Lymph Circulation in the Liver

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ABSTRACT

The liver produces a large amount of lymph, which is estimated to be 25 to 50 % of lymph flowing through the thoracic duct. The hepatic lymphatic system falls into three categories depending on their locations: portal, sublobular, and superficial lymphatic vessels. It is suggested that 80 % or more of hepatic lymph drains into portal lymphatic vessels, while the remainder drains through sublobular and capsular lymphatic vessels. The hepatic lymph primarily comes from the hepatic sinusoids. Our tracer studies, together with electron microscopy, show many channels with collagen fibers traversing through the limiting plate and connecting the space of Disse with the interstitial space either in the portal tracts, or around the sublobular veins. Fluid filtered out of the sinusoids into the space of Disse flows through the channels traversing the limiting plate either independently of blood vessels or along blood vessels and enters the interstitial space of either portal tract or sublobular veins. Fluid in the space of Disse also flows through similar channels traversing the hepatocytes intervening between the space of Disse and the hepatic capsule and drains into the interstitial space of the capsule. Fluid and migrating cells in the interstitial space pass through prelymphatic vessels to finally enter the lymphatic vessels. The area of the portal lymphatic vessels increases in liver fibrosis and cirrhosis and in idiopathic portal hypertension. Lymphatic vessels are abundant in the immediate vicinity of the hepatocellular carcinoma (HCC) and liver metastasis. HCCs expressing vascular endothelial growth factor-C are more liable to metastasize, indicating that lymphangiogenesis is associated with their enhanced metastasis. Anat Rec, 291:643–652, 2008.

Key words: lymp circulation; lymphatic vessel; liver; electron microscopy; corrosion case; KOH-maceration

As in other organs, the lymphatic vessels in the liver function as a tissue drainage system and an immunological control system. The lymphatic vascular system consists of noncontractile initial lymphatic network and collecting lymphatic vessels. Initial lymphatic vessels are tubulosaccular and have many valves that allow unidirectional lymph flow. The basement membrane of the initial lymphatic vessels is discontinuous or absent. Lymphatic endothelial cells (LECs) are strongly attached at the anchoring filaments to the surrounding collagen and elastin fibers (Leak and Burke, 1966, 1968). LECs show tight junctions, single contact (or overlapping) junctions, and interdigitated junctions. During expansion of the initial lymphatic vessels, overlapping junctions can be opened, thus allowing fluid to flow from the interstitium into the lumen, while during compression, overlapping junctions can be closed, thereby retarding the return of lymph flow into the interstitium. Collecting lymphatic vessels are, on the other hand, located downstream of the initial ones and serve as a drainage system. Collecting lymphatic vessels are endowed with smooth muscle cells and valves. Recently, some markers specific to LECs have been discovered, which greatly promotes lymphatic research. The markers include Prox-1 (Wigle and Oliver, 1999), Podoplanin (Wetterwald et al., 1996; Breiteneder-Geleff et al., 1999), LYVE-1 (Banerji et al.,

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1999), vascular endothelial growth factor (VEGF) receptor-3 (Kaipainen et al., 1995), Macrophage mannose receptor 1 (Irjala et al., 2001), CCL21 (Gunn et al., 1998), Desmoplakin (Ebata et al., 2001), Plakoglobin (Petrova et al., 2002, Hirakawa et al., 2003), and Integrin α9 (Huang et al., 2000).

The liver produces a large volume of lymph, which is estimated to be 25 to 50% of lymph flowing through the thoracic duct (Barrowman, 1991). The hepatic lymphatic vessels fall into three categories depending on their locations: portal, sublobular, and superficial (or capsular) lymphatic vessels (Lee, 1923; Comparini, 1969; Trutmann and Sasse, 1994). It is suggested that 80% or more of hepatic lymph drains into portal lymphatic vessels, while the remainder drains through sublobular and capsular lymphatic vessels (Popper and Schaffner, 1957; Ritchie et al., 1959; Yoffey and Courtice, 1970).

It had long been a mystery how fluid and migrating cells in the hepatic sinusoids reach lymphatic vessels in the liver. Our recent studies strongly suggest that fluid in the space of Disse passes through channels between hepatocytes of the limiting plate and through the space along the initial segment of the hepatic sinusoids (or inlet venules) to enter the interstitial space of the portal tract and finally drains into portal lymphatic vessels (Ohtani et al., 2003). Fluid in the space of Disse also travels through channels between hepatocytes to enter sublobular and superficial lymphatic vessels (Poonkhum et al., 2003). In this study, we review the distribution of lymphatic vessels in the liver, the ultrastructure of fluid pathways from the space of Disse to lymphatic vessels, and the lymphatic vascular system in pathological conditions of the liver.

DISTRIBUTION OF PORTAL LYMPHATIC VESSELS

Mall (1901) showed that color gelatin injected into the portal vein first appeared in the perisinusoidal space (or the space of Disse), then reached the perilobular space, that is, the space of Mall, and finally entered portal lymphatic vessels. Corrosion casting/scanning electron microscope (SEM) studies showed lymphatic vessels around interlobular veins, arteries and bile ducts, which extended distally as far as the terminal portal tract in rabbit (Yamamoto and Phillips, 1986; Ohtani, 1989; Fig. 1). The resin injected into the common bile duct in retrograde direction to bile flow leaks out of the bile duct at the periphery of the hepatic lobules and fills the lymphatic vessels in the portal tract. This is well correlated with the fact that biliary constituents enter the lymphatic vessels following bile duct obstruction (Bloom, 1923). The portal lymphatic vessels are composed of straight vessels and anastomosing short side branches. The anastomoses are especially rich at the bifurcation of the portal tracts and form a network (Yamamoto and Phillips, 1986). The lymphatic corrosion casts show many distinct notches indicative of locations of valves. Immunohistochemistry to markers specific to lymphatic vessels such as LYVE-1 (Banerji et al., 1999) and Prox-1 (Wigle and Oliver, 1999) shows the existence of lymphatic vessels in the portal tract (Carreira et al., 2001).

DISTRIBUTION OF SUBLOBULAR LYMPHATIC VESSELS

Sublobular lymphatic vessels reportedly exist in many mammals, including rabbits, dogs, cats, and humans (Lee, 1923; Yoffey and Courtice, 1970; Nishi, 1983; Trutmann and Sasse, 1994). Complete ligation of the thoracic duct in the cat shows expanded sublobular lymphatic vessels as well as expanded sinusoids, the space of Disse, and the channels connecting the space of Disse and that of perihepatic interstitial tissue (Poonkhum et al., 2003). Sublobular lymphatic vessels lead into lymphatic vessels running along the inferior vena cava.

DISTRIBUTION OF SUPERFICIAL LYMPHATIC VESSELS

According to Rusznyak and his colleagues (1967), superficial lymphatic vessels in human liver form a very dense network and their efferent vessels travel in several directions. Some of the lymphatic vessels coming from the central area run in the falciform ligament toward the diaphragm, others pass downward into the lymph nodes of the porta hepatis. The lymphatic vessels from the lateral area of the liver convexity advance in the triangular ligament toward the diaphragm and lead into the pancreaticolienal lymph nodes. The lymphatic vessels in the coronary ligament drain into those along the inferior vena cava. The superficial lymphatic vessels from the concave part of the liver curvature run in various directions toward their regional lymph nodes.

ORIGIN OF THE PORTAL LYMPH

Our previous study has demonstrated that the hepatic sinusoids and the space of Disse significantly expand when the thoracic duct is completely ligated (Poonkhum et al., 2003). This fact indicates that hindrance of lymph drainage of the liver causes hepatic sinusoids and the space of Disse to expand, suggesting that macromolecules and hepatic lymph fluid come from the hepatic sinusoids. The hepatic artery is responsible for 25% of the hepatic blood flow (Fawcett, 1994; Saxena et al., 1999), and primarily supplies the peribiliary plexus of the intrahepatic bile duct (Ohtani and Murakami, 1978; Ohtani, 1979). As filtration through the walls of blood capillaries is responsible for the origin of lymph (Starling, 1896), it is probable that the interstitial fluid in hepatic lymphatic vessels also originates from these arteries. However, 75% of the blood in the liver comes from the portal vein and almost all the blood of the liver flows through sinusoids. Furthermore, the protein concentration of hepatic lymph is approximately 80% of the plasma protein concentrations (Yoffey and Courtice, 1970; Courtice et al., 1974), suggesting that hepatic lymph derives from highly permeable sinusoids rather than true capillaries of peribiliary plexuses (Gemmel and Heath, 1972; Wright et al., 1983; Wisse et al., 1985).

Considering the large volume of portal lymph in connection with the structure of the portal capillaries, the portal tracts themselves do not appear to be a major source of portal lymph; indeed, Heath and Lowden (1998) reported that the space of Disse is continuous with the interstitial space of the portal tracts at the origin of the sinusoids (or inlet venule). Our recent study

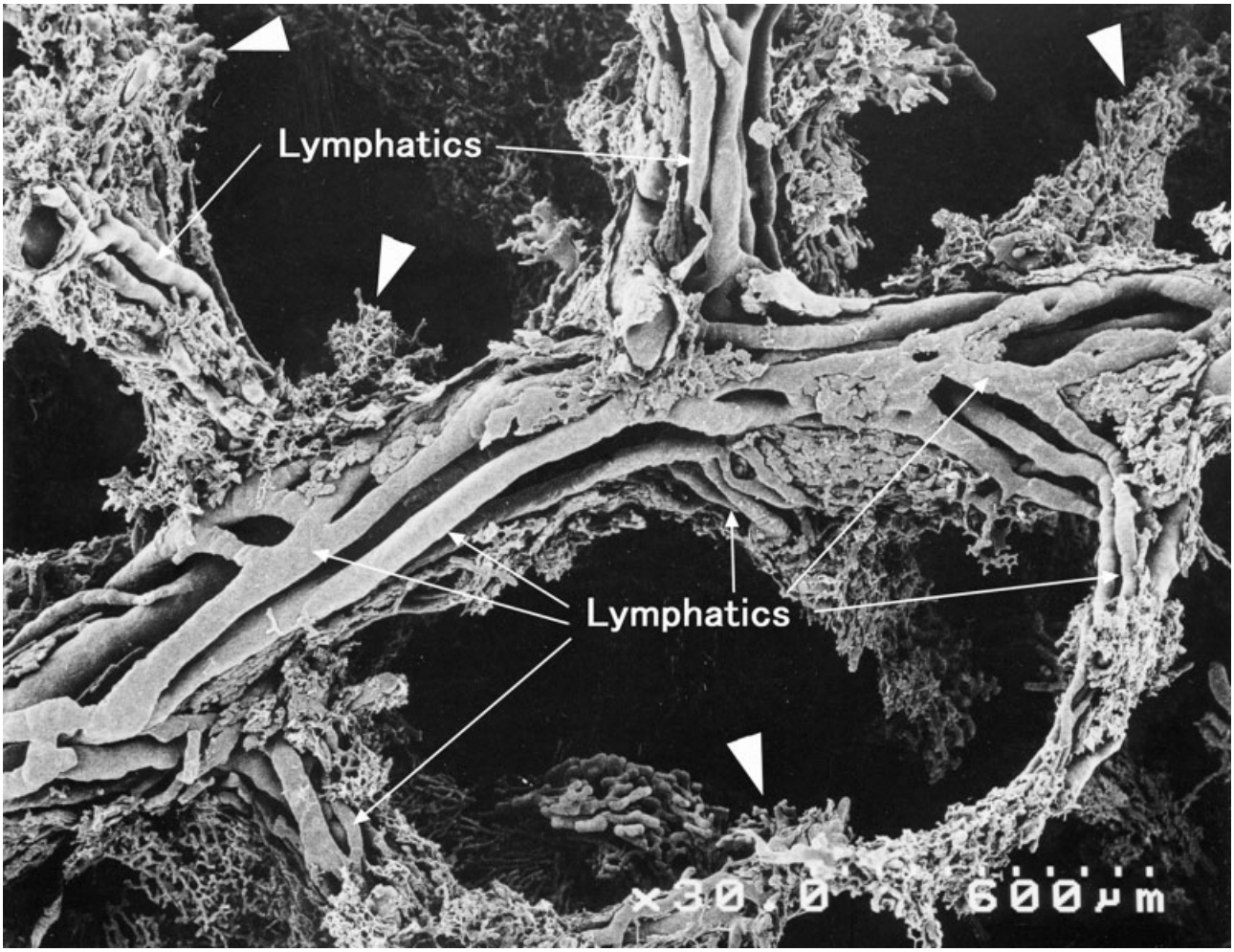

Fig. 1. Scanning electron micrograph of the lymphatic corrosion cast of the rabbit liver. The lymphatic network in the portal tract extends as far as terminal portal tract. Arrows indicate partially filled sinusoids in the vicinity of the portal tract.

has revealed that, in addition to the pathways reported by Heath and Lowden (1998), there are many channels penetrating through the portal limiting plate to connect the space of Disse with the interstitial space of the portal tract (Ohtani et al., 2003) (see below).

Corrosion casting/SEM has shown that the portal lymphatic networks develop around the portal triads, and they extend distally as far as the terminal portal tract in rabbits, guinea pigs, and rats (Yamamoto and Phillips, 1986; Ohtani, 1989). There are no tendencies that the portal lymphatic vessels run preferentially along the interlobular arteries, veins, or bile ducts. These also seem to support the hypothesis that the portal lymph comes mainly from the hepatic sinusoids.

ORIGIN OF THE SUBLOBULAR AND SUPERFICIAL LYMPH

Reportedly, the vasa vasorum of hepatic veins are supplied by the hepatic (Saxena et al., 1999), internal thoracic, and phrenic arteries (Tajiri, 1960; Elias and Sherrick, 1969), but it is in general not well developed. The peribiliary plexus exists only in the portal tract, but not in the sublobular interstitial space. The liver capsule does not possess its own blood vessels, but is separated by only one cell layer of hepatocytes from the hepatic sinusoids. These findings suggest that the sublobular and capsular lymph also originates from the hepatic sinusoids.

FLUID PATHWAYS FROM THE HEPATIC SINUSOIDS TO THE INTERSTITIAL SPACE OF THE PORTAL TRACTS

Our tracer study showed that horseradish peroxidase (HRP) injected into the blood vascular system of the rat appeared in the hepatic sinusoids, in the space between limiting plate hepatocytes, and in the space of Mall (Ohtani et al., 2003). At the initial segment of the hepatic sinusoids, there are interstitial space containing collagen fibers between sinusoidal endothelial cells and hepatocytes forming the portal limiting plates (i.e., portal limiting plate hepatocytes; Fig. 2). There are also spaces or channels which penetrate through the portal

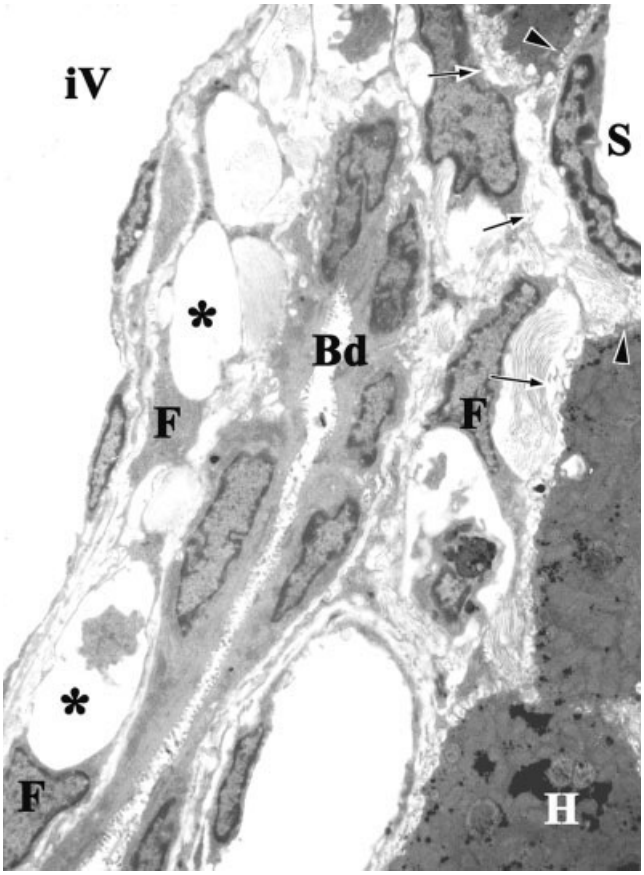

Fig. 2. Transmission electron-micrograph of intact rat liver. Arrowheads indicate transition of the space of Disse at the initial segment of sinusoids (S) to the space of Mall (arrows). Processes of fibroblast-like cells (F) form spaces (*) that mimic lymphatic vessels, in which migrating cells (presumably dendritic cells and/or lymphocytes) can be seen. Original magnification, ×3,000.

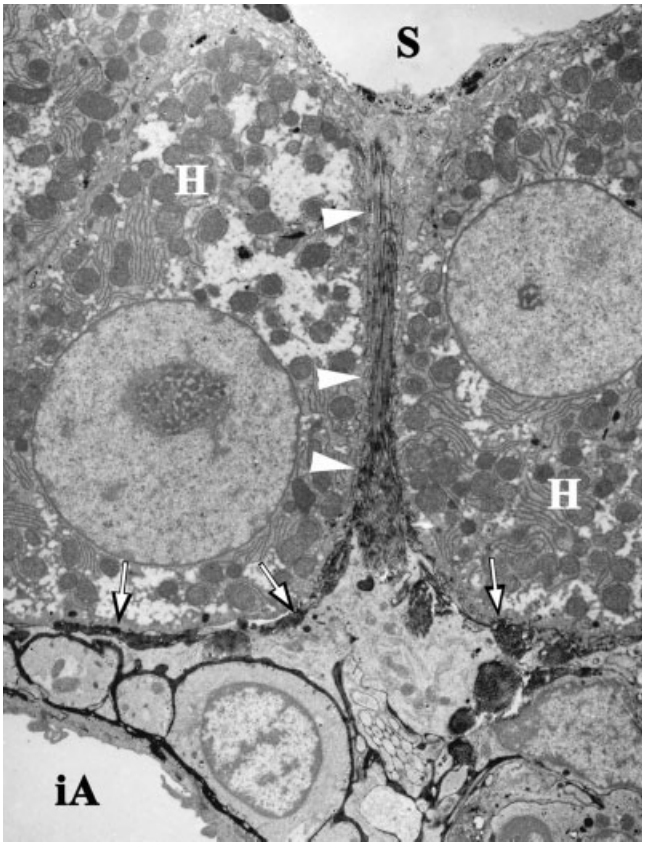

Fig. 3. Transmission electron-micrograph of the horseradish peroxidase (HRP) -injected rat liver. HRP reaction products can be seen in the sinusoids (S), in the space of Disse, in the space (arrowheads) between limiting plate hepatocytes (H), and in the space of Mall (arrows). Also note collagen fibers with HRP in the space between limiting plate hepatocytes.

limiting plate with collagen fibers, independent of the blood vessels. In line with early studies by Mall (1901) and Viragh et al. (1978), these findings indicate that fluids in the space of Disse pass through the space between limiting plate hepatocytes to enter the space of Mall as well as through the space around the initial segment of the hepatic sinusoids (or inlet venules).

Transmission electron microscopy (TEM) of the rat liver injected with HRP into the blood vascular system showed that collagen fibers are also present in the space where HRP appeared (Ohtani et al., 2003; Fig. 3). This seems to indicate that the collagen fiber network provides the liver with fluid pathways as well as skeletal framework (Ohtani, 1988, 1992). We re-examined the organization of the collagen fiber network in the liver by the alkali-water maceration/SEM technique, which was introduced by ourselves (Ohtani, 1987; Ohtani et al., 1988; Poonkhum et al., 2003).

There are much more collagen fibers in the liver than commonly assumed from observation of the tissue sections. There are condensations of collagen fibers in the Glisson's sheaths. Some collagen fibers run along the inlet venules to continue with those in the space of Disse, while others travel independently of blood vessels through the layer of the periportal limiting plate and connect with those in the space of Disse (Ohtani, 1988, 1992; Poonkhum et al., 2003; Fig. 4).

We have examined the ultrastructure of the periportal limiting plate by the KOH-maceration/SEM method (Ushiki and Ide, 1988). KOH-maceration at 60°C for 10 min followed by microdissection under a binocular microscope exposes the surface of the limiting plate (Ohtani et al., 2003). SEM of the samples shows many openings of channels extending through the limiting plate (Fig. 5). These openings are generally located in the areas where three hepatocytes meet. The density of the openings is approximately 1.3×10^3/mm. Undigested collagen fibers can sometimes be observed to emerge from the channels between limiting plate hepatocytes. Accidentally fractured limiting plates also show channels containing undigested collagen fibers, which pass through the limiting plate to connect the space of Disse with the interstitial space of the portal tract (Ohtani et al., 2003). Thus, it is evident that the space of Disse is in continuity with the interstitial space of the portal tract or space of Mall through the channels traversing the periportal limiting plate as well as the space along

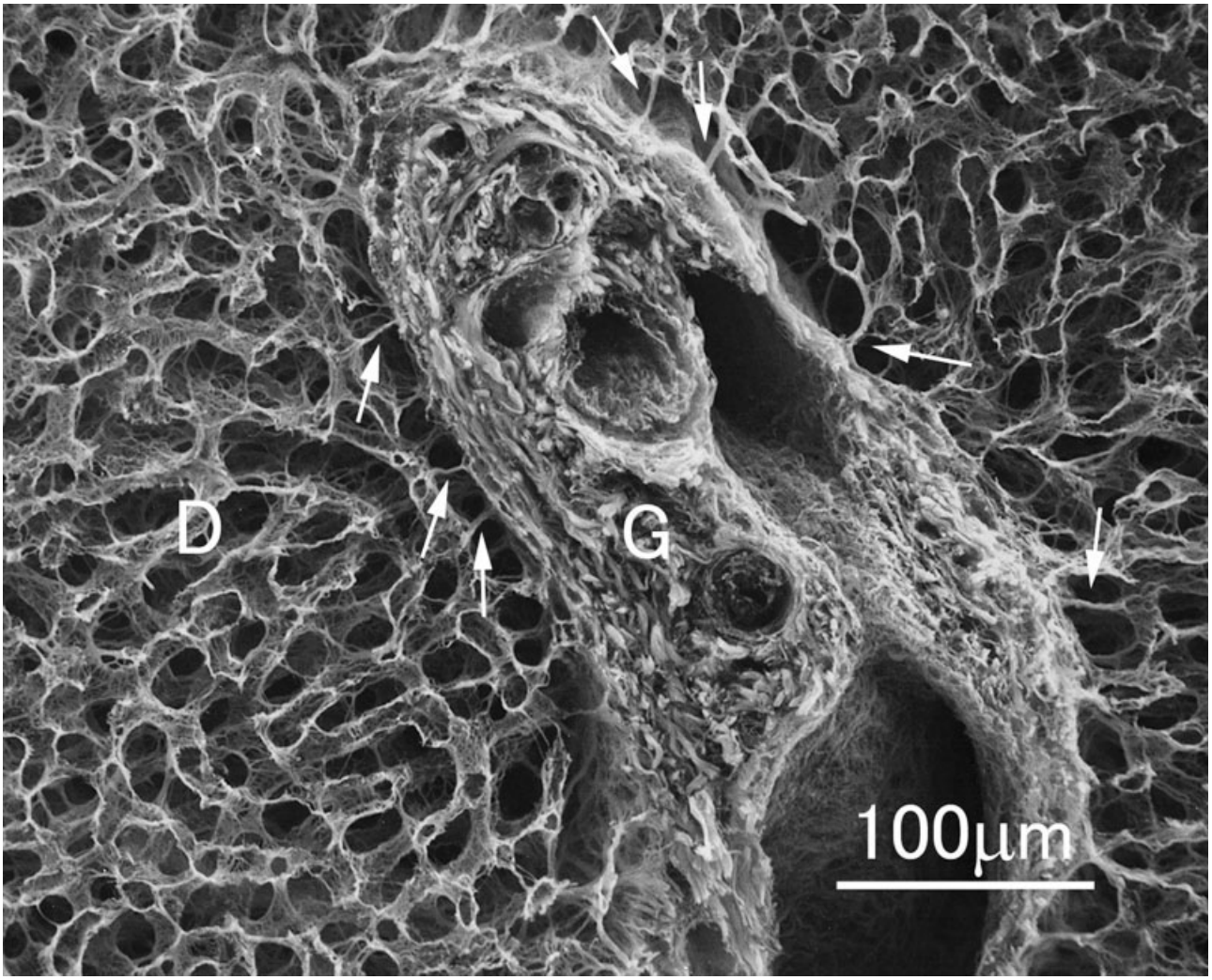

Fig. 4. Scanning electron-micrograph of collagen fiber network of the human liver. There is a condensation of collagen fibers in the Glisson's sheath (G). The collagen fibers in the space of Disse (D) form sheathes for housing the hepatic sinusoids. Arrows indicate collagen fibers passing through the layer of periportal limiting plate independently of blood vessels.

the inlet venules. The normal blood pressure in the portal vein is 7 mmHg, while the interstitial pressure of the portal tract is 5.8 mmHg (Laine et al., 1979). Because the hepatic sinusoids are highly permeable and thus oncotic pressure along the sinusoids is negligible, fluid in the hepatic sinusoids can flow through the channels traversing the limiting plate to the interstitial space of the portal tract in accordance with hydrostatic pressure gradient. The interlobular bile duct is surrounded by the peribiliary capillary plexus (Ohtani and Murakami, 1978; Ohtani, 1979). The peribiliary capillary consists of endothelial cells of a continuous type (Barrowman and Granger, 1984). In accordance with the force of the Starling, fluid is filtered through the peribiliary capillaries into the surrounding connective tissue. However, Földi (1974) estimated that the peribiliary capillary plexus contributes less than 10% to the total lymph output from the liver.

Taken together, it is likely that fluid filtered out of the hepatic sinusoids into the space of Disse flows through the channels traversing the limiting plate either independently of blood vessels or along inlet venules to reach the interstitial space of the portal tract.

PATHWAYS FOR BLOOD–LYMPH TRANSLOCATION OF MIGRATING CELLS

The channels traversing the periportal limiting plate also can be pathways for free cells such as dendritic cells and lymphocytes to migrate from the hepatic sinusoids to the interstitial space of the portal tract. Indeed, our TEM of lipopolysaccharide-injected rat liver has shown that cells, presumably dendritic cells, in the hepatic sinusoids or between limiting plate hepatocytes, extend their long pseudopodia through channels in the limiting plate to the interstitial space of the portal tract. The

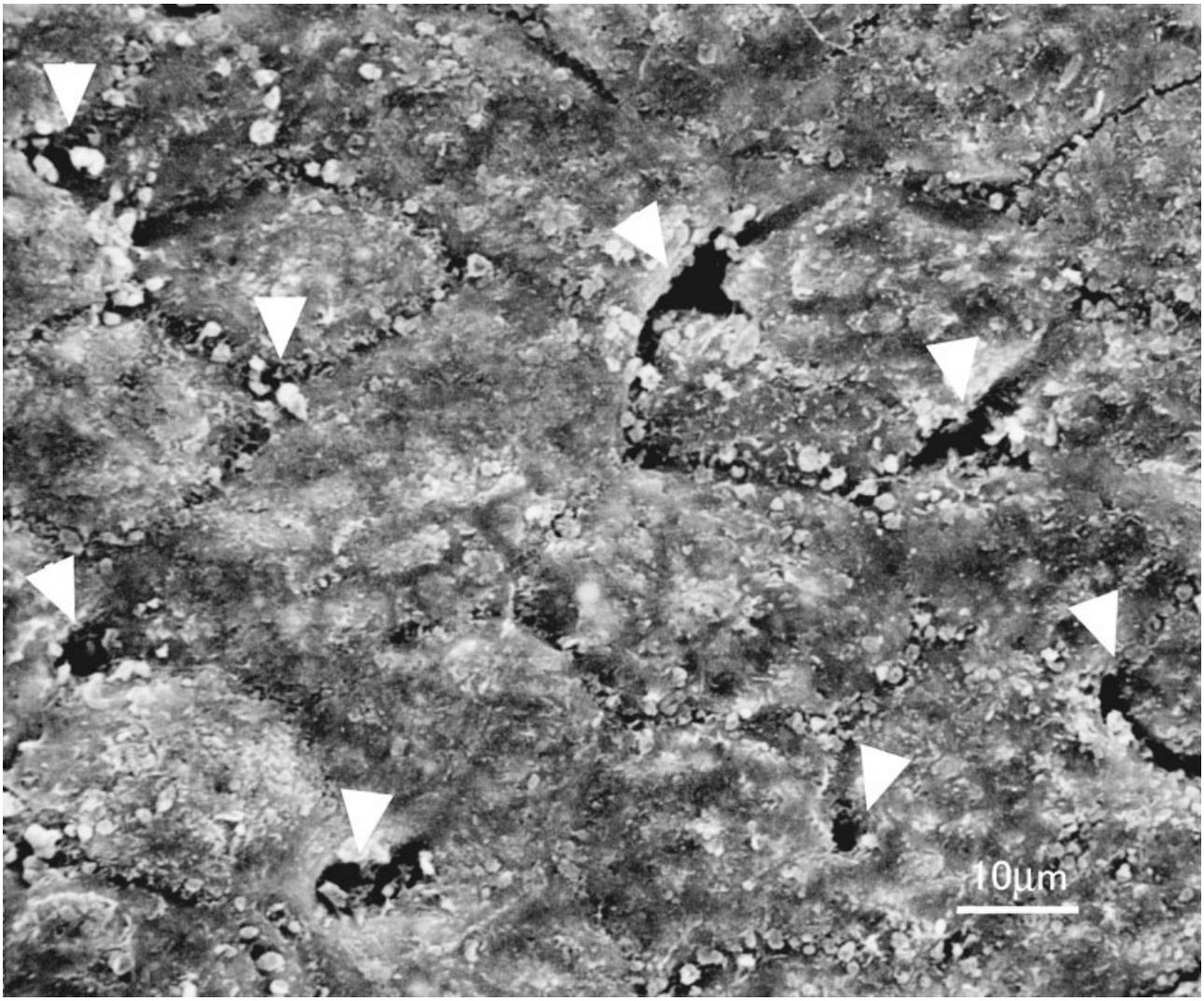

Fig. 5. Scanning electron micrograph of the rat liver treated with the KOH-maceration technique, showing surface view of the portal tract side of limiting plate. There are many openings (arrowheads) of channels between limiting plate hepatocytes.

morphology of these cells strongly suggests that the cells migrate from the hepatic sinusoids through the channels in the limiting plate to the interstitial space of the portal tract. It has been reported that mature dendritic cells in the blood can transmigrate only from the blood vessels of the liver and spleen (Kudo et al., 1997; Matsuno and Ezaki, 2000). Dendritic cell release is enhanced by an IV injection of endotoxin (Young et al., 1994; MacPherson et al., 1995). Thus, it is likely that the cells transmigrating through the limiting plate are mostly dendritic cells. As lymphocytes also translocate from the blood to the hepatic lymph, some of the migrating cells may be lymphocytes.

FLUID PATHWAYS FROM HEPATIC SINUSOIDS TO SUBLOBULAR INTERSTITIAL SPACE

Collagen fibers in the liver form a continuum as a skeletal framework of the liver (Ohtani, 1988, 1992; Poonkhum et al., 2003). Collagen fibers in the space of Disse are continuous with those around the central vein, which in turn increase in number toward the sublobular vein and the hepatic vein and finally continue into those around the vena cava. In addition, many collagen fibers traversing the hepatic limiting plate independently of blood vessels connect collagen fibers in the space of Disse with those around the sublobular veins. Furthermore, our TEM has shown that many channels with collagen fibers pass through the limiting plate: the channels communicate the space of Disse to the sublobular interstitial space. Our tracer studies have shown that HRP injected into the systemic vein flows along collagen fibers in the liver (Ohtani et al., 2003). In this context, it is likely that fluid in the space of Disse flows through the channels along collagen fibers traversing the hepatic limiting plate. Fluids in the space of Disse also flow through spaces along collagen fibers connecting those around sinusoids with central veins into the interstitial space of the sublobular and hepatic veins. Fluid in the

interstitial space around the sublobular vein finally enters sublobular lymphatic vessels.

Sublobular lymphatic vessels in cat livers are found in the sublobular venous walls of approximately 200 μm or more in thickness (Poonkhum et al., 2003). Sublobular lymphatic vessels reportedly exist in many mammals, including rabbits, dogs, cats, and humans (Lee, 1923; Ritchie et al, 1959; Rusznyak et al, 1967; Comparini, 1969; Yoffey and Courtice, 1970; Nishi, 1983; Trutmann and Sasse, 1994). Rusznyak and his colleagues (1967) reported that, in cats, most of the efferent hepatic lymph vessels run caudally along the portal vein and there are no, or scarcely any, lymphatic vessels running in a cranial direction along the branches of the hepatic vein. The present study, however, shows that the sublobular lymphatic vessels are fairly developed in cat livers. Rat livers, however, do not possess sublobular lymphatic vessels (Niiro and O'Morchoe, 1986). These findings appear to indicate that sublobular lymphatic vessels exist only in a thick venous wall and that the development of the sublobular lymphatic vessels shows species differences.

Shibayama and his coworkers (1991) proposed that the obstruction of sublobular lymphatic vessels may result in some veno-occlusive lesions in patients with carcinoma in the liver. The sublobular lymphatic vessels may be involved in intrahepatic remetastases of colorectal cancer (August et al., 1985).

FLUID PATHWAYS FROM THE SPACE OF DISSE TO THE INTERSTITIAL SPACE OF THE LIVER CAPSULE

Our TEM results demonstrate that the space of Disse around the hepatic sinusoids close to the portal tract communicates through the spaces containing collagen fibers between hepatocytes with the interstitial space of the hepatic capsule (Ohtani et al., 2003). Our tracer study has shown that HRP appears along collagen fibers running from the space of Disse through the space between hepatocytes to the interstitial space of the hepatic capsule. Collagen fibers in the space of Disse are connected with those in the hepatic capsule (Ohtani, 1988, 1992; Poonkhum et al., 2003). These findings seem to indicate that fluids in the hepatic sinusoids located close to the hepatic capsule can flow at least in part to the interstitial space of the hepatic capsule, and finally enter the capsular lymphatic vessels.

PRELYMPHATIC AND LYMPHATIC VESSELS IN THE PORTAL TRACT

Our TEM results show many oval spaces incompletely lined with fibroblast-like cells in the portal tract (Ohtani et al., 2003; Fig. 2). Thus, the interstitial space of the portal tract shows a porous appearance. Observations of serial sections suggest that the spaces form a tubular structure partly lined with fibroblast-like cells. The spaces in question frequently contain lymphocytes and/or dendritic cells. Therefore, it is likely that the spaces or tubular structures, herein termed prelymphatic vessels (Ohtani et al., 2003), serve as pathways for migrating cells such as lymphocytes and dendritic cells as well as fluid draining into the portal tract.

How do prelymphatic vessels continue to lymphatic vessels? We have so far failed to demonstrate any direct transition of prelymphatic vessels to lymphatic vessels. As prelymphatic vessels are only incompletely lined with fibroblast-like cells and initial lymphatic vessels open to the interstitial space, fluid, and cells can probably easily move from prelymphatic vessels to lymphatic vessels. Further studies with a variety of methods are mandatory to determine whether prelymphatic vessels directly continue to the lymphatic vessels. We should also examine the nature of the fibroblast-like cells lining prelymphatic vessels in relation to lymphatic endothelial cells.

COMMUNICATIONS BETWEEN THE PORTAL AND SUBLOBULAR LYMPHATIC SYSTEMS

Sublobular and portal lymphatic vessels are sometimes enclosed in a common investment of connective tissue. The sharing of connective tissue of both kinds of lymphatic vessels has been reported in rabbits (Nishi, 1983), cats (Lee, 1923), dogs (Ritchie et al, 1959), and humans (August et al., 1985). In mice and rats, sublobular veins sometimes cross over interlobular veins (Wagenaar et al, 1994; Morikawa et al., 2000). Liver lymph flow reportedly relates directly to hepatic venous pressure in dogs and cats (Barrowman and Granger, 1984). Blood pressure of the portal vein is higher than that of the hepatic vein: normal blood pressure in the portal vein is 7 mmHg and that in the inferior vena cava is 2 mmHg (Laine et al., 1979). These facts suggest that some of the interstitial fluid in the portal tract may flow to the interstitial space around the sublobular veins to enter the sublobular lymphatic vessels.

LYMPHATIC VESSELS IN PATHOLOGICAL CONDITIONS OF THE LIVER

It is known that increased portal lymph flow occurs in diffuse abnormalities of liver architecture such as fibrosis and cirrhosis (Ludwig et al., 1968; Witte et al., 1969). Indeed, Barrowman and Granger (1984) report that lymph flows from the liver in cirrhotic rats are increased 30-fold, and that liver lymph flows correlate well with portal venous pressure. Furthermore, they demonstrate that the highly permeable blood–lymph barrier of the normal liver becomes markedly restrictive in cirrhotic animals (Barrowman and Granger, 1984). Vollmar et al. (1997), in their intravital fluorescence microscopy of CCl_4-induced fibrosis liver in the rat, show a strong negative correlation between portal lymphatic network density development and macromolecular trans-sinusoidal exchange. Their study provides the direct evidence for the pivotal role of lymphatic function for macromolecular transport in case of deteriorated sinusoidal hepatocellular exchange capacity. Oikawa et al. (1998) report that the area of portal lymphatic vessels increases in idiopathic portal hypertension (IPH), also known as Banti's syndrome, suggesting that the increased lymphatic area may be associated with a reduction in portal blood flow and increased lymph flow, and that the latter may in turn reduce the high portal vein pressure in IPH.

Tumor metastasis to lymph nodes by means of the lymphatic vascular system results in poor prognoses of patients with cancers. Reportedly, in human heptocellular carcinoma (HCC) and some metastasized tumors, LYVE-1- and Prox 1-positive lymphatic vessels are abundant in the immediate vicinity of the tumors (Carreira

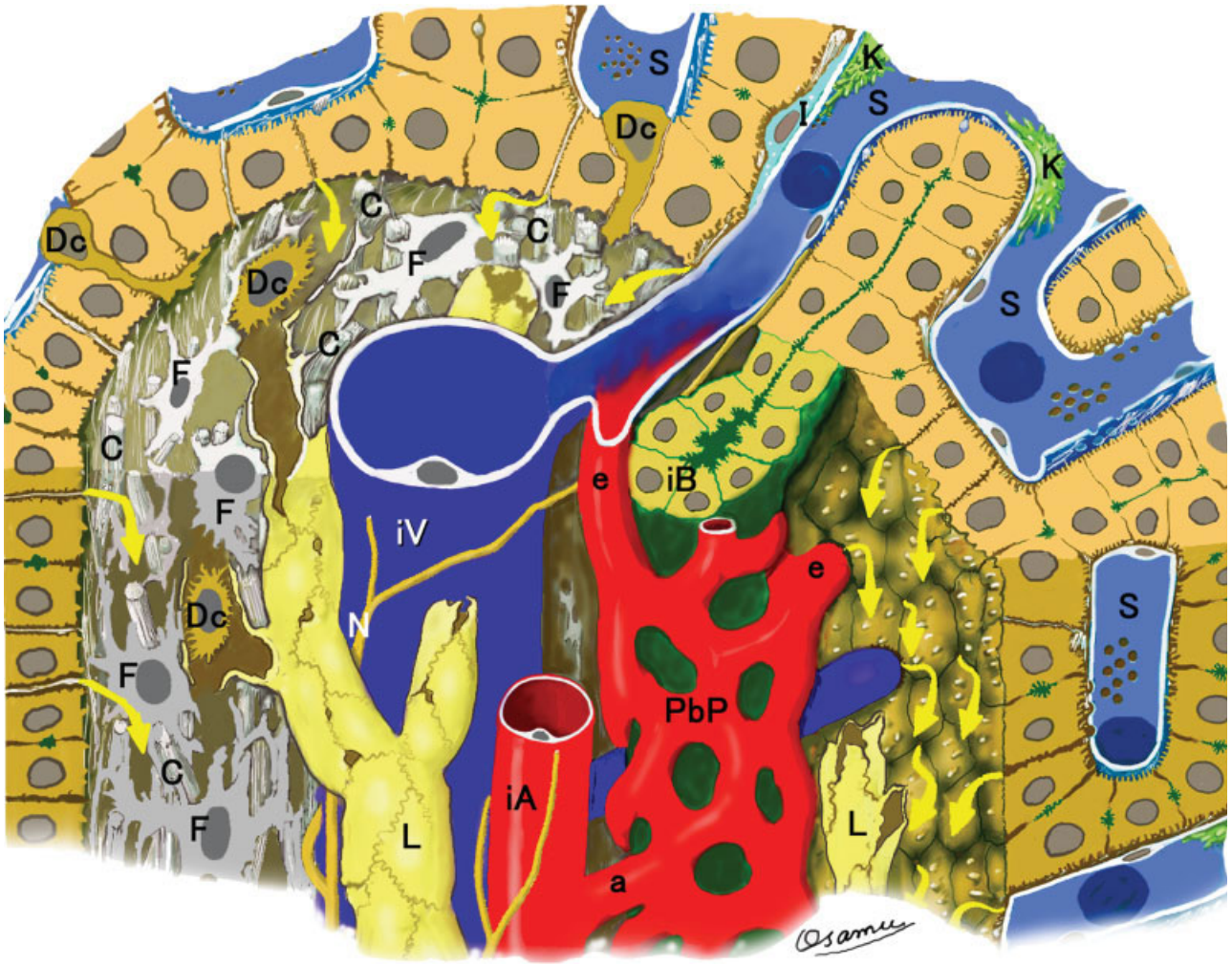

Fig. 6. A schematic representation of pathways of fluid and migrating cells such as dendritic cells (Dc) extending from the sinusoids (S) through the space of Disse, channels in the limiting plate, and interstitial space of the portal tract to portal lymphatic vessels (L). Arrows indicate the presumable flow direction. C, collagen fibers; iA, interlobular artery; iV, interlobular vein; iB, interlobular bile duct; F, fibroblast; I, Ito cell (or stellate cell); K, Kupffer cell; N, nerve; PbP, peribiliary capillary plexus; a, afferent vessel of PbP; e, efferent vessel of PbP.

et al., 2001). Recent studies by others show that poorly differentiated HCCs express VEGF-C significantly stronger than well- or moderately differentiated HCCs, and the incidence of metastasis is higher in patients with VEGF-C expressing HCC than those without (Yamaguchi et al., 2006). These findings seem to indicate that lymphangiogenesis is associated with enhanced metastasis as reported in other human cancer (Achen et al., 2005; Tobler and Detmar, 2006; Thiele and Sleeman, 2006).

CONCLUSION

The hepatic lymphatic system falls into three categories depending on their location: portal, sublobular, and superficial lymphatic vessels. The hepatic lymph primarily comes from the hepatic sinusoids. Fluid filtered out of the sinusoids into the space of Disse flows through the channels traversing the limiting plate either independently of blood vessels or along blood vessels and enters the interstitial space of either the portal tract, sublobular veins, or the hepatic capsule. Fluids and migrating cells in the interstitial space pass through prelymphatic vessels to finally enter the lymphatic vessels. Pathways for movement of fluid and cells from hepatic sinusoids to the portal lymphatic vessels are summarized in Figure 6.

In addition, the present study briefly reviews the lymphatic vascular system in portal hypertension and liver cancers. Little is known about the development of hepatic lymphatic vessels in the fetal and early postnatal liver, which is a topic that warrants to be studied.

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