

Architecture of the Liver and Biliary Tract

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ABSTRACT

The liver is the largest mass of glandular tissue in the body. It has several endocrine and exocrine functions derived from the single parenchymal cell type; hepatocyte. Hepatocytes are large polygonal cells and rich in organelles including rough and smooth surfaced endoplasmic reticulum, several Golgi complexes, mitochondri, peroxisomes, lysosomes etc., and inclusions including glycogen granules and lipid droplets. Bile secretion represents exocrine function of the liver. Bile produced within the cytoplasm of the hepatocytes, is secreted into a series of bile canalicules, canals and ducts and finally into the lumen of the duodenum.

In this chapter I tried to summarize histological architecture of the liver via describing the classical liver lobule, portal lobule and liver acinus, ultrastructural features of the hepatocytes and perisinusoidal cells, and histological features of the biliary tree including bile canaliculi, canals of Hering, intrahepatic bile ducts and extrahepatic bile ducts. Additionally, I summarized the cholestasis-related hepatic histological alterations and ultrastructural changes within the hepatocytes based on primarily my recent experimental studies.

Key words: Biliary tree; Cholestasis; Hepatocyte; Liver

INTRODUCTION

The liver located in the upper right quadrant of the abdominal cavity is the largest mass of the glandular tissue of the body. It is both an endocrine and exocrine organ. It is an endocrine organ because it produces various substances including plasma proteins such as albumin, prothrombin, fibrinogen etc. and releases them into the blood stream. It is an exocrine organ because it produces bile and secretes it into the duodenum via biliary tract. The liver also plays important roles in deposition of vitamins, degradation of drugs and toxin (detoxification), and in glucose and cholesterol metabolism etc. [1,2].

The liver is enclosed by capsule of fibrous connective tissue called Glisson's capsule. The connective tissue of the fibrous capsule of Glisson is continuous with the loose connective tissue stroma surrounding liver lobules. In humans, however, there is normally very little interlobular connective tissue. It is mainly composed of parenchyma consisting of plates of hepatocytes separated by sinusoidal capillaries. The morphological and functional units of the liver are lobules and acini. There are three ways to describe the structure of the liver in terms of these units. These are classical hepatic lobule, portal lobule and liver acinus.

*The classical liver lobule: The classical liver lobule, hexagonal in shape, consists of anastomosing plates of hepatocytes separated by sinusoid capillaries that contain both venous and arterial blood derived from portal vein (75 %) and hepatic artery (25 %); respectively. At the center of the lobule is a large venule; the terminal hepatic venule or central vein into which sinusoid capillaries drain. At the angles of the hexagon are portal areas in which loose connective tissue, ultimately continuous with the capsule of the liver, characterized by the presence of the portal triads including branches of hepatic artery, portal vein and bile duct (Figure 1).

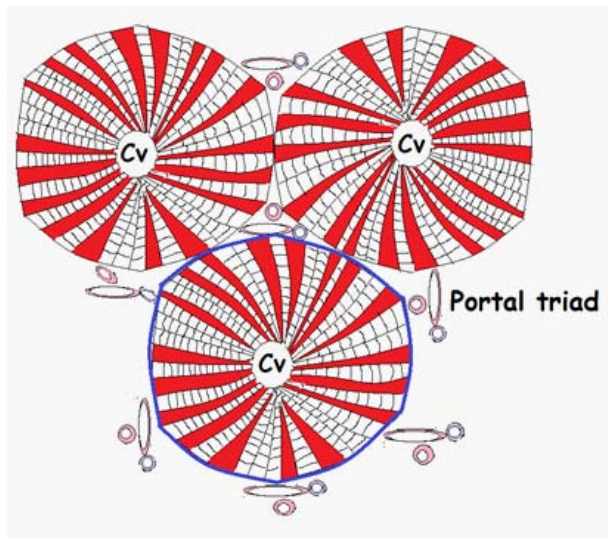


Figure 1: Diagram of classical liver lobule. Pale columns represent hepatocytes rows, red columns represent sinusoid capillaries. Note that at the centre of the lobule central vein is located (Drawn by Esrefoglu M).

***The portal lobule:** The portal lobule, triangular in shape, emphasizes the exocrine function of the liver, namely bile secretion. At the centre of the portal lobule, a portal space containing portal triad is located. At each edge, one central vein is individually placed (Figure 2). The portal lobule includes those portions of three classical liver lobules that secrete bile that drains into its axial bile ducts. The direction of bile flow is from central vein to portal space via bile canaliculi and bile canals whereas the direction of blood stream is from portal space to central vein via sinusoids.

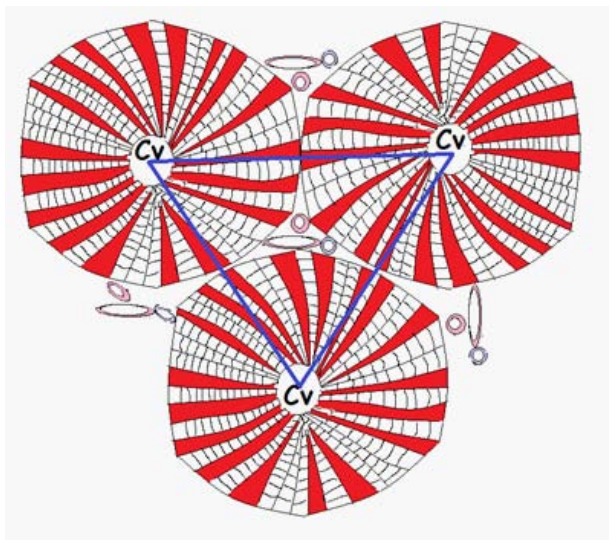


Figure 2: Diagram of the portal lobule. Note that at the centre of the lobul, portal space is located (Drawn by Esrefoglu M).

***The liver acinus:** The liver acinus, elliptic in shape, is an area of which long axis extends from one central vein to the next one and short axis extends from one portal space to the next one. The liver acinus is the best to describe the differences in terms of blood perfusion, metabolic activity and liver pathology among the hepatocytes located in different zones. Zone 1 is closest to the short axis and the blood supply from the vessels of portal space whereas zone 3 is the farthest part of short axis and closest to central vein (Figure 3). Variations in enzyme activity, the number and size of organelles are seen between zones 1 to 3. The cells of zone 1 are the first to receive oxygen and to regenerate, but they are last to die. Conversely the cells of zone 3 are the first to undergo necrosis. In rats with experimental obstructive jaundice, changes including centrilobular hepatocellular swelling and necrosis, hepatocanalicular cholestasis, intrahepatic bile duct proliferation, periportal and parenchymal polymorphonuclear leukocyte, and lymphocyte infiltration have been detected [3-5]. It has been observed that the features of liver regeneration following the occurrence of such changes that originated from zone 2, extends to zone 1 and occasionally to zone 3 [5].

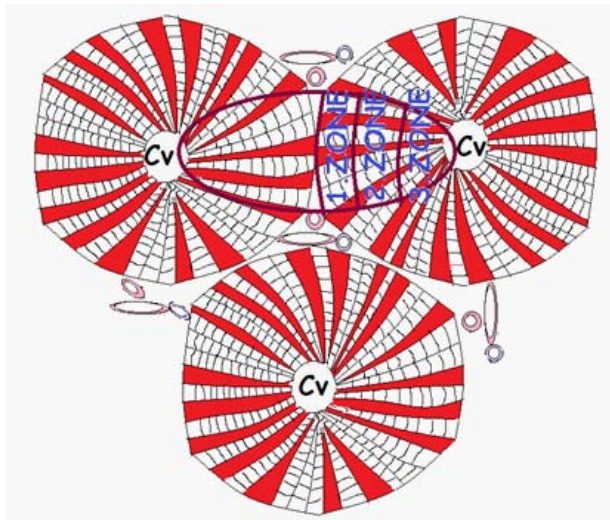


Figure 3: Diagram of the liver acinus (Drawn by Esrefoglu M).

ULTRASTRUCTURE OF THE HEPATOCYTES

Hepatocytes are large, polygonal cells with large spherical nuclei. They are organized as cellular rows extending from central vein to the periphery of the classical liver lobule (Figure 4). The hepatocyte cytoplasm is generally acidophilic; some small patchy areas may be basophilic that represents rough endoplasmic reticulum (RER) and ribosomes. They have a well-developed RER (Figure 5) as well as smooth surfaced endoplasmic reticulum (SER), numerous mitochondria (Figure 5, Figure 6), multiple small Golgi complexes, large numbers of peroxisomes (Figure 5), ribosomes, large amounts of glycogen deposits (Figure 5, Figure 6), lipid droplets of various sizes (Figure 6), and various amounts of lysosomes [1,6-8].

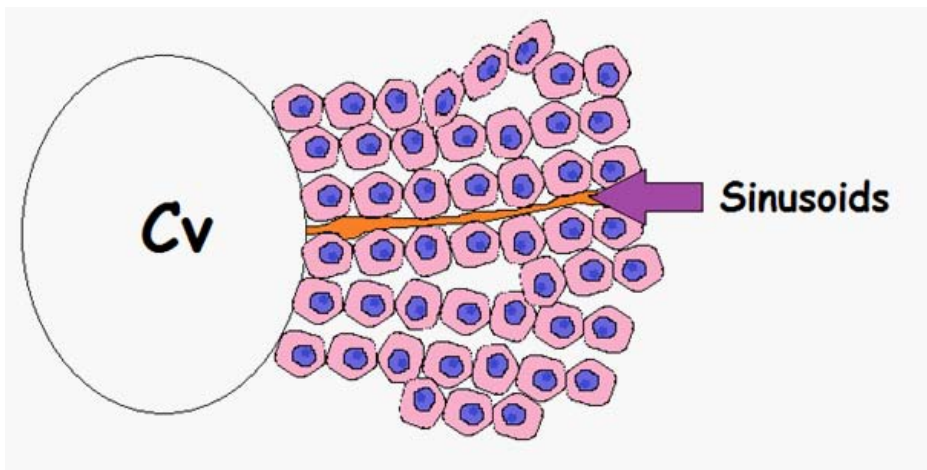


Figure 4: Radial organization of the hepatocytes from central vein to the periphery is shown (Drawn by Esrefoglu M).

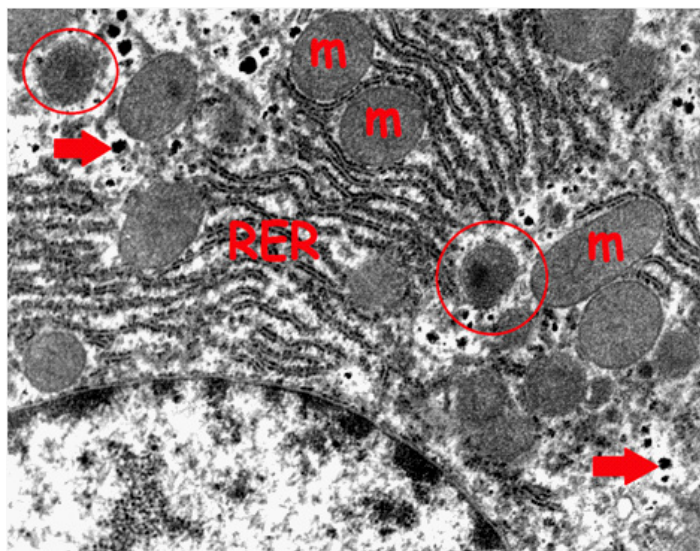


Figure 5: Extensive RER, many mitochondria (m), peroxisomes (in circle) and glycogen granules (arrows) are observed in the cytoplasm of a rat hepatocyte. X 10.000.

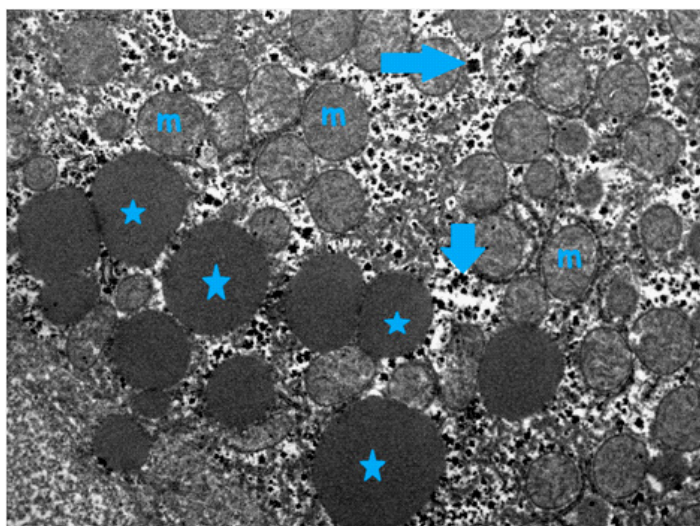


Figure 6: Many mitochondria (m), glycogen granules (arrows) and lipid droplets (asterisks) are observed in the cytoplasm of a rat hepatocyte. X 10.000.

Hepatocytes are vulnerable to various types of injury due to their high metabolic activity thus high oxygen consumption. Cholestasis induces various alterations including necrosis, apoptosis, portal fibrosis, leukocyte infiltration, cholangitis etc. [3,4,9]. Experimental cholestasis also results in many degenerative changes, such as edema (Figure 7), vacuolization, mitochondrial degeneration (Figure 7, Figure 8), endoplasmic reticulum dilatation, lysosome accumulation and necrosis (Figure 8) [10].

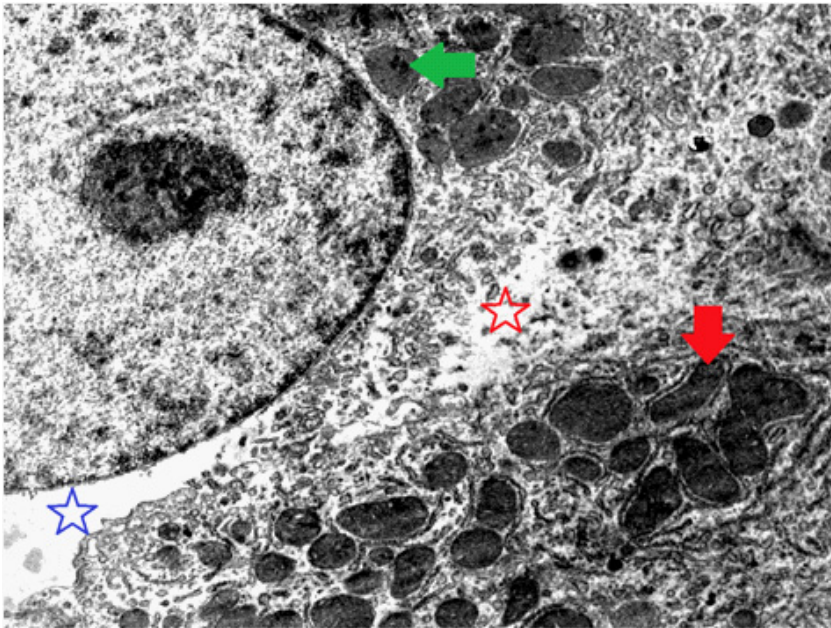


Figure 7: Cytoplasmic edema (red asterisk) (especially in perinuclear area; blue asterisk) and mitochondrial degeneration are shown (red arrow shows increase in the matrix density, blue arrow shows myelinic figure formation within the matrix). X 8.000.

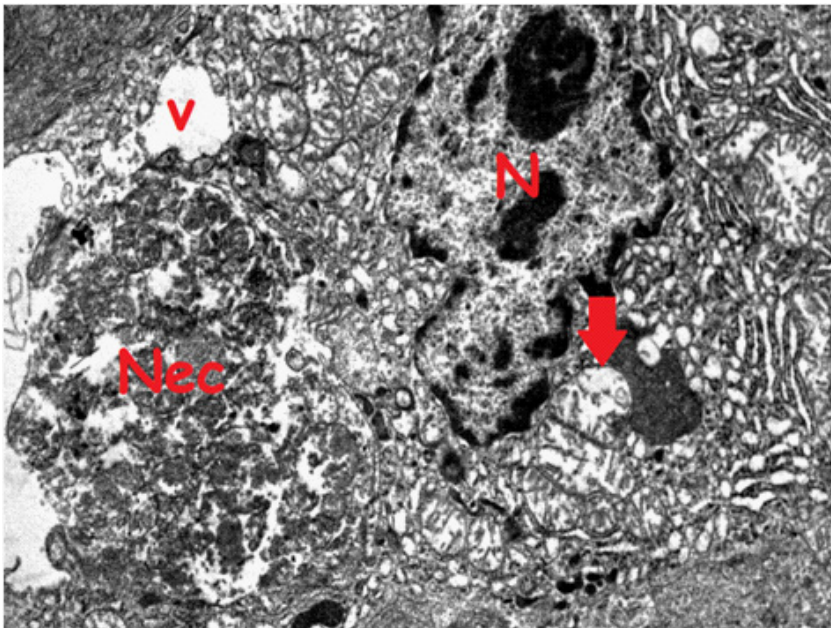


Figure 8: Nuclear irregularity, vacuole formation (v), mitochondrial degeneration (swelling and cristae loss) (red arrow), and necrosis (Nec) are obvious. Note that degenerated organelles are spilled out to the extracellular space. X. 8.000.

PERISINUSODAL AREA

Hepatic sinusoids are large capillaries lined with a discontinuous endothelium with discontinuous basal lamina. Endothelial cells are separated from each other's and additionally have large fenestrae (gaps). Perisinusoidal area is a very intriguing area in terms of the organization of perisinusoidal space (space of Disse) and the presence of various cell types with various functions. The cell types located within the perisinusoidal area are Kupffer cells, Ito cells (hepatic stellate cells), and Pit cells.

Kupffer cells, derived from monocytes, belong to mononuclear phagocyte system. Their processes attach to the sinusoidal wall. They span the lumen, may partially occupy it. The most attractive feature of these cells is the presence of numerous lysosomes within their cytoplasm (Figure 9). Since they are involved in the breakdown of senile erythrocytes as well as harmful foreign material, they have cell fragments and iron in the form of ferritin.

Ito cells, also found in perisinusoidal area, are of mesenchymal origin. They are the primary site for hepatic vitamin A in the form of retinyl esters within cytoplasmic lipid droplets (Figure 10). Additionally they are capable of producing matrix proteins, collagen, and growth factors, etc. They may present antigens to natural killer cells, so they should be considered as antigen-presenting cells. They can contract by the presence of desmin and smooth muscle α -actin and thus may regulate the diameter of the sinusoids. They are related with portal hypertension. In some pathological conditions (e.g. cirrhosis) they differentiate into myofibroblasts, synthesize collagens type I and III resulting in fibrosis [1,2].

Some studies have shown that oxidative stress has important functions in the course of cholestasis [3,4,9,10-12]. Rat models with ligated bile ducts show the symptoms, which are similar to those observed in humans with biliary hepatic fibrosis. Duct occlusion results in activation of hepatic stellate cells as well as induction of hepatocyte death by necrosis and apoptosis, proliferation of bile duct epithelial cells, and promotion of fibrosis development [13,14]. Since hepatic fibrosis lesions contain a large number of α -smooth muscle actin-positive cells, which might have originated from hepatic stellate cells/myofibroblasts, it is suggested that Ito cells play a key role in the pathogenesis of liver fibrosis induced by hepatic cholestasis [15].

Pit cells are the other type of hepatic sinusoidal cells, defined morphologically as large granular lymphocytes and functionally as liver-associated natural killer cells.

They are accepted to be synonym with natural killer cells of other organs although there are expected natural killer cells in liver. They share several morphological properties with natural killer cells, and at least some are probably observed as pit cells under an electron microscope. They are situated inside the sinusoidal lumen, adhering to the endothelial cells and Kupffer cells. They contain multivesicular body-related dense granules and rod-cored vesicles. The number and size of granules and vesicles differ between hepatic natural killer cells and peripheral blood

cells, suggesting possible differentiation of the latter into the former in the microenvironment of the liver [16]. Pit cells may reside in the liver about 2 weeks, under the supportive influence of Kupffer cells [2].

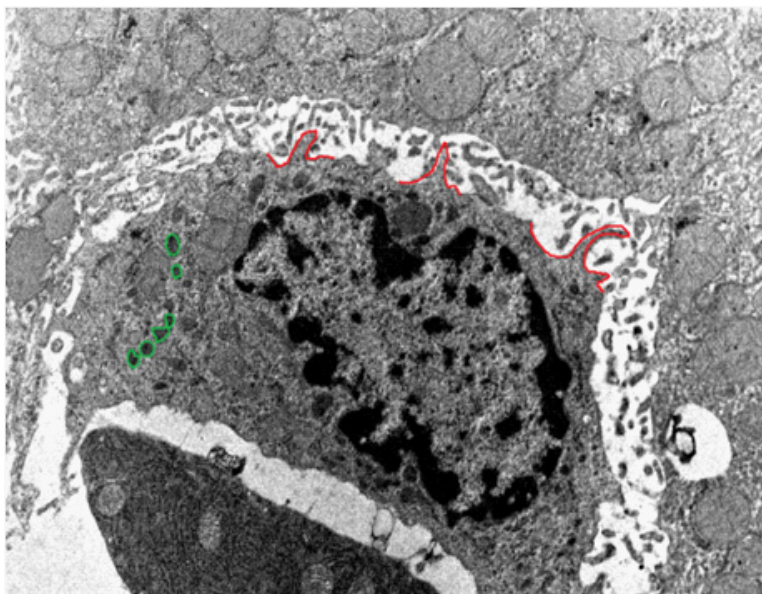


Figure 9: A Kupffer cell containing many lysosomes (some of those are marked by green lines) is observed to attach to the wall of the sinusoid capillary by projections (some of those are marked by red lines). X 8.000.

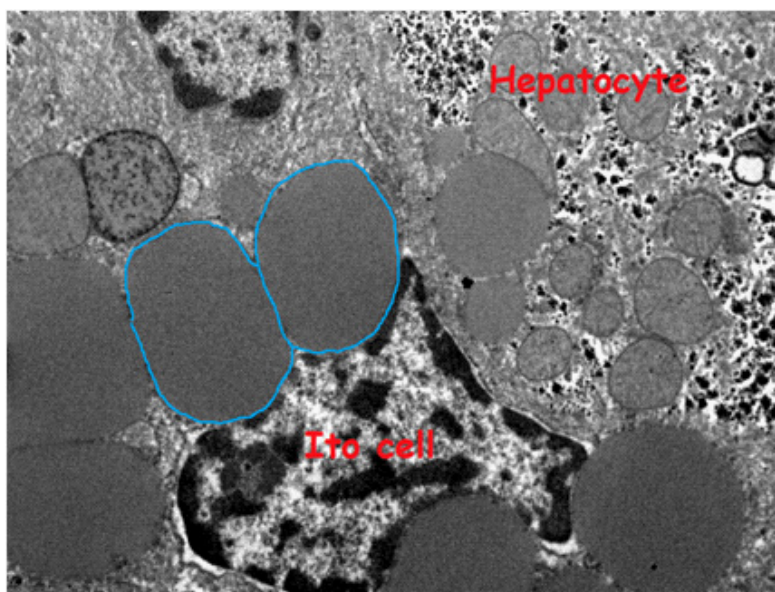


Figure 10: An Ito cell containing many lipid droplets (two of those are lined by blue lines) is observed at the perisinusoidal area. X 10.000.

ARCHITECTURE OF THE BILIARY TRACT

The smallest branches of the biliary tree are the bile canaliculi. Thus hepatocytes secrete bile firstly into the bile canaliculi. In fact, bile canaliculi are narrow components of intercellular space (Figure 11) isolated from the rest of intercellular compartment by tight junctions including mainly zonula adherents and desmosomes. Microvilli of two adjacent hepatocytes extend into canaliculus lumen (Figure 12).

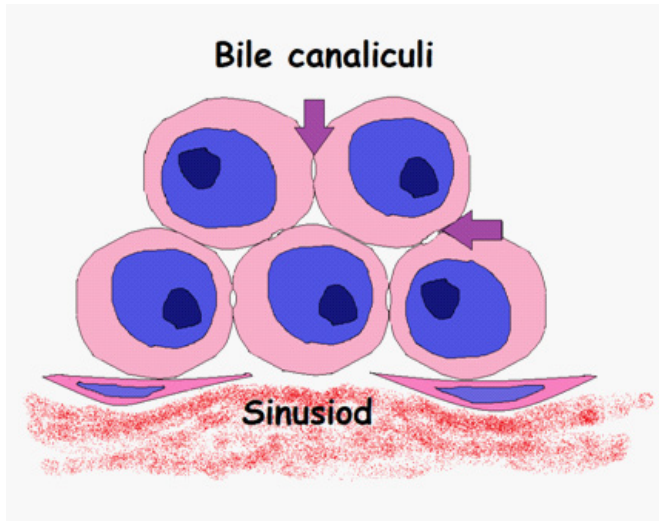


Figure 11: Bile canaliculi between adjacent hepatocytes are shown (Drawn by Esrefoglu M).

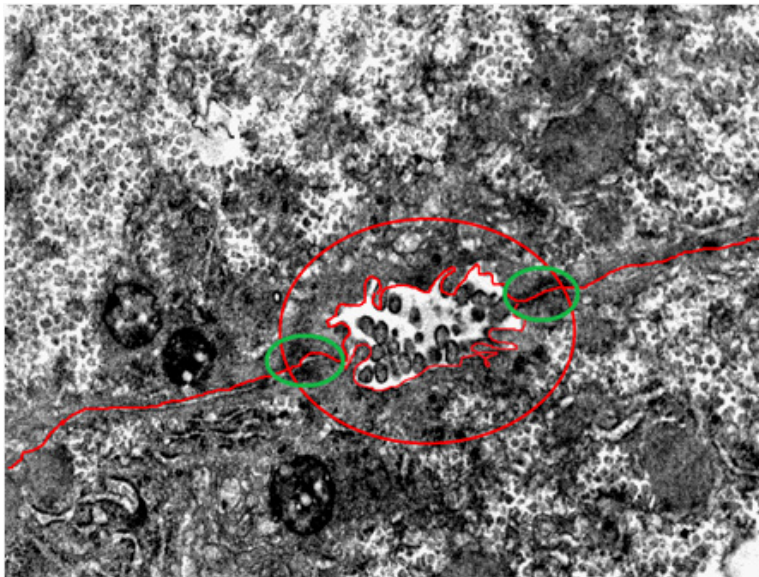


Figure 12: Bile canaliculus, a small area of intercellular space between two adjacent hepatocytes, is shown. Note the junctional complexes at the edges (in green circle) and microvilli at the surface. X 16.000.

Bile canaliculi is continuous with small ducts (or canals) located in the periphery of the classical liver lobules. These ducts surrounded with single cuboidal epithelium are called as canals of Hering. The epithelium of the canal of Hering is made of two types of cells, hepatocytes and cholangiocytes. Epithelial cells possess microvilli at their apical surfaces and tight junctions at their lateral surfaces. The canal of Hering exhibits contractile activity that assists with unidirectional bile flow toward the portal canal. Moreover, biliary tree is capable to monitor bile flow and regulate its content by changing its composition. Functional disturbance of contractile activity as well as injury or destruction of the canals of Hering may contribute to intrahepatic cholestasis (obstruction of the bile flow) [1,2].

Due to the unique location that is between hepatocytes and cholangiocytes, the canal of Hering is thought to serve a reservoir of liver stem/progenitor cells [17]. The cell compartment that resides in the canal of Hering has been called the progenitor (in humans) or the oval cell compartment (in rodents) [17,18]. In humans the canal extends to the proximate third of the lobule whereas in rodents it can barely extend beyond the limiting plate [19]. The 'oval cells' of the epithelium can differentiate into both hepatocytes and cholangiocytes. Thus, it would be more appropriate to use the term 'hepatic progenitor cells' instead of 'oval cells' [20]. The transdifferentiation of oval cells to hepatocytes may determine survival when it occurs during liver failure in humans.

The canals of Hering are continuous with the small interlobular bile ducts that form part of the portal triad. These ducts are lined by cholangiocytes that are cuboidal at the beginning and gradually become columnar. These cells possess many microvilli at their apical sites as those of the extrahepatic bile ducts and gallbladder (Figure 13). Larger bile ducts are surrounded dense connective tissue containing collagen and elastic fibers and, additionally smooth muscle cells approaching to the hilum. Finally, interlobular ducts join to form the right and left hepatic ducts, which in turn join to form the common hepatic duct. Extrahepatic bile ducts lined by tall columnar epithelium have all layers of the alimentary canal, except the muscularis mucosa. Common bile duct extends to the wall of the duodenum at the ampulla of Vater. A thickening of muscularis externa constitutes sphincter of Oddi which surrounds the openings of both pancreatic and common hepatic ducts.

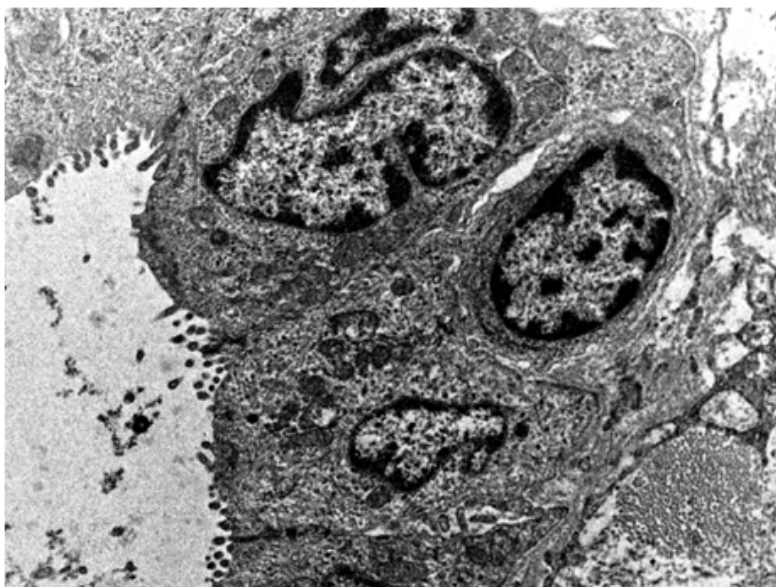


Figure 13: A bile duct lined by simple columnar epithelium with apical microvilli is surrounded with the connective tissue of portal space. X 8.000.

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