Regulation of DCT1 and IREG, the intestinal iron transporters, in hereditary hemochromatosis

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BACKGROUND: Hereditary hemochromatosis (H.H.), a common genetic disorder, is caused by loss of function mutations in the gene encoding the MHC I protein, HFE. It has been reported that HFE interacts with the transferrin receptor (TfR), and that in the case of H.H. this interaction is disrupted, giving rise to iron overload throughout the body. Intestinal crypt cells express HFE and TfR, but lack DCT1, the apical intestinal iron transporter. In contrast, mature villus cells show DCT1 expression, but no HFE. In the intestine the mRNA levels of DCT1 and of the basolateral iron exit system consisting of the iron transporter IREG and the multi copper oxidase hephaestin are tightly controlled by serum iron levels. These findings let us speculate that HFE and TfR sense serum iron in proximal crypt cells of the small intestine to regulate the expression of the proteins involved in iron absorption in villus cells, including DCT1, IREG/Hephaestin, probably via basolateral iron absorption in crypt cells and via iron responsive elements/iron responsive proteins. In patients suffering from H.H., this regulation may be disturbed, leading to a higher expression rate of proteins involved in iron absorption in mature villus and in increased body iron absorption.

METHODS: To determine whether DCT1, IREG, and hephaestin mRNAs are increased in H.H. patients compared to controls, we performed real time quantitative PCR using the LightCycler® from Roche/Boehringer. The gene-specific detection was performed by using the fluorescence resonance emission transfer technology with oligonucleotide probes specific for the individual gene sequence. To determine the number of mRNA copies in intestinal biopsies from H.H. patients and control individuals we prepared calibration curves using in vitro transcribed cRNAs.

RESULTS: In H.H. patients DCT1 expression in the intestine was increased ~2-5 fold compared to control individuals. Furthermore, in control samples there was a clear correlation between iron status and DCT1 expression. Patients suffering from iron depletion (microcytic anemia) showed upregulation of DCT1. With respect to the basolateral iron transporter IREG, we also observed regulation as a function of serum iron levels and upregulation in H.H. patients. Hephaestin did not exhibit any changes in expression levels.

CONCLUSION: We show that in H.H. patients the expression of the genes involved in iron absorption in the human intestine are no longer regulated properly, giving rise to excessive iron absorption and chronic accumulation of iron in liver, heart, brain, etc.