

## **PS-1.2 RIP1-dependent programmed necrosis is negatively regulated by caspases during hepatic ischemia-reperfusion (W)**

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### Einleitung:

Programmed necrosis (necroptosis), a newly discovered form of the cell death is mediated by Receptor-Interacting Protein (RIP1) and plays a pivotal role after myocardial, renal, and cerebral ischemia-reperfusion (I/R). The relevance of necroptosis in the postischemic liver remains, however, unclear. The aim of this study was to analyze the role of programmed necrosis during hepatic I/R.

### Material und Methoden

Under inhalation anesthesia, C57BL6 mice were subjected to warm hepatic I/R (90min/240min). The animals were pretreated either with the RIP1 inhibitor necrostatin-1 (Nec-1, 3.5µg/kg) or vehicle (Nec-1<sub>inactive</sub>; 3.5µg/kg) administered systemically prior ischemia. Sham-operated animals served as controls (n=6 each group). The inflammatory response was evaluated by intravital microscopy. The hepatic transaminases ALT/AST in plasma as well as the activity of caspase-3 in tissue were determined as markers of hepatocellular injury.

### Ergebnisse

Leukocyte recruitment to the liver ( $21 \pm 2$  rolling leukocytes/mm<sup>2</sup>s and  $215 \pm 22$  adherent leukocytes/mm<sup>2</sup>), sinusoidal perfusion failure ( $19 \pm 2\%$  non-perfused sinusoids) as well as the transaminase activities (AST  $9758 \pm 2408$ , ALT  $2072 \pm 657$  U/L) were strongly increased upon I/R as compared to the sham-operated mice. Inhibition of the RIP1-dependent pathway with Nec-1, however, did not attenuate I/R-induced leukocyte migration, perfusion failure, and hepatocellular injury. Western-Blot analysis showed a baseline RIP1 expression in livers from sham-operated mice, whereas RIP1 expression was not detectable in both Nec-1-treated and vehicle-treated I/R group. Caspase-3 activity was significantly elevated in both postischemic groups.

### Schlussfolgerung

Our *in vivo* data show that RIP1-mediated necroptosis is not present in the liver after I/R. Since caspases are able to cleave RIP1, we suggest that I/R-triggered caspase activation negatively regulates necroptosis and, thereby, determines apoptosis as a preferred route of cell death after hepatic I/R.