Life savers in the gut

January 9 2008

Researchers from the European Molecular Biology Laboratory (EMBL) have discovered that proteins that regulate the body's iron household play a vital role in making sure enough nutrients and water are absorbed in the intestine. Mice lacking these proteins suffer from weight loss and dehydration, the scientists report in the current issue of *Cell Metabolism*.

Iron is a central component of red blood cells and has many other important functions throughout the body. Since too little or too much iron is dangerous for our health a range of regulatory proteins tightly controls iron metabolism. EMBL scientists now assessed the role of two of these proteins, iron regulatory proteins 1 and 2 (IRPs), for the first time in living mice and found that their effects are much broader than previously assumed.

“We generated the first living organism lacking both IRPs in one of its organs," says Bruno Galy, who carried out the research in the lab of Matthias Hentze at EMBL. “This was extremely challenging, because if both proteins are switched off throughout the whole body, the mouse dies before birth. But if you switch off only one IRP, the one that is still intact substitutes and you can hardly see any effects."

Surprisingly, the lack of IRPs in the intestine did not upset the mice's iron household in blood and tissues. Instead the mice suffered from other, unexpected problems: they weighed only half of their normal littermates, suffered from severe dehydration and died only 4 weeks after birth. The general nutrient and water absorption in the gut was impaired. A closer look at the intestinal tissues revealed that their

structure and organisation were completely disturbed, which likely affects all absorption processes that happen in intestinal cells. The findings show that IRPs are essential for intestinal function and the survival of an organism, but the details of how they accomplish their effects is unclear.

Although the global iron household was unaffected by the lack of intestinal IRPs, the scientists observed changes in the local handling of iron in the gut. IRPs control the abundance of iron transporters in the membrane of intestinal cells. Without the IRPs less iron importers are found in the membrane facing the gut, but iron exporters on the interface with the blood stream are increased. The results are less iron absorption, but more export of the metal into the bloodstream. In the short term this will keep the global iron content stable while depleting the iron stores of intestinal cells, which could be the reason for their disturbed structure and tissue organisation.

“Since IRPs were discovered 20 years ago we have not been able to pin down what exactly they are doing,?says Matthias Hentze, Associate Director and group leader at EMBL. “The new insights provided by our mouse model greatly advance our understanding of their function in iron metabolism and reveal that IRPs play a vital role for the survival of an organism." The findings might help inform the development of strategies to control iron absorption in the intestine, which might pave the way for alternative therapeutic approaches to treat iron overload disorders such as hemochromatosis.

Source: European Molecular Biology Laboratory