New insights into intestinal iron absorption*

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Introduction

In the May issue of Science, Du et al. described the novel and exciting finding that the transmembrane serine protease 6 (TMPRSS6) senses iron deficiency [1]. In their study, Du et al. described a mutant mouse, which is characterized by progressive loss of body hair and microcytic anaemia. The phenotype was found to result from reduced intestinal iron absorption caused by high levels of hepcidin. Iron deprivation and anaemia suppressed hepcidin mRNA levels in the livers of wild-type mice, whereas high mRNA levels persisted in the livers of anaemic mutant mice. The high hepcidin levels in the mutant mice resulted from a splice defect in the Tmprss6 gene. This suggests that TMPRSS6 physiologically downregulates hepcidin mRNA transcription and thus promotes iron uptake [1].

(Patho-)Physiology of enteric iron uptake

Physiologically, intestinal iron absorption amounts to 1–2 mg iron per day calculated from a dietary iron intake of 12–18 mg/day. Mucosal iron absorption is determined by the amount of iron in the body iron stores and the level of erythropoiesis [2]. Dietary iron consists of haem iron and non-haem iron. Meat contains large amounts of haem iron, while vegetables are a poor source of iron. Haem iron is readily taken up by a specific transporter and degraded by haem oxygenase liberating Fe^{2+}, which enters the intracellular iron pool. In the duodenum, non-haem Fe^{3+} is reduced to Fe^{2+} by ferric reductase (DcytB) (Figure 1). Subsequently, Fe^{2+} is transported across the apical enterocyte membrane by DMT1, a proton-coupled divalent metal transporter. Within the intestinal cells, Fe^{2+} enters mainly either the storage pool (stored in intracellular ferritin) or the transport pool (transported to the basolateral membrane and exported by ferroportin). Iron incorporation into serum apotransferrin is facilitated by the oxidation of Fe^{2+} to Fe^{3+} catalyzed by hephestin [2,3]. Intestinal iron absorption increases with a decline in body iron stores, while intestinal iron absorption is inhibited by iron overload.

Iron deficiency is the most common cause of anaemia. Iron deficiency is caused by stimulated erythropoiesis, reduced dietary iron intake, inhibition of intestinal iron absorption, inhibition of iron release from macrophages and enterocytes and/or by iron losses. Several factors such as iron overload, pro-inflammatory cytokines [4,5], HFE (haemochromatosis protein) [6], transferrin receptor 2 [7], haemojuvelin [8], the transcription factor Smad4 [9] and/or bone morphogenetic protein-2, -4 and -9 [10] promote expression of Hamp, the gene encoding hepcidin (Figure 1). The liver-derived peptide hepcidin inhibits intestinal iron absorption and cellular iron release. Vice versa, iron deficiency, hypoxia and stimulation of erythropoiesis inhibit hepcidin production. Mice with constitutive over-expression of hepcidin die from severe iron-deficient anaemia [11], while mutations in the hepcidin gene result in a severe form of juvenile haemochromatosis [12].

The mechanism of how hepcidin production in the liver blocked, is thus far unknown. Recently, the serine protease TMPRSS6 was discovered to be an essential component of a pathway that detects iron deficiency. In both humans and mice, the major site of TMPRSS6 expression is the liver. TMPRSS6 likely participates in a transmembrane signalling pathway triggered by iron deficiency. This pathway may interact with suppressive element(s) in the Hamp promoter, inhibiting hepcidin transcription in response to various stimuli (Figure 1). Overexpression or dysregulation of TMPRSS6 might cause iron overload, whereas mutational inactivation of TMPRSS6 (as demonstrated in mask mice) lowers the physiological body iron content [1].

What is in it for the practising nephrologist?

Hepcidin controls the whole-body iron content. Iron deficiency, hypoxia and stimulated erythropoiesis inhibit hepcidin production and thereby allow intestinal iron...
Iron deficiency activates the serine protease TMPRSS6. The protease then inhibits hepcidin transcription and thereby allows intestinal iron absorption and cellular iron release.

Conflict of interest statement. None declared.

References

1. Du X, She E, Gelbart T et al. The serine protease TMPRSS6 is required to sense iron deficiency. Science 2008; 320: 1088–1092

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