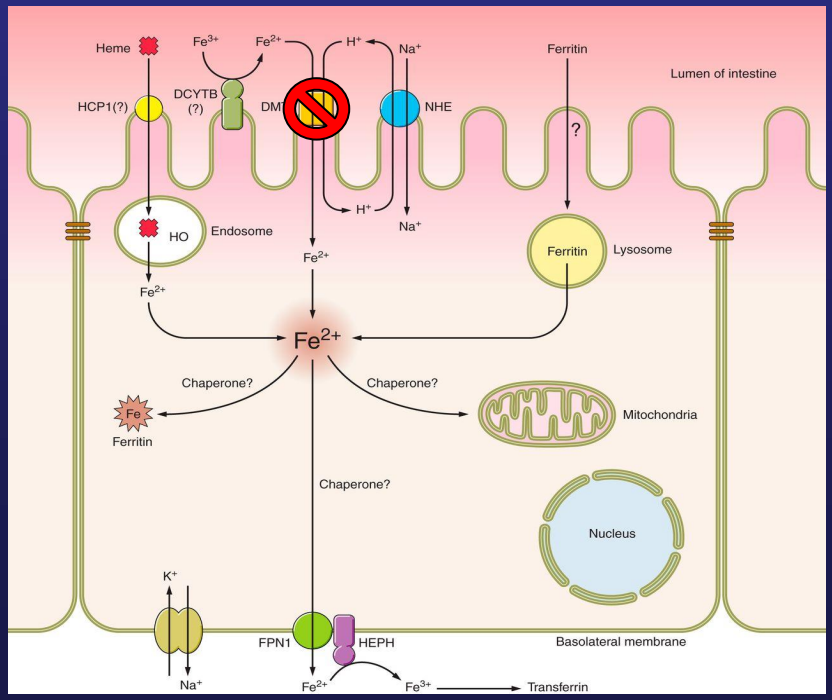
Treatment for Iron-overload Disorders

- Phlebotomy (HH)
  - Not specific for iron
  - Weekly
  - Maintenance phlebotomy
    - Over lifetime as needed
- Iron chelators (βTI)
  - Numerous side-effects



Novel Approach to Prevent Excess Iron Absorption

- Knockdown or block Dmt1
- Rationale:
  - DMT1 required for NHI absorption
  - DMT1 may be hepcidin target
- Key Question: could DMT1 also be involved in HI absorption?



Targeting Intestinal DMT1 in HH and βTI

(1) DMT is required for iron loading in HH and βTI
(2) Targeting intestinal DMT1 could be an effective adjunctive txt for iron overload.

Loading in Murine Hereditary Hemochromatosis

Xiaoyu Wang,[1] Mingzhen Zhang,[3,4] Shireen R.L. Flores,[1] Regina R. Woloshun,[1] Chunhua Yang,[4] Liangjie Yin,[2] Ping Xiang,[1,6] Xiaodong Xu,[2] Michael D. Garrick,[7] Sadasivan Vidyasagar,[2] Didier Merlin,[4,5] and James F. Collins[1]

[1]Food Science & Human Nutrition Department, University of Florida, Gainesville, FL, USA; [2]Department of Radiation Oncology, University of Florida, Gainesville, FL, USA; [3]Institute of Medical Engineering, School of Basic Medical Science, Health Science Center, Xi'an Jiaotong University, Xi'an, China; [4]Center for Diagnostics and Therapeutics, Institute for Biomedical Science, Georgia State University, Atlanta, GA, USA; [5]Atlanta Veterans Affairs Medical Center, Decatur, GA, USA; [6]State Key Lab of Pollution Control and Resource Reuse, School of the Environment, Nanjing University, Nanjing, China; [7]Department of Biochemistry, State University of New York (SUNY), Buffalo, NY, USA

In vivo silencing of intestinal DMT1 mitigates iron loading in β-thalassemia intermedia (*Hbb*$^{th3/+}$) mice

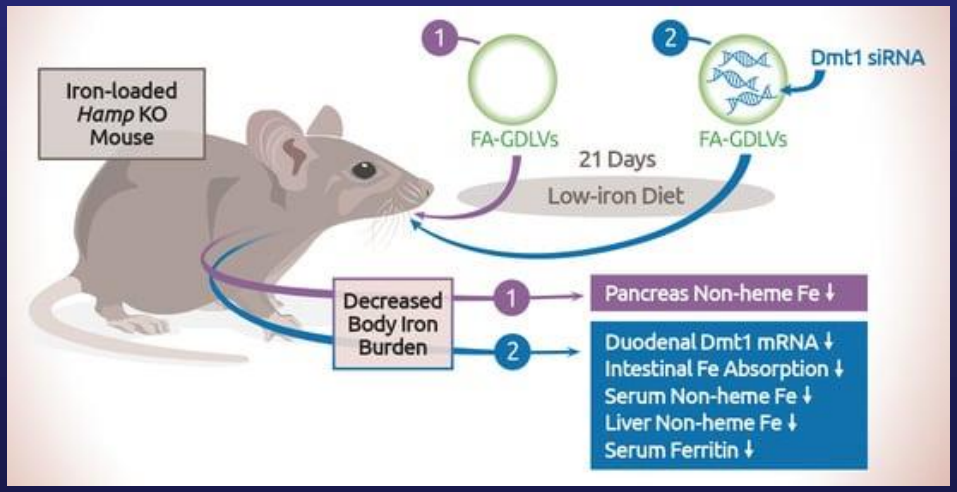
Yang Yu [1], Regina R Woloshun [1], Jennifer K Lee [1], Pearl O Ebea-Ugwuanyi [1], Jacob S Shine [1], Sean Zhu [1], Yue He [1], James F Collins [1,*]

nutrients MDPI

Nutrients. 2021 May 15;13(5):1686. doi: 10.3390/nu13051686

Oral Administration of Ginger-Derived Lipid Nanoparticles and Dmt1 siRNA Potentiates the Effect of Dietary Iron Restriction and Mitigates Pre-Existing Iron Overload in *Hamp* KO Mice

Xiaoyu Wang [1,2,†], Mingzhen Zhang [3,4,†], Regina R Woloshun [2], Yang Yu [2], Jennifer K Lee [2], Shireen R L Flores [2], Didier Merlin [3,5], James F Collins [2,*]



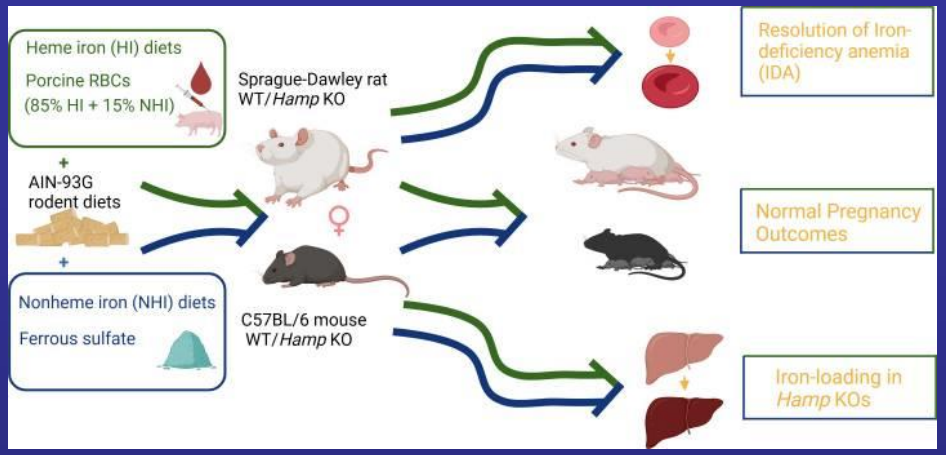
New Models of Intestinal Heme-Iron (HI) Absorption

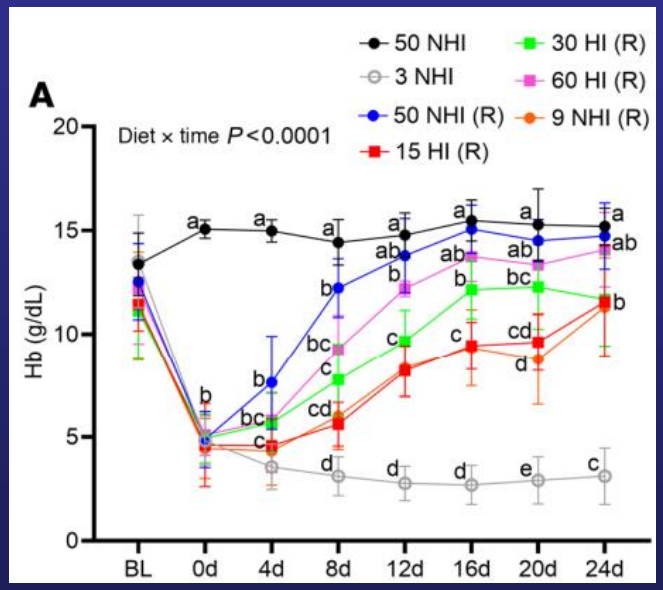
JCI insight
Published by The American Society for Clinical Investigation | Founded 1908

JCI Insight. 2025 Jun 9;10(11):e184742. doi: 10.1172/jci.insight.184742

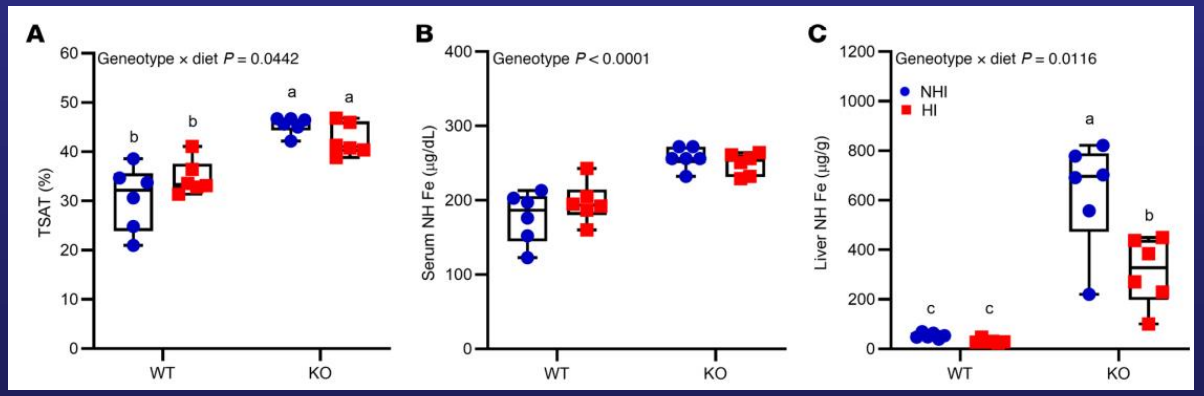
Development of rat and mouse models of heme-iron absorption

Jennifer K Lee [1], Yue He [1], Shireen RL Flores [1], Regina R Woloshun [1], Xiaoyu Wang [1], Jacob S Shine [1], Pearl O Ebea-Ugwuanyi [1], Sitara Sriram [1], Melissa Fraga [1], Sean Zhu [1], Yang Yu [1], Iqbal Hamza [2,3], James F Collins [1,✉]





A 60-ppm HI diet was effective at correcting the anemia in iron-depleted mice.



Consumption of a 50-ppm NHI diet or a 50-ppm HI–enriched diet leads to iron loading in Hamp-KO C57BL/6 mice.

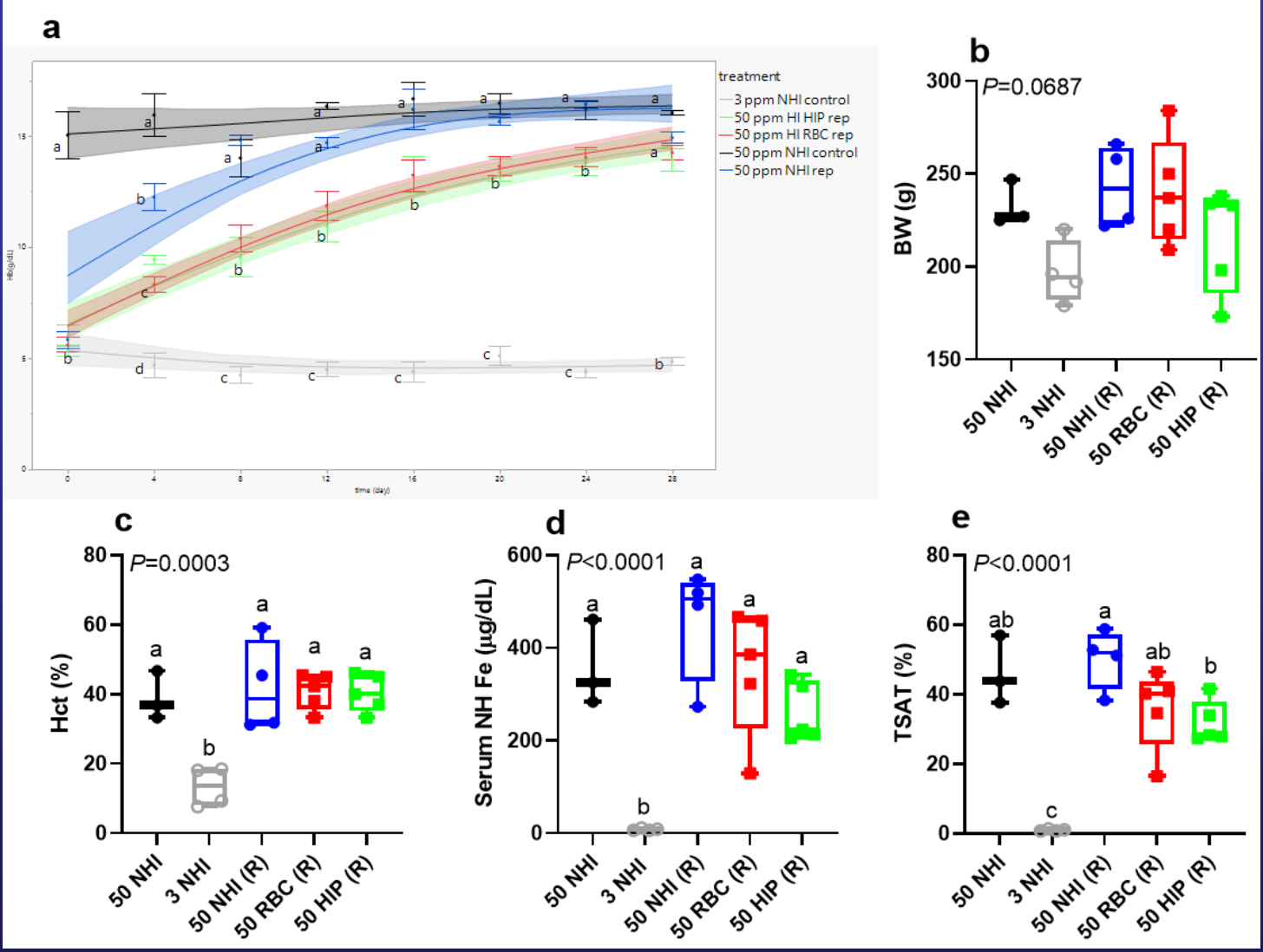
Elucidating mechanisms of HI absorption could inform the development of new approaches to modulate intestinal iron absorption in disease states

Dietary Heme-Iron Polypeptide (HIP) Resolves Anemia in Iron-deficient Rats

50 ppm RBC and HIP diets corrected IDA in SD rats

Depletion-repletion experimental design

Unpublished Data
Collins Lab



- A nutritional paradigm to study HI absorption has been successfully developed
- Next: Use these models to test the role of key transporters or enzymes in HI absorption

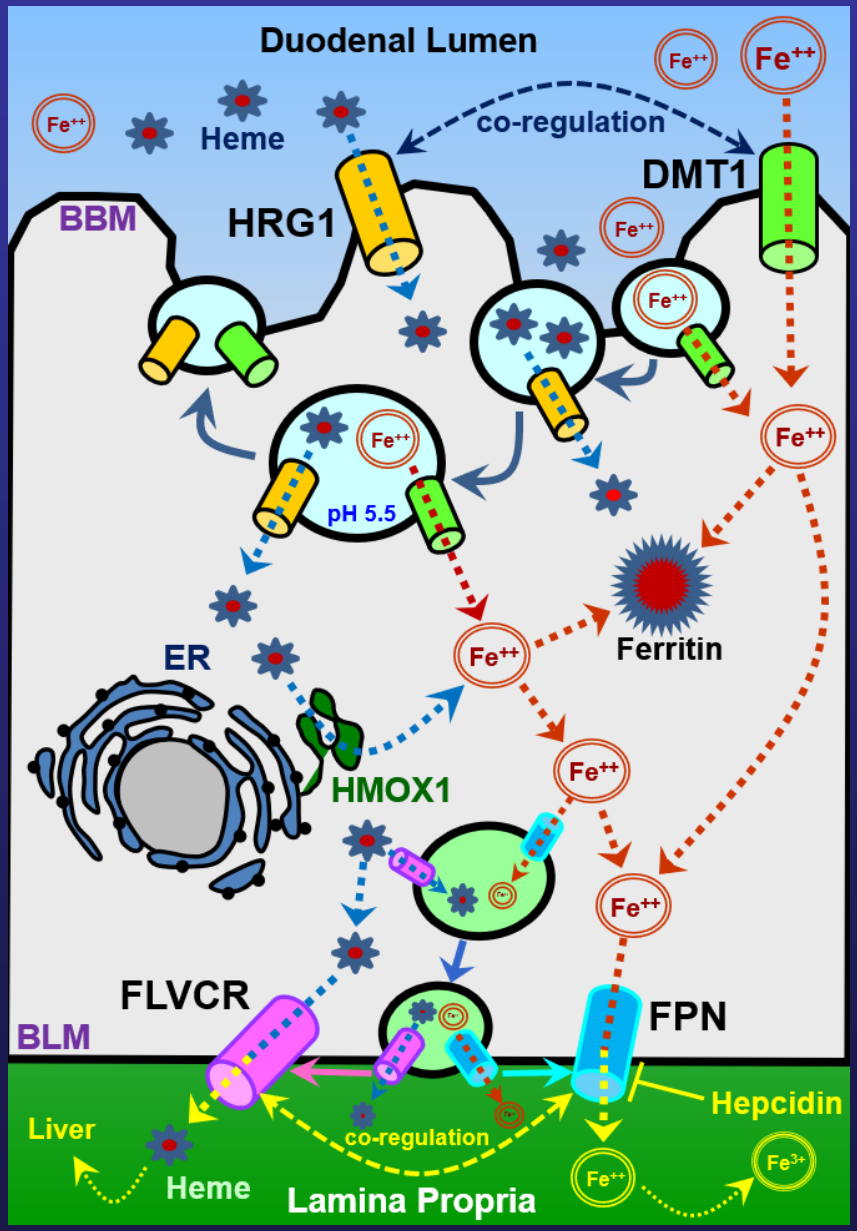
Testing the role of Intestinal DMT1 in HI Absorption

- Iron derived from heme (HI)- highly bioavailable in humans
  - Absorption increases during iron deficiency
- Dietary HI contributes to iron loading in HH
- Mechanisms of HI absorption unknown

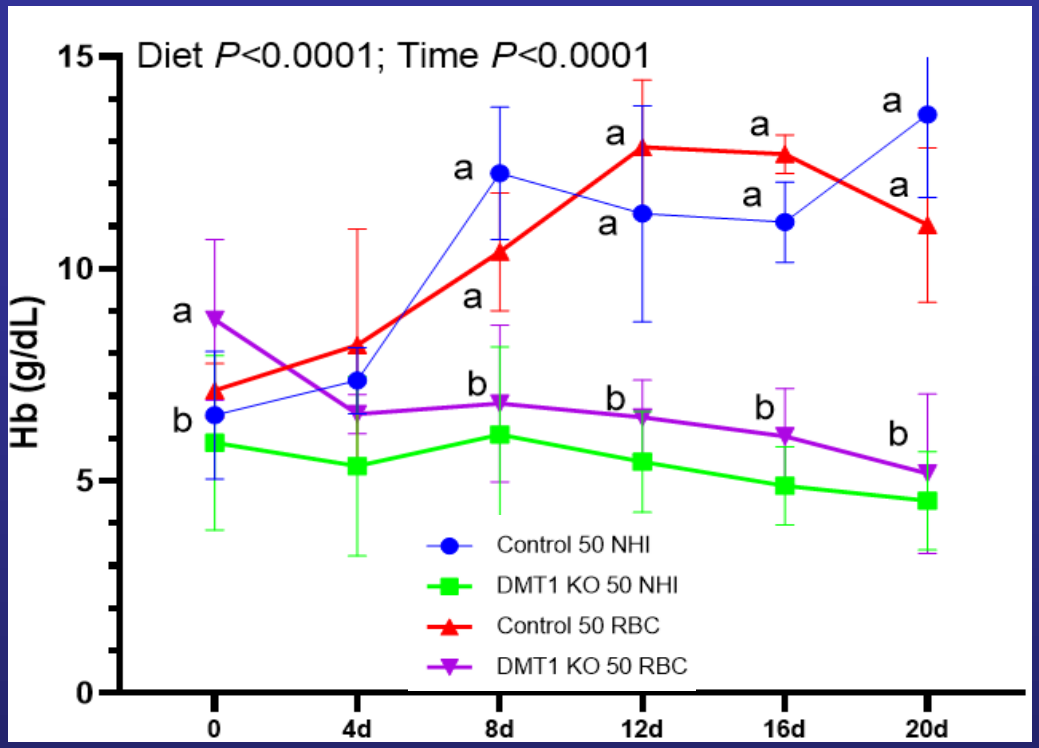
- Most plausible scenario (based upon published literature)
  - Receptor-mediated endocytosis of heme
  - Heme is transported out of endosomes into cytosol
  - Heme is catabolized by HMOX in the ER
  - Released iron joins intracellular iron pool (along with dietary NIH)

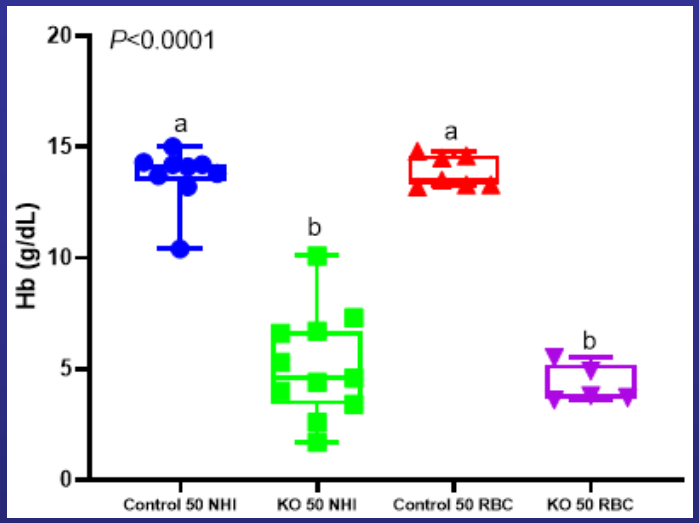
  - Alternative pathway: heme is catabolized in endosomes / lysosomes, and the released iron is then transported into the cytosol by DMT1

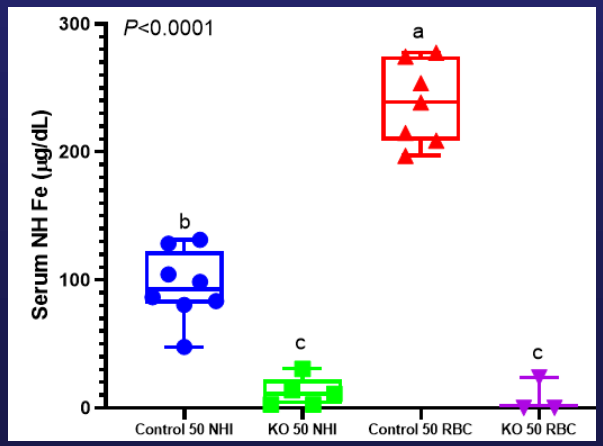
Possible Model of Iron Absorption

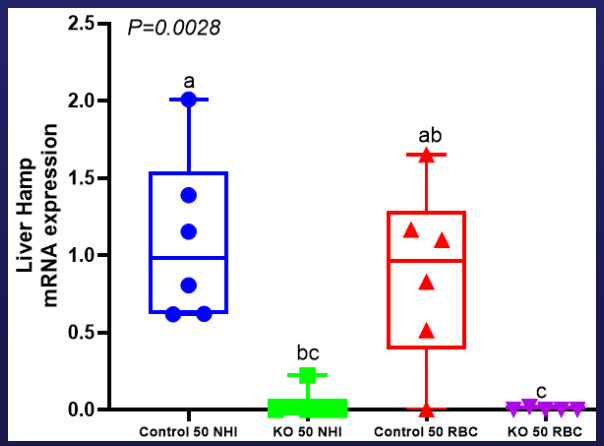


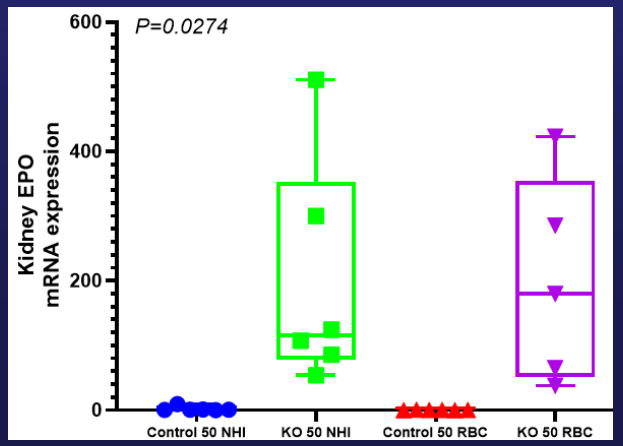
Intestinal DMT1 is Required for the Absorption of NHI and HI





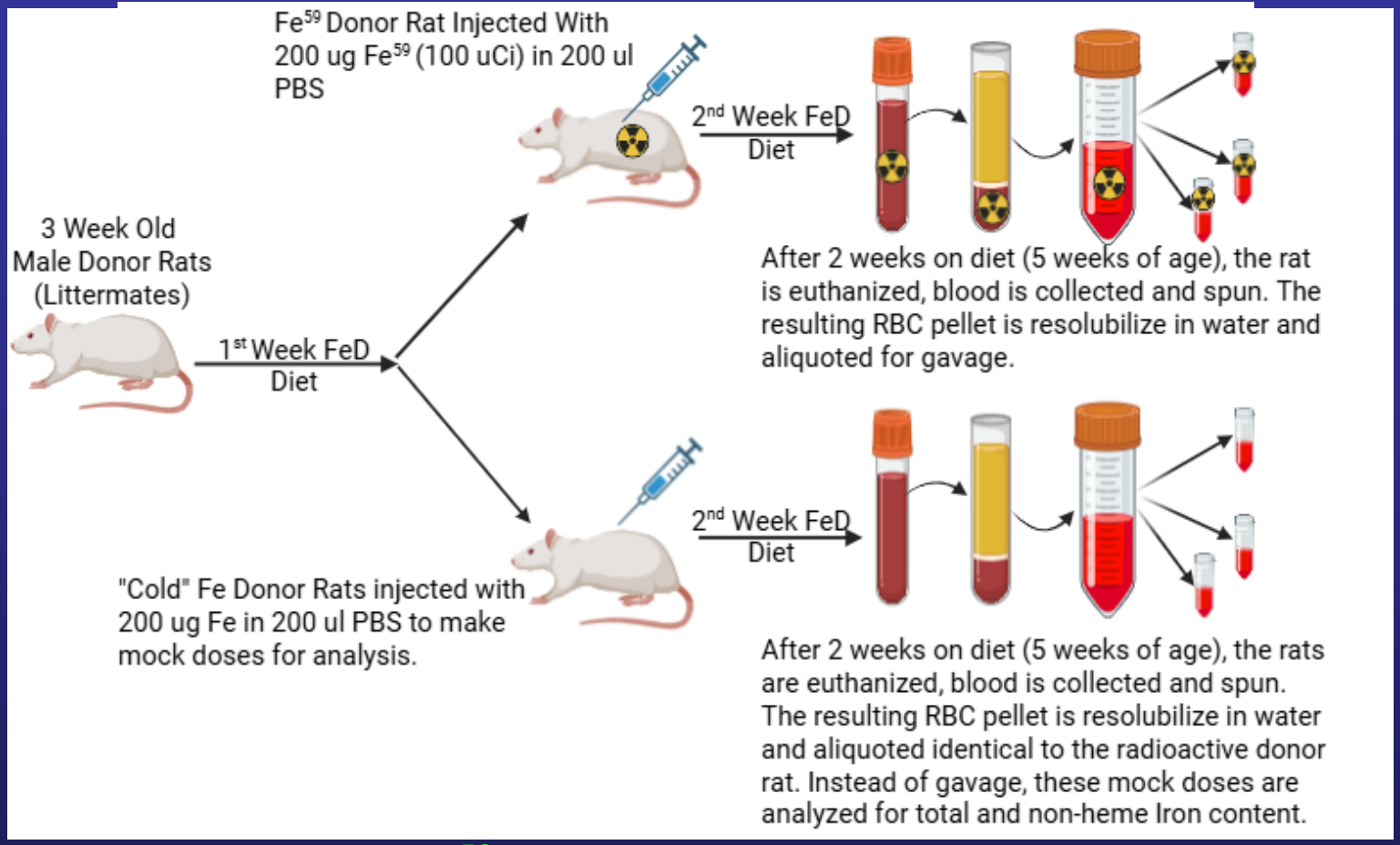






Unpublished Data; Collins Lab

Intestinal DMT1 is Required for HI Absorption During IDA



24-hour ^{59}Fe-heme Absorption Study

RBCs isolated from ID rats contained ~95% HI / 5% NHI

Intestine Specific DMT1 KO Mice

Unpublished Data; Collins Lab

Overall Conclusions

- DMT1 is required for the absorption of both main forms of dietary iron (NHI and HI)
- Enhancing DMT1 expression / activity could improve absorption of oral iron salts and heme-iron-based dietary supplements during IDA
- Blocking intestinal DMT could be an effective adjunctive treatment to mitigate ion loading in HH and βTI

Acknowledgements

- Supported by NIDDK and ODS
- R01DK074867, R01DK109717, R56DK137863, R01DK134583

(Left to right)
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