How iron levels are sensed in the liver and what can module iron deposition under disease conditions?

Iron is a microelement that plays a crucial role in various vital functions (e.g. it is indispensable for hemoglobin synthesis in red blood cells). Due to its chemical properties, however, excessive iron may be harmful, and thus can cause organ damage, ultimately leading to disease. Therefore, iron availability must be tightly controlled and gaining new knowledge about genes and processes that affect iron balance is important for human health.

It has been known for decades that disorders associated with inappropriately high or low body iron status belong to the most common diseases worldwide. Surprisingly, only in the last 18 years the molecular mechanisms that control iron levels in the human body have been revealed. A small hormone produced by liver hepatocytes called hepcidin has been discovered as a key regulator of systemic iron homeostasis, that prevents excessive iron absorption. Later, scientists identified another secreted protein, a cytokine called bone morphogenetic protein (BMP) 6, which acts as a key upstream hepcidin regulator. It is well-established that BMP6 acts as a sensor of systemic iron status, and modulates hepcidin levels according to body iron needs. Interestingly, recent data showed that BMP6 synthesis occurs not in hepatocytes, but in less abundant liver cells: endothelial cells that line hepatic blood vessels. Strikingly, the molecular mechanisms which are responsible for BMP6 regulation by iron supplies are still not known. Based on our preliminary data, we would like to explore a hypothesis, that the iron content of hepatocytes, but not of the endothelial cells is sensed in the liver endothelia cells to induce BMP6. Our results suggest that such a signaling mechanism can be provided by ferritin, a protein that normally stores iron inside the cells, but may undergo secretion from iron-loaded hepatocytes and stimulate BMP6 expression levels in the endothelium. In our work, we will use hepatic and endothelial cell cultures to look for all missing factors that could be involved in this sensing pathway. We will also aim to validate our findings in primary cells and in mice. If confirmed, such a novel mechanism will increase our understanding of cell-to-cell communication in liver: it would show that iron-loaded hepatocytes send ferritin to endothelial cells to produce BMP6, which then, in turn, stimulates hepcidin back in hepatocytes.

Another line of our research will focus on a situation when iron sensing by BMP6 and hepcidin fails, and too much iron accumulates in the body. Under such conditions most of this excessive iron goes to the liver hepatocytes, eventually leading to their failure, and increasing risk of cancer. Iron accumulation in the liver is a common medical problem: it underlies a very common genetic disease hemochromatosis (that may affect 1 in 200 individuals) and is also often associated with other common liver diseases. ZIP14 is a metal transporter that is the key factor underlying hepatic iron accumulation in disease. Surprisingly, not much is known about mechanisms that affect levels of ZIP14 expression in hepatocytes. Therefore, we would like to comprehensively look for factors that regulate ZIP14 in the liver cells. To this aim, we will employ an innovative genetic engineering system - CRISPR/Cas9. Over only last few years, this technology has been adapted from Bacteria defense mechanisms and became a breakthrough and versatile technology to modify mammalian genomes. Using CRISPR/Cas9 genome editing, we have already generated a hepatic cell model, where the levels of the ZIP14 expression could be monitored using a fluorescent protein. Next, we will employ CRISPRs to inactivate all genes in the genome and search for those, that alter ZIP14 expression. We will further characterize the most promising hits from this screen and ultimately assess if they affect hepatic iron overload under disease conditions. Of medical importance, our work can reveal factors which could be targeted by drugs to prevent iron loading of the liver. My identifying new genes that affect ZIP14 levels, our data may also help to understand why only some patients with hemochromatosis are at risk to accumulate iron, and some do not show clinical symptoms.