C/EBP Homologous Protein (CHOP) protects against Acetaminophen-Induced Liver Injury by regulating FOS-mediated Autophagy

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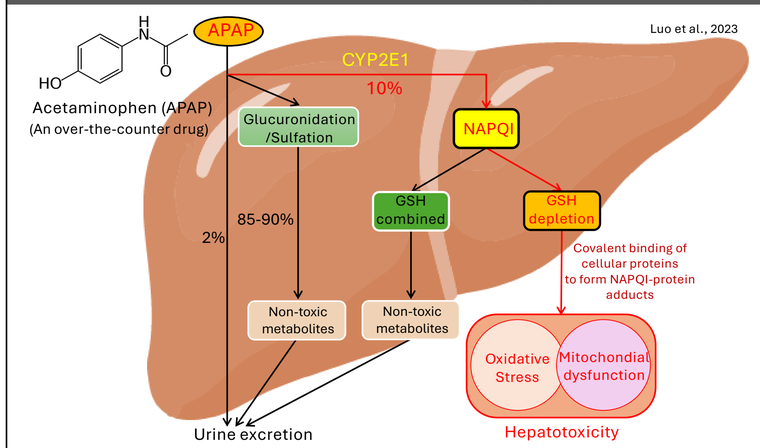
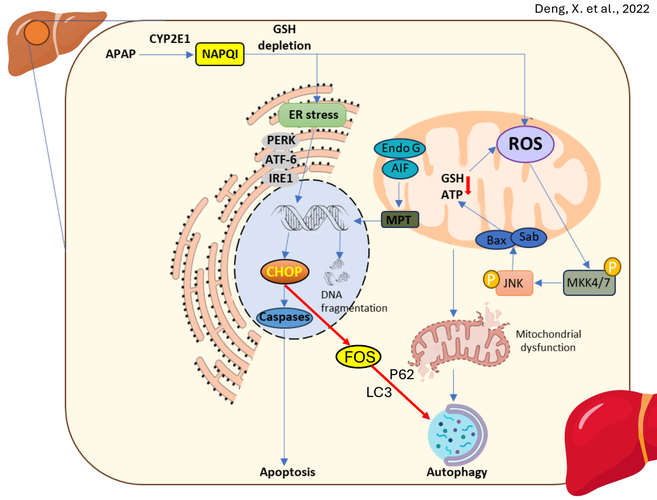
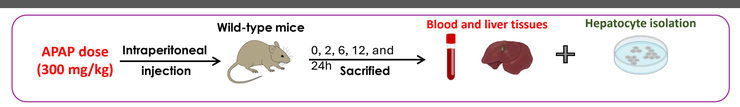
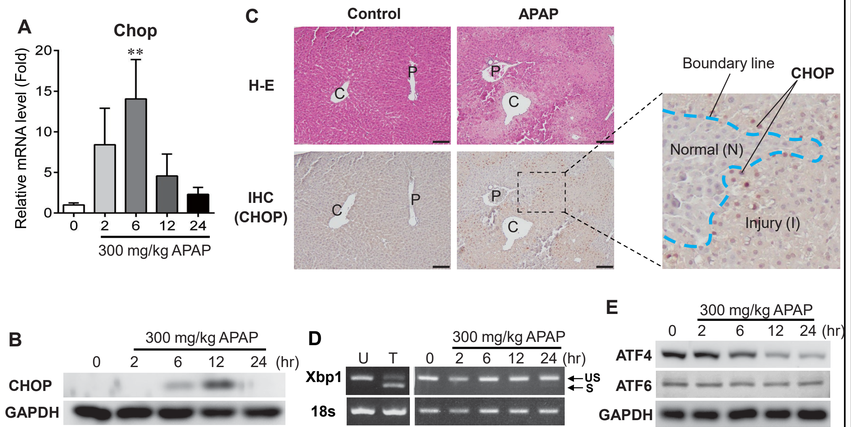
1. Acetaminophen (APAP) metabolic pathways & Intracellular signaling events in APAP-induced liver injury



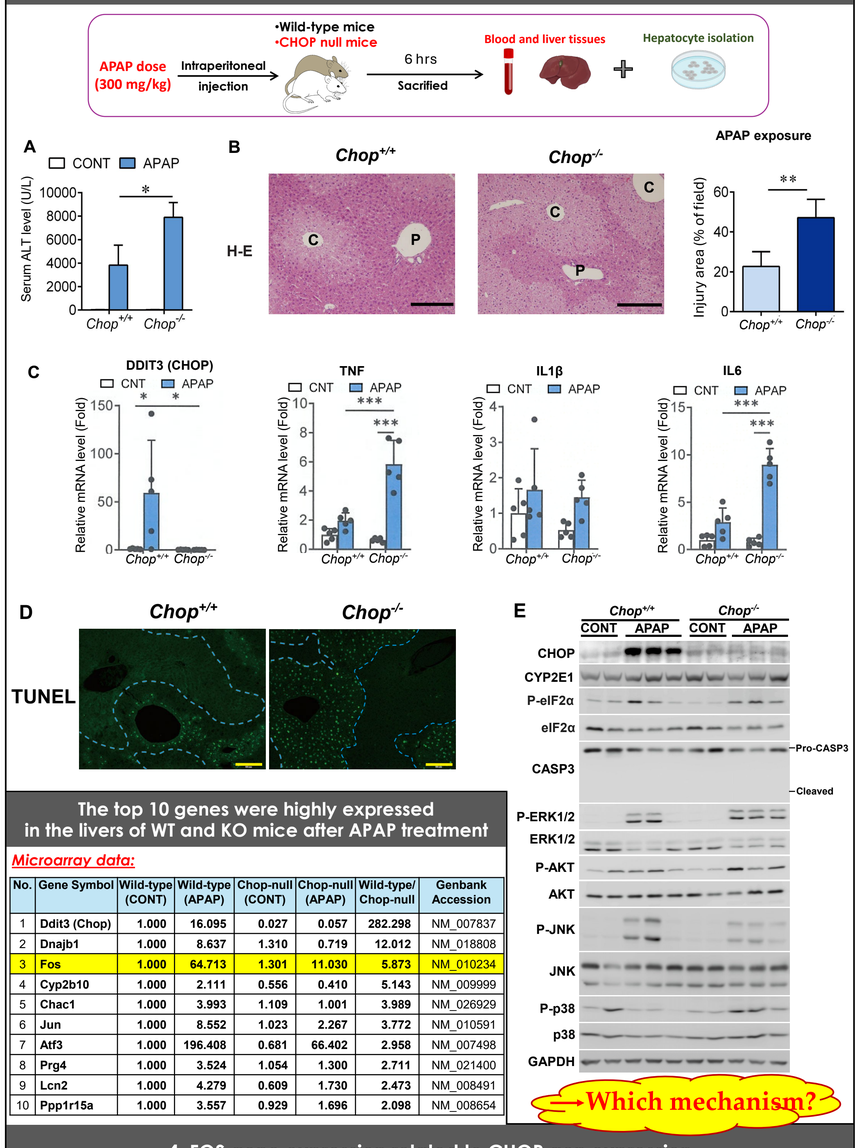


2. APAP promoted CHOP expression independent of Endoplasmic Reticulum Stress





3. CHOP regulated and protected the liver from APAP-induced liver injury

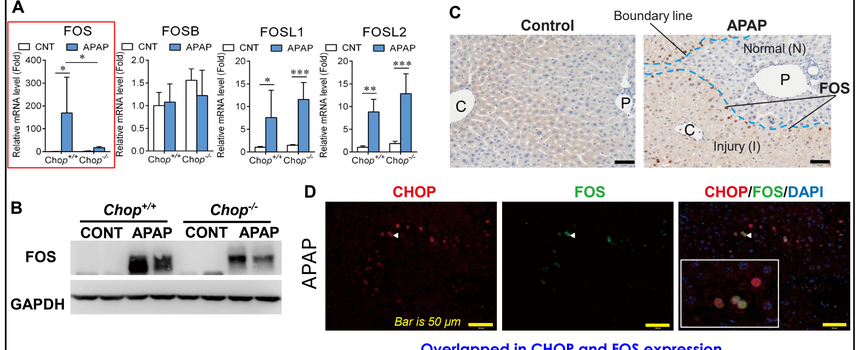


The top 10 genes were highly expressed in the livers of WT and KO mice after APAP treatment

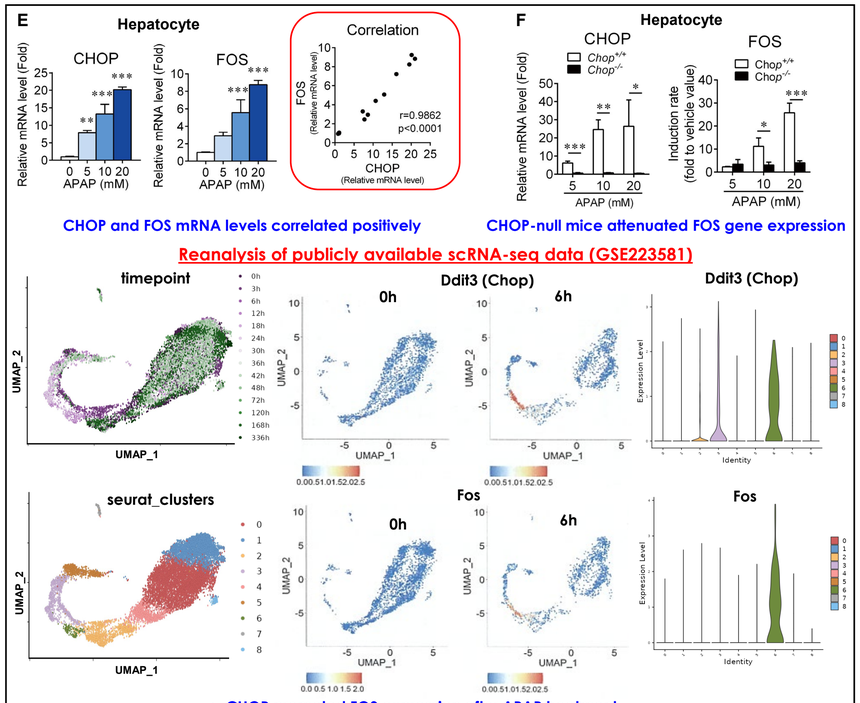
Microarray data:

No.	Gene Symbol	Wild-type (CONT)	Wild-type (APAP)	Chop-null (CONT)	Chop-null (APAP)	Wild-type/ Chop-null	Genbank Accession
1	Ddit3 (Chop)	1.000	16.095	0.027	0.057	282.298	NM_007837
2	Dnajb1	1.000	8.637	1.310	0.719	12.012	NM_018808
3	Fos	1.000	64.713	1.301	11.030	5.873	NM_010234
4	Cyp2b10	1.000	2.111	0.556	0.410	5.143	NM_009999
5	Chac1	1.000	3.993	1.109	1.001	3.989	NM_026929
6	Jun	1.000	8.552	1.023	2.267	3.772	NM_010591
7	Atf3	1.000	196.408	0.681	66.402	2.958	NM_007498
8	Prg4	1.000	3.524	1.054	1.300	2.711	NM_021400
9	Lcn2	1.000	4.279	0.609	1.730	2.473	NM_008491
10	Ppp1r15a	1.000	3.557	0.929	1.696	2.098	NM_008654

4. FOS gene expression related to CHOP gen expression



Overlapped in CHOP and FOS expression



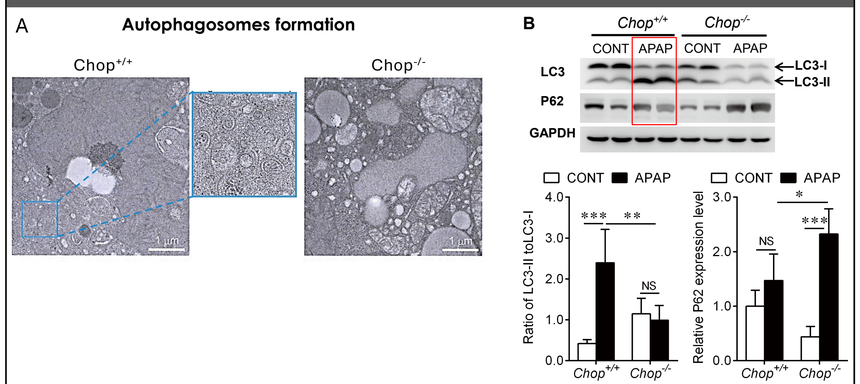
CHOP and FOS mRNA levels correlated positively

CHOP-null mice attenuated FOS gene expression

Reanalysis of publicly available scRNA-seq data (GSE223581)

CHOP promoted FOS expression after APAP treatment

5. CHOP regulated FOS-mediated autophagy



APAP induced autophagy in Wild-type mice but not in *Chop*-null mice

Abstract

Aims: Acetaminophen (APAP) is a common medication for treating fever, pain or inflamation, but its overdose causes severe liver injury through oxidative stress. This study aimed to clarify how C/EBP homologous protein (CHOP) protects hepatocytes by regulating FOS and autophagy.

Methods: Wild-type (WT) and CHOP-null (KO) mice were injected with APAP (300 mg/kg). Liver injury and gene expression were examined by histology, qPCR, Single-Cell RNA sequencing data processing and western blotting. The protective effect of FOS was also evaluated in hepatocytes under oxidative stress conditions.

Results: After APAP exposure, CHOP and FOS expression markedly increased and overlapped between the normal and injuried area in WT mice, while FOS expression was greatly reduced in KO mice. APAP-induced autophagy was observed in WT mice but not in KO mice by increase protein ratio of LC3-II/LC3-I and the degradation of protein p62. In vitro, FOS overexpression reduced oxidative stress–induced hepatocyte death, suggesting its cytoprotective role downstream of CHOP.

Conclusions: CHOP protects against APAP-induced liver injury by regulating FOS-mediated autophagy. The CHOP–FOS axis may serve as a crucial mechanism for maintaining hepatocyte survival under oxidative stress.

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