Functional recovery after liver resection
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General introduction and outline of the thesis
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Liver fat accumulation, i.e. steatosis, is a dramatically growing clinical problem because of the close connection of the disease etiology with Western lifestyle; obesitas, diabetes and metabolic syndrome. This particular entity of steatosis is described as non-alcoholic fatty liver disease (NAFLD) but steatosis can develop also after a variety of insults, including a spectrum of diseases and substances. Steatosis can be classified either by the extent (percentage of hepatocytes containing fat) and/or the type (fat infiltration presenting either as small or large vesicles within hepatocytes, i.e. micro- and macrovesicular steatosis, respectively). Currently the most commonly used staging, based on the extent of steatosis, divides steatosis into mild (30% of hepatocytes affected), moderate (30-60% affected) and severe (>60% affected) forms.

Steatosis was originally considered as a benign condition without any influence on the outcome of patients undergoing hepatic resection. However, there is an increasing amount of evidence that even the mildest form of steatosis affects recovery after liver resection by increasing postoperative morbidity and, even in some cases, mortality. Regardless of developments made in the field of medical oncology, surgical resection remains the only potentially curative treatment for patients with liver malignancy. For patients with compromised liver, i.e. steatosis, fibrosis or cirrhosis, a larger remnant liver is required to ensure uneventful postoperative recovery after major liver resection. Sufficient recovery of hepatocellular volume and function is of vital importance to avoid postoperative complications related to hepatic dysfunction as severe acute liver failure still has a mortality of up to 80%.

The major issue in patients with compromised liver is the lack of reliable methods to estimate preoperatively the safe extent of resection. In these patients, the actual liver volume does not always correlate with hepatic function and for this reason, conventional radiological modalities fall short. The gold standard for diagnosis of steatosis remains histopathological evaluation of multiple biopsies as radiological modalities do not demonstrate the pathological features of steatosis severity scoring, such as fibrosis and the extent of inflammation. However, as already a single biopsy bares a risk of bleeding and multiple biopsies are usually required due to the heterogeneous distribution of steatosis in liver parenchyma, it is neither routinely recommended nor performed. In view of the magnitude of steatosis in the future, new pharmacological interventions are being developed. This research is, however, hindered by the lack of reliable non-invasive methods to follow-up and to determine the success of the intervention, i.e. reduction of the severity of steatosis.

The aim of this thesis is to explore new avenues for diagnosis and treatment of steatosis and to provide insights in the mechanisms involved in the increased vulnerability of steatotic livers during liver resection. These aspects were addressed both from the experimental and clinical perspective of liver surgery in steatotic livers.

In the chapter 2, the currently most common hepatic parenchymal disease, liver steatosis, is introduced and the clinical presentation defined. Significant features of steatosis demographics and diagnostics are presented together with the key pathogenic features.
of the disease. The clinical relevance of steatosis is evaluated with special emphasis on its consequences for liver resection and liver transplantation, both in the setting of orthotopic liver transplantation and living donor liver transplantation. Steatosis is clearly associated with impaired patient outcome after liver resection. Also, studies have shown that steatosis affects primary function and secondary outcome of patients after living donor liver transplantation, a form of transplantation encompassing major liver resection on the part of the donor. Present knowledge of the influence of steatosis in liver surgery gained from experimental and clinical studies is reviewed and discussed in detail. Furthermore, the underlying hepatocellular metabolic and pathologic derangements induced by fat accumulation, as far as involved in the increased vulnerability of steatotic livers, are discussed in depth.

In chapter 3, the development of steatosis in two experimental models of diet-induced steatosis was investigated. NAFLD presents with a broad spectrum of hepatocellular parenchymal changes ranging from mild hepatocyte fat accumulation to a more severe inflammatory form, known as steatohepatitis (NASH). NASH is considered the irreversible end stage of NAFLD in which progressive fibrosis leads to fulminant parenchymal cirrhosis and even to death. The dietary models were chosen as they currently are considered the only experimental models featuring progressive inflammation, in contrast to steatosis models based on genetic alteration of the leptin pathway (ob/ob mice, Zucker rats). The clinically relevant, biochemical and histopathological features of progression of NAFLD were investigated with the aim of application of these experimental models in future studies.

Hepatocellular function correlates with parenchymal volume in patients with normal liver parenchyma. However, in cases of parenchymal liver disease, function is often impaired while the volume of liver increases or remains constant. Especially after liver resection, when the liver compensates for the loss of tissue by hepatocyte proliferation, actual liver volume is a poor discriminator of hepatocellular function. Current, widely applied imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI) do not provide information concerning parenchymal function. The widely used non-invasive standard tests for the assessment of hepatic function, such as plasma levels of transaminases and bilirubin, are more parameters of hepatocellular damage than function. There is also a growing clinical demand for non-invasive modalities for the follow-up of steatosis as the amount of patients with parenchymal liver diseases on the basis of steatosis, is expected to increase in the future. In chapter 4, the functional imaging techniques currently used clinically to evaluate liver function are reviewed. This is of importance when the limits of safe liver resection need to be defined in order to avoid postoperative complications related to insufficient remnant liver. Recent developments in the assessment of hepatocellular function are discussed and the latest knowledge of the clinical application of nuclear imaging techniques are reviewed in the context of liver surgery.