P058

The role of p-JNK expression on hepatocyte necrosis and autophagy in the cholestatic liver

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Introduction : Clinically, liver fibrosis and cholestasis are two major disease entities, ultimately leading to hepatic failure. Although autophagy plays a substantial role in the pathogenesis of these diseases, its precise mechanism has not been determined yet.

Methods : Mouse models of liver fibrosis or cholestasis were obtained following the serial administration of thioacetamide or surgical bile duct ligation (BDL), respectively. Next, after obtaining liver specimens at specific time points, we compared the expression of apoptotic (cleaved caspases), necrotic (phospho-c-Jun N-terminal kinase [p-JNK] and CD68), and autophagy markers (microtubule-associated protein light chain 3B [LC3B] and p62) in the fibrotic or cholestatic mouse livers, using polymerase chain reaction, western blot analysis, immunohistochemistry, and immunofluorescence.

Results : Following BDL, although there was a time-dependent increase of necrotic markers (p-JNK and CD68), no significant expression changes were detected in pro-apoptotic markers (cleaved cascades) over time. In addition, autophagy marker studies indicated that whereas autophagy was upregulated in fibrotic livers, it was downregulated in cholestatic livers. We also observed mild to moderate activation of p-JNK in fibrotic livers, whereas cholestatic livers demonstrated a significantly higher p-JNK activation.

Conclusions : Whereas fibrotic livers exhibited a mild to moderate increase in p-JNK expression related with the induction of autophagy and apoptotic cell death, cholestatic livers exhibited a marked increase in p-JNK expression which could be associated with the reduction of autophagy and a subsequent increase in necrosis.

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