The transcription factor CHOP, a central component of the transcriptional regulatory network induced upon CCl4 intoxication in mouse liver, is not a critical mediator of hepatotoxicity.

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Abstract

Since xenobiotics enter the organism via the liver, hepatocytes must cope with numerous perturbations, including modifications of proteins leading to endoplasmic reticulum stress (ER-stress). This triggers a signaling pathway termed unfolded protein response (UPR) that aims to restore homeostasis or to eliminate disturbed hepatocytes by apoptosis. In the present study, we used the well-established CCl4 hepatotoxicity model in mice to address the questions whether CCl4 induces ER-stress and, if so, whether the well-known ER-stress effector CHOP is responsible for CCl4-induced apoptosis. For this purpose, we treated mice with a high dose of CCl4 injected i.p. and followed gene expression profile over time using Affymetrix gene array

analysis. This time resolved gene expression analysis allowed the identification of gene clusters with overrepresented binding sites for the three most important ER-stress induced transcription factors, CHOP, XBP1 and ATF4. Such result was confirmed by the demonstration of CCl4-induced XBP1 splicing, upregulation of CHOP at mRNA and protein levels, and translocation of CHOP to the nucleus. Two observations indicated that CHOP may be responsible for CCl4-induced cell death: (1) Nuclear translocation of CHOP was exclusively observed in the pericentral fraction of hepatocytes that deteriorate in response to CCl4 and (2) CHOP-regulated genes with previously reported pro-apoptotic function such as GADD34, TRB3 and ERO1L were induced in the pericentral zone as well. Therefore, we compared CCl4 induced hepatotoxicity in CHOP knockout versus wild-type mice. Surprisingly, genetic depletion of CHOP did not afford protection against CCl4-induced damage as evidenced by serum GOT and GPT as well as quantification of dead tissue areas. The negative result was obtained at several time points (8, 24 and 72 h) and different CCl4 doses (1.6 and 0.132 g/kg). Overall, our results demonstrate that all branches of the UPR are activated in mouse liver upon CCl4 treatment. However, CHOP does not play a critical role in CCl4-induced cell death and cannot be considered as a biomarker strictly linked to hepatotoxicity. The role of alternative UPR effectors such as XBP1 remains to be investigated.

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