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Letter to the editor

Skin hepcidin overexpression is sufficient to promote systemic iron deficiency

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It has long been recognized that iron is essential for healthy skin and it is widely assumed, although poorly documented, that alteration of skin iron dynamics doesn't impact systemic metabolism. However, recent advances, particularly those involving genetic mouse models, challenge this view. To further document whether disrupted local iron homeostasis can directly impact systemic iron metabolism, we thought to use our recently generated transgenic mouse model with keratinocyte-specific hepcidin overexpression. Here we show that localized epidermal *Hamp1* induction causes skin iron accumulation but profound reductions in plasma iron and ferritin levels leading to iron-deficiency anemia. These systemic alterations occur despite compensatory mechanisms such as increased erythropoiesis and hepatic hepcidin suppression, demonstrating that excessive epidermal hepcidin can override classical liver-mediated endocrine systemic control. Our finding identifies the epidermis as an active regulator of systemic iron homeostasis and reveal that dysregulated skin-derived hepcidin may contribute to iron deficiency that frequently accompanies dermatological disorders marked by accelerated epidermal turnover such as psoriasis.

Systemic iron deficiency has been frequently described in pathological conditions marked by accelerated epidermal turnover, such as psoriasis[1–4]. Several mechanisms have been proposed to explain this association. On one hand, rapidly proliferating keratinocytes have heightened metabolic and biosynthetic demands, including a requirement for iron to support DNA synthesis, mitochondrial activity, and cellular respiration. On the other hand, increased desquamation accelerates iron loss at the skin surface, since exfoliation constitutes the primary physiological route of iron excretion in mammals. Early clinical observations by Prystowsky and colleagues and others have long suggested that both increased iron utilization and epidermal iron loss may synergize to produce iron-deficiency anemia in hyperproliferative skin disorders[1–

[5]. Despite these hints, the molecular mechanisms linking epidermal activity to systemic iron pools have remained insufficiently defined.

Under physiological conditions, systemic iron homeostasis depends largely on liver-derived hepcidin, a peptide hormone that orchestrates both intestinal absorption of dietary iron and macrophage-mediated iron recycling[6] . Hepcidin functions by binding to ferroportin (FPN), the only known cellular iron exporter, expressed predominantly on the surface of enterocytes, and macrophages. Upon binding hepcidin, FPN is internalized and degraded, reducing iron efflux into the bloodstream[7]. Increased hepcidin therefore suppresses dietary iron absorption and limits iron release from macrophages, whereas low hepcidin stabilizes FPN and increases plasma iron availability. This finely tuned system is essential because mammals lack a regulated pathway for iron excretion; daily iron losses occur passively, primarily through sloughing of skin and mucosal epithelia. Remarkably, epidermal desquamation accounts for approximately 20-25% of total daily iron loss, highlighting the importance of skin biology in iron economy. Supporting the relevance of epidermal iron handling, Milstone *et al.* demonstrated that, in three transgenic mouse models, increased epidermal iron import and increased iron desquamation lead to reduction of systemic iron levels. In addition, Asano *et al.* reported that mice with keratinocyte-specific deletion of FPN develop pronounced skin scaling when fed an iron-rich diet, whereas on an iron-poor diet, these animals become anemic more rapidly than their wild-type counterparts[8]. These observations underscore that the epidermis is not a passive endpoint in iron homeostasis; instead, it plays an active, although previously underappreciated, role in regulating systemic iron availability.

In the current study, we though to expand on this concept by examining whether epidermal hepcidin overproduction is sufficient to perturb whole-body iron balance. For that we use our

transgenic mouse model (Hamp1 KI-Ker), in which Hamp1 is selectively overexpressed in keratinocytes (Figure 1A-B), and asked whether keratinocyte-derived hepcidin can not only affects local skin pathology[9] but also contributes to systemic metabolic alterations, specifically iron deficiency. The animal studies described here were reviewed and approved (Agreements n° APAFIS 40199-2022102719322238 v8) by the Ministry of Higher Education, Research and Innovation.

As expected, immunohistochemical analysis revealed a significant reduction in ferroportin expression in the skin, consistent with local hepcidin activity (Figure 1C). As previously described, Hamp1 KI-Ker mice exhibited cutaneous accumulation of iron, greater epidermal proliferation and acanthosis[9] compared with their control littermates.

We observed that Hamp1 KI-Ker mice present with significant reduced plasma iron and ferritin levels, compared to control littermates (Figure 1D), indicating depleted circulating and stored iron pools. Consistent with iron-restricted erythropoiesis, hematological parameters, including Hemoglobin, MCH (Mean Corpuscular Hemoglobin), MCV (Mean Corpuscular Volume) and MCHC (Mean Corpuscular Hemoglobin Concentration) were all significantly decreased in Hamp1 KI-Ker mice (Figure 1E), confirming a systemic iron-deficiency phenotype. In line with this, plasma erythropoietin (EPO) levels and red blood cell (RBC) counts were elevated (Figure 1F) reflecting normal physiological attempt to compensate for reduced hemoglobin synthesis by stimulating erythropoiesis. Increased erythropoietic activity is known to induce the erythroid hormone erythroferrone (ERFE), which acts as a key mediator linking erythropoiesis to systemic iron homeostasis. ERFE expression was found significantly elevated in the spleen and in the plasma of Hamp1 KI-Ker mice compared with control littermates (Figure 1G), further confirming the iron deficiency phenotype. In turn, ERFE is known to repress hepatic hepcidin expression, through modulation of the BMP/Smad signaling pathway, for iron mobilization. In agreement with this mechanism, hepatic hepcidin expression was markedly suppressed in

Hamp1 KI-Ker mice (Figure 2A), as well as two canonical BMP/Smad target genes, *Atoh8* and *Id1*, in the liver of transgenic Hamp1 KI-Ker mice (Figure 2B). By contrast, Fgl1, another recently identified hepatocyte-derived regulator implicated in hepcidin suppression during anemia and hypoxia[10], was not differentially expressed in Hamp1 KI-Ker mice, suggesting that ERFE is the predominant erythroid signal associated with hepcidin repression in this model (Figure 2C).

Noteworthy, although liver hepcidin expression was drastically reduced, plasma hepcidin levels were only modestly decreased (Figure 2A), suggesting that skin-derived hepcidin likely contributes to the systemic hepcidin pool. As expected from the systemic iron deficiency phenotype, liver iron content was significantly decreased (Figure 2D). The normalization of hepatic *Hamp1* mRNA levels to liver iron concentration reinforces the interpretation of inappropriate suppression relative to iron stores (Figure 2E).

Our results suggest that, although the liver senses systemic iron depletion and downregulates hepcidin, this reduction in hepatic hepcidin is insufficient to counterbalance the iron sequestration occurring in the hyperproliferative epidermis

To determine whether impaired intestinal absorption or defects in iron recycling contributed to the anemia, we examined key markers of these pathways. Duodenal DMT1 (Figure 2F) and FPN (Figure 2G) expression remained unchanged in Hamp1 KI-Ker mice, arguing against defective dietary iron uptake. In contrast, splenic FPN expression was slightly increased (Figure 2H), consistent with enhanced iron recycling by macrophages in response to systemic iron deficiency.

Overall, our findings demonstrate that localized epidermal overexpression of hepcidin is sufficient to induce systemic iron deficiency. This provides strong *in vivo* evidence that keratinocytes actively shape systemic iron homeostasis. The observed phenotype is likely

driven by increased iron retention in keratinocytes combined with heightened epidermal iron demand, a mechanism consistent with previous observations in hyperproliferative skin diseases. These insights illuminate an emerging skin-liver axis in iron regulation, where signals originating in the epidermis modulate endocrine control of iron availability. It should be noted, however, that a limitation of the present model is that Hamp1 KI-Ker mice develop a severe phenotype and die prematurely[9] making it difficult to fully disentangle the contribution of hepcidin-independent mechanisms, such as chronic inflammation or epidermal barrier defects, from the iron-regulatory effects of hepcidin itself.

Importantly, this work has broader implications. Many dermatological diseases characterized by altered proliferation, chronic inflammation, or barrier disruption, such as psoriasis, atopic dermatitis, and chronic wounds, are associated with anemia or iron-misdistribution syndromes whose origin has remained elusive[1–4,11–15]. Our data suggest that dysregulated epidermal hepcidin production may contribute to these systemic manifestations, providing a new conceptual framework for understanding and potentially treating iron imbalance in the context of skin disease. We need to point out that the Hamp1 KI-Ker model likely represents an extreme scenario of skin hepcidin excess, and that the systemic iron-deficiency phenotype we observe may not be directly recapitulated in human psoriasis or other hyperproliferative dermatoses in which hepcidin upregulation is spatially restricted. Future studies employing inducible or spatially restricted overexpression systems will be necessary to attribute the systemic iron phenotype more precisely to epidermal hepcidin itself. Nevertheless, this model provides proof-of-principle that keratinocyte-derived hepcidin is, in principle, capable of overriding hepatic endocrine control, and raises the possibility that lesion-restricted increases in epidermal hepcidin may contribute to the systemic iron perturbations documented in these diseases.

In conclusion, this study highlights the epidermis as a previously underrecognized regulator of systemic iron metabolism. By demonstrating that keratinocyte-derived hepcidin can override hepatic regulation and induce iron deficiency, our work provides new mechanistic insight with significant implications for both basic science and clinical dermatology.

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Figure legends

Figure 1. **Hepcidin overexpression in keratinocytes leads to a marked deregulation of systemic iron metabolism.**

(A) Schematic of the Hamp1 knock-in keratinocyte-specific model (Hamp1 KI-Ker). (B) Hepcidin expression by quantitative PCR (qPCR) -left- and hepcidin immunohistochemistry (IHC) in the skin representative of 5 Hamp1 KI-Ker mice and 5 control littermates (Hamp1 CMV lox-STOP-lox) -right-. (C) FPN expression by IHC (representative of 9 Hamp1 KI-Ker and 5 control littermates). Quantification of IHC staining analysis by « ImageJ plugin IHC profiler ». Each dot represents the mean of 3 measurements taken from one microscopic slide per mouse. (D) Plasma iron (µmol/L) and ferritin (µg/L) levels. (E) Blood count parameters: Hgb (g/dL), HCT (%), MCV (fL), MCH (pg), MCHC (g/dl) (F) EPO (pg/ml) and RBC (10^{12}/L) in Hamp1 KI-Ker and control littermates. (G) *Erfe* expression by qPCR in the spleen and in the serum (ELISA) of Hamp1 KI-Ker and control littermates.

3 to 4 week old male and female mice were used. (B-C): the bar represents 50 µm. Lamina slide scanner, Perkin Elmer. Data are means ± SD. Data were analyzed by unpaired Student t test *P < 0.05, **P < 0.01, ****P < 0.0001). Hamp1 CMV lox-STOP-lox are represented by black dots and Hamp1KI-Ker mice by blue dots.

Figure 2. Intestinal and systemic iron transporter expression in Hamp1 KI-Ker and Hamp1 CMV lox-STOP-lox mice.

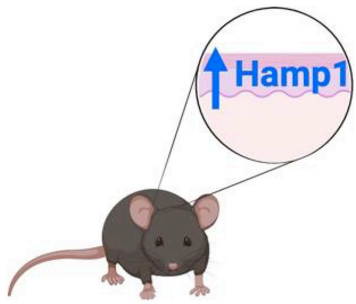
(A) Liver and plasma hepcidin expression measured by qPCR and ELISA respectively. (B) *Atoh8, Id1* and (C) *Fgl1* expression (qPCR) in the liver of Hamp1KI-Ker and control littermates (Hamp1 CMV lox-STOP-lox mice). (D) Liver iron (quantified by the Bothwell method). (E) Normalization of hepatic *Hamp1* mRNA levels to liver iron concentration. (F) DMT1 expression by western-bot and (G) FPN expression by IHC (representative of 9 Hamp1 KI-Ker

and 5 control littermates) in the duodenum of Hamp1 KI-Ker and control littermates. The bar represents 25 µm. Lamina slide scanner, Perkin Elmer. Quantification of IHC staining analysis by « ImageJ plugin IHC profiler ». Each dot represents the mean of 3 measurements taken from one microscopic slide per mouse. (H) FPN expression by western-bot in the spleen of Hamp1 KI-Ker and control littermates.

3 to 4 week old male and female mice were used. Data are means ± SD. Data were analyzed by unpaired Student t test (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001). Hamp1 CMV lox-STOP-lox are represented by black dots and Hamp1KI-Ker mice by blue dots.

FIGURE 1

A



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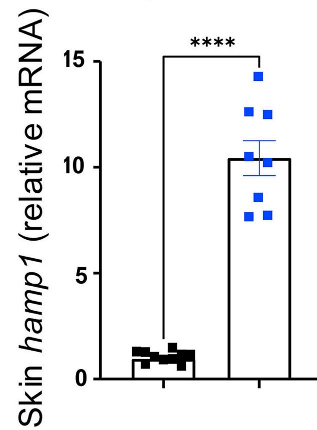

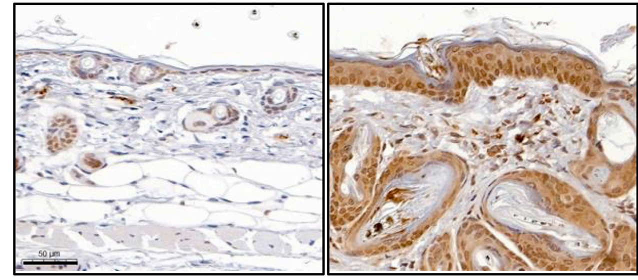

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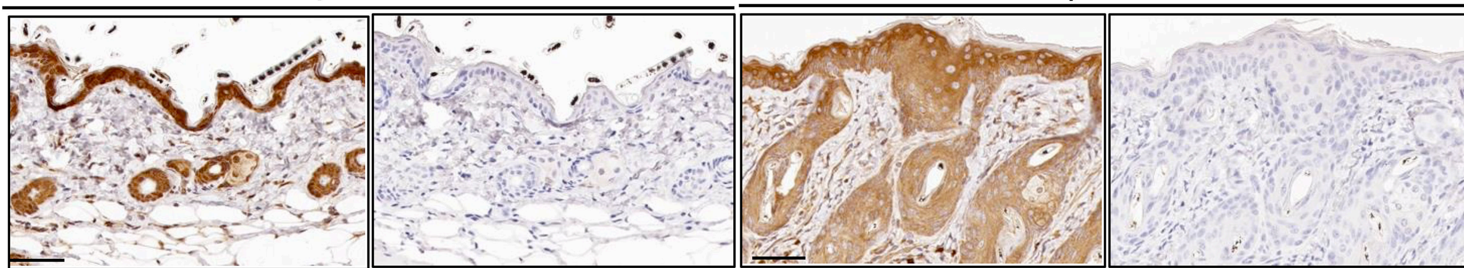

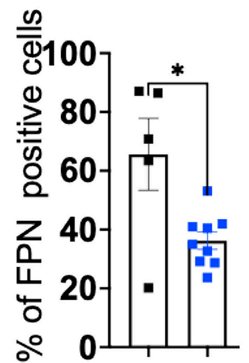

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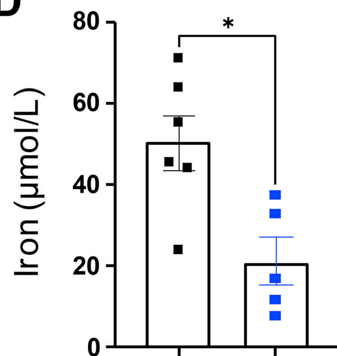
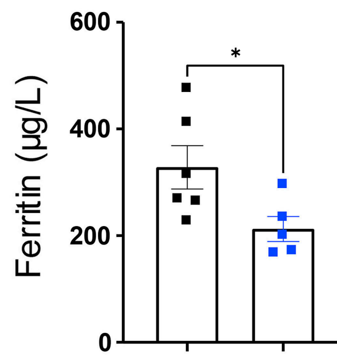
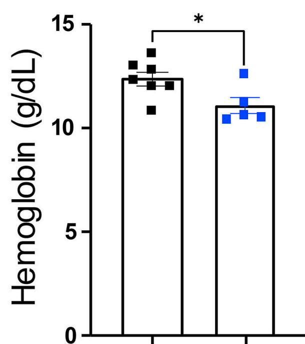


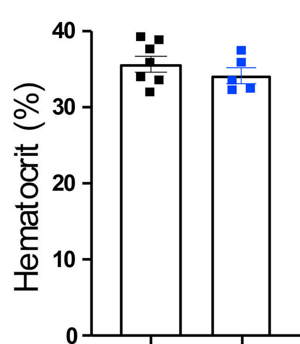


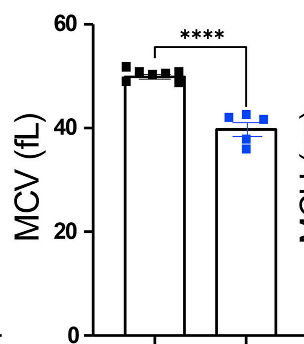
Hamp1 CMV lox-STOP-lox

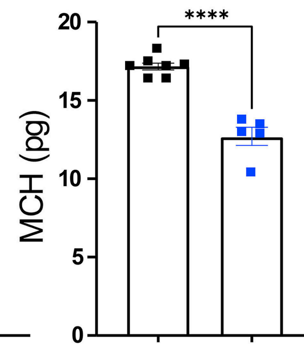
Hamp1 KI-Ker

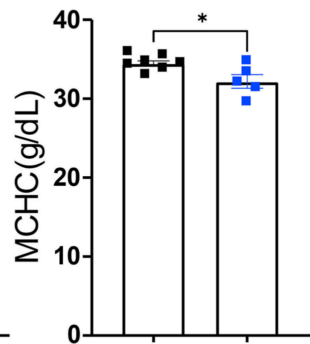
E











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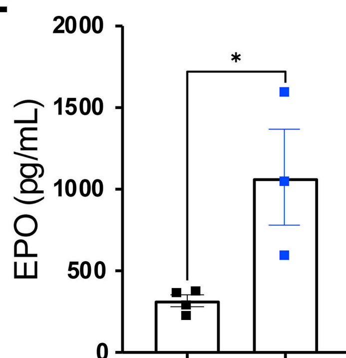

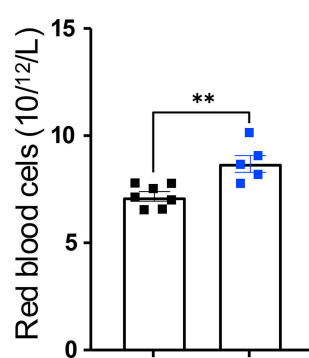

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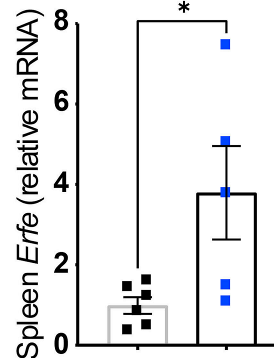

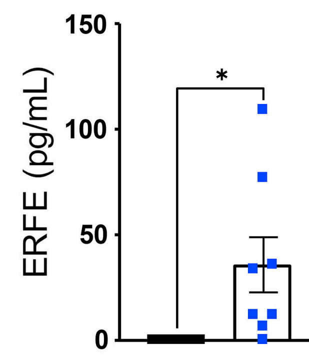

FIGURE 2