Overview

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Anatomy and Physiology of the Liver

The liver is one of the metabolically most active and versatile organs. It has a dual blood supply: about 25 % comes via the hepatic artery and about 75 % is delivered via the portal vein, which drains blood coming from the intestine. Accordingly, it is the first organ to get in contact with intestinally absorbed nutrients, ingested toxins, and products from intestinal microorganisms. Thus, major tasks of the liver are (1) to process and store nutrients contained in the intestinal or splanchnic blood and to guarantee an adequate nutrient supply for other organs during both the absorptive and postabsorptive state; (2) to detoxify and excrete xeno- and endobiotics into the bile; (3) to participate in pathogen defense and immune functions and to trigger acute phase responses in inflammation; and (4) to fulfill other homeostatic functions such as maintenance of acid-base and glucose homeostasis (see chapter "Diabetes mellitus"), synthesis of most plasma proteins (see chapter "Overview" under the part "Blood"), triglyceride and cholesterol metabolism and transport (see chapter "Hyperlipidemia"), and hormone processing and secretion. Furthermore, bile acids (BAs) are synthesized in the liver, which aid in triglyceride digestion in the intestine (see chapter "Overview" under the part "Gastrointestinal tract") and are increasingly recognized as important signaling molecules and coordinators of interorgan metabolism.

Seventy percent of the hepatic cell mass are made up by liver parenchymal cells (PCs, also called hepatocytes), whereas the remainder comprises different non-parenchymal cell types. These include the fenestrated sinusoidal endothelial cells, Kupffer cells as liver-resident macrophages, vitamin A storing hepatic stellate cells, large granular lymphocytes called pit cells, cholangiocytes, and progenitor cells (called "oval cells" in rodents). The latter are located at the canals of Hering (intrahepatic bile ductules) and can differentiate into PCs or cholangiocytes. Hepatic stellate cells are mesenchymal stem cells and are located in the space of Disse (Fig. 1), which has characteristics of a stem cell niche [1]. Following liver injury, liver regeneration is primarily achieved by division of preexisting PCs, but under conditions of impaired replication ability of PCs, stem cell-based liver regeneration comes into play, which involves oval cells and hepatic stellate cells [2].

The various cell types in the liver are embedded in the liver acinus into a structural-functional organization with complex intra- and intercellular communication. The acinus represents the functional unit of the liver and extends from the terminal portal venule along the sinusoid to the terminal hepatic venule (Fig. 1). Along the acinus,

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E. Lammert, M. Zeeb (eds.), *Metabolism of Human Diseases*,
DOI 10.1007/978-3-7091-0715-7_27,

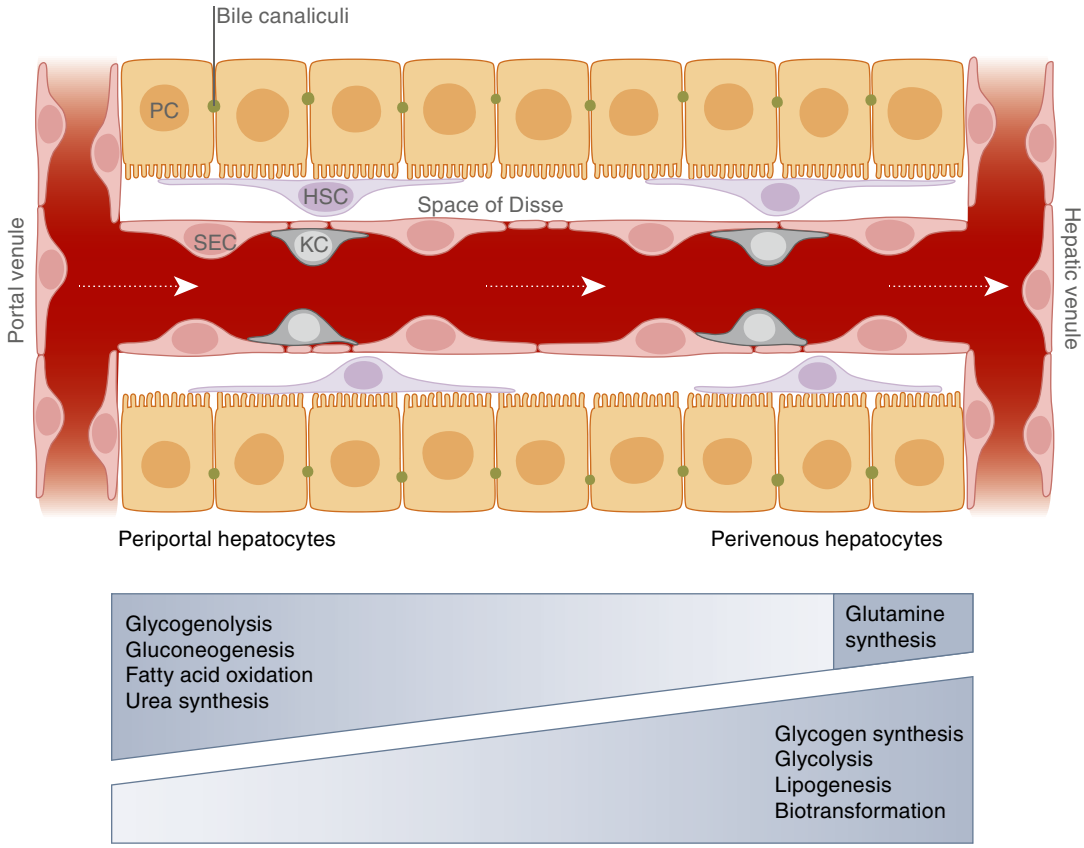

Fig. 1 Acinar organization and metabolic zonation. The liver acinus is the functional unit of the liver and extends from the terminal portal venule to terminal hepatic venule. Schematic presentation of the cells constituting the acinus, i.e., parenchymal cells (*PCs*, also called hepatocytes), liver macrophages (Kupffer cells, *KCs*), sinusoidal endothelial cells (*SECs*), and hepatic stellate cells (*HSCs*) located in the space of Disse. PCs are polar cells and adjacent PCs form the bile canaliculus with their apical membrane. Along the acinus, metabolic pathways show gradients or are heterogeneously distributed ("metabolic zonation")

the portal-venous blood, which mixes with blood from the hepatic artery in the inflow segment of the acinus, passes 20–30 PCs. These are morphologically very similar but differ in their enzyme and transporter equipment (the so-called PC heterogeneity or metabolic zonation) [3]. Metabolite, hormone, and oxygen gradients but also signals from neighboring cells are thought to be responsible for this metabolic zonation. Periportal PCs, i.e., those located at the sinusoidal inflow, are primarily engaged in gluconeogenesis, fatty acid oxidation, and urea synthesis, whereas glycolysis, lipogenesis, and biotransformation predominate in perivenous PCs (located at the sinusoidal outflow). Glutamine synthetase is exclusively localized in a small perivenous PC subpopulation, the so-called perivenous scavenger cells, which eliminate ammonia, eicosanoids, and other signaling molecules with high affinity before the sinusoidal blood enters the systemic circulation.

Liver-Specific Metabolic Pathways and Processes

Plasma Protein Synthesis

Except for immunoglobulins, most circulating plasma proteins are synthesized in the liver. These include albumin, which is responsible for transport

of some lipophilic substances (in the bloodstream) and regulation of oncotic pressure, and acute phase proteins, which are synthesized and secreted by PCs in response to cytokines such as tumor necrosis factor α (TNFα), interleukin-1, and interleukin-6, which are produced by macrophages including Kupffer cells, endothelial cells, and fibroblasts at sites of injury. The plasma concentrations of acute phase proteins (such as C-reactive protein) can increase within hours after a local inflammatory reaction up to several hundredfold and apart from opsonization (see chapter " Overview" under the part "Immune system"); their role mainly resides in a local restriction of inflammatory processes.

Nutrient Metabolism

The liver is the central organ of glucose homeostasis and acts as a "glucostat." In the absorptive phase, when plasma insulin levels increase, the liver synthesizes and stores glycogen from gluconeogenic precursors in periportal PCs and from absorbed glucose in perivenous PCs, whereas glucose becomes mobilized from glycogen in the postabsorptive state, when insulin levels are low and glucagon levels are high (see chapters "Overview" under the part "Pancreas" and "Diabetes mellitus"). After exhaustion of glycogen stores, gluconeogenesis mainly from glucogenic amino acids, glycerol, and lactate is stimulated through induction of enzymes of amino acid metabolism, gluconeogenesis, and the urea cycle, whereas glycolytic enzymes become repressed in perivenous PCs. The shift from net glucose consumption to net glucose output in the postabsorptive state is therefore accomplished by increasing the flux through the periportal gluconeogenic pathway and a simultaneous decrease of glycolytic flux in perivenous PCs [3]. The liver is also a major organ for synthesis of triglycerides, cholesterol, and sphingolipids and secretes very low-density lipoproteins (see chapter "Hyperlipidemia"). In the postabsorptive state, fatty acid oxidation provides energy for the liver; ketogenesis and ketone body release from the liver can provide energy for other organs, such as the brain (see chapter "Overview" under the part "Brain").

Urea Synthesis and Acid-base Homeostasis

One liver-specific pathway is urea synthesis [4] from bicarbonate (HCO_3^-) and ammonium (NH_4^+), which are generated in almost stoichiometric amounts during complete amino acid oxidation. Urea synthesis can be viewed as an energy-driven neutralization of the strong base HCO_3^- by the weak acid NH_4^+:

$$2NH_4^+ + 2HCO_3^- \rightarrow \text{urea} + CO_2 + 3H_2O$$

Thus, the role of urea synthesis resides not only in the removal of potentially toxic ammonium ions but also in the removal of bicarbonate. Through a pH-regulated partitioning of hepatic ammonium disposal via either bicarbonate-consuming urea synthesis or via glutamine synthesis (from glutamate and ammonium), the liver can adjust the rate of bicarbonate disposal to the needs of systemic acid-base homeostasis. The structural-functional organization of urea and glutamine synthesis in the liver acinus allows for this role: in periportal PCs, ammonium is disposed of via urea synthesis, whereas downstream perivenous scavenger cells maintain ammonia homeostasis by high-affinity disposal via glutamine synthesis. In the kidney, ammonia is then liberated from glutamine by renal glutaminase and excreted into the urine. Glutamine uptake, glutaminase, and carbonic anhydrase V in periportal PCs are major sensitively acid-base regulated steps, which adjust flux through the HCO_3^--disposing urea cycle. Selective destruction of perivenous scavenger cells or specific knockdown of glutamine synthetase in these cells triggers hyperammonemia.

Bile Formation and Bile Acid Secretion

Another liver-specific pathway is biliary excretion of endo- and xenobiotics and bile formation [5]. PCs are polar cells, in which the basolateral (sinusoidal) membrane faces the bloodstream, whereas the apical (canalicular) membrane of

two adjacent PCs forms the bile canaliculus, which is sealed by tight junctions. Bile formation is an osmotic process, which is driven by the coordinated action of transport systems in the sinusoidal and canalicular membranes of the PC and subsequent water flow. PCs metabolize cholesterol to lipid-soluble, unconjugated BAs, which are later conjugated to become water-soluble. At the sinusoidal membrane, conjugated BAs are taken up by the Na^+-taurocholate cotransporting protein (NTCP), whereas sinusoidal uptake of unconjugated BAs, bilirubin (a catabolite of heme), and other anions is accomplished by the organic anion transporting protein (OATP) family (Fig. 2). Canalicular secretion is achieved by transport ATPases, such as the bile salt export pump (BSEP), and the bilirubin-transporting multidrug resistance-related protein (MRP2, Fig. 2).

In addition to bilirubin and BAs, cholesterol, phospholipids, and other substances are also secreted into the canaliculi via specific transporters, such as the aminophospholipid transporter FIC1 (from familial intrahepatic cholestasis), the cholesterol transporter ABCG5/G8 (ATP-binding cassette G5/G8), and the multidrug resistance protein 1 and 3, the latter of which acts as a flippase and transports phospholipids from the inner to the outer leaflet of the canalicular membrane (Fig. 2).

The BSEP and MRP2 are regulated at the level of gene expression but also on short-term time scale by dynamic insertion/retrieval of the transporters into/from the canalicular membrane. High BA concentration (overload) in PCs activates the nuclear transcription factor farnesoid X receptor (FXR), which upregulates the BSEP and MRP2 expression and downregulates expression of NTCP and cholesterol-7α-hydroxylase, a rate-controlling step of BA synthesis. In cholestasis, a condition of impaired bile formation, compensatory BA efflux pathways via MRP3 and 4 located at the sinusoidal part of the PC membrane become activated (Fig. 2). These responses protect PCs against intracellular BA accumulation, which is toxic and can lead to PC apoptosis [5].

In addition to FXR, bile acids can activate TGR5, a G protein-coupled BA receptor in the plasma membrane of cholangiocytes, Kupffer cells, sinusoidal endothelial cells, and other cell types. This triggers cAMP formation, which protects sinusoidal endothelial cells and cholangiocytes against BA-induced apoptosis, increases bile flow through stimulation of Cl^- secretion by cholangiocytes, and ameliorates cytokine formation by Kupffer cells.

A small fraction of BAs is reabsorbed from the bile duct by the apical sodium-dependent bile salt transporter (ASBT), excreted into the blood via the organic solute and steroid transporter αβ (OSTαβ), and recirculated to the liver, a process called cholehepatic shunting (Fig. 2).

Detoxification

Detoxification of endo- and xenobiotics involves biotransformation of these compounds. Such reactions convert lipophilic compounds into polar, water-soluble metabolites. In a first step (biotransformation phase I), such compounds become hydroxylated or N- or O-dealkylated by cytochrome P450 enzymes and undergo oxidative deamination or hydrolysis. Such reactions introduce or expose reactive groups, which are used in phase II of biotransformation for conjugation reactions, leading to the formation of hydrophilic compounds, which can be excreted into the bile or urine. Such conjugation reactions include glucuronidation, sulfation, or coupling to glutathione or amino acids such as glycine, taurine, or glutamine. Phase III of biotransformation describes the excretion of such conjugates into bile or blood via canalicular transporters (e.g., MRP2) or sinusoidal OATPs, respectively.

Phase I–III enzyme activities can be induced by endo- and xenobiotics after their binding to nuclear receptors, such as constitutive androstane receptor or the pregnane X receptor (also called steroid and xenobiotic-sensing nuclear receptor). After heterodimerization with the retinoid X receptor, these act as transcription factors inducing a variety of genes involved in biotransformation, such as cytochrome P450 family 3A (CYP3A), glutathione-S-transferases, or OATP2. Aromatic hydrocarbons are sensed by the aryl hydrocarbon receptor (AHR), which together with the aryl hydrocarbon receptor nuclear translocator (ARNT) acts as a ligand-activated transcription factor, which regulates the expression of phase I and II enzyme activities. Biotransformation reactions can also give rise to toxic products. One

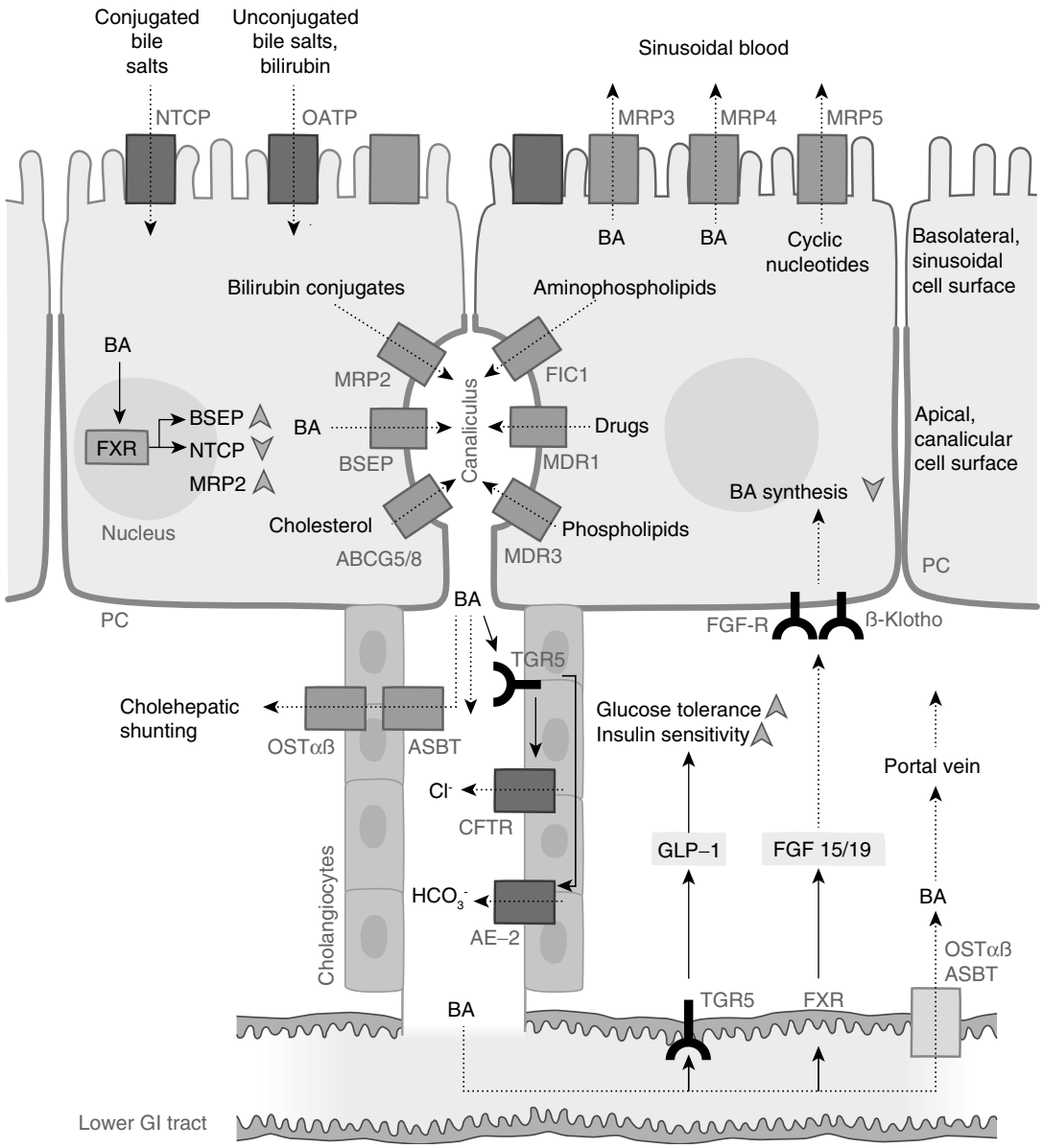

Fig. 2 Schematic representation of hepatobiliary transport systems, bile formation, and bile acid signaling. Conjugated and unconjugated bile acids (*BAs*) are taken up from the blood into the liver parenchymal cells (*PCs*) via Na^+-taurocholate cotransporting protein (*NTCP*) and organic anion transport protein (*OATP*), respectively. High levels of BAs in the PC can activate the farnesoid X receptor (*FXR*) to reduce the BA load (by reducing uptake and increasing excretion, left PC). Under conditions of cholestasis, BAs can be exported into the blood by means of multidrug resistance-associated proteins 3–5 (MRP3-5, right PC). Both mechanisms help to prevent BA-induced liver damage. Biliary excretion of various substances is accomplished by specific transport ATPases in the canalicular, apical membrane of the PC. In the bile duct, a small fraction of BAs is reabsorbed by the apical sodium-dependent bile salt transporter ASBT, excreted into the blood via the organic solute and steroid transporter (*OST*) αβ and recirculated to the liver ("cholehepatic shunting"). In the bile duct, cholangiocytes sense the bile acid concentration via the G protein-coupled bile acid receptor TGR5 causing an increase in chloride excretion into the lumen to increase bile flow. In the intestine, BAs can activate their receptors FXR and TGR5 in order to signal back to the liver and to secrete glucagon-like peptide-1 (*GLP-1*), respectively. GLP-1 increases glucose tolerance. The signal to the liver downstream of FXR is relayed via fibroblast growth factor (*FGF*) 15/19. This activates its receptor (*FGF-R/β-Klotho*) on PCs to repress further BA synthesis. Additionally, BAs are also reabsorbed in the terminal ileum and transported back to the liver ("enterohepatic circulation of BAs") *BSEP* bile salt export protein, *ABCG5/G8* ATP-binding cassette G5/G8 cholesterol transporter, *MDR* multidrug resistance protein, *FIC1* familial intrahepatic cholestasis aminophospholipid transporter, *CFTR* cystic fibrosis transmembrane conductance regulator, *AE-2* anion exchanger 2

example is the formation of genotoxic derivatives of benzopyrene. Another example is paracetamol (acetaminophen) toxicity. This drug is partly converted to a highly toxic quinone derivative, which is immediately detoxified by S-conjugation with glutathione. However, after depletion of glutathione stores, this highly reactive intermediate forms protein adducts, which can produce acute liver necrosis.

Inside-Out: Metabolites of the Liver Affecting Other Tissues

BAs also serve as signaling molecules in other tissues because the bile acid receptors FXR and TGR5 are also found in extrahepatic tissues (Fig. 2). TGR5 activation in enteroendocrine intestinal cells triggers release of glucagon-like peptide-1 (GLP-1) from the ileal L cells, thereby stimulating insulin secretion from β cells (see chapter "Overview" under the part "Pancreas") delaying gastric emptying and improving insulin sensitivity, thus increasing glucose tolerance (see chapter" Diabetes mellitus") [6]. Activation of FXR in the ileum by BAs triggers formation and release of fibroblast growth factor 15/19, which returns to the liver and activates the fibroblast growth factor receptor/ß-Klotho complex to downregulate hepatic de novo bile acid synthesis [7] and to protect the liver during cholestasis [8] (Fig. 2).

Another example for inside-out signaling is the hepatorenal reflex, which is activated by amino acids most likely through induction of PC swelling and an increase of the sinusoidal blood pressure and which triggers a decrease of glomerular filtration rate (GFR) in the kidney (see chapter "Overview" under the part "Kidney") via the afferent vagal nerves and sympathetic efferent nerves [9]. Renal water retention triggered by this reflex may counteract splanchnic blood pooling in the absorptive state. The latter describes the circumstance that after a rich meal, a large volume of blood is diverted to the intestine to facilitate digestion and absorption, resulting in postprandial hypotension. Thus, the hepatorenal reflex contributes to maintain sufficient blood pressure to perfuse vital organs, such as the brain.

Failure of the liver to eliminate NH_4^+, which arises during intestinal and hepatic metabolism, can lead to hyperammonemia and ammonia toxicity in the brain (hepatic encephalopathy; see chapter "Cirrhosis"), which is characterized by a low-grade cerebral edema and an oxidative/nitrosidative stress response [10].

Outside-In: Metabolites of Other Tissues Affecting the Liver

There are several ways how metabolites from other tissues can affect liver function. These include hormones and cytokines released from extrahepatic sites. For example, insulin from pancreatic β cells (see chapter "Overview" under the part "Pancreas") binds to insulin receptors on PCs in the postabsorptive state and increases nutrient anabolism, such as glycogen synthesis. In addition, nutrients and toxins directly affect liver function through alterations of PC hydration. PC hydration is dynamic and is controlled by a variety of transport systems in the plasma membrane of PCs, which can create or dissipate osmotic gradients. For example, an increased amino acid load to the liver leads to an osmotic water shift into the PC due to cumulative amino acid uptake driven by the transmembrane sodium gradient. This increase of PC volume represents an independent signal regulating liver function. PC swelling increases bile flow (choleresis), inhibits protein and glycogen breakdown, stimulates protein and glycogen synthesis, and acts as an antiapoptotic and proliferative signal. Opposite responses are triggered by PC shrinkage. Control of liver cell functions by fluctuations of PC hydration or PC volume is mediated by osmosensing and osmosignaling pathways [11]. Integrins were identified as important osmosensors in response to PC swelling, activating osmosignaling pathways [12]. Conversely, cell shrinkage is sensed by an increased concentration of intracellular chloride and involves endosomal acidification, ceramide formation, activation of protein kinase Cζ and NADPH oxidase with subsequent formation of reactive oxygen species and further signaling events.

Final Remarks

The liver plays a major role in intermediary metabolism, maintenance of homeostatic functions, immune responses, and endo- and xenobiotics excretion into bile. These functions are impaired in a variety of diseases, such as hepatitis or cirrhosis (see chapter "Cirrhosis").

For more in-depth surveys on liver function, the reader is referred to textbooks of hepatology [13, 14].

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