Pathways of Hepatic Regeneration and Pharmacological Approaches for Hepatoprotection: A Brief Approach

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ABSTRACT
Liver is one of the most important organs in the metabolism of food, drugs, endogenous and exogenous substances. Problems related to liver such as acute or chronic inflammation, toxin/drug-induced hepatitis, cirrhosis and hepatitis are well-known nowadays due to our exposure to different environmental pollutants like chemicals, toxins, viruses etc. Liver disease can result from dosage-dependent hepatotoxicity or from adverse reactions to drugs used in therapeutic dosage. The anatomical structures of a liver that has undergone partial hepatectomy are therefore distinctly different from those of the original liver. The restoration process of liver volume in humans is initiated by the replication of various types of intra hepatic cells, followed by an increase in cell size. Efforts to develop pharmacologic means for liver protection from damage during regeneration have identified a few molecular targets.

Key words: Microanatomy, regeneration pathway, hepatic dysfunctions, pharmacological hepatoprotection

INTRODUCTION
It is well recognized that liver is one of the most important organs in the metabolism of food, drugs, endogenous and exogenous substances. Profuse supply of blood and the presence of many redox systems (e.g., cytochromes and various enzymes) causes liver to convert these substances into different kinds of inactive, active or even toxic metabolites. Problems related to liver such as acute or chronic inflammation, toxin/drug-induced hepatitis, cirrhosis and hepatitis are well-known nowadays due to our exposure to different environmental pollutants like chemicals, toxins, viruses etc. (Dhiman and Chowla, 2005).

Liver: Liver is the largest organ in the body weighing 1200-1500 g. It is a key organ in regulating homeostasis within the body. The liver is one of the few organs which can regenerate after injury or disease. Total liver blood flow is about 1300 mL min⁻¹ (Roger and Edwards, 2003).

Structure of liver: The liver consists of four sections, or lobes. There are two main lobes-the right lobe, which is by far the larger and the left lobe. Two small lobes lie behind the right lobe (Fig. 1).

Microanatomy of liver: Liver essentially made up of a series of channels or sinusoids, running between plates of hepatocytes. These are lined by endothelial cells. Specialised phagocytic (reticulo
endothelial) cells (Kupffer cells) are also present in sinusoids. Each lobe is consisting of multisided units called lobules. Most livers have between 50,000 and 100,000 lobules. Each lobule consists of a central vein surrounded by tiny liver cells grouped in sheets or bundles. These cells perform the work of the liver. Cavities known as sinusoids separate the groups of cells within a lobule. The sinusoids give the liver a spongy texture and enable it to hold large amounts of blood (Fig. 2) (Cunningham and Van Horn, 2003). The liver consists of four systems:
Hepatocyte (liver cell) system
- Biliary tract system
- Blood circulatory system
  - Dual blood circulatory system:

The blood in the liver is supplied by two sets of blood circulatory systems:

- Systemic circulation
- Portal circulation
- Blood flow of the liver: 1,300 cc of blood flow into the liver every minute, it is about 1/4 of the cardiac output
- 3/4 of the blood in the liver is supplied by the portal system and the remaining 1/4 is supplied by hepatic artery from systemic circulation
- The liver receives blood from both the intestine and the heart. The blood then flows through a latticework of tiny channels inside the liver. Blood from the intestine and heart then mix together and flow back to the heart through the hepatic vein
- Reticulo-endothelial system
  - Kupffer cells: highly mobile macrophages, attached to the endothelium, phagocytic
  - Lipocytes (Ito cells): fat-storing cells in the sinusoids
  - Pit cells: highly mobile, natural killer lymphocytes attached to the endothelium
  - Endothelial cells (Cunningham and Van Horn, 2003)

Hepatic dysfunctions: Liver disease can result from dosage-dependent hepatotoxicity or from adverse reactions to drugs used in therapeutic dosage. The idiosyncratic hepatotoxins can cause clinical syndromes that mimic all known liver diseases, so that drugs must be considered as the possible causal agent for all unexplained cases of liver disease (Javed et al., 2009).

Many hepatic dysfunctions are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.

- Hepatitis, inflammation of the liver, caused mainly by various viruses but also by some poisons, autoimmunity or hereditary conditions
- Cirrhosis is the formation of fibrous tissue in the liver, replacing dead liver cells. The death of the hepatic cells can for example be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals
- Hemochromatosis, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage
- Cancer of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract)
- Wilson’s disease, a hereditary disease which causes the body to retain copper
- Primary sclerosing cholangitis, an inflammatory disease of the bile duct, autoimmune in nature.
- Primary biliary cirrhosis, autoimmune disease of small bile ducts
- Budd-Chiari syndrome, obstruction of the hepatic vein
- Gilbert’s syndrome, a genetic disorder of bilirubin metabolism, found in about 5% of the population (David and Thomas, 2003)
Liver regeneration: The human body acts to partial hepatectomy not by regenerating lost segments but by inducing hyperplasia in the liver remnant. The anatomical structures of a liver that has undergone partial hepatectomy are therefore distinctly different from those of the original liver. The restoration process of liver volume in humans is initiated by the replication of various types of intra hepatic cells, followed by an increase in cell size. The onset and peak of hepatocyte replication vary among species. In humans, replication of hepatocytes generally starts within 1 day after a major resection. Non parenchymal cells, such as endothelial cells, Kupffer cells (macrophages resident in the liver) and biliary-duct cells, replicate in a delayed fashion. After completion of replication, growth consisting of an increase in cell size occurs over several additional days (Taub, 2004; Michalopoulos and DeFrances, 2005; Fausto et al., 2006). The initiation and synchronization of replication in different types of hepatic cells depend on the degree of the resection, tissue damage, or both. Low-grade tissue damage (e.g., toxic or ischemic injury) or a comparatively small resection (removal of less than 30% of the liver) substantially reduces the replication rate, which also appears to be less synchronized than after a large resection (removal of 70% of the liver) (Taub, 2004; Fausto et al., 2006; Nocito et al., 2007). After a massive resection, up to 90% of the hepatocytes appear to replicate (Taub, 2004).

Molecular basis of liver regeneration: Liver regeneration has been studied in murine models, an approach that permits the determination of cellular events and the analysis of the molecular triggers governing regeneration (Taub, 2004; Michalopoulos and DeFrances, 2005; Fausto et al., 2006). In short, the process of liver regeneration involves mediators similar to those found in acute inflammation. Usually, hepatocytes are in the quiescent G0 phase. After resection, the remaining hepatocytes enter the G1 phase. Cytokines derived predominantly from Kupffer cells prime hepatocytes; tumor necrosis factor α (TNF-α) and, then, interleukin-8 are released, contributing to the initiation of the cell cycle (Cressman et al., 1996; Yamada et al., 1997). Mitogenic factors are needed for the regenerative process to enter the S phase, primarily growth factors such as epidermal growth factor, hepatocyte growth factor and transforming growth factor α (TGF-α) (Mead and Fausto, 1989; Pediaditakis et al., 2001). Integration of these signals induces full and synchronized regeneration. Failure to activate this signal cascade can result in a delay in the onset of regeneration, inadequate recovery of liver volume and finally clinical signs of liver failure (Tian et al., 2006).

Termination of the regenerative steps appears to be controlled by the action of transforming growth factor β (TGF-β) and other members of the activin family (Strain et al., 1987). Two newer reports shed further light on the mechanisms of regeneration. In one report from our group, platelets (thrombocytes) were shown to be critically involved in regeneration (Lesurtel et al., 2006). Serotonin, a neurotransmitter transported within the peripheral circulation by platelets, appears to be a co-mitogen that is essential for liver regeneration. Mice deficient in tryptophan hydroxylase (Taub, 2004), which lack peripheral serotonin, have diminished hepatocyte proliferation after partial hepatectomy (Lesurtel et al., 2006).

According to another recent report, bile acids also seem to influence regeneration. In experiments in animal models in which bile-acid pools were high, regeneration was complete, whereas low bile flow was associated with reduced hepatocyte replication. The signal responsible for this feedback mechanism of regeneration is a nuclear bile receptor, the farnesoid X receptor. This mechanism may be important in integrating the metabolic load of the liver and may have a direct action on regeneration (Huang et al., 2006). The integration of all these signals is important for full and synchronized regeneration.
Pharmacological approaches for hepatoprotection: Efforts to develop pharmacologic means for liver protection from damage during regeneration have identified a few molecular targets. It has recently been shown that pentoxifylline (Trental, Hoechst-Roussel), an inhibitor of TNF-α synthesis in Kupffer cells that has other properties such as vasodilatation and induction of the interleukin-6 pathway, decreases the likelihood of inadequate liver function in the liver remnant in a murine model of partial liver transplantation (Tian et al., 2005). Pretreatment of a small graft (30% of the total liver volume) and of the recipient with pentoxifylline prevents lethal outcomes and fully restores regeneration (Cressman et al., 1996). Acetylcysteine, a precursor of glutathione, has been widely explored as a protective molecule. Clinical trials of its use in the perioperative treatment of patients undergoing liver transplantation showed reduced levels of circulating selectins (Weigand et al., 2001) and a reduction in the severity of rejection in pediatric patients undergoing hepatic transplantation (Bucuvalas et al., 2001), but neither study showed an overt benefit for the patient.

Other molecules, such as cardiotrophin-1, a member of the interleukin-6 cytokine family, have shown a hepatoprotective potential in preventing regeneration and in animal survival after 90% hepatectomy in rats (Bustos et al., 2003). Drugs with a reduction in portal pressure, such as somatostatin (Xu et al., 2006), fingolimod (FTY720, Novartis Pharma) (Zhao et al., 2004), or the low-dose nitric oxide donor PK 409 provided significant protection in animal models of small graft transplantation. These drugs have additional activities that might contribute to protection, such as down-regulation of endothelin-1, up-regulation of heme oxygenase-195 or interleukin-10, (Man et al., 2004) and activation of Akt signaling, which has been shown to be related to cell survival (Zhao et al., 2004). An immunosuppressive agent, sirolimus (Rapamune, Wyeth-Ayerst), has also been shown to reduce injury and improve survival-effects that may be related to suppression of the activation of hepatic stellate cells in a model of partial graft transplantation in cirrhotic rats (Man et al., 2006). Although, these strategies have been successful in animal models, their usefulness in humans remains to be demonstrated in clinical trials.

REFERENCES