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Review

Molecular mechanisms of hepatic apoptosis regulated by nuclear factors

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ABSTRACT

Apoptosis is a prominent characteristic in the pathogenesis of liver disease. The mechanism of hepatic apoptosis is not well understood. Hepatic apoptosis alters relative levels of nuclear factors such as Foxa2, NF-κB, C/EBPβ, and p53. Regulation of nuclear factors modulates the degree of hepatic apoptosis and the progression of liver disease. Nuclear factors have distinctive mechanisms to mediate hepatic apoptosis. The modification of nuclear factors is a novel therapeutic strategy for liver disease as demonstrated by pre-clinical models and clinical trials.
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Contents

Abbreviations: TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; ELISA, enzyme-linked immunosorbent assay; DNA, deoxyribonucleic acid; TNFα, tumor necrosis factor-alpha; Foxa2, forkhead box protein A2; HNF6, hepatocyte nuclear factor 6; C/EBPα, CCAAT–enhancer-binding protein alpha; C/EBPβ, CCAAT–enhancer-binding protein beta; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p53, protein 53; AFP, alpha-fetoprotein; PEPCK, phosphoenolpyruvate carboxykinase; ER stress, endoplasmic reticulum stress; EMSA, electrophoretic mobility shift assay; ChIP assay, chromatin immunoprecipitation assay; IAP, inhibitors of apoptosis; XIAP, X-linked inhibitor of apoptosis protein; cIAP1/2, cellular inhibitor of apoptosis 1/2; MPT, mitochondrial permeability transition; TG, triglyceride; CREB, cAMP response element-binding protein; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; GST, glutathione S-transferases; MTP, microsomal triacylglycerol transfer protein; IGF1, insulin-like growth factor 1; stat5, signal transducer and activator of transcription 5; CYP7A1, cholesterol 7-alpha hydroxylase; Foxm1, forkhead box m1; TGFb2R, TGF-beta 2 receptor; cAMP, cyclic adenosine 3′,5′-monophosphate; TLR, toll-like receptor; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; anti-ds-DNA, double-stranded DNA; CDK, cyclin-dependent kinases; TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; CRC, colorectal carcinogenesis; NKT cells, natural killer T cells; MCD diet, methionine choline-deficient diet; PPAR-γ, peroxisome proliferator-activated receptor gamma; SREBP-1c, sterol regulatory element binding protein 1c; LXRα, liver X receptor alpha; IRS, insulin receptor substrate

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1. Introduction

Hepatocytes make up 70–85% of liver mass. The gene of hepatocytes encodes unique expression of plasma proteins, bile synthesis, clotting factors and enzymes related to the metabolic activity of glucose, fat and drugs [1]. Therefore, the liver performs multiple essential functions, e.g. homeostasis of serum proteins, bilirubin excretion, coagulation, metabolism of glucose and lipid, and detoxification. Clinically, liver dysfunction as a progressive outcome of liver disease is exacerbated by hepatic apoptosis. Hepatic apoptosis, induced by causative factors such as alcohol, viruses, toxic bile acids, fatty acids, drugs and immune response, is a prevalent mechanism in the pathogenesis of liver disease. Hepatic apoptosis can be determined by common techniques, including TUNEL staining, DNA fragmentation as visualized by DNA laddering assay, histone ELISA, mitochondrial cytochrome *c* release, translocation of the pro-apoptotic Bcl-2 family member Bax to the mitochondria, caspase activity and the hepatoprotective effect of pancaspase inhibitors following pretreatment [2–5]. Hepatocyte apoptosis is also discovered via particular morphology in single cells by electron microscopy and flow cytometry study of phosphatidylserine externalization [6,7]. Plentiful studies in recent years have demonstrated that apoptotic liver injury alters relative levels of nuclear factors Foxa2, NF-κB, C/EBPβ and p53 (Table 1). The regulation of some nuclear factors modulates the degree of hepatic apoptosis as well as intervenes in the progression of liver disease.

2. Relationship between expression of certain nuclear factors and hepatic apoptosis

2.1. Foxa2

2.1.1. Introduction of Foxa2

Foxa2, previously known as hepatocyte nuclear factor 3β (HNF3β), is a member of the forkhead class of DNA-binding proteins that are transcriptional activators for the regulation of cell differentiation and metabolism. Foxa2 plays important roles in different stages of mammalian life, beginning with early development, continuing during organogenesis, and finally in metabolism and homeostasis in the adult. At the onset of gastrulation, Foxa2 functions in the establishment of tissue-specific gene expression and regulation of gene expression in differentiated tissues such as the liver, pancreas, lungs and prostate [8]. Ablation of Foxa2 in mice results in embryonic lethality because of severe defects in the development of the organs [9]. In postnatal life, Foxa2 is repressed by insulin to mediate fasting responses [10]. The expression of Foxa2 acts on glucose homeostasis and lipid metabolism [11]. Moreover, Foxa2 is a transcription activator for liver-specific genes such as AFP, albumin, transthyretin, and PEPCK [12].

2.1.2. Expression of Foxa2 and hepatic apoptosis

Apoptosis could be induced in primary hepatocytes by either glycochenodeoxycholate (GCDC) or lipopolysaccharide (LPS). Hepatocyte

Table 1
Expression of nuclear factors involves the pathogenesis of liver injury.

Nuclear factors	Liver disease	Expression of nuclear factors during liver injury
Foxa2	Cholestasis	Toxic bile salts reduce Foxa2 abundance, increase endoplasmic reticulum stress, and inhibit cIAP1 expression [13,14].
	NAFLD	Foxa2 modulates the insulin-related gene expression and regulates lipid metabolism via the PI3K–Akt signaling pathway [17,18].
	Hepatitis B	Foxa2 inhibits nuclear hormone receptor-mediated HBV replication in mouse fibroblasts. Foxa2 transcriptional interference may regulate HBV RNA synthesis and viral replication [19,20].
	Hepatitis C	HCV infection differentially modulates FoxO1 and Foxa2 activation and affects insulin-induced metabolic gene regulation in human hepatocytes [17].
	PBC	Foxa2 expression is altered in different stages of primary biliary cirrhosis and chronic biliary obstruction [13,14,51].
NF-κB	ALD	Chronic alcohol-mediated decrease in cAMP can prime macrophages to enhance LPS-inducible NF-κB activation and TNFα expression [61,62].
	Hepatitis C	NF-κB activation is detected during HCV infection. TNFα and TLR 3 and 7 mRNAs are also up-regulated in ALD and HCV as compared with normal liver, TNFα and TLR7 being the highest in hepatitis C. Strong induction of interferon beta is found in hepatitis C, but not in ALD or normal liver tissue [67].
	Cholestasis	NF-κB is required for hepatocyte proliferation in bile duct ligated mouse. NF-κB mediates the up-regulation of iNOS that is further augmented by oxidative stress. NF-κB is activated in hepatocytes and functions to reduce liver injury during obstructive cholestasis [68–70].
C/EBPβ	NAFLD	C/EBPβ deletion increases mitochondrial function and protects mice from LXR-induced hepatic steatosis [77].
	Hepatitis C	Increased C/EBPβ and NS5A may be essential components leading to increased gluconeogenesis associated with HCV infection [78].
	ALD	C/EBPβ and C/EBPδ expression is elevated in the early phase of ethanol-induced hepatosteatosis in mice [79].
	Cholestasis	C/EBPα and C/EBPβ regulate the iNOS expression, which may further modulate hepatocyte apoptosis during cholestatic liver injury [80].
p53	HCC	HBV infection had prevalent GC → TA transversion mutation at the third position of codon 249 of the p53 gene. The HBx protein of HBV also promotes cell cycle progression, increases the expression of telomerase reverse transcriptase, inactivates negative growth regulators, and binds to and inhibits the expression of p53 (anti-apoptotic activity) and other tumor suppressor genes and senescence-related factors. Some reports also evidence the role of hepatitis C virus in the pathogenesis of HCC [95,96]
	Hepatitis B	Tumor development correlates precisely with p53 binding to HBx in the cytoplasm and complete blockage of p53 entry into the nucleus. Functional inactivation but not structural mutation of p53 causes liver cancer HCC [95,96].
	NAFLD	p53 in hepatocytes regulates steatohepatitis progression by controlling p66Shc signaling, ROS levels, and apoptosis. Moreover, p53/p66Shc signaling in the liver appears to be a promising target for the treatment of NASH [94]
	AIH	DNA damage may trigger the production of anti-p53 in patients with autoimmune liver disease including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and AIH/PBC overlap syndrome (AIH/PBC OS). The emergence of anti-p53 is likely to be useful for discriminating AIH or AIH/PBC OS from PBC and helpful for predicting favorable prognoses in patients with AIH (100).

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