Mechanisms of oxidative stress-induced cell death in hepatocytes

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CHAPTER 1

Scope of the thesis

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Most chronic liver diseases, such as non-alcoholic steatohepatitis (NASH), chronic cholestasis and alcoholic and chronic viral hepatitis, are almost invariably accompanied by exposure to reactive oxygen species (ROS). In addition to oxidative stress, liver cells are also exposed to cytokines and bile acids during chronic liver injury. Under these circumstances, cell damage followed by cellular death occurs, which may lead to liver injury and loss of liver function. There are no effective treatments available for chronic liver disorders yet.
Hepatocytes, the parenchymal cells of the liver, are well equipped with protective mechanisms to prevent cell death. Once these protective pathways are activated, the balance will be in favour of cell survival. However, the balance between cell survival and cell death is delicate and easily disrupted during liver injury, leading to massive cell death and loss of liver function. Hence, knowledge about the cellular mechanisms leading to cell death is of relevance as it may enable the identification of novel therapeutic tools to treat liver diseases.
The aim of this thesis is to elucidate the mechanisms of oxidative stress-induced hepatocyte cell death, in order to develop strategies to protect hepatocytes and prevent liver injury.

In **chapter 2**, the current knowledge on oxidative stress induced cell death, with special emphasis on liver cells, is reviewed. In **chapter 3**, the mechanisms of cell death induced by different ROS are elucidated. Furthermore, the role of different signal transduction pathways (MAPK and NF-κB) and ROS detoxification mechanisms in ROS-induced cell death are investigated.
Heme oxygenase-1 (HO-1) is an important stress-responsive cytoprotective protein. In **chapter 4**, we describe the regulation of HO-1 in an in vivo model of chronic cholestasis (bile duct ligation model) and in acute inflammation. Furthermore, the protective role of HO-1 against oxidative stress-induced apoptosis was investigated in primary hepatocytes. In addition, we study the contribution of carbon monoxide, a product of heme oxygenase-1, to the protective role of HO-1 against oxidative stress-induced apoptosis and we examine the mechanism involved in this process.

Chapter 5 describes the protective effect of metformin, an insulin sensitizing drug frequently used in the treatment of type 2 diabetes, against oxidative stress-induced apoptosis in primary rat hepatocytes. We also examine the mechanisms involved in the process.
Exposure to oxidative stress is also a hallmark of cholestatic liver diseases. Patients with cholestatic liver disease are often treated with ursodeoxycholic acid (UDCA), but its protective mechanism of action has not been elucidated yet.

Chapter 6 of this thesis reports the possible mechanisms behind the anti-apoptotic action of taurine-conjugated UDCA.

In conclusion, this thesis describes various modes of cell death induced by ROS and provides tools to selectively interfere with this process. This knowledge may contribute to the development of novel therapies for liver disorders.