



## Samenvatting proefschrift Golnar Karimian

**'Signal transduction pathways in hepatocyte cell death: New targets for therapy'**

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Cholestatic and steatotic liver diseases comprise a significant share of the total burden of chronic liver diseases. Both cholestatic and steatotic liver diseases are associated with a high morbidity and mortality. Existing therapeutic agents are either not very effective or are associated with severe difficulties. One of the reasons for the lack of effective treatment for cholestatic and steatotic liver diseases is the lack of detailed knowledge about the pathogenetic mechanisms of these diseases. Both groups of diseases are characterized by a gradual and progressive loss of viable hepatocytes leading to liver inflammation, fibrogenesis and end-stage liver disease. Hepatocyte cell death can occur via either apoptosis or necrosis (or intermediate forms). Knowledge about the cellular mechanisms regulating death and survival of liver cells is of clinical and scientific interest for developing new therapeutic strategies. The aim of this thesis is to elucidate the mechanisms of cell death in hepatocytes, in order to develop strategies to protect hepatocytes and prevent liver injury. Three models of hepatocyte cell death were studied: glycochenodeoxycholic acid (GCDCA)-induced cell death as a model for bile acid toxicity, tumor necrosis factor  $\alpha$  (TNF $\alpha$ )/ actinomycin D (ActD, an inhibitor of transcription) as a model for cytokine-induced toxicity and menadione-induced cell death (menadione is a superoxide anion donor) as a model for oxidative stress-induced toxicity. These models are clinically relevant as these toxic stimuli are present at increased levels in most liver diseases. This thesis describes that hepatocyte death and survival are regulated at the cross-roads of intracellular organelles (e.g., mitochondria and endoplasmic reticulum), membrane-bound receptors (such as GPCRs and EGFR) and cell survival signaling pathways (such as ERK, PI3K and PKC). ◀

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