Unravelling the effect of intra- and intercellular processes on acetaminophen-induced liver injury

Main author: Muriel Heldring (Leiden University (LU))

Co-authors: Angela Shaw, Margriert Palm, Joost Beltman

INTRODUCTION

In high dosages, acetaminophen (APAP) can cause severe liver damage, but susceptibility to liver failure varies across individuals. APAP-induced liver injury and recovery is regulated by an intricate system of intra- and extracellular molecular signalling which involves various cell types, such as hepatocytes, residential Kupffer cells and macrophages. High APAP blood concentrations lead to accumulation of toxic metabolites which causes necrotic damage in centrilobular hepatocytes, where cytochrome P450-mediated metabolism is fast and detoxification by glutathione is low. In addition, these toxic metabolites cause oxidative stress and activate p53 and the associated DNA damage response. The p53-dependent transcriptional activation of p21 can induce senescence in hepatocytes surrounding the necrotic area. Macrophages that are recruited to the damaged site for removal of necrotic debris simultaneously stimulate senescence and proliferation in undamaged hepatocytes. The regenerative capacity within a liver lobule therefore depends on the balance between the extent of damage and the number of remaining healthy cells.

METHODOLOGY

To gain insight in the importance of distinct intra- and extracellular processes for successful recovery, we integrated hepatocellular acetaminophen metabolism, DNA damage response induction and cell fate into a spatially explicit multiscale mechanistic model. We used the Cellular Potts model framework to design a two-dimensional hexagonal structure of one liver lobule with the central vein in the centre surrounded by hepatocytes and Kupffer cells and with portal veins in the corners. Hepatocellular APAP uptake and metabolism, implemented with differential equations, caused accumulation of toxic metabolites and could induce changes into senescent or necrotic cell states. Chemokine excretion led to recruitment of macrophages to the damaged site and clearance of necrotic debris. In addition, macrophages could promote senescent and proliferative events through chemokine signalling. We performed sensitivity analysis of various model parameters to unravel the relevance of different processes in the systems sensitivity to APAP-induced adversity.

RESULTS

We examined the importance of zonated APAP metabolism on the extent of damage by elimination of zonal differences in cytochrome P450 and glutathione abundance. Our model simulations suggested that impaired APAP detoxification can greatly sensitise the system to irreparable necrotic damage. Investigation of the role of the DNA damage response in liver recovery showed that augmented p53 inhibition can positively influence the regenerative capacity of the liver after a chemical insult. Moreover, macrophage-dependent stimulation of p21 production is a potent stimulant of senescence, whereas the effectiveness of p21 determines proliferative events. Thus, intracellular protein dynamics and intercellular communication are important determinants for recovery.

DISCUSSION

Here, we aimed to combine essential determinants of APAP-induced adversity and recovery in liver tissue in one comprehensive model. Through integration of processes at different levels of biological organisation, we were able to quantitatively determine the effect of changes in subcellular dynamics on system outcome. Alterations in the lobular structure of the model or replacement of modules such as drug metabolism could make this model applicable to other organisms or drugs. Our approach demonstrates how modelling can be used to identify the main sources of interindividual variability, thereby improving our understanding of adversity in drugs and chemicals.