Gastroenterology 2014;147:765–783

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Cell Death and Cell Death Responses in Liver Disease: Mechanisms and Clinical Relevance

Tom Luedde,[1] Neil Kaplowitz,[2] and Robert F. Schwabe[3,4]

[1]Department of Medicine III, University Hospital RWTH Aachen, Aachen, Germany; [2]Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California; and [3]Department of Medicine, [4]Institute of Human Nutrition, Columbia University, New York, New York

Hepatocellular death is present in almost all types of human liver disease and is used as a sensitive parameter for the detection of acute and chronic liver disease of viral, toxic, metabolic, or autoimmune origin. Clinical data and animal models suggest that hepatocyte death is the key trigger of liver disease progression, manifested by the subsequent development of inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. Modes of hepatocellular death differ substantially between liver diseases. Different modes of cell death such as apoptosis, necrosis, and necroptosis trigger specific cell death responses and promote progression of liver disease through distinct mechanisms. In this review, we first discuss molecular mechanisms by which different modes of cell death, damage-associated molecular patterns, and specific cell death responses contribute to the development of liver disease. We then review the clinical relevance of cell death, focusing on biomarkers; the contribution of cell death to drug-induced, viral, and fatty liver disease and liver cancer; and evidence for cell death pathways as therapeutic targets.

Keywords: Apoptosis; Necrosis; Necroptosis; Necrosome; DAMP; Viral Hepatitis; NASH; Clinical Trial; Hepatocellular Carcinoma; Alcoholic Liver Disease; DILI; Caspases; RIP3; RIP Kinases.

The presence of hepatocyte death, reflected by increased levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), is the most widely used parameter to screen for and monitor patients with liver disease. Moreover, these markers drive therapeutic decisions; have prognostic value for patients with hepatitis B virus (HBV)[1–4] and hepatitis C virus (HCV)[5–8] infections, nonalcoholic steatohepatitis (NASH),[9–11] and autoimmune hepatitis[12]; and correlate with overall and liver-specific mortality in the general population.[13–15] These well-established facts emphasize the importance of cell death as the ultimate driver of liver disease progression and the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).

In the healthy liver, cell death controls organ homeostasis, with a tight equilibrium between the loss and replacement of hepatocytes.[16] Turnover is low in the normal liver, with approximately 0.05% of hepatocytes at any given time being removed by apoptosis, mostly in zone 3.[17,18] This is reflected by almost undetectable ALT levels in healthy subjects. Despite the fact that most hepatic cell types rest in G_0 phase, the liver is endowed with an astounding ability to regenerate in response to massive hepatocellular death or loss of functional liver mass.[19] This regenerative ability not only reflects essential metabolic functions of the liver but is also directly related to its high vulnerability to insults causing massive hepatic cell death, such as food-derived toxins or infections with hepatotropic viruses, bacteria, and parasites. As such, the wide range of metabolic and detoxifying functions predisposes hepatocytes to xenobiotic- and toxin-induced injury. Rapid regeneration represents an efficient mechanism to avoid the loss of key hepatic functions in this setting. Although acute liver failure caused by foodborne poisons and infections may have posed the biggest threat in former times, the bulk of modern liver diseases result from chronic disease processes such as chronic viral hepatitis, nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD). In these settings, the hepatic response to cell death, which is primarily geared toward restoring hepatic architecture and function in response to an acute threat to life (by providing extracellular matrix for mechanical stability and triggering hepatocyte regeneration to restore functional liver mass), becomes maladaptive and promotes the development of tissue fibrosis, cirrhosis, and HCC. The contribution of cell death to liver disease is cell-, stage- and context-specific. Although increased cell death may be a key driver of many chronic disease processes, including fibrogenesis and hepatocarcinogenesis (Table 1), loss or malfunction of programmed cell death (PCD) induction in subsets of

Abbreviations used in this paper: **ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; DAMP, damage-associated molecular pattern; DILI, drug-induced liver injury; ER, endoplasmic reticulum; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HMGB1, high-mobility group box 1; HSC, hepatic stellate cell; IDILI, idiosyncratic drug-induced liver injury; JNK, c-Jun N-terminal kinase; K18, keratin 18; miR, microRNA; MLKL, mixed lineage kinase domain-like protein; MPT, mitochondrial permeability transition; NAC, *N*-acetylcysteine; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor κB; PCD, programmed cell death; RIP, receptor-interacting protein; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor–related apoptosis-induced ligand; XIAP, X-linked inhibitor of apoptosis protein.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.07.018

Table 1. Evidence From Animal Models for Cell Death as a Driver of Liver Disease

		Mode of cell death that promotes disease			
	Experimental evidence	Apoptosis	Necroptosis	Necrosis	References
Acetaminophen	Rip3 knockout protects from early liver injury		X		40
	Cyclosporin A inhibits acetaminophen hepatocyte toxicity in vitro and liver injury in vivo			X	36,46
Hepatic I/R injury	Cyclophilin D knockout inhibits necrotic cell death in hepatocytes and cardiac ischemia-reperfusion injury	X			33
Fibrosis	Spontaneous fibrosis in Mcl1 hepatocyte knockout mice	X			54
	Bcl_{x1} hepatocyte knockout develops fibrosis	X			55
	Necrotic injury models (CCl_4 , APAP) result in fibrosis			X	Common models in the literature
	Tak1- and Nemo-hepatocyte-specific knockout mice develop spontaneous liver fibrosis	X			90,152,167
	Caspase inhibitor IDN-6556 inhibits fibrosis after bile duct ligation	X			144
NASH	Decreased inflammation and fibrosis in mice with ablation of RIP3 after MCD diet		X		146
	Caspase inhibitor VX-166 inhibits inflammation and fibrosis in the MCD model	X			145,204
ALD	Reduced steatosis, injury, and inflammation in Rip3-deficient mice				41
HCC	Spontaneous HCC in Mcl1 hepatocyte knockout mice	X			56
	Spontaneous HCC in mice with Mcl1 or Bcl_{x1} hepatocyte knockout, and inhibition of hepatocarcinogenesis by additional Bak knockout	X			150
	Spontaneous HCC development in mice with hepatocyte-specific Nemo or Tak1 knockout	X			90,152,167
	Reduced HCC development by caspase-8 ablation in Tak1 hepatocyte-specific knockout mice, increase HCC development by Rip3 knockout in Tak1 hepatocyte-specific knockout mice	X			105

I/R, ischemia reperfusion.

epithelial cells contributes to the malignant transformation and constitutes a hallmark of cancer.[20] Likewise, whereas increased cell death in hepatocytes contributes to fibrogenesis, cell death in fibrogenic cells is an important mechanism for resolution of liver fibrosis.[21] Our review focuses on cell death, but it is also likely that cellular injury (not full-blown cell death) triggers stress responses that contribute to disease development. However, these aspects will not be covered in this review.

In view of the fundamental role of cell death in virtually all hepatic diseases, precise knowledge of mechanisms regulating cell death and cell death responses is essential to understand the pathophysiology of liver disease and develop new therapeutic approaches.

Regulation of Cell Death in the Liver

Cell death occurs not only as a passive response to physicochemical stress or noxious insults but may also be actively induced by the host via PCD. PCD plays an active role in development and organismal homeostasis.[22] Accordingly, inhibition of PCD by genetic ablation of key cell death regulators leads to hepatic hyperplasia.[23] Moreover, PCD is directly involved in the defense against pathogens, including hepatotropic viruses,[24] and represents a key mechanism preventing malignant transformation.[20] Traditionally, 2 distinct forms of cell death have been recognized: apoptosis as the mediator of PCD, actively induced by specific signaling cascades and occurring in a