Liver Physiology

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1. BILE ACIDS AND BILE

In the terminal ileum, bile acids present in the lumen are recuperated and returned to the liver where they are taken up into hepatocytes and excreted into the bile again. This enterohepatic circulation retains over 95% of the bile acids. Each day, only 400–500 mg of bile acids are produced, balancing the small physiologic fecal loss (excretion into urine is normally negligible). In 24 h, approximately 12–25 g of bile acids are secreted into the intestine, turning the whole pool over up to 10 times a

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day. Cholesterol is the starting molecule in the synthesis of bile acids. Conversion of cholesterol into bile acids occurs via two pathways: the classical (or neutral) pathway and the alternative (or acidic) pathway. The classical pathway contributes 75% of the bile acid pool. Reactions leading to primary bile acids, cholic acid and chenodeoxycholic acid, include initiation (hydroxylation in position 7), modification of the sterol ring, oxidation, shortening of the side chain, and conjugation with glycine or taurine. Once secreted into the intestinal lumen, the anaerobic flora metabolizes the primary bile acids into secondary bile acids. The major reaction is 7α-dehydroxylation to give deoxycholic acid from cholic acid and lithocholic acid from chenodeoxycholic acid. Secondary bile acids are reabsorbed by the enterohepatic circulation and reconjugated within the hepatocytes before they are secreted into the bile system. Once transported back to the liver, secondary bile acids can be further processed to form tertiary bile acids such as sulfolithocholic acid and ursodeoxycholic acid, which normally contribute marginally to the bile acid pool. Bile acids are derived from cholesterol and their excretion facilitates biliary cholesterol excretion, influencing cholesterol homeostasis. Resins binding bile acids in the intestinal lumen increase their fecal output, stimulate synthesis of bile acids, and, indirectly, act as hypocholesterolemic agents. In contrast, cholestatic liver diseases are characterized by hypercholesterolemia.

Conjugated bile acids have powerful detergent-like properties that are important in stabilizing the physical state of bile and in promoting fat digestion and absorption. Bile acids support digestion of nutritional components by formation of micelles and activation/stabilization of enzymes such as pancreatic lipase, phospholipase A, and Pancreatic cholesterol esterase. Micelle formation relies on the amphiphilic nature of bile acids, which are hydrophile on one end while lipophile on the other. This mechanism allows biliary excretion of lipophilic compounds such as cholesterol. To prevent cell damage by formation of micelles while transporting bile acids inside the cell, bile acids bind to specific intracellular transport proteins.

Physiologically 600-ml bile is produced daily. It consists of 400-ml canalicular bile formed in the bile canaliculi between hepatocytes and 200-ml ductular bile collected in the bile ducts lined up by cholangiocytes. Hepatocytes and cholangiocytes are polarized cells with basolateral sides and an apical side. Several ATP-dependent pumps are embedded into the canalicular membrane of the hepatocytes at their apical side. These pumps accumulate bile acids, phospholipids, and organic anions in the canalicular bile. Bile salt export pump (BSEP) is one of them, permitting the excretion of conjugated bile acids against a concentration gradient (1). Intestinal recycling of bile acids occurs via

a Na^+-dependent carrier (apical sodium bile acid transporter (ASBT)) located on the apical side of enterocytes in the terminal ileum as well as on the apical side of hepatocytes and cholangiocytes. Organic solute and steroid transporters (Ostα, Ostβ) have been shown to be essential transporters on the basolateral side of enterocytes and cholangiocytes. These bile acids are taken up back into the hepatocytes by another Na^+-dependent transporter, Na^+-Taurocholate cotransporting polypeptide (NTCP). This system avoids precious cholesterol metabolites to be lost with feces and also permits a cross talk between the intestine and the liver.

Bile acids are now recognized to be important signaling molecules linking feeding to metabolism regulation (2). Their increased intestinal presence postprandially informs adjacent transmitters and metabolic pathways of the availability of nutrients. Bile acids bind and activate a specific G-protein-coupled receptor, TGR5 (also called GPBAR1, membrane bile-acid receptor or BG37) as well as an intracellular receptor, FXR (farnesoid X receptor). FXR belongs to the group of nuclear hormone receptors and functions as a transcription factor. FXR affects not only bile acid metabolism, but also cholesterol metabolism, triglyceride metabolism, and glucose metabolism. In liver, kidney, and intestinal tissues, FXR hinders accumulation of bile acids and thereby prevents toxic damage. In the liver, FXR intensifies bile acid conjugation which consecutively increases bile flow by enhanced excretion of bile acids from hepatocytes into bile canaliculi. In the intestine, FXR activation leads to increased expression of the ileal bile acid binding proteins (*I-BABP, FABP6*), of the basolateral bile acid transporters and of the secreted growth factor, fibroblast growth factor 19 (*FGF19*). Bile acids influence energy homeostasis via the TGR5 pathway. Furthermore, after cellular uptake bile acids exert direct signaling functions in cholangiocytes and hepatocytes via calcium, PKC, MEK, ERK, and PI3K pathways, altering gene expression, cell proliferation, apoptosis, and secretion.

2. THE LIVER AS A FACTORY

Protein metabolism. In contrast to muscle cells, which synthesize protein for their own use, hepatocytes synthesize proteins of importance altruistically for the whole organism. The majority of the circulating proteins are synthesized by hepatocytes. These proteins comprise cargo proteins (e.g., albumin, transferrin, ceruloplasmin, haptoglobin, lipoproteins), immune-related proteins (proteins of the complement system, acute-phase proteins), and coagulation factors.

C-reactive protein is an acute-phase protein, whose hepatocellular production is massively stimulated by cytokines such as IL-6 and IL-1. Albumin is the most abundant plasma protein maintaining intravascular oncotic pressure; its determination reflects the synthesis capacity of the liver over the past few weeks since its half-life is 21 days. To assess the hepatocellular synthesis capacity for a shorter time (hours), the determination of the coagulation factors is appropriate.

Aminotransferases transfer an amino group from a donor molecule to a recipient molecule. Aspartate aminotransferase facilitates the conversion of aspartate and α-ketoglutarate to oxaloacetate and glutamate, and vice versa, whereas alanine aminotransferase facilitates the conversion of alanine and α-ketoglutarate to pyruvate and glutamate, and vice versa. AST can be cytosolic and mitochondrial, whereas ALT is strictly cytosolic. These enzymes are intensively expressed in cells involved in physiologic protein metabolism, particularly hepatocytes and muscle cells. Elevated serum aminotransferase levels are nonspecific markers for hepatocellular damage.

Proteins are degraded by two major pathways: the autophagic–lysosomal pathway and the ubiquitin–proteasome-related pathway. Autophagy engulfs part of the cytoplasm in vacuoles whose content is digested by lysosomal enzymes after fusion with lysosomes. In the ubiquitin–proteasome pathway, proteins are tagged for degradation by enzymatic linkage with ubiquitin residues.

Carbohydrate metabolism. To maintain blood glucose levels within physiologic range, the liver functions as recipient, store, donator, and creator. Up to 90% of the intestinally absorbed glucose is taken up by the liver. Glucose passes membranes via glucose transporters (GLUT family of transporters; GLUT-2, 9, and 10 are expressed in the liver). Once in the cytoplasm, glucose is phosphorylated by hexokinase or glucokinase to access cellular metabolism. Glucokinase is expressed only in the liver and phosphorylates only glucose. Glucokinase activity is particularly important postprandially since its velocity is maximal at much higher concentrations of glucose than hexokinase. Glucose-6-phosphate is sequentially transformed into glucose-1-phosphate by phosphoglucomutase and into uridine-diphosphate-glucose by glucose-1-phosphouridyltransferase to be finally stored as glycogen. The arborescent structure of glycogen with a central anchor protein termed glycogenin links up to 50,000 molecules of glucose while keeping them easily accessible for reintegration into metabolism. Glucose-6-phosphate is not solely the initial compound for glycolysis; it can also enter the pentose phosphate pathways via glucose-6-phosphate dehydrogenase to produce NADPH and precursors for nucleotides. Other carbohydrates like fructose and galactose are enzymatically transformed to join the glycolysis pathway.

When glucose blood levels drop, glucagon and adrenaline stimulate via cAMP a protein phosphorylase reverting glycogen to glucose-1-phosphate (α-glycanphosphorylase) and to glucose-6-phosphate (phosphoglucomutase). G-6-P is converted to glucose by glucose-6-phosphatase. Once glycogen storage has been emptied, glucose needs to be synthesized from other sources. Two third of the glucose derived from neoglucogenesis is synthesized from lactate, which results from anaerobic metabolism and can be supplied to the liver by the muscles. Glucose can also be produced from amino acids, mostly alanine, and from glycerine which is a degradation product of triglycerides. Gluconeogenesis is triggered by hormonal signals. Glucagon increases gluconeogenesis in the short term, while glucosteroids enhance gluconeogenesis in the long term. Insulin inhibits gluconeogenesis. A hallmark of hepatic insulin resistance is the failure of insulin to inhibit hepatic glucose output.

Lipid metabolism. Within each liver lobule, there is zonation of the metabolic functions. The periportal zone is where oxidative energy metabolism, amino acid catabolism, cholesterol metabolism, and fatty acid β-oxidation take place, whereas the perivenous zone is where de novo lipid synthesis, ketogenesis and xenobiotic metabolism occur. Liposynthesis occurs by esterification of free fatty acids via acetyl-CoA and glycerol and is driven by glycerophosphate acyltransferase (GPAT), which is activated by nutritional status and insulin and inhibited by glucagon. De novo lipogenesis of free fatty acids from acetyl-CoA is regulated by insulin via activation of sterol regulatory element-binding protein-1c (SREBP-1c), which controls the transcription of lipogenic enzymes such as fatty acid synthase. Insulin stimulates the conversion of carboxyl-CoA to malonyl-CoA, a key regulator for the distribution of free fatty acids toward esterification or oxidation. Low levels of malonyl-CoA direct free fatty acids to the mitochondriae and β-oxidation via carnitine palmitoyltransferase-1 (CPT-1), an outer mitochondrial membrane enzyme. High levels of malonyl-CoA inhibit CPT-1, thus enhancing esterification of free fatty acid into triglycerides. Fatty acids can also be oxidized in peroxisomes (β-oxidation) and microsomes (ω-oxidation). Triglycerides stimulate apolipoprotein B (Apo-B) synthesis and are secreted as VLDL-Apo-B. Insulin inhibits Apo-B synthesis and impairs secretion of triglycerides as VLDL.

The regulators. AMP-dependent protein kinase (AMPK) and mammalian target of rapamycin (mTOR) adapt hepatocellular metabolism to energy status. Activated AMPK switches energy-consuming anabolic lipogenic pathways to ATP-producing catabolic pathways (3). Multiple cues activate AMPK; hypoxia, ATP depletion, starving, chronic alcohol consumption, oxidative stress, adiponectin, leptin, and drugs such as metformin or thiazolinediones. AMPK

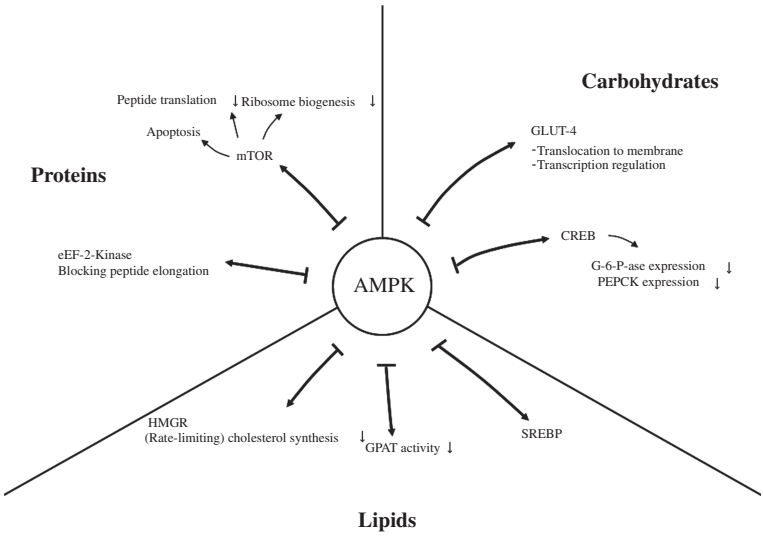

Fig. 1. AMPK influences several main metabolic processes as central turntable. mTOR: mammalian target of rapamycin, a protein complex regulating cell cycle and growth. GLUT-4: insulin-dependent transmembrane glucose transporter protein. CREB: c-AMP response element binding protein, a nuclear transcription regulator. PEPCK: phosphoenolpyruvat carboxykinase, speed-limiting gluconeogenesis enzyme, catalyzing metabolism from oxalacetat via guanosintriphosphat to phosphoenolpyruvat. SREBP: sterol regulatory element binding protein, a transcription factor regulating cholesterol metabolism via activation of gene translation. GPAT: glycerol-3-phosphate acyltransferase, the initial step enzyme in glycerolipid synthesis. HMGR: HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis via the mevalonate pathway.

controls acetyl-CoA-carboxylase 1 reducing lipogenesis, acetyl-CoA-carboxylase 2 increasing fat oxidation, HMG-CoA-reductase lowering cholesterol synthesis, or mTOR lowering protein synthesis (Fig. 1).

Peroxisome proliferator-activated receptors (PPARs) are transcription factors essential for the regulation of cell differentiation and metabolism (4). PPARs sense lipid signals and are to be considered "lipostats": endogenous fatty acids activate PPAR-α, while leukotrienes and prostaglandins activate PPAR-γ. They are also the targets of several metabolic drugs. Fibrates activate PPAR-α and glitazones activate PPAR-γ. PPAR-α stimulates hepatocellular fatty acid uptake and catabolism. PPAR-γ is highly expressed in adipose tissue, where it regulates adipogenesis and adipose tissue integrity. PPAR-γ is usually

poorly expressed in the liver, but its levels increase significantly during lipid accumulation in both hepatocytes and stellate cells. Activation of hepatic PPAR-γ decreases steatosis and reduces profibrogenic processes.

LXR is a nuclear receptor whose ligands are oxysterols. LXR is involved in the regulation of cholesterol, bile acid, and triglyceride metabolism as well as in inflammatory response and energy balance. LXR stimulates cholesterol synthesis and biliary secretion. LXR activates SREBP-1c inducing lipogenesis. LXR promotes glucose utilization by inhibiting expression of glucose-6-phosphatase and induction of glucokinase expression.

Iron. The liver regulates iron homeostasis and is the main body store for iron. Iron is taken up by enterocytes in a highly regulated manner, since it is not excreted and loss of iron is not controlled. Intestinal iron absorption is regulated by hepcidine, which is mainly produced by hepatocytes and to a lesser amount by adipocytes and macrophages. Hepcidine concentrations increase under inflammatory conditions or iron overload and decrease in case of anemia or hypoxic conditions (5). Expression of hepcidine is activated by bone morphogenic protein, which is controlled by hemojuvelin (HJV), HFE, and transferrin receptor 2 (Tfr-2) proteins. Hepcidine inhibits the expression of the ferroportin transporter, a membrane transporter protein releasing iron from the enterocyte. Once released from the enterocyte, iron binds to transferrin, the main iron transport protein of the body. Iron uptake into the hepatocytes is mediated by transferrin receptor 1 (Tfr-1). Tfr-1 is upregulated by hypoxia-inducible factor, IL-2, mitogens, growth factors, or other cytokines. Proliferating cells, in need of iron for growth, express more Tfr-1. HFE, the defective protein in hereditary hemochromatosis, competes with transferrin for binding to Tfr-1. Transferrin is also endocytosed via Trf-2, but with an affinity 25–30 times lower; Trf-2 seems to act as a transferrin saturation sensor.

Copper. Copper is essential for life as it plays a key role as a cofactor for various enzymes. As copper is cytotoxic, it is accompanied by specific protector proteins, which carry and transfer copper to its intracellular destination. At the level of the plasma membrane, copper-transporting ATPases (Cu-ATPases) with two isoforms (ATP7A and ATP7B) play a central role in copper homeostasis by supporting transmembranous copper exchange. ATP7A is responsible for copper transport across the basolateral membrane of enterocytes into the circulation. ATP7B expressed in hepatocytes is responsible for copper excretion into bile. ATP7B deficiency leads to Wilson's disease with intracellular copper accumulation (5).

3. THE LIVER AS A DETOXIFIER

The liver is the central organ for detoxification of exo- and endogenous substances. While water-soluble substances can be excreted by the kidneys, lipophilic substances have to be transformed in the hepatocytes before excretion. Biotransformations within the liver include not only detoxification, but also activation of certain compounds (e.g., prodrugs). Detoxification processing can be divided into three phases. In a first phase, lipophilic substances are conjugated with an additional reactive group enhancing the polarity of the molecule. These groups most often consist of either $–NH_2$, –COOH, –OH, or –SH groups. Conjugation is achieved by oxidation/hydroxylation, reduction, or hydrolysis, depending on the group to be added. Clinical importance of these processes has been shown best for the microsomal mixed-functional monooxygenases, which contain the cytochromes P450. Cytochromes P450 consist of several dozens of enzymes—among others those metabolizing drugs such as the CYP3A4, which influences pharmacokinetics and interactions of many drugs. The large number of cytochrome isoenzymes explains the stunning diversity in individual drug metabolization. Phase I reaction may be sufficient to render substances hydrophilic and enhance kidney excretion.

The second phase conjugates phase I products with other liver-derived substances such as glucuronic acid, amino acids, activated sulfuric acid or mercapturic acid. The newly generated conjugate provides an increased hydrophilicity due to its most often acid characteristics and therefore can be excreted more easily by the kidneys or into the intestinal lumen by bile excretion.

The third phase consists of transmembrane transporters. Noxious compounds conjugated with charged moieties such as glucuronide, glutathione, and sulfate are subsequently pumped into bile across the canalicular membrane by different ATP-binding cassette (ABC) transporters. These involve ABCC2 (MRP2), which largely transports organic anions; ABCG2 (breast cancer-related protein (BCRP)), which transports many charged and uncharged compounds; and ABCB1 (MDR1 P-glycoprotein), which mainly transports uncharged or cationic amphiphilic compounds. Conjugated compounds can also be transported back into the blood by pumps such as ABCC3, ABCC4, and ABCC5, resulting in urinary excretion after filtration or active excretion in the kidney.

3.1. Specific Detoxification Pathways

Bilirubin. Bilirubin concentration in the serum consists of a balance of pigment production and elimination. An end product of heme and

hemoproteins, most bilirubin reaches the bloodstream from the spleen, entering the liver via the portal vein. Hepatocyte uptake happens Na^+ independent, by organic anion transporter proteins (OATPs) in a glutathione countertransport manner at the sinusoidal surface of the hepatocyte. Intracellular bilirubin is linked to ligandin and Z-protein, specific cytosolic proteins, thus preventing intracellular toxicity. Glucuronidation for excretion takes place in the smooth endoplasmic reticulum by the rate-limiting enzyme uridine diphosphoglucuronate-glucuronosyl transferase (UDP-GT), resulting in hydrophilic bilirubin glucuronide. Excretion into the bile is ATP-dependent as transmembrane efflux is provided by conjugated export pump MRP2 (see above). Small amounts of bilirubin are secreted to the plasma via MRP3. Within the intestinal tract, bile-derived bilirubin is metabolized by gut bacteria via β-glucuronidase for oxidation to stercobilin, which is excreted within feces or in small amounts by the kidneys after reuptake by small intestinal endothelium and further metabolization to urobilirubin (6).

Alcohol. The mainstay of alcohol degradation consists of the alcohol dehydrogenase enzyme, though hepatocytes own a microsomal oxidative system located within the ER and catalase within the peroxisomes. The presence of different isoenzymes of ADH explains the individually different capability to cope with ingested alcohol, furthermore, as ADH activity is maximally saturated from 0.3 to 0.5‰ and cannot be upregulated or induced by chronic exposition. ADH metabolizes alcohol to aldehyde acetate, which is highly toxic and has to be further degraded within the microsomes by aldehyde dehydrogenase to acetate acid. Acetate acid is then integrated as acetyl-CoA into the citric acid cycle as well as into the lipid acid cycle and the cholesterin synthesis. ADH is a zinc-depending enzyme, a feature relevant in chronic alcohol abuse, as chronic alcohol consumption most often leads to zinc deficiency. The degradation of alcohol is highly oxygen-dependent and may consume up to 90% of the whole hepatocellular oxygen uptake, meanwhile inhibiting or affecting other oxygen-dependent processes. In chronic alcohol consumption, alcohol specific ADH cannot be induced, whereas the microsomal oxidative system in the ER consisting of cytochrome P450 isoenzymes, primarily unspecific for alcohol, can be upregulated and therefore becomes more and more important as consumption of higher amounts endures. Alcohol induces CYP2E1 subtype, which releases reactive oxygen species and contributes to oxidative stress. Finally, alcohol can also be degraded by catalase, a peroxisomal enzyme degrading H_2O_2 into water and O_2 and reducing alcohol to acetaldehyde only if higher concentrations occur (>1‰) (7).

Ammonium. Ammonium (NH_4^+) derives mainly from the colonic bacterial flora by degradation of proteins and urea. The liver produces and metabolizes ammonium within the urea/ornithine cycle. Urinary ammonium excretion amounts to approximately 20–40 mmol/l urine. Ammonium detoxification in the liver is dependent on two systems: the urea/ornithine cycle, which is the mainstay of ammonium detoxification, and the glutamate cycle, which is not liver-specific. In the urea/ornithine cycle, which is liver-specific, ammonium and bicarbonate are conjugated into the mitochondria by carbamylphosphate synthetase to form carbamylphosphate. Carbamylphosphate is transformed to citrulline via the ornithine carbamylphosphate transferase. Citrulline is further metabolized within the cytoplasm via arginine for urea production providing ornithine as a spin-off. The glutamate cycle conjugates ammonium with α-ketoglutaric acid to produce glutamine, which represents the nontoxic transport form of ammonium. The urea/ornithine cycle depends on high ammonium concentrations and is therefore located in the periportal area and detoxifies the bulk of the portal venous ammonium load. It is vulnerable to exogenous/intestinal toxic substances. The glutamine synthesis is located perivenously and due to its high affinity is less dependent on ammonium concentrations. Importantly, the urea/ornithine cycle and the glutamate cycle are linked to the plasma bicarbonate level as bicarbonate acts as substrate for urea production and glutamine synthesis is dependent on plasma pH levels. Hepatic urea synthesis is a major pathway for the removal of metabolically generated bicarbonate (8).

4. THE LIVER AS A FILTER

The liver is receiving two third of its blood supply from the intestine. This blood full of nutrients contains many antigens, which are filtered through the hepatic sinusoids by cells of the innate immunity system. The innate immunity system is the first line of defense against pathogens recognizing them via pattern recognition receptors such as the toll-like receptors. The liver is enriched with cells of the innate immune system including Kupffer cells (KCs), dendritic cells (DCs), and natural killer (NK) cells (9). Lipopolysaccharides (LPS), which derive from the cell wall of gram-negative bacteria, are present in concentrations up to 1 ng/ml in the portal blood, whereas LPSs are not detectable in the peripheral blood because they have been cleared

in the liver. Liver sinusoidal endothelial cells (LSECs), KCs, and DCs function as antigen-presenting cells (APCs). The KCs are mobile macrophages which position themselves within the sinusoids to contact circulating lymphocytes and engage antigens. KCs are activated by various bacterial antigen stimuli such as LPS and bacterial superantigens. Once activated, KCs produce cytokines (IL-6, TNF, IL-12, and IL-18), influencing the function of other cell types present in their vicinity (hepatocytes, LSECs, and NKs). IL-1β, IL-6, TNF-α, and leukotrienes recruit neutrophils. Neutrophils phagocyte bacterial antigens presented by APCs and secrete cytokines to stimulate other innate immune cells and promote attraction and activation of CD4+ and CD8+ cells. Neutrophil recruitment can significantly contribute to liver injury (10).

LSECs express mannose and scavenger receptors and antigen-uptake molecules. LSECs also support immune pathways by expressing costimulatory CD 40, CD 80, and CD86, similar to mature DCs. Receptor-mediated uptake of antigens and MHC class II expression is downregulated by TNF-α and IL-10, while activation of the mannose receptor (e.g., by bacterial walls) induces expression of IL-12, IL-1β, IL-6, und TNF-α. LSECs are affected by aging, leading to age-related pseudocapillarization of the sinusoids which is characterized by the loss of fenestration and deposition of collagen in the space of Dissé.

NK and NKT cells, which are identified by expression of CD56, have the ability to quickly produce high amounts of cytokines. Their strategic localization in the sinusoids enables NK and NKT cells together with KCs and LSECs to provide an effective first-line innate immune defense against invading pathogens, toxins, food antigens, and circulating tumor cells (11). The liver is exposed to millions of antigens and exobiotics. If every contact would stimulate the immune system, the liver would be in a permanent state of inflammation. Therefore, one of the important functions of the hepatic immune system is the promotion of active tolerance. KCs are crucial for the development of hepatic antigen tolerance. Depletion of KCs impairs antigen tolerance leading to upregulation of T cells (12). Transformation of CD4 T cells to different T-helper (Th) cells or regulatory T (Treg) cells expressing different chemokines (Th1: IFN-γ, Th2: IL-4, IL-10, Th17: IL-17) plays a key role in liver immunotolerance. Short-term inhibition of T-cell stimulation by CTLA-4 and long-term inhibition by PD-1 are nonredundant mechanisms of enduring hepatic immunotolerance (13) (Fig. 2).

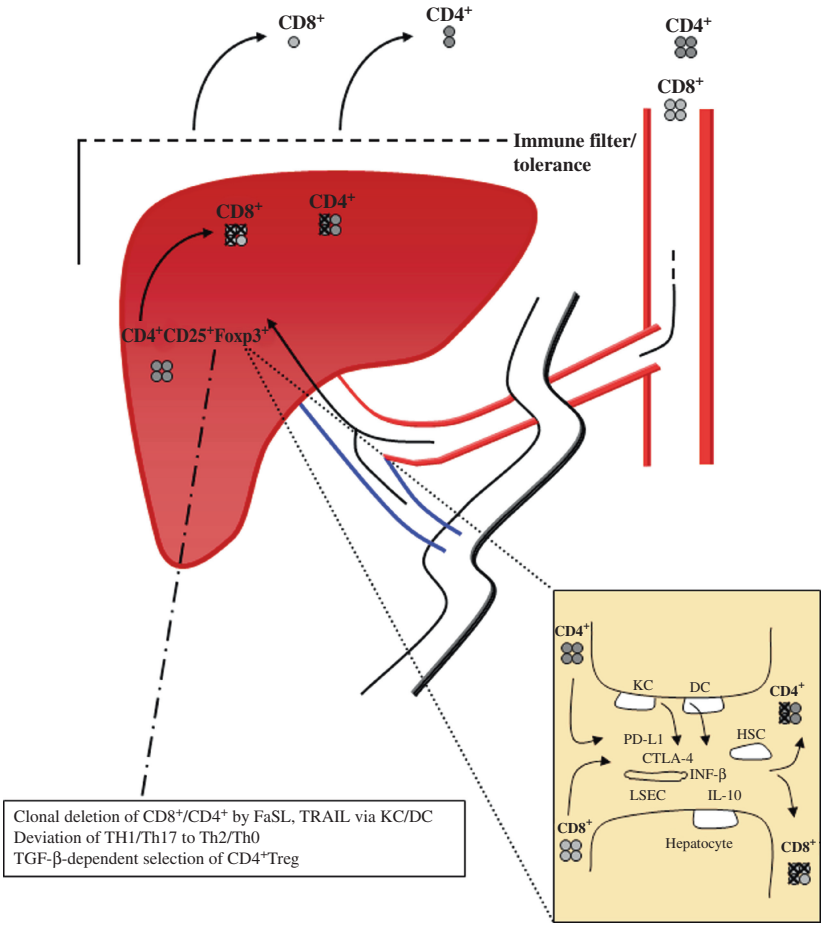

Fig. 2. Immunofunctions of the liver. Mechanical filter function for portal venous inflow due to diameter of the sinusoids. Mechanisms of tolerance: $CD4^+CD25^+Foxp3^+$ Treg cells (graveyard/killing field theory) regulate $CD8^+$ and $CD4^+$ numbers by cell contact, as do Th1 and Th3 cells. Hepatic immune deviation via LSEC "veto" and DC, suppressing IFN-γ-producing Th1-CD4 cells while engaging IL-4 and IL-10 producing Th2-CD4 cells. Furthermore, LSECs, KCs, hepatocytes, and stellate cells produce PD-L1 and CTLA-4, thus suppressing CD4- and CD8-cell function up to induction of apoptosis.

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