blood® commentary

RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Falabrègue et al, page 2863

Luminal hepcidin targets intestinal DMT1

James F. Collins | University of Florida

In this issue of *Blood*, Falabrègue et al[1] identify a new function for the iron-regulatory hormone hepcidin by showing that it acts within the intestinal lumen to target the iron importer divalent metal-ion transporter 1 (DMT1) and block iron absorption.

Iron is an essential nutrient for humans and other mammals. Given that iron deficiency and iron overload are both associated with significant morbidity and mortality, body iron levels must be maintained within narrow physiological limits. Moreover, given that no active, regulated mechanism exists to excrete excess iron, intestinal iron absorption is tightly controlled. Hepcidin is a peptide hormone that is a regulator of systemic iron homeostasis. Hepcidin lowers serum iron by blocking ferroportin (FPN)-mediated iron export from cells that absorb iron (enterocytes) or store/recycle iron (reticuloendothelial macrophages, hepatocytes). Historically, hepcidin was thought to be produced and secreted mainly by the liver, and the iron exporter FPN was presumed to be its major, if not only, target. More recent investigations have revealed that hepcidin is synthesized in many different cell and tissue types, and more localized autocrine/paracrine functions of hepcidin are emerging.[2] So far, extrahepatic hepcidin has been shown to mainly function the same as liver-derived hepcidin by blocking iron efflux via FPN in various cells.

In this exciting, paradigm-shifting study published by the French research groups of Peyssonnaux and Vaulont, a new function of hepcidin was described in which it does not act via the blood and FPN is not the molecular target.[1] These authors developed a genetically engineered mouse model in which a murine *Hamp* transgene (encoding hepcidin) was constitutively transactivated by a strong viral (cytomegalovirus) promoter but only in the intestinal epithelium (using the villin1/Cre system). They initially noted that mice with elevated intestinal hepcidin production developed hypoferremia and iron-deficiency anemia within a few weeks of birth. The endogenous hepatic *Hamp* gene was repressed in these mice, probably because of iron depletion/hypoxia, but, perhaps surprisingly, overproduction of intestinal hepcidin increased circulating hepcidin levels by approximately twofold. Despite higher hepcidin levels, intestinal FPN levels did not decrease, which is consistent with previous reports that suggested that intestinal FPN is not regulated by hepcidin.[3,4] Falabrègue et al then made the potentially seminal discovery that hepcidin was also present within the intestinal lumen and that this was associated with decreased iron import into duodenal enterocytes and reduced expression of the main intestinal (nonheme) iron transporter DMT1. Given these unanticipated outcomes, the authors next sought to develop an experimental protocol to deliver hepcidin intraluminally to test the influence of exogenous hepcidin on DMT1 expression and iron absorption. For these studies, they used a mouse model of the iron-loading disorder hereditary hemochromatosis (HH), namely liver-specific, *Hamp* knockout (KO) mice. The approach was to engineer food-grade *Lactococcus lactis* to express murine *Hamp* and secrete hepcidin. Peroral administration of the hepcidin-secreting bacteria decreased DMT1 expression and iron absorption within hours of administration, and daily administration of the bacteria for 4 weeks prevented iron overload in liver-specific *Hamp* KO mice. The authors postulated that this approach could be effective at mitigating iron loading in humans with HH or other iron-overload disorders.

Hepcidin was previously shown to be produced by intestinal dendritic cells in a mouse model of intestinal inflammation in which it targeted FPN and caused iron sequestration in phagocytes, thereby altering the gut microbiota and facilitating intestinal repair.[5] The current study by Falabrègue et al expands our knowledge of the possible functions of intestinal hepcidin and has provided critical new insight into the mechanisms that regulate iron homeostasis. The importance of this study comes from 3 key observations, namely (1) when *Hamp* is constitutively transactivated throughout the epithelium of the small and large intestines, hepcidin can be secreted into the blood in significant amounts and also into the intestinal lumen; (2) luminal hepcidin regulates iron absorption by reducing iron import into duodenal enterocytes via DMT1; and (3) luminal hepcidin blunts excessive iron absorption and mitigates iron loading in a mouse model of HH. The approach and outcomes of this investigation also raise several intriguing questions. First and foremost, do intestinal epithelial cells secrete hepcidin into the intestinal lumen under physiological conditions and, if so, by what cell type(s) and in which gut segment(s)? Second, what about in inflammatory states, when hepatic *Hamp* is transactivated by proinflammatory cytokines? Does intestinal hepcidin production also increase in response to

inflammation and thus contribute to the development of the anemia of inflammation (by blocking iron absorption and reducing serum iron)? Third, could luminal secretion of hepcidin be an artifact of the overexpression system used in which CRE expression, driven by the villin1 promoter, transactivates a *Hamp* transgene throughout the epithelium of the entire intestinal tract?[6] This concern, however, is mitigated by the discovery that intraluminal hepcidin downregulates iron absorption via interaction with DMT1, a clearly nonrandom regulatory process that has developed through evolutionary time, thus highlighting the potential physiological relevance of the luminal hepcidin-DMT1 interaction. And finally, how would this new proposed function of hepcidin translate to diets containing both nonheme and heme iron as in the prototypical, omnivorous human diet? This is a particularly important question because, in this study, mice were (presumably) fed diets containing only nonheme iron and DMT1 transports only nonheme iron. It is possible that blunting DMT1 expression could also decrease heme-iron absorption,[7] but whether DMT1 is important for this process has not been clarified.

In summary, this investigation by the research groups of Peyssonnaux and Vaulont points toward a potential new function of hepcidin in which iron absorption is regulated from the apical surface of enterocytes by the hepcidin-DMT1 interaction as opposed to the traditional function of hepcidin that acts from the blood side on FPN. Although key concepts remain to be tested in future work, the intriguing outcomes of this study could, as postulated by the authors, lead to the development of new therapeutic approaches to prevent the excessive intestinal iron absorption that typifies genetic iron-overload disorders.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Falabrègue M, Aurrand C, Cazaulon L, et al. Intestinal hepcidin overexpression promotes iron deficiency anemia and counteracts iron overload via DMT1 downregulation. *Blood*. 2025;146(24):2863-2869.
2. Daher R, Lefebvre T, Puy H, Karim Z. Extrahepatic hepcidin production: the intriguing outcomes of recent years. *World J Clin Cases*. 2019;7(15):1926-1936.
3. Brasse-Lagnel C, Karim Z, Letteron P, Bekri S, Bado A, Beaumont C. Intestinal DMT1 cotransporter is down-regulated by hepcidin via proteasome internalization and degradation. *Gastroenterology*. 2011;140(4):1261-1271.e1.
4. Laftah AH, Ramesh B, Simpson RJ, et al. Effect of hepcidin on intestinal iron absorption in mice. *Blood*. 2004;103(10):3940-3944.
5. Bessman NJ, Mathieu JRR, Renassia C, et al. Dendritic cell-derived hepcidin sequesters iron from the microbiota to promote mucosal healing. *Science*. 2020;368(6487):186-189.
6. el Marjou F, Janssen KP, Chang BH, et al. Tissue-specific and inducible Cre-mediated recombination in the gut epithelium. *Genesis*. 2004;39(3):186-193.
7. West AR, Oates PS. Mechanisms of heme iron absorption: current questions and controversies. *World J Gastroenterol*. 2008;14(26):4101-4110.

https://doi.org/10.1182/blood.2025031293

CLINICAL TRIALS AND OBSERVATIONS

Comment on Chari et al, 2902

Improving MM outcomes with bispecific antibody combinations

Faith E. Davies and Gareth J. Morgan | NYU Langone Health

In this issue of *Blood*, Chari et al[1] address a conundrum in relapsed refractory multiple myeloma (RRMM), as to whether adding a routinely used drug to a novel drug has more impact than would be expected from using both drugs as single agents. Put another way, can we develop synergistic combinations to improve outcomes in this poor prognosis group of patients? In the conventional approach to drug development, the aim is to evaluate the safety and efficacy of the drug as a single agent, followed by additional studies evaluating combinations. When building combinations, it is important to incorporate non–cross-reacting agents and to balance clinical effectiveness with safety and tolerability and not to just simply build an alphabet soup of letters into a catchy acronym. A basic rule of thumb for drug combinations is that there should be 1) a biological rationale and mechanism for building the combination and it should overcome resistance based on a synergistic interaction between the agents, 2) an ability to induce high response and survival rates, and 3) a lack of combined toxicity making the combination tolerable and safe to deliver.

The introduction of bispecific antibodies (BsAbs) has revolutionized the treatment of RRMM with unprecedented response rates and long progression-free survivals (PFSs) but relapse has remained a clinical problem. Since their introduction we have learnt a lot about how to manage their toxicities, however, a concern has been that combinations may increase toxicity. The results of TRIMM-2, where talquetamab is combined with daratumumab, negate this fear with excellent response rates pushing the field to exploring further combinations.[1]

CD38 monoclonal antibodies such as daratumumab are well-established therapies for MM, which combine well with most other myeloma therapies (eg, proteasome inhibitors [PIs], immunomodulatory drugs [IMiDs]) without a significant increase in toxicity.[2] More recently, talquetamab, a GPRC5D-targeting BsAb has been approved by