Best Practice & Research Clinical Gastroenterology 27 (2013) 471–483

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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Mechanisms of liver involvement in systemic disease

Lori Edwards, MD, Ph.D, FRCPC, Assistant Professor of Pathology, Staff Pathologist [a,1],
Ian R. Wanless, MD, FRCPC, Professor of Pathology, Staff Pathologist [b,*]

[a] Department of Laboratory Medicine and Pathobiology, University of Toronto, Canada
[b] Department of Pathology, Dalhousie University, Canada

Keywords:
Immunity, innate
Immunity, adaptive
Liver cirrhosis
Hypertension, portal
Cytokines
Reactive oxygen species
Hyperinsulinism
Obesity
Liver ischaemia
Apoptosis

A B S T R A C T

The liver may be injured during the course of many systemic diseases. The mechanisms of injury can be broadly divided into four pathways: vascular, toxic, immune, and hormonal. Vascular obstruction may be an early event but is also the late common pathway from all mechanisms. Despite the large number of possible initiating factors, the end results are few, including death of hepatocytes or cholangiocytes, leading to the stereotyped syndromes of acute liver failure, non-cirrhotic portal hypertension, or cirrhosis. This small number of outcomes is a reflection of the few anatomic patterns that can be generated by microvascular obstruction. Vascular obstruction may occur by thrombosis, inflammation, or congestive injury. The innate immunity pathway is activated by endotoxin and other agents, leading to inflammatory infiltration, release of cytokines and reactive oxygen species, and necrosis. The adaptive immune pathway involves the generation of antibodies and antigen-specific cell-mediated attack on hepatic cells. Hormonal effects are principally involved when overnutrition leads to hyperinsulinemia followed by hepatocellular necrosis.

* Corresponding author. Present address: Queen Elizabeth II Health Sciences Centre, Division of Anatomic Pathology, MacKenzie Building, 7th Floor, 5788 University Ave, Halifax, NS B3H 1V8, Canada.
E-mail addresses: lori.edwards@medportal.ca (L. Edwards), iwanless@eastlink.ca (I.R. Wanless).
[1] Present address: Trillium Health Partners, 100 Queensway West, Mississauga, ON L5B 1B8, Canada.

1521-6918
http://dx.doi.org/10.1016/j.bpg.2013.08.002

The liver may be injured during the course of many diseases that are systemic or predominantly involve other organs. In this setting, the mechanisms of liver injury can be broadly classified as vascular, toxic, immune, and hormonal, as summarized in Fig. 1. Despite the large number and variety of initiating factors, the end results are few, including death of hepatocytes or cholangiocytes leading, in severe cases, to the stereotyped anatomical and clinical patterns of portal hypertension, with or without cirrhosis.

The vascular pathway usually culminates in obstruction to blood flow with secondary portal hypertension or parenchymal extinction. The innate immunity pathway may involve diverse agents, especially derived from gut flora or medications, leading to activation of the innate immune system. The adaptive immune pathway may involve antibody or cell-mediated mechanisms directed against hepatic cells. The hormonal pathway is principally involved when overnutrition leads to hyperinsulinemia.

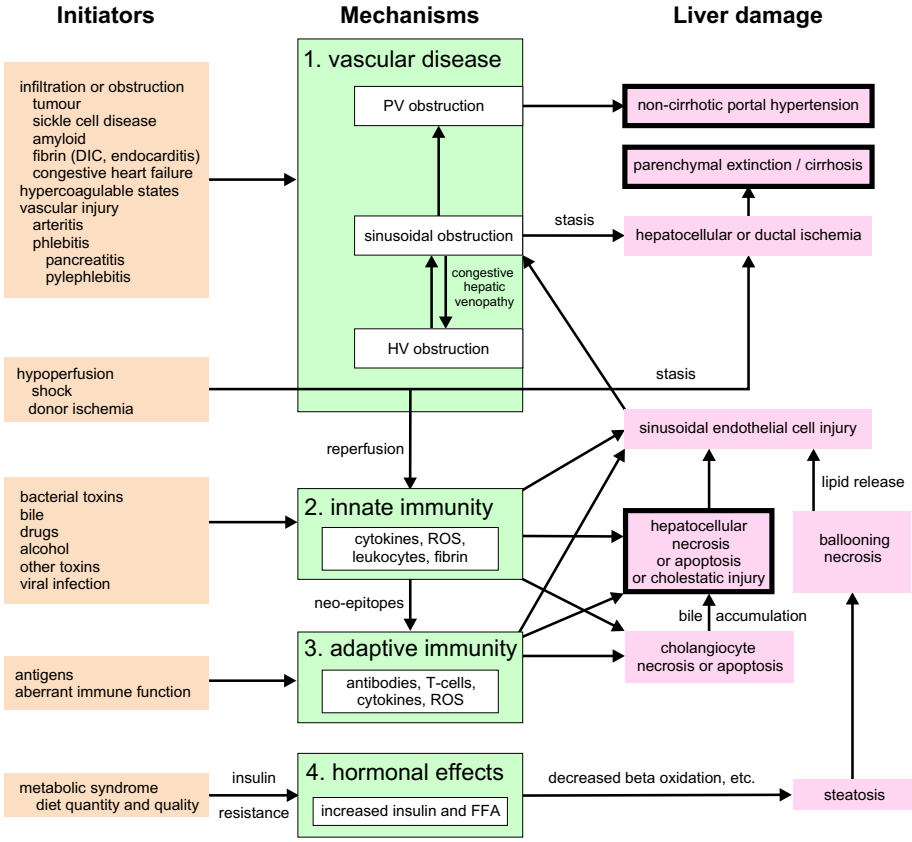

Fig. 1. Diagram showing the four main mechanisms of liver injury. These mechanisms can be initiated by many different factors but the resulting patterns of liver injury are really only three (heavy boxes). These three patterns are governed by the severity and distribution of vascular obstruction (Mechanism 1). All four mechanisms may lead to death of hepatocytes, cholangiocytes, or sinusoidal endothelial cells. With acute injury from mechanisms 2, 3, or 4 there is minimal vascular obstruction and the clinical effects are related to the loss of function of hepatic cells. If loss of function is not lethal, the effects of secondary vascular obstruction become clinically dominant. Chronic portal vein obstruction leads to non-cirrhotic portal hypertension. Chronic vascular outflow obstruction leads to cirrhosis. Vascular disease (Mechanism 1) is usually followed by obstruction, either by thrombosis or inflammatory injury. In shock or in the donor liver, ischaemia often occurs without vascular obstruction. The innate and adaptive immune systems (Mechanisms 2 and 3) cause a variety of insults leading to death of any type of liver cell. When these injuries cause sinusoidal obstruction, secondary ischaemia causes chronic liver disease. The most important hormonal effect (Mechanism 4) is hyperinsulinemia. In concert with elevated free fatty acids (FFA), steatosis and ballooning necrosis occur. Release of toxic lipids from dying hepatocytes leads to secondary inflammation and exacerbation of vascular obstruction.