Review Article

Crosstalk of liver immune cells and cell death mechanisms in different murine models of liver injury and its clinical relevance

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BACKGROUND: Liver inflammation or hepatitis is a result of pluripotent interactions of cell death molecules, cytokines, chemokines and the resident immune cells collectively called as microenvironment. The interplay of these inflammatory mediators and switching of immune responses during hepatotoxic, viral, drug-induced and immune cell-mediated hepatitis decide the fate of liver pathology. The present review aimed to describe the mechanisms of liver injury, its relevance to human liver pathology and insights for the future therapeutic interventions.

DATA SOURCES: The data of mouse hepatic models and relevant human liver diseases presented in this review are systematically collected from PubMed, ScienceDirect and the Web of Science databases published in English.

RESULTS: The hepatotoxic liver injury in mice induced by the metabolites of CCl_4, acetaminophen or alcohol represent necrotic cell death with activation of cytochrome pathway, formation of reactive oxygen species (ROS) and mitochondrial damage. The Fas or TNF-α induced apoptotic liver injury was dependent on activation of caspases, release of cytochrome c and apoptosome formation. The ConA-hepatitis demonstrated the involvement of TRAIL-dependent necrotic/necroptotic cell death with activation of RIPK1/3. The α-GalCer-induced liver injury was mediated by TNF-α. The LPS-induced hepatitis involved TNF-α, Fas/FasL, and perforin/granzyme cell death pathways. The MHV3 or Poly(I:C) induced liver injury was mediated by natural killer cells and TNF-α signaling. The necrotic ischemia-reperfusion liver injury was mediated by hypoxia, ROS, and pro-inflammatory cytokines; however, necroptotic cell death was found in partial hepatectomy. The crucial role of immune cells and cell death mediators in viral hepatitis (HBV, HCV), drug-induced liver injury, non-alcoholic fatty liver disease and alcoholic liver disease in human were discussed.

CONCLUSIONS: The mouse animal models of hepatitis provide a parallel approach for the study of human liver pathology. Blocking or stimulating the pathways associated with liver cell death could unveil the novel therapeutic strategies in the management of liver diseases.

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KEY WORDS: liver immunobiology; hepatitis; therapy; mode of cell death

Introduction

The liver is a pivotal organ of the body and plays a crucial role in taking up of nutrients from the gastrointestinal tract, storage of nutrients, metabolism, homeostasis, detoxification, immune regulation and tolerance, synthesis of bile, serum proteins, coagulating factors and complement proteins of the immune system. The liver is regarded as special immunological organ due to its enriched resident immune cell population like natural killer (NK) cells, NKT cells (formally called pit cells), Kupffer cells (KCs, resident macrophages of liver), dendritic cells (DCs), hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSEC), innate lymphoid cells (ILCs), B cells, T cells and cells of myeloid lineage.[1] The ILCs are distinctly classified as ILC1s, ILC2s and ILC3s depending upon cytokine production and transcription factors involved in their development and function. ILC1s produce interferon-γ (IFN-γ) and they are dependent of transcription factor T-bet, ILC2s secrete Th2 cytokines such as IL-4, IL-5, IL-9, IL-13 and

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amphiregulin and require GATA3, and ILC3s produce IL-17 and/or IL-22 dependent on RORγt regulation.[2] The liver encounters many circulating antigens and toxins of gut origin. In such a precarious milieu, the liver must have a robust immunologic mechanism to deal with constant exposure to potential insult.

The liver is an organ with dual face immunological functions. On one hand, immune reactions against harmless antigens have to be avoided (immune tolerance), but on the other hand, to combat against the hepato-tropic infectious agents (viruses, bacteria, parasites), effective immune responses have to be induced.[3, 4] The "dual edge" functions are regulated and controlled by the resident immune cells of the liver by secreting chemical mediators such as chemokines (for chemotaxis, recruitment of immune cells) and cytokines (pro-inflammatory and anti-inflammatory functions) collectively called as "microenvironment". The pathophysiology of acute liver injury is orchestrated by the interplay of immune cells, cytokines, and parenchymal liver cells. The exacerbated immune responses following entry of antigens result in liver inflammation. Acute hepatitis is defined by liver cell death, cellular disarray and immune cells infiltration in the liver. The type of antigen, immunological reaction, cell death pathways or mode of liver cell death determines the fate of liver or immuno-pathogenesis of liver diseases (acute vs chronic) with distinct mechanisms of disease.

Animal models of hepatitis provide an excellent tool to understand the pathophysiological mechanisms and to correlate the data with clinical findings. The use of animal models in scientific research is appreciable due to mimicry with many human pathologies, easy availability of technical tools for analysis, reproducibility of data, close relevance to human parameters (physiology/metabolism), a minimal hazard to personnel and genetic deletion or insertion to study the effect of a specific gene. The animal models serve as an alternative approach for certain infectious diseases in human caused by HBV, HCV, influenza virus and HIV. Among various existent animal models of acute hepatitis, the present review summarized the mouse models of acute hepatitis with principal cellular and effective molecular players involved in liver cell death. The murine models of acute hepatitis have been categorized depending upon the nature of hepatitis inducing agent, i.e. hepatotoxin, autoimmune, immune cell dependent, Toll-like receptor (TLR) agonists, viral and fulminant hepatic models.

The hepatocytes express death receptors like Fas (CD95), TRAIL-R1 (DR4), TRAIL-R2 (DR5), TNFR1 and TNFR2 on their surface and the immune cells express death ligands like FasL, TRAIL, and TNF-α.[5] The interaction of these death ligands and receptors in different liver diseases lead to liver cell death (apoptosis, necrosis or necroptosis) and it determines the outcome of a disease. Briefly, the apoptosis is a highly organized and genetically controlled type of cell death mediated by distinct extrinsic (death receptor dependent) and intrinsic (mitochondrial/caspase dependent) pathways. The key features of the apoptotic mode of cell death are membrane blebbing, shrinkage of the cell, chromatin condensation, nuclear fragmentation and formation of apoptotic bodies.[6] Necrosis is characterized by oncosis (swelling) and the formation of plasma membrane blebs (devoid of organelles) and rupture of the plasma membrane[6] accompanied by a complete release of cellular constituents into the extracellular environment.

Evolving data[5-7] have evidenced involvement of a novel cell death pathway in liver pathology termed as necroptosis. The term "programmed necrosis" or "necroptosis" was described as an alternative receptor interacting protein kinase (RIPK) mediated form of cell death initiated by necrosis factor receptors, Fas and TNF-related apoptosis inducing ligand (TRAIL).[7] The necroptosis pathway is initiated by TNF receptors mainly dependent on RIPK1/RIPK3 activation and it is identified as "back up" cell death mechanism of apoptosis. Necroptosis is marked by cell and organelle swelling, extensive formation of intracellular vacuoles and rapid rupture of the plasma membrane.[6, 8] The execution of necroptosis starts from binding and trimerization of death ligands (TNF-α, FasL, and TRAIL) to their cognate receptors. Briefly, the downstream events of TNF-induced necroptosis are initiated by the activation/trimerization of TNF and its receptor (TNFR1) that promotes the formation of complex I (containing signaling molecules TRADD, TRAF2, TRAF5, cIAP1, cIAP2 and RIP1) and complex II (caspase-8-dependent cleavage of RIPK1 and RIPK3). Moreover, the interplay of RIPK1, capase-8 and substrate of RIPK3 called as phosphorylated mixed lineage kinase domain-like (MLKL) defines the mode of cell death. The RIPK3-MLKL pathway (ubiquitylation) is essential to drive the necroptotic cell death while RIPK1-caspase-8 activation is required for the apoptotic cell death.[9] However, in the absence of caspase-8, RIPK1 stimulates necroptotic cell death.[9] It has been shown that necroptosis plays a crucial role in immune cell mediated hepatitis in mice because the inhibitors of necroptosis (i.e., necrostatin-1 and PJ34) protected liver injury in mice.[10, 11] Necrostatin-1 (Nec-1), a small tryptophan-based compound, an inhibitor of RIPK1 activity (phosphorylation), blocks the interaction between RIPK1 and RIPK3 and inhibits necroptosis. Nec-1 is widely used in cellular and animal disease models to prevent the necroptotic cell death.[12] The present review comprehen-