https://doi.org/10.48047/AFJBS.6.2.2024.2696-2702

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Brief Overview about Histological organization of the liver

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Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 10 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi: 10.48047/AFJBS.6.2.2024.2696-2702

Abstract: The liver is the largest gland in the body, weighing approximately 1500 g. It is located in the upper right-hand quadrant of the abdominal cavity, just inferior to the diaphragm. The liver is subdivided into four lobes (right, left, quadrate, and caudate) of which the first two constitute its bulk. It is completely enveloped by peritoneum except its bare area. Hepatocytes are arranged in such a manner that each cell not only comes in contact with other hepatocytes but also borders the space of Disse. Thus, the plasma lemma of hepatocytes to have lateral and sinusoidal domains. The lateral domains of the hepatocyte cell membrane from labyrinthine intercellular space ,1 to 2 µm in diameter, known as bile canaliculi lobules. leakage of bile from bile canaliculi is prevented by the formation of tight junctions between adjoining liver cells. At the sinusoidal domain, microvilli projecting from basal surface of hepatocytes increase the surface area available for exchange of materials between hepatocytes and plasma by much as six times. The epithelial cells of the canals of Hering and of the bile ducts secrete a bicarbonate-rich fluid like that produced by the duct system of the pancreas. The formation and release of this alkaline buffer is controlled by the hormone secretin, produced by diffuse neuroendocrine system (DNES) cells of the duodenum. This fluid acts with fluid from the pancreas, to neutralize the acidic chyme that enters the duodenum

Keywords: *Histological organization of the liver*

Introduction

The liver is the largest gland in the body, weighing approximately 1500 g. It is located in the upper right-hand quadrant of the abdominal cavity, just inferior to the diaphragm. The liver is subdivided into four lobes (right, left, quadrate, and caudate) of which the first two constitute its bulk. It is completely enveloped by peritoneum except its bare area [1].

Embryologically the liver started as a small bud emerging from the foregut endoderm. This process is initiated by signaling molecules like fibroblast growth factors (FGFs) and bone morphogenetic proteins (BMPs). At the 3rd to 4th week of gestation the liver bud grows and undergoes expansion and branching to develop into mature organ. This maturation is tightly regulated by various signaling pathways and transcription factors [2]. (Fig. A)

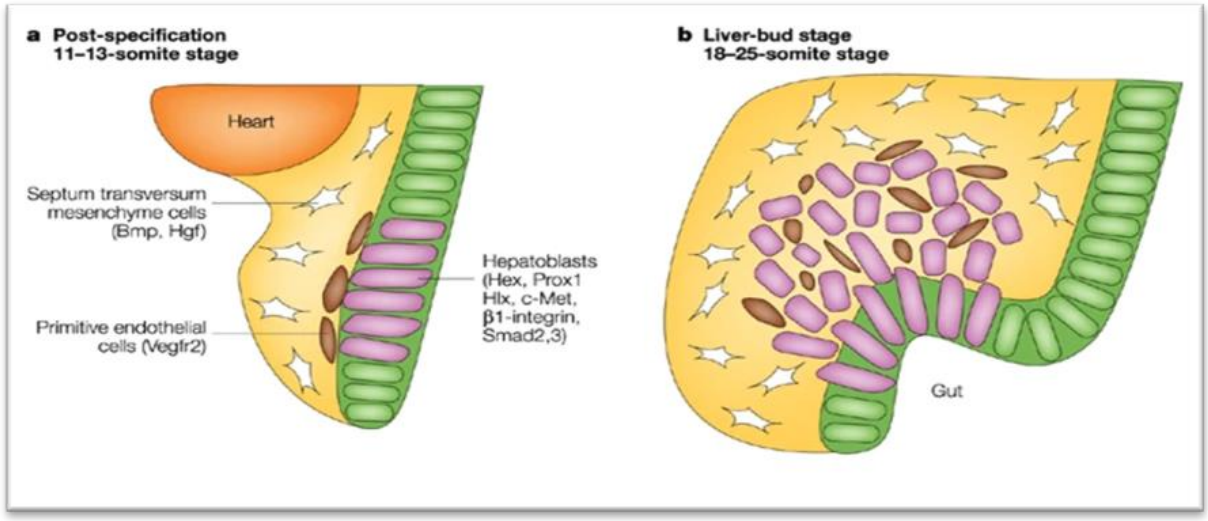

Fig. (A): Development of the liver bud [3].

Tomaz et al. [4] mentioned that when the hepatic endoderm is specified to give rise to hepatoblast. These cells express some genes to become either fully differentiated to hepatocytes or bile duct cells (cholangiocytes). Mesoderm-derived cells such as endothelial cells and hematopoietic cells also contribute to liver development. It migrated to the liver and colonized at specialized niches, giving rise to various blood cell lineages since the liver serves as a hematopoietic organ during embryonic development contributing to the production of blood cells (Fig. B) [5].

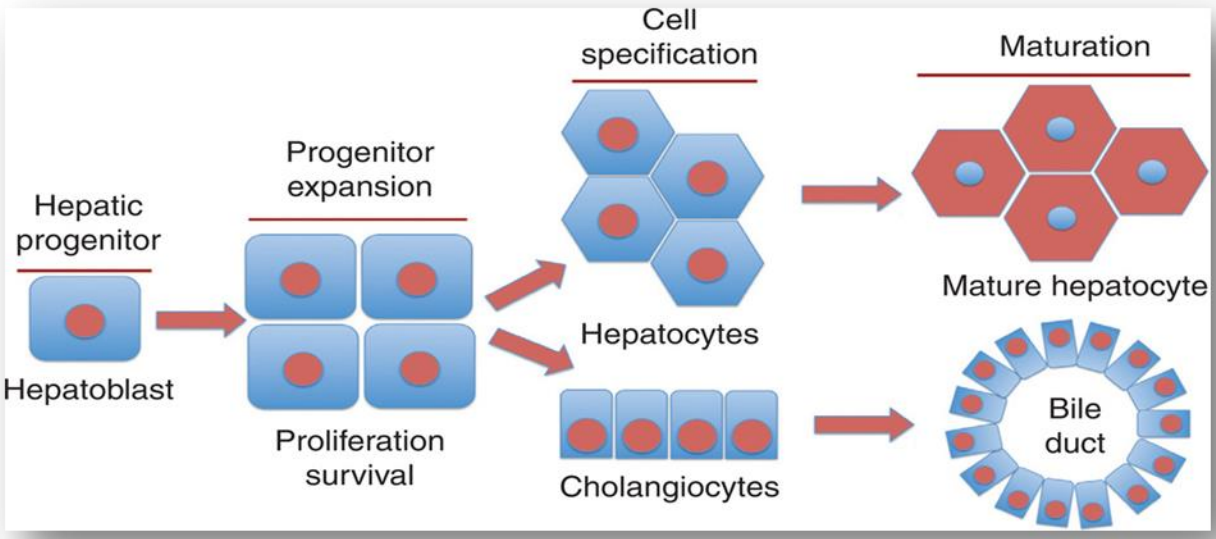

Fig.(B): hepatic morphogenesis [6].

Histological organization of the liver

The liver stroma is composed of fibrous connective tissue capsule (Glisson capsule) and network of reticular fibers. While the parenchyma of the liver includes parenchymal cells (hepatocytes) and non-parenchymal cells include Von Kupffer cells, Ito stellate cells, Pit cells and endothelial cells, hepatic sinusoids between the plates of hepatocytes, perisinusoidal spaces (space of Disse) which lie between the sinusoidal endothelium and the hepatocytes [7].

Kwon et al. [8] reported that there are three ways to describe the structural organization of the liver cells into a functional units. The first way is the classic hepatic lobule, which is hexagonal (polygonal) in shape. This hexagon formed of cellular anastomosing plates of hepatocytes radiating from central vein (in the center). These plates are organized as sheets, one or two cells thick arranged around the central vein like spokes of wheel. Blood sinusoids located between the cellular sheets are approximately 9-12 μm in width and lined by endothelium. At the corner of hexagon, there are portal areas containing branches of hepatic arteriole, a portal venule and a bile ductule (Fig. c) [9].

The second way is the portal lobule which surrounds the portal triad. It is a triangular in shape, with the central vein located at its apex. These triads are crucial for the liver's function as they provide the liver cells with oxygenated blood, nutrients, and bile. The hepatic artery supplies oxygen-rich blood to the liver, the portal vein carries nutrient-rich blood from the digestive system, and the bile duct transports bile produced by the liver cells to the gallbladder or small intestine for digestion. This intricate network ensures proper liver function, including metabolism, detoxification, and bile production [10].

The third way is liver acinus which is a diamond-shaped area that has three zones and correlates to blood perfusion, metabolic activity, and liver pathology [11]. The hepatic acinus is divided into three regions or zones of approximately equal size. Zone one is nearest to the blood supply (periportal) while zone three includes the terminal hepatic venule (central vein). Zone two is located between zones one and three [12].

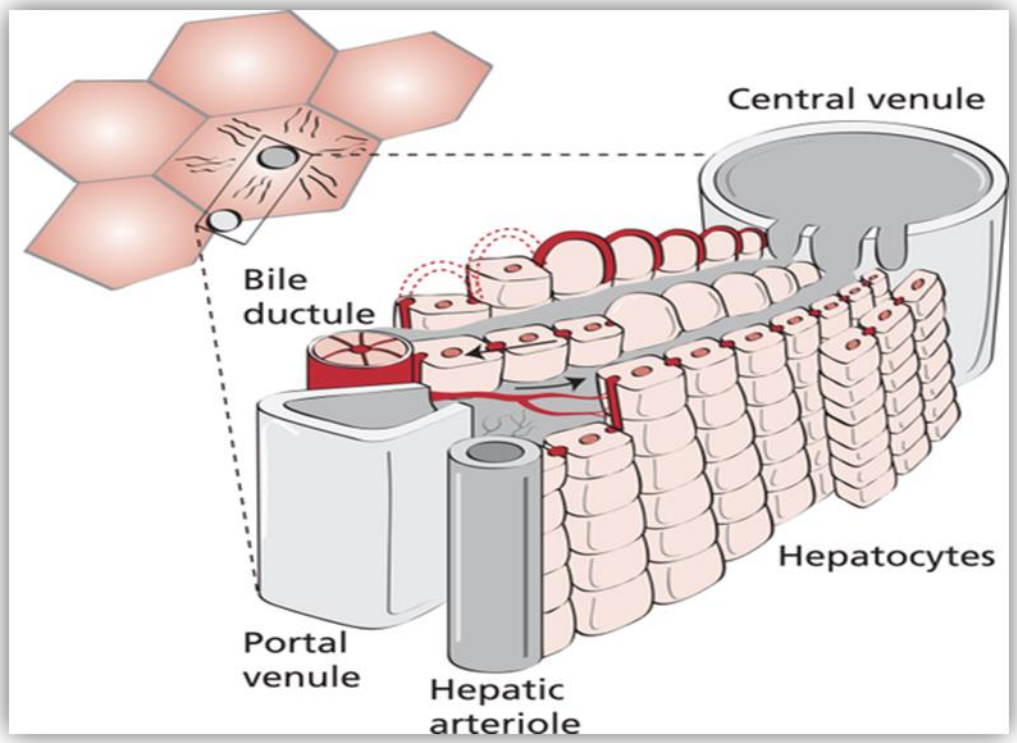

Fig.(c) classic hepatic lobule [13].

Hepatocytes that constitute 80% of liver cells are relatively long-lived compared to digestive system cells as their average life span is about 5 months. These cells are capable of regeneration when liver substance is lost due to hepatotoxic processes, disease, or surgery [14].

The hepatocyte nucleus typically appears large, round to oval, occupies the center of the cell and contains a prominent nucleolus, reflecting its high metabolic activity and protein synthesis capacity. Most hepatocytes are binucleated with two or more nucleoli. The nucleoli of these cells are euchromatic with scattered clumps of

heterochromatin in the nucleoplasm and as a distinct band under the nuclear envelope. [15]. The cytoplasm has a variable appearance depending on the nutritional status of the individual. When well-nourished, hepatocytes store significant quantities of glycogen and process large quantities of lipid. Both metabolites are partially removed during routine histological preparation, leaving irregular unstained areas within the cytoplasm [16].

The hepatocyte cytoplasm is strongly acidophilic due to numerous mitochondria with fine basophilic granularity due to extensive free ribosomes and rough endoplasmic reticulum. [17]. Mitochondria are the main energy source in hepatocytes and play a major role in extensive oxidative metabolism and normal function of the liver. This key role also assigns mitochondria a gateway function in the center of signaling pathways that mediate hepatocyte injury. Rough endoplasmic reticulum (rER) and free ribosomes are demonstrated as basophilic regions which are responsible for production of plasma proteins and coagulation factor. [18].

Golgi apparatus is extensive as many as 50 Golgi units, each consisting of three to five closely stacked cisternae, plus many large and small vehicles [19]. Elements of the Golgi apparatus near the bile canaliculus are believed to be associated with the exocrine secretion of bile. Golgi cisternae and vesicles near the sinusoidal surfaces of the cell, contain electron-dense granules 25 to 80 nm in diameter that are believed to be VLDL and other lipoprotein precursors. These substances are subsequently released into the circulation as part of the endocrine secretory function of the hepatocytes [20].

The smooth endoplasmic reticulum (sER) in hepatocytes may be extensive but varies with metabolic activity. The sER contain enzymes involved in degradation and conjugation of toxins and drugs as well as enzymes responsible for synthesizing cholesterol and lipid portion of lipoproteins. Fine brown granules of lipofuscin pigment are present in variable amounts and increase with aging [21].

Hepatocytes have as many as 200 to 300 peroxisomes per cell. They are relatively large and vary in diameter. Peroxisomes are a major site of oxygen use and, in this way, perform a function like that of mitochondria. They contain a large amount of oxidase that generates toxic hydrogen peroxide, H2O2. The enzyme catalase, also residing within peroxisomes, degrades hydrogen peroxide to oxygen and water [22]. In fact, about one-half of the ethanol that is ingested is converted to acetaldehyde by enzymes contained in liver peroxisomes. In humans, catalase and D-amino acid oxidase, as well as alcohol dehydrogenase, are found in peroxisomes. In addition, peroxisomes are also involved in breakdown of fatty acids as well as gluconeogenesis and metabolism of purines [23].

Lipofuscin pigment in hepatocytes appears as fine, yellow-brown granular deposits, primarily situated near the cell nucleus. This pigment is a product of lysosomal digestion, consisting of oxidized proteins and lipids, and increases with age, serving as a marker of cellular aging and oxidative stress. Lipofuscin accumulation indicates lysosomal inefficiencies and oxidative damage, and is commonly seen in chronic liver diseases, such as cirrhosis and chronic hepatitis, as well as in certain metabolic disorders [24].

Hepatocytes are arranged in such a manner that each cell not only comes in contact with other hepatocytes but also borders the space of Disse. Thus, the plasma lemma of hepatocytes to have lateral and sinusoidal domains. The lateral domains of the hepatocyte cell membrane from labyrinthine intercellular space ,1 to 2 µm in diameter, known as bile canaliculi lobules. leakage of bile from bile canaliculi is prevented by the formation of tight junctions between adjoining liver cells. At the sinusoidal domain, microvilli projecting from basal surface of hepatocytes increase the surface area available for exchange of materials between hepatocytes and plasma by much as six times [25].

Hepatic sinusoids are large, irregularly shaped spaces that are lined by thin discontinuous fenestrated endothelial cells. These fenestrations allow for the passage of small molecules and particles between blood and hepatocytes [26]. There is a space lie between the endothelium and hepatocytes named space of Disse. This space contains microvilli that increase the surface area for nutrient absorption and exchange. Also, the space of Disse contains Sinusoidal macrophages (Von Kupffer cells), hepatic stellate cells and reticular fibers. It is considers as the site of exchange of materials between blood and liver cells [27].

Von Kupffer cells are resident macrophages which associate the sinusoidal lining cells in the sinusoids. Frequently, phagosomes of Kupffer cells contain endocytosed particulate matter and cellular debris, especially erythrocytes that are being destroyed by these cells. So they are responsible for iron recycling and removal of aged RBCS. Electron micrographs of Kupffer cells displayed numerous filopodia like projections, mitochondria, some rER, as mall Golgi apparatus, an abundance of lysosome and late endosomes. Because these cells don't make intercellular junctions with the neighboring cells, it has been suggested that they may be migratory scavengers [28].

Hepatic stellate cells (HSCs) (Ito cells) or hepatic lipocytes are fat storing cells that have been noted in the space of Disse .It is believed that hepatic stellate cells store vitamin A, manufacture and release type III collagen into the space of Disse ,secrete growth factors required by the liver for generating new hepatocytes and form fibrous connective tissue to replace hepatocytes damaged by toxins [29].

Pit cells are liver-specific natural killer (NK) cells and belong to the group of sinusoidal cells, together with Kupffer, endothelial, and fat-storing cells. They are lymphoid cells containing specific granules and proliferate locally. They probably originate from the bone marrow, circulate in the blood, and marginate in the liver, where they develop into pit cells by lowering their density and increasing the number of granules. They display short pseudopodia and cytoplasmic granules [30].

The liver has a dual blood supply, receiving oxygenated blood from the left and right hepatic arteries (25%) and hemoglobin-rich blood from the spleen as well as nutrient-rich blood from the digestive tract via the portal vein (75%). The vessels enter the liver at the porta hepatis and leave it at its posterior aspect through the hepatic veins, which deliver their contents into the inferior vena cava. Bile also leaves the liver at the porta hepatis by way of the right and left hepatic ducts, to be delivered to the gallbladder for concentration and storage [31].

Hepatic lymph originates in the space of Disse. Plasma that remains in it drains into the periportal connective tissue, where a small space called space of Mall. From this collecting site, the fluid enters lymphatic capillaries that travel with the other components of the portal triad [32]. The lymph moves in progressively larger vessels, in the same direction as the bile from the level of the hepatocytes, directed toward the portal canals and eventually to the hilum of the liver. About 80% of the hepatic lymph passes in this pathway and drains into the thoracic duct, forming the major portion of the thoracic duct lymph [33].

The liver is innervated by both the sympathetic and the parasympathetic nerve systems. These nerves are derived from the splanchnic and vagal nerves that surround the portal vein, hepatic artery, and bile duct. The afferent fibers deliver information regarding osmolality, glucose level, and fatty acid level in the portal vein to the central nervous system (CNS). In contrast, efferent fibers are crucial in the regulation of metabolism, blood flow, and bile secretion. Furthermore, liver innervation can be affected by hepatic fibrosis, regeneration, and circadian rhythm. Knowledge of these mechanisms can be applied for potential liver disease treatment [34].

Referred pain is visceral pain perceived as somatic pain through the dermatomes of the skin which are innervated by the cutaneous nerves of the spinal cord T5 to L3. It is essentially information that is carried by visceral afferent fibers via the thoracic and lumbar splanchnic nerves. The liver and the gallbladder are governed by the sixth to the ninth thoracic spinal nerves and present as referred pain in the epigastric region of the abdomen, as well as to the right hypochondrium [35].

The biliary tree is a system of channels of increasing diameter that bile flows through from the hepatocytes to the gallbladder and then to the intestine. In the adult human liver, there are more than 2 km of interconnecting bile ductules and ducts of different sizes and shapes. These structures are not only passive conduits, but they are also capable of modifying bile flow and changing its composition in response to hormonal and neural stimulation [36].

The biliary tree is lined by simple cuboidal epithelial cells called cholangiocytes, which monitor bile flow and regulate its content. Bile (produced by hepatocytes) is collected by the bile canaliculi and drains to the canals of Hering. From there, it continues to flow into the intrahepatic bile ductulus and further into the interlobular

bile ducts (part of the portal triad). Interlobular ducts eventually merge to form the left and right hepatic ducts that exit the liver in the porta hepatis. Extrahepatic bile ducts carry the bile to the gallbladder and eventually into the duodenum [37].

The epithelial cells of the canals of Hering and of the bile ducts secrete a bicarbonate-rich fluid like that produced by the duct system of the pancreas. The formation and release of this alkaline buffer is controlled by the hormone secretin, produced by diffuse neuroendocrine system (DNES) cells of the duodenum. This fluid acts with fluid from the pancreas, to neutralize the acidic chyme that enters the duodenum [38]..

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