CCAAT-Enhancer-Binding Protein Homologous Protein Promotes Liver Ischemia and Reperfusion Injury by Inhibiting Beclin-1-mediated Autophagy in Hepatocytes


ABSTRACT

Background and Aims: Critical role of endoplasmic reticulum (ER) stress has been found in ischemia and reperfusion (IR) injury models. However, the role of CCAAT-Enhancer-Binding Protein Homologous Protein (CHOP) signaling in liver IR injury still remains unclear. The aim of this study is to determine the role and its underlying mechanisms of CHOP signaling in liver IR injury.

Method: Wild-type (WT) and CHOP KO mice were subjected to a murine liver partial warm ischemia model. Liver injury and hepatocellular apoptosis was compared between groups. Autophagy and its regulatory signaling pathways were assessed in both the liver tissues and the primary hepatocytes.

Results: CHOP KO significantly decreased liver IR injury, as evidenced by lower ALT and AST levels and better preserved liver architecture. Liver IR induced marked hepatocellular apoptosis, as indicated by Hoechst/PI staining and western blot analysis of cleaved Caspase-3, BCL-2, and BCL-XL. CHOP KO mice demonstrated much less hepatocellular apoptosis but enhanced autophagy. Primary hepatocytes were isolated and subjected to a stress injury model in vitro. CHOP KO mice decreased cell death, as measured by LDH and CCK8 assay. Autophagy was enhanced in CHOP KO hepatocytes as evidenced by LC3B staining and the electron microscope examination. Beclin-1 activation was significantly increased in CHOP KO hepatocytes post IR. Functionally, Beclin-1 siRNA or autophagy specific inhibitor 3-MA effectively blocked autophagy in hepatocytes and abrogated the protective role of CHOP KO in hepatic IR injury.

Conclusion: Our results indicated that CHOP activation protected liver IR injury by inhibiting Beclin-1-mediated autophagy in hepatocytes. Strategies targeting CHOP or autophagy signaling may provide therapeutic effects against liver IR injury in patients.

OBJECTIVE

To determine the role of CHOP signaling in IR-stressed liver parenchymal cells.

METHODS

SUMMARY

- CHOP KO significantly protected livers against IR injury.
- CHOP KO promoted autophagy in livers post IR.
- Autophagy inhibition by 3-MA abrogated the protective role of CHOP KO in both liver IR model in vivo and hepatocyte H/R model in vitro.
- Beclin-1 was significantly activated in CHOP KO primary hepatocytes post H/R.
- Autophagy inhibition by Beclin-1 siRNA abrogated the protective role of CHOP KO in H/R induced cell injury.

CONCLUSIONS

CHOP KO alleviates liver IR injury and inhibits hepatocellular apoptosis via promoting Beclin-1 dependent autophagy activation in hepatocytes.

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