1st Faculty of Medicine, Charles University in Prague
Study program: Molecular and Cellular Biology, Genetics and Virology

Proteomic analysis of liver iron overload

Mgr. Denisa Myslivcová, Ph.D.
Supervisor: RNDr. Jiří Petrák, Ph.D.

Abstract

Iron is an essential cofactor for a multitude of proteins of diverse biological function (oxygen transport by hemoglobin, oxidation-reduction reactions, cellular proliferation, etc.)
The dark side of the metal is, that in excess, it can be toxic and due to reactive oxygen species (ROS) is able to cause oxidative damage to DNA, proteins and biological membranes (Fenton reaction). So the concentration of the metal in mammalian body must be kept within defined limits. In humans there is no active mechanism for the excretion of iron, iron levels are tightly regulated by specialized proteins. Disruption of iron metabolism can lead to iron deficiency or iron overload. Iron overload is involved in the pathogenesis of many human diseases. One of them is hereditary hemochromatosis (HH) type I, which is associated with mutations in the *HFE* gene, that can result in liver fibrosis, cirrhosis, diabetes, etc.

Our knowledge of pathophysiological processes connected with or triggered by iron deposition in liver is very limited. We studied the effect of iron overload in liver cells. Influence of acute and chronic iron overload was investigated in human hepatoma HepG2 cells and C57BL/6J mice. Molecular mechanisms of genetic iron overload was studied in mouse model of hereditary hemochromatosis ($HFE^{-/-}$ mice). In our project, we used the classical method of expression proteomics – combination of 2-DE with mass spectrometry.
We focused our studies of molecular pathophysiology of liver iron overload on the three central questions:

- What changes in protein expression induces acute iron-overload in liver cells?
- What changes in protein expression triggers chronic iron overload in liver?
- Are there any liver protein expression changes specific for hereditary hemochromatosis that are not caused by iron overload?

We identified three distinct sets of proteins involved in 1) response of liver (hepatoma) cells to acute iron toxicity, 2) response of liver to chronic nutritional iron overload and 3) pathophysiological mechanisms of hereditary hemochromatosis type I.

The results of our study have provided us with new information that will serve as a basis for future detailed studies addressing particular roles of individual candidate proteins or pathways in the context of iron metabolism. Such studies are prerequisite for detailed understanding of molecular mechanisms involved in iron metabolism. Without the understanding of molecular pathophysiology it is impossible to imagine any progress in the development of new methods in prevention and therapy of diseases connected with iron metabolism, namely hemochromatosis and anemia, from chronic diseases.