Cooperation of Liver Cells in Health and Disease

Davit Tophuria[1], Maia Matoshvili[2], Levan Benashvili[3], Inga Kakhniashvili [4]

Tbilisi State Medical University
Departments: Human Normal Anatomy[1], Dermatology and Venereology[2], Topographic Anatomy and Operative Surgery[3], Clinical Skills[4]

[1]Supervisor MD, PhD, Associate Professor; [2]MD, PhD, Assistant Professor; [3]MD, PhD Assistant Professor;
[4]PhD student

Summary

The enormous number of different liver functions are carried out by parenchymal and four main types of nonparenchymal cells, either alone or in cooperation. Although the liver tissue is uniform on the level of histology, it is heterogenous on the level of morphometry and histochemistry. This heterogeneity is related to the blood supply; cells located in the upstream or periportal zone differ from those in the downstream or perivenous zone in their equipment with key enzymes, translocators, receptors, and subcellular structures and therefore have different functional capacities.

Abbreviations: SEC-sinusoidal endothelial cells, KC-Kupffer cells, IHL-intrahepatic lymphocytes, ECM-extracellular matrix, APC-antigen-presenting cells, LPS-lipopolysaccharide, NK- natural killer cells.
Key Words: *Liver Cells, Health, Disease.*

The liver lobule is formed by parenchymal cells, i.e., hepatocytes and nonparenchymal cells. In contrast to hepatocytes that occupy almost 80% of the total liver volume and perform the majority of numerous liver functions, nonparenchymal liver cells, which contribute only 6.5% to the liver volume, but 40% to the total number of liver cells, are localized in the sinusoidal compartment of the tissue. The walls of hepatic sinusoid are lined by three different cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells (HSC, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells). Additionally, intrahepatic lymphocytes (IHL), including pit cells, i.e., liver-specific natural killer cells, are often present in the sinusoidal lumen. It has been increasingly recognized that both under normal and pathological conditions, many hepatocyte functions are regulated by substances released from neighboring nonparenchymal cells. Liver sinusoidal endothelial cells constitute the lining or wall of the hepatic sinusoid. They perform important filtration function due to the presence of small fenestrations that allow free diffusion of many substances, but not of particles of the size of chylomicrons, between the blood and the hepatocyte surface. SEC show huge endocytic capacity for many ligands including glycoproteins, components of the extracellular matrix (ECM; such as hyaluronate, collagen fragments, fibronectin, or chondroitin sulphate proteoglycan), immune complexes, transferrin and ceruloplasmin. SEC may function as antigen-presenting cells (APC) in the context of both MHC-I and MHC-II restriction with the resulting development of antigen-specific T-cell tolerance. They are also active in the secretion of cytokines, eicosanoids (i.e., prostanoids and leukotrienes), endothelin-1, nitric oxide, and some ECM components.Kupffer cells are intrasinusoidally located tissue macrophages with a pronounced endocytic and phagocytic capacity. They are in constant contact with gut-derived particulate materials and soluble bacterial products so that a subthreshold level of their activation in the normal liver may be anticipated. Hepatic macrophages secrete potent mediators of the inflammatory response (reactive oxygen species, eicosanoids, nitric oxide, carbon monoxide, TNF-alpha, and other cytokines), and thus control the early phase of liver inflammation, playing an important part in innate immune defense. High exposure of Kupffer cells to bacterial products, especially endotoxin (lipopolysaccharide, LPS), can lead to the intensive production of inflammatory mediators, and ultimately to liver injury.

Besides typical macrophage activities, Kupffer cells play an important role in the clearance of senescent and damaged erythrocytes. Liver macrophages modulate immune responses via antigen presentation, suppression of T-cell activation by antigen-presenting sinusoidal endothelial cells via paracrine actions of IL-10, prostanoids, and TNF-alpha, and participation in the development of oral tolerance to bacterial superantigens. Moreover, during liver injury and inflammation, Kupffer cells secrete enzymes and cytokines that may damage hepatocytes, and are active in the remodeling of extracellular matrix. Hepatic stellate cells are present in the perisinusoidal space. They are characterized by abundance of intracytoplasmic fat droplets and the presence of well-branched cytoplasmic processes, which embrace endothelial cells and provide focally a double lining for sinusoid. In the normal liver HSC store vitamin A, control turnover of extracellular matrix, and regulate the contractility of sinusoids. Acute damage to hepatocytes activates transformation of quiescent stellate cells into myofibroblast-like cells that play a key role in the development of inflammatory fibrotic response. Pit cells represent a liver-associated population of large granular lymphocytes, i.e., natural killer (NK) cells. They spontaneously kill a variety of tumor cells in an MHC-unrestricted way, and this antitumor activity may be enhanced by the secretion of interferon-gamma. Besides pit cells, the adult liver contains other subpopulations of lymphocytes such as gamma delta T cells, and both "conventional" and "unconventional" alpha beta T cells, the latter containing liver-specific NK T cells. The development of methods for the isolation and culture of main liver cell types allowed to demonstrate that both nonparenchymal and parenchymal cells secrete tens of mediators that exert multiple paracrine and autocrine actions. Co-culture experiments and analyses of the effects of conditioned media on cultures of another liver cell type have enabled the identification of many substances released from non-parenchymal liver cells that evidently regulate some important functions of neighboring hepatocytes and non-hepatocytes. To the key mediators involved in the intercellular communication in the liver belong prostanoids, nitric oxide, endothelin-1, TNF-alpha, interleukins, and chemokines, many growth factors (TGF-beta, PDGF, IGF-I, HGF), and reactive oxygen species (ROS). Paradoxically, the cooperation of liver cells is better understood under some pathological conditions (i.e., in experimental models of liver injury) than in normal liver due to the possibility of comparing cellular phenotype under in vivo and in vitro conditions with the functions of the injured organ. The regulation of vitamin A metabolism provides an example of the physiological role for cellular cross-talk in the normal liver. The majority (up to 80%) of the total body vitamin A is stored in the liver as long-chain fatty acid esters of retinal, serving as the main source of retinoids that are utilized by all tissues throughout the body. Hepatocytes are directly involved in the uptake from blood of chylomicron remnants, and the synthesis of retinol-binding protein that transfers retinol to other tissues. However, more than 80% of the liver retinoids are stored in lipid droplets of hepatic stellate cells. HSC are capable of both uptake and release of retinol depending on the body's retinol status. The activity of some major enzymes of vitamin A metabolism have been found to be many times higher per protein basis in stellate cells than in hepatocytes. Despite progress in the understanding of the roles played by these two cell types in hepatic retinoid metabolism, the way in which retinoids move between the parenchymal cells, stellate cells, and blood plasma has not been fully elucidated. Sinusoidal blood flow is, to a great extent, regulated by hepatic stellate cells that can contract due to the presence of smooth muscle alpha-actin. The main vasoactive substances that affect constriction or relaxation of HSC derive both from distant sources and from neighboring hepatocytes (carbon monoxide, leukotrienes), endothelial cells (endothelin, nitric oxide, prostaglandins), Kupffer cells (prostaglandins, NO), and stellate cells themselves (endothelin, NO). The cellular cross-talk reflected by the fine-tuned modulation of sinusoidal contraction becomes disturbed under pathological conditions, such as endotoxemia or liver fibrosis, through the excess synthesis of vasoregulatory compounds and the involvement of additional mediators acting in a paracrine way. The liver is an important source of some growth factors and growth factor-binding proteins. Although hepatocytes synthesize the bulk of insulin-like growth factor I (IGF-I), also other types of nonparenchymal liver cells may produce this peptide. Cell-specific expression of distinct IGF-binding proteins observed in the rat and human liver provides the potential for specific regulation of hepatic IGF-I synthesis not only by growth hormone, insulin, and IGF-I, but also by cytokines released from activated Kupffer (IL-1, TNF-alpha, TGF-beta) or stellate cells (TGF-alpha, TGF-beta). Hepatic stellate cells may affect turnover of hepatocytes through the synthesis of potent positive as well as negative signals such as, respectively, hepatocyte-growth-factor or TGF-beta. Although hepatocytes seem not to produce TGF-beta, a pleiotropic cytokine synthesized and secreted in the latent form by Kupffer and stellate cells, they may contribute to its actions in the liver by the intracellular activation of latent TGF-beta, and secretion of the biologically active isoform. Many mediators that reach the liver during inflammatory processes, such as endotoxins, immune-complexes, anaphylatoxins, and PAF, increase glucose output in the perfused liver, but fail to do so in isolated hepatocytes, acting indirectly via prostaglandins released from Kupffer cells. In the liver, prostaglandins synthesized from arachidonic acid mainly in Kupffer cells in a response to various inflammatory stimuli, modulate hepatic glucose metabolism by increasing glycogenolysis in adjacent hepatocytes.

The release of glucose from glycogen supports the increased demand for energetic fuel by the inflammatory cells such as leukocytes, and additionally enables enhanced glucose turnover in sinusoidal endothelial cells and Kupffer cells which is necessary for effective defense of these cells against invading microorganisms and oxidative stress in the liver. Leukotrienes, another oxidation product of arachidonic acid, have vasoconstrictive, cholestatic, and metabolic effects in the liver. A transcellular synthesis of cysteinylleukotrienes (LTC4, LTD4, and LTE4) functions in the liver: LTA4, an important intermediate, is synthesized in Kupffer cells, taken up by hepatocytes, converted into the potent LTC4, and then released into extracellular space, acting in a paracrine way on Kupffer and sinusoidal endothelial cells. Thus, hepatocytes are target cells for the action of eicosanoids and the site of their transformation and degradation, but can not directly oxidatearachidonic acid to eicosanoids.

Conclusion

The liver is a heterogeneously complex organ and understanding the 3-dimensional structure, physiology, and cellular components is integral to the interpretation of genomic and proteomic data as well as disease pathogenesis and prevention. Future elucidation of the heterogeneity and complexity of the liver, for example using emerging genomics and imaging technology, will help in the fight against liver disease and cancer and find new targets for therapy.