

Introduction to Review Series

Liver injury and liver protection: mechanisms and novel treatment strategies

Worldwide an increasing impact of liver disease is being recognized. Moreover, liver injury due to pharmacological treatment or surgical intervention plays an important role. Recent years have brought new insights into the pathomechanisms of liver injury. In some cases this provides the basis for novel therapeutic strategies. Thus, in the age of translational research hepatology gives an excellent example for progress. To pick just one of many novel strategies: in hepatic ischemia–reperfusion injury early generation of sinusoidal oxidative stress has been identified as major factor. Consequently, the application of extracellular antioxidants such as glutathione with the beginning of reperfusion has been developed as protective strategy. Within a few years the link from animal experiments to clinical trials has been made.

For this review series some of the most interesting pathomechanisms and intriguing treatment strategies will be displayed. The issues are being covered by leading experts in the field whose expertise is well documented by their publications in well-recognized journals.

Jaeschke and Hasegava characterize the contribution of neutrophils to acute liver injury and in particular to necrotic cell death. A time-dependent three-step mechanism comprises accumulation of neutrophils in hepatic sinusoids, extravasation in the liver parenchyma and finally oxidative damage to hepatocytes. Reactive oxidants species also are a major mediator of Kupffer cell-induced liver injury as described by Bilzer et al. While Kupffer cells, the largest population of resident macrophages in the body, play a major role following bacteraemia and other stimuli they seem to be of particular importance in hepatic ischemia–reperfusion injury. Based on this observation the group has elaborated a clinically applicable antioxidative strategy to prevent ischemia–reperfusion injury of the liver. Nitric oxide in contrast seems to be a two-edged sword in hepatic pathophysiology. While it seems to inhibit apoptosis in acute liver failure, it promotes liver injury in conditions such as ischemia–reperfusion and haemorrhagic shock. Never-

theless, strategies may be developed to attenuate liver injury by use of NO as outlined by Timothy R. Billiar's group.

In contrast to necrosis, apoptosis is usually not accompanied by inflammatory responses, but nevertheless involved in several forms of liver injury. While impairment of apoptosis may contribute to hepatocellular carcinoma (HCC), augmentation of apoptosis has a potentially devastating effect. Thus, modulation of apoptosis in the liver – either by increasing or decreasing – seems to have important therapeutic implications as outlined by Galle and colleagues. In this respect, knowledge of the molecular pathways involved in hepatocellular apoptosis and moreover in survival pathways during liver injury is essential to delineate novel protective strategies. The liver is endowed with a series of natural protective and regenerative mechanisms that likely evolved to preserve this organ from the many potential harmful agents it may face. Among them, the nuclear factor (NF)- κ B pathway early emerged as a key intracellular mediator of protective signaling in the hepatocyte. Trautwein et al. present the latest studies performed in genetically modified mice that begin to unravel the complex role of the NF- κ B pathway in different liver cell types during acute and chronic injury. Fernandez-Checa et al. review the evidence supporting a new role for glycosphingolipids in liver injury. Tumor necrosis factor-induced generation of this class of lipids has been recently recognized to impinge on the development of pathological processes such as alcohol-induced liver disease.

While alcoholic liver disease has long been recognized as a major risk factor for cirrhosis, recent years have suggested non-alcoholic steatohepatitis as another important cause of liver disease. Interestingly, only a minority of subjects exposed to alcohol abuse or obesity and metabolic syndrome, respectively, will finally develop fibrosis and cirrhosis. Thus, environmental and, moreover genetic risk factors seem to be decisive and have partly been identified. The contribution of C. Day provides the most recent insights in

these fascinating studies. Regarding treatment the modulation of inflammatory cytokines should play a major role given the pathophysiological background outlined above. Tilg et al. summarize the data available so far with inhibition of tumor necrosis factor- α and administration of interleukin-10 or the adipokine adiponectin, respectively.

J. Rosello-Catafau et al. delineate the cellular and molecular mechanisms involved in ischemia-reperfusion injury, and in the protective strategy of ischemic preconditioning. The identification of such mechanisms may pave the way to the development of novel pharmacological interventions to protect small liver grafts and steatotic livers, and thus alleviate the scarcity of suitable cadaveric grafts. Liver surgery may be dangerous particularly to patients with compromised organ function such as fatty liver or cirrhosis. Recently, novel strategies which prevent blood loss and may reduce ischemia-reperfusion injury have been studied in patients by Pierre-Alain Clavien and his group.

Ideally, liver support could be supplied with human hepatocytes or stem cell-derived hepatocyte-like cells. Many years of research in this field, however, have not solved to overcome major obstacles such as *in vitro* expansion, homing and engraftment of such cells. F. Faendrich et al. have just recently introduced a fascinating concept: dedifferentiation of peripheral blood monocytes and differentiation into neohepatocytes. If transferable to the clinical setting this could revolutionize the treatment of various forms of liver failure.

HCC is the fifth most common tumor worldwide. Unfortunately, curative treatment strategies are available only for a minority of patients. Within this context Jesus M. Prieto and collaborators describe new players and potential targets for liver cancer. The implementation of novel tools for high-throughput analysis of gene expression will undoubtedly help to improve the early diagnosis, molecular classification and prediction of outcomes in HCC. Pineau et al. review the contribution of genomics, while F. J. Corrales et al. delineate the application of proteomics to HCC gene expression profiling.

Obviously, the articles will reflect the view of the various authors. Nevertheless, for the sake of readability and clarity the chapters do provide a similar outline, restricting themselves to a few tables/figures and some of the most important references. It is our hope that this review series will provide an excellent overview of the most intriguing topics of liver injury and liver protection. Furthermore, it should stimulate discussion and development in this rapidly moving and important field.

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