
Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell

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Laurie D. DeLeve

Abstract

The hepatic sinusoidal endothelial cell is highly differentiated, with unique morphology and function. It provides a porous barrier that facilitates access of the hepatocyte to oxygen and small molecules in the microcirculation. Other specialized functions include clearance of colloids and macromolecules, promotion of hepatic stellate cell quiescence, and induction of immune tolerance. The hepatic sinusoidal endothelial cell may be injured by a variety of toxins, ischemia–reperfusion, and even bacteria, leading to vascular liver diseases such as sinusoidal obstruction syndrome, nodular regenerative hyperplasia, and peliosis hepatis.

Keywords

Liver • Liver circulation • Endothelial cells • Hepatic veno-occlusive disease • Nodular regenerative hyperplasia

Introduction

The liver sinusoidal endothelial cell (LSEC) has a number of important functions, as will be addressed below. To summarize these functions, LSECs: (1) provide a porous barrier that facilitates oxygenation of hepatocytes and enhances hepatocyte exposure to macromolecules in the portal circulation; (2) clear colloids and macromolecules from the circulation; (3) act as a gatekeeper against hepatic stellate cell (HSC) activation; and (4) provide a microcirculation.

Wisse was first able to demonstrate that the endothelial cells lining the hepatic sinusoids were distinct from Kupffer cells using electron microscopic studies of the perfusion-fixed liver [1, 2]. The next major step forward in LSEC research was the description of a method to isolate a pure population of LSEC using elutriation [3, 4]. Isolation by elutriation requires specialized equipment, which has limited the number of laboratories working in this field. Subsequent development of a method using density gradient centrifugation with selective adherence has provided an alternative method for rapid and inexpensive isolation of LSEC [5]. In recent years, several methods have been described for LSEC isolation using immunomagnetic separation. Immunomagnetic separation yields a very small fraction of the number of cells isolated by either of the two earlier methods, with the inherent risk

L.D. DeLeve (✉)
Division of Gastrointestinal and Liver Diseases,
University of Southern California,
Keck School of Medicine, 2011 Zonal Avenue- HMR 603,
Los Angeles, CA 90033, USA
e-mail: deleve@usc.edu

that subpopulations are being isolated. Most of the immunomagnetic protocols have not yet validated that the cells being isolated have both ultra-structural features and functional characteristics specific to LSEC. With proper validation, the use of immunomagnetic separation should facilitate more widespread study of LSEC.

SEC Phenotype

Two specific phenotypic features can be used to definitively identify LSEC. By electron microscopy [1, 2], LSEC have nondiaphragmed fenestrae organized in clusters termed sieve plates. Functionally, endocytosis of labeled formaldehyde-treated serum albumin or collagen alpha chains can be used to identify LSEC (see Sect. Function and Dysfunction). Although there are a number of surface markers present on LSEC (Table 2.1), few if any are specific for LSEC within the liver.

Morphology

Endothelial Cell Fenestration

The permeability of endothelial barriers is dependent on the structure of the cell itself and the underlying basement membrane. Endothelial cells are divided into continuous or discontinuous cells.

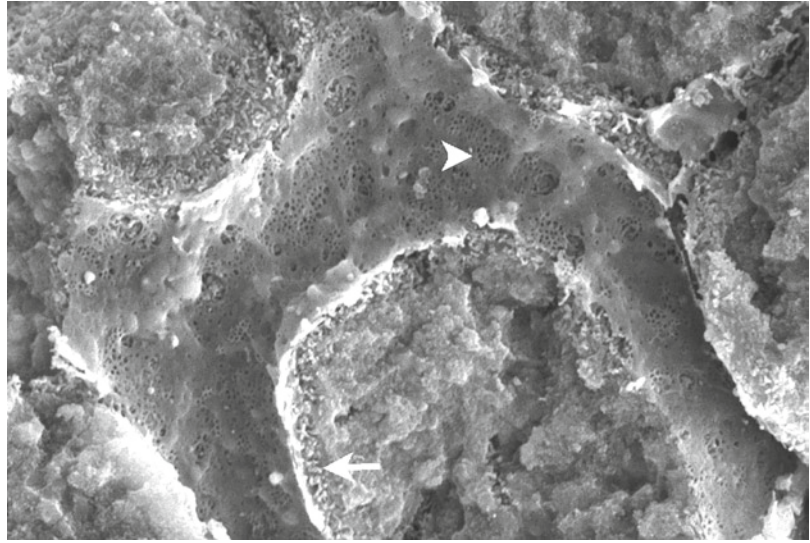
Continuous endothelial cells have continuous cytoplasm and fusion of the luminal and abluminal plasma membrane only occurs at cell junctions. The subset of discontinuous endothelium that has larger gaps or pores is referred to as fenestrated cells. Fenestrae traverse the cytoplasm and connect the luminal and abluminal cytoplasmic membrane. Fenestrae can be closed with a diaphragm or completely open. With the exception of the LSEC and renal glomerular endothelial cell, fenestrated endothelial cells in the mammal are diaphragmed. The LSEC and the glomerular endothelial cell differ from each other in that the LSEC does not have an organized basement membrane and the glomerular endothelial cell does. Thus, the LSEC has a unique morphology in that it is the only mammalian cell with both open fenestrae and the lack of an organized basement membrane. The LSEC is therefore the most permeable of all mammalian endothelial cells. The fenestrae in LSEC are grouped together in clusters, termed sieve plates (Fig. 2.1).

The LSEC morphology varies across the sinusoid. LSEC in the periportal region are smaller than perivenular LSEC. Compared to perivenular LSEC, periportal LSEC have fewer fenestrae per sieve plate and fenestrae that are slighter larger in size, but overall porosity (percentage of the cell surface occupied by fenestrae) of periportal LSEC is lower than of perivenular LSEC.

Table 2.1 Selected markers present on LSEC

CD31 or PECAM-1	Classic endothelial cell marker present on cell surface, facilitates transendothelial migration of leukocytes [6]. Absent from cell surface of LSEC, but present in cytoplasm [7]
CD45	Leukocyte common antigen. Present on 85–90% of LSEC isolated by elutriation [8]
CD33	A myeloblast antigen, also present on the LSEC surface [8]
CD4	Present on T cells, monocytes, macrophages, dendritic cells, and LSEC [9]
ICAM-1	Ligand for LFA-1 on leukocytes [9]
CD36	Thrombospondin-1 receptor [9]
Fcγ(gamma) receptor IIb ₂	Predominant receptor on LSEC for the Fc receptor of immunoglobulin G, endocytoses immune complexes. Present on dendritic cells
Stabilin-2	Main scavenger receptor on LSEC, thought within the liver to be unique for LSEC [10–12]
Integrin α(alpha) ₁ β(beta) ₁	Preferentially binds collagen IV [13]
Integrin α(alpha) ₅ β(beta) ₁	Binds fibronectin [13]
Other antigens reported on LSEC include LYVE-1, MCAM (CD46), MHC class I and class II molecules, CD80, CD86, CD40	

Fig. 2.1 Hepatic sinusoid. Scanning electron microscopy picture of hepatic sinusoid. *Arrowhead* indicates a sieve plate in the LSEC. *Arrow* indicates hepatocyte villi in the space of Disse



Other Sinusoidal Endothelial Cells

Sinusoids are tortuous terminal blood vessels with a discontinuous endothelial lining and either a discontinuous basement membrane or the lack of an organized basement membrane. In addition to the liver, both the spleen and bone marrow have sinusoids. Both the spleen and bone marrow have interendothelial slits that open up to allow migration of cells through the sinusoids, providing the discontinuity of lining. Splenic sinusoidal endothelial cells have continuous cytoplasm, but a discontinuous basement membrane that forms ring-like structures around the sinusoid [14–16]. The bone marrow has diaphragmed, fenestrated endothelial cells and a discontinuous, irregular basement membrane [17, 18].

Regulation of SEC Phenotype

Fenestrated endothelial cells occur in proximity to epithelial cells with a high constitutive expression of vascular endothelial growth factor (VEGF) [19]. In the liver, the LSEC phenotype is maintained by paracrine secretion of VEGF by hepatocytes and HSCs [7, 20] and a downstream autocrine loop of VEGF-stimulated NO production by eNOS in the LSEC [7].

Function and Dysfunction

Barrier Function

Oxygen Delivery

The liver has a dual blood supply. About 70% of the blood is poorly oxygenated blood from the portal vein and the remaining 30% is well-oxygenated blood from the hepatic artery. The combination of open fenestrae, thin cytoplasm, and lack of an organized basement membrane reduces the distance required for oxygen diffusion and thereby facilitates oxygen delivery to the hepatocyte to compensate for the relatively low pO_2 in sinusoidal blood.

Loss of fenestration, thickening of the cytoplasm, and development of an organized basement membrane is called capillarization [21]. Capillarization precedes fibrosis in chronic liver disease and has been observed in both humans and experimental animals [21–27]. A forme fruste of capillarization, termed pseudocapillarization by LeCouteur and colleagues, occurs with aging in humans and experimental animals (see Chap. 3). In both capillarization and pseudocapillarization, there is evidence of hepatocyte hypoxia. In the cirrhotic liver, oxidative drug

metabolism is decreased and can be restored with oxygen supplementation [28–30]. In pseudocapillarization, there is a decline in high-energy phosphate and other metabolites in the hepatocyte, indicative of hepatocyte hypoxia [31]. In the latter case, this occurs without fibrosis or other structural changes that could account for the hypoxia. There are no studies to document whether functions other than oxidative metabolism are impaired by the barrier to oxygenation induced by capillarization.

Passage of Small Molecules

Based on the observation that chylomicron remnants that pass into the space of Disse are smaller than the size of fenestrae, it was postulated many years ago that LSEC fenestration acts as a sieve for chylomicron remnant clearance [1, 32, 33]. This observation gained renewed interest with the recognition of aging-related pseudocapillarization. Chylomicron remnants are thought to play an important role in initiating atherosclerosis [34, 35]. Decreased chylomicron remnant clearance with aging-related LSEC defenestration may contribute to aging-related hyperlipidemia and atherosclerosis [36–38] (see Chap. 3).

In most vascular beds, protein-bound drug is restricted to the circulation and uptake into tissues is restricted to free or unbound drug, but in the liver protein-bound drugs pass into the space of Disse. Consequently, in one pass through the liver free drug in the space of Disse can be cleared by hepatocytes, which allows bound drug to reequilibrate with the free, and the newly formed free drug can be cleared. This allows drug clearance to exceed the free fraction in the liver. The combination of decreased drug clearance and the decline in oxidative drug metabolism (see above) in capillarization and pseudocapillarization is predicted to contribute to the impaired drug disposition in chronic liver disease and the aging liver. However, in both aging and cirrhosis there are also changes in liver blood flow and liver mass, so that it is difficult to determine the relative contribution of changes in LSEC to the decline in drug clearance and drug metabolism.

Scavenger Function of LSEC

LSEC and Kupffer cells play complementary roles in the clearance of waste from portal vein blood. LSEC clear colloids and macromolecules, whereas Kupffer cells phagocytose the larger particulate matter and insoluble waste. As described by Smedsrød et al. [39], there are several factors that make LSEC such effective and important scavengers. The liver, and therefore the LSEC, is the first checkpoint for macromolecules and antigens that enter the portal circulation from the intestine. LSEC clearance is facilitated by the slow and intermittent flow through the sinusoids, the large surface area of LSEC, the numerous positively charged coated pits that aid endocytosis of negatively charged molecules, and the presence of three distinct endocytosis receptors. Finally, LSEC are well suited for disposal of waste products, because of high specific activity of lysosomal enzymes that is as high or even higher than that of Kupffer cells [40].

The three LSEC endocytosis receptors are the collagen- α (alpha)-chain/mannose receptor, the hyaluronan/scavenger receptor, and the Fc γ (gamma) IIb₂ receptor. The collagen- α (alpha)-chain/mannose receptor (CD206) clears circulating collagen alpha chains, i.e., denatured collagen of several types of collagen, and glycoconjugates with terminal mannose, such as lysosomal enzymes, procollagen type I carboxyterminal propeptides, and tissue type plasminogen activator [41, 42]. The hyaluronan/scavenger receptor, SR-H (stabilin-1 and stabilin-2), is the main functional scavenger receptor on the LSEC [10–12]. The hyaluronan/scavenger receptor clears hyaluronan, chondroitin sulphate, formaldehyde-treated serum albumin (FSA, used as a test ligand for scavenger receptor-mediated endocytosis), procollagen type I and III N-terminal peptides, nidogen, acetylated and oxidized low density lipoprotein [43–45], plasma coagulation products, and advanced glycation end-products [46]. The LSEC Fc receptor, Fc γ (gamma) IIb₂ (CD32b or SE-1), clears immune complexes formed with Ig G [47, 48].

Aging-related pseudocapillarization and liver disease-related capillarization both lead to a decline

in endocytosis [49, 50]. The pathophysiological consequences of the decline in LSEC scavenger function have not been studied.

Stellate Cell Quiescence

In vitro studies show that LSEC maintain stellate cell quiescence and induce reversion of activated stellate cells to quiescence [51]. When LSEC dedifferentiate to a defenestrated “capillarized” phenotype, this paracrine effect on stellate cells is lost and stellate cell become activated. LSEC capillarization in vivo precedes fibrosis in both human chronic liver disease and in experimental animal models. The in vitro studies suggest that LSEC capillarization not only precedes fibrosis, but also is permissive for fibrosis and that reversal of capillarization could promote resolution of fibrosis. Studies reported in abstract form provide in vivo confirmation that reversal of capillarization promotes reversion of stellate cells to quiescence and reversal of fibrosis [52].

Other LSEC Functions

Two other LSEC functions have not been well studied in chronic liver disease and will only be briefly mentioned.

Immune Function

LSEC may function as an antigen-presenting cell that induces tolerance [53–60]. This effect is consistent with several observations that suggest that the liver can induce tolerance: the success of transplantation of MHC-incompatible livers, induction of immune tolerance to antigens presented in the portal circulation, and the reduction in rejection when the venous drainage of a graft is through the portal vein [61].

Drug Metabolism

Although the specific activity of metabolic enzymes is generally much higher in parenchymal cells, LSEC have both phase I and II enzymes [62, 63]. The ability of LSEC to metabolically activate drugs

may contribute to some forms of toxin-induced injury [64–66], particularly given the relatively low glutathione detoxification capacity [67]. There are currently no studies of whether LSEC drug metabolism is altered in chronic liver disease.

Vascular Liver Disease and LSEC (Table 2.2)

Sinusoidal Obstruction Syndrome (SOS)

For decades, SOS was called hepatic veno-occlusive disease. Given that 45% of patients with mild and moderate SOS and 25% of patients with severe SOS after myeloablative regimens do not have involvement of the central venules [68] and that the disease is initiated by damage at the level of the sinusoids (see below), this is a misnomer. This led to the new name, SOS [69], which also serves to distinguish it from liver pathology with veno-occlusive lesions seen in alcoholic liver disease and liver transplantation, sometimes termed hepatic veno-occlusive disease in the literature.

SOS occurs in only two settings. It can be induced by ingestion of pyrrolizidine alkaloids, as first described in South Africa and later described in Jamaica [70–72]. The second setting is due to specific medications alone (see Table 2.3) or medications in combination with irradiation of the liver. The major plant species containing pyrrolizidine alkaloids, *Crotalaria*, *Heliotropium*, and *Senecio*, can be found all around the world. However, pyrrolizidine alkaloid-induced SOS is most commonly seen in undernourished individuals in underdeveloped countries. It can be seen sporadically in individuals that ingest “bush teas” or during local

Table 2.2 Vascular liver injury with LSEC involvement

Sinusoidal obstruction syndrome
Radiation-induced liver disease
Ischemia–reperfusion injury ^a
Heterogeneous liver perfusion
Peliosis hepatitis

^aSee Chap. 5

epidemics, when crops are contaminated by plants containing pyrrolizidine alkaloids. In contrast to the iatrogenic form, pyrrolizidine alkaloid-induced SOS is commonly a more chronic disease. The most common setting for SOS in North America and Western Europe is after myeloablative hematopoietic cell transplantation. It is seen sporadically after chemotherapy unrelated to hematopoietic cell transplantation and with certain immunosuppressive drugs.

Table 2.3 Drugs associated with sinusoidal obstruction syndrome

Actinomycin D
Azathioprine
BCNU ^a
Busulfan ^b
Cyclophosphamide ^b
Cytosine arabinoside
Dacarbazine
Dimethylbusulfan ^c
Gemcitabine ^c
Gemtuzumab-ozogamicin
Mithramycin
Oxaliplatin
6-Thioguanine
Urethane

^a Only in high doses

^b Only at high doses and in combination regimens

^c Rare case reports

Mechanism of Injury (Fig. 2.2)

In vitro studies with drugs and toxins that cause SOS demonstrated that these compounds are selectively more toxic to LSEC, either due to enhanced metabolic activation in the LSEC or due to relatively weak detoxification [64, 66, 73]. SOS has also been studied in a reproducible animal model induced by monocrotaline, a pyrrolizidine alkaloid [74]. This model has the same signs and symptoms as human SOS and follows a more acute course, similar to that seen in humans after high-dose chemotherapy. Monocrotaline is P450 activated to a monocrotaline pyrrole and metabolic activation occurs in both hepatocytes and LSEC. One of the four known adducts of monocrotaline pyrrole is actin [75]. In LSEC, monocrotaline causes depolymerization of F-actin, which in turn leads to increased expression of matrix metalloproteinase-9 (MMP-9) [76], an enzyme that is exocytosed from cytoplasmic granules and then digests extracellular matrix in the space of Disse. The combination of depolymerization of F-actin, an element of the cell skeleton, and digestion of the extracellular matrix tethering of the LSEC leads to rounding up of the LSEC and formation of gaps in the endothelial barrier [77]. With obstruction of sinusoids by swollen LSEC and gaps in the endothelial barrier, the space of Disse becomes

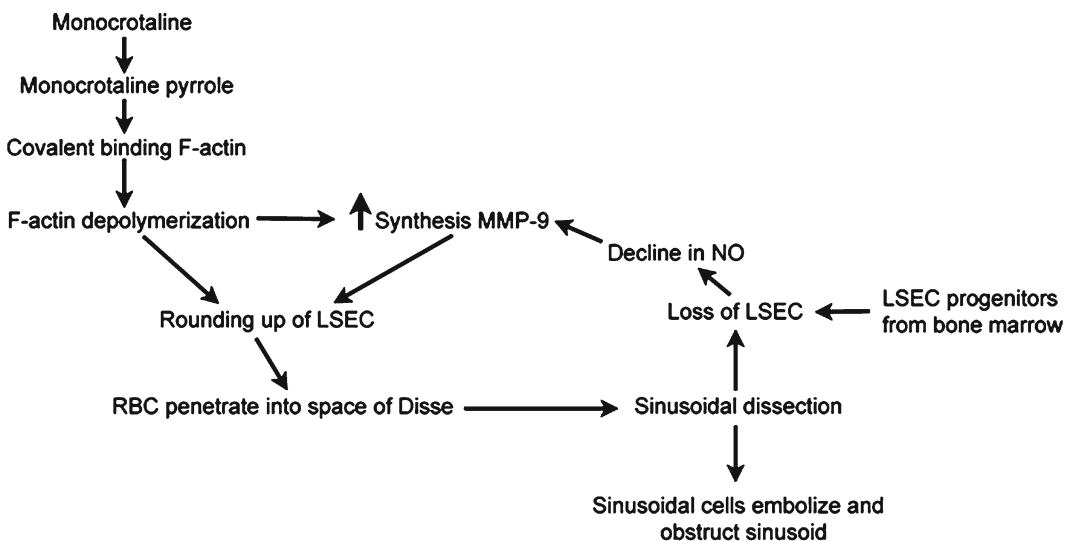


Fig. 2.2 Scheme illustrating mechanism of SOS

the pathway of least resistance. Red cells penetrate between LSEC and eventually blood begins to flow through the space of Disse, dissecting off LSEC and stellate cells. Sinusoidal cells embolize downstream, blocking sinusoidal blood flow. Other changes occur that lead to the perpetuation of the changes described above. At the same time that LSEC round up, the number of Kupffer cells in the liver decreases markedly [74]. Nitric oxide (NO) levels fall in parallel to the decline in Kupffer cells [78]. As the number of viable LSEC declines, there is an additional and parallel drop in NO. NO is known to tonically inhibit MMP synthesis [79–81] and delivery of a liver-specific NO prodrug prevents the increase in MMP-9 synthesis and activity in this model. Monocrotaline depletes LSEC glutathione (GSH) and support of LSEC GSH prevents the development of SOS in the model. GSH inhibits MMP-9 activity [82]. Thus, the decline in NO permits the increased synthesis of MMP-9 and the fall in GSH permits increased MMP-9 activity. All of the events described above are initiating events that occur before there is clear-cut histological evidence of injury and form a feed-forward loop of injury. The more MMP-9 synthesis is upregulated, the more LSEC are lost, the greater the decline in NO, and the less MMP-9 synthesis and activity are inhibited. Inhibition of MMP-9, treatment with a liver-specific NO donor, or support of GSH all prevent development of SOS, demonstrating that the LSEC injury initiates SOS and that protection of the LSEC prevents SOS.

There is a second component to SOS that distinguishes it from other forms of LSEC injury. The normal response to endothelial cell injury is to increase the number of endothelial progenitor cells in the bone marrow and mobilization of these cells to the circulation. In monocrotaline-induced SOS, LSEC progenitors in the bone marrow are reduced by 50% and circulating progenitors are reduced by over 95% [8], demonstrating monocrotaline toxicity to the progenitors. Infusion of LSEC progenitor cells completely prevents SOS. In contrast, when a subtoxic dose of monocrotaline is given to bone marrow-suppressed rats, severe SOS ensues, demonstrating that bone marrow suppression unmasks a subclinical

injury. Thus, SOS is due to both LSEC injury and to monocrotaline-induced impairment of repair by bone marrow-derived progenitors. This then explains why SOS occurs almost exclusively after either exposure to pyrrolizidine alkaloids or to chemotherapy regimens that are both toxic to LSEC and that are myeloablative.

In addition to the changes to the LSEC, SOS can also lead to occlusion of the hepatic venules. There is a rough correlation with severity of disease and extension of the injury to the venules [68]. Central vein endothelial cells are damaged and subendothelial edema contributes to the early occlusion of the venules. The impediment to sinusoidal and venular blood flow leads to hepatocyte necrosis. Thus, in early SOS there is congestion, centrilobular hemorrhagic necrosis, extensive centrilobular loss of CD31 positive LSEC, loss of central vein endothelium, and occlusion of the central vein by subintimal edema.

Late SOS is characterized by marked sinusoidal fibrosis and fibrotic occlusion of central veins. LSEC tonically suppress stellate cell activation [51], so that widespread, prolonged loss of LSEC [77] permits stellate cell activation and sinusoidal fibrosis.

Clinical Features of SOS

This section will discuss chemo-irradiation induced SOS: there is much more extensive literature on this than on pyrrolizidine alkaloid-induced SOS and the author assumes that readers of this text are more likely to see chemo-irradiation induced SOS.

Causes of SOS (Table 2.3)

The highest risk for SOS is induced by myeloablative chemotherapy in preparation for hematopoietic cell transplantation (including bone marrow transplantation). Cyclophosphamide by itself does not cause SOS, but two of the highest risk myeloablative regimens contain cyclophosphamide [83]. Busulfan does not cause SOS when given alone, but the busulfan–cyclophosphamide myeloablative regimen is a very high-risk regimen. In contrast, the myeloablative regimen busulfan–fludarabine has a much lower incidence

of SOS. Another high-risk regimen is cyclophosphamide combined with total body irradiation (TBI). The doses of TBI used are not in the hepatotoxic range when used alone, but the risk of SOS in the cyclophosphamide–TBI regimen increases with higher doses of TBI [83].

Gemtuzumab-ozogamicin is a humanized monoclonal antibody to CD33, a myeloblast antigen that is linked to the toxin calicheamicin and is used in the treatment of acute myeloid leukemia. Of note, LSEC express CD33 on their surface [8]. As a single agent, gemtuzumab-ozogamicin has a relatively low incidence of SOS. Patients with acute myeloid leukemia may undergo myeloablative hematopoietic cell transplantation and, if the disease relapses, may then be treated with gemtuzumab-ozogamicin, or the converse order of treatments may be used. The incidence of SOS increases markedly when a patient has been exposed to both gemtuzumab-ozogamicin and myeloablative chemotherapy and this risk is greater when the two modalities are given within several months of each other [84–86]. It is not known why there is a persistently increased risk of SOS in the first few months after myeloablative chemo-irradiation or gemtuzumab-ozogamicin, but it is tempting to speculate that this may indicate persistent suppression of the bone marrow LSEC progenitor response.

Treatment of Wilms' tumor with actinomycin D has a significant risk for SOS. The risk is highest when the tumor is in the right kidney, when actinomycin D is given in combination with abdominal irradiation and when a single high dose is given instead of repeated administration of lower doses [87–89]. Among the remaining medications listed in Table 2.3, there are numerous reports of SOS related to standard chemotherapy with dacarbazine, cytosine arabinoside, or oxaliplatin. There are also case series of SOS related to immunosuppression with azathioprine for kidney or liver transplantation and to 6-thioguanine used for inflammatory bowel disease or psoriasis.

Incidence: The incidence of SOS has dropped over the years. This can largely be attributed to the shift towards nonmyeloablative regimens,

e.g., fludarabine plus low-dose TBI, which are not hepatotoxic. There are substantial differences in the incidence of SOS across transplant centers, which depends on the regimens used (TBI dose used, use of gemtuzumab-ozogamicin), patient exclusion criteria (preexisting liver disease, prior transplantation), and diagnostic criteria [83]. As McDonald has pointed out in a recent review, although the frequency of SOS varies at different centers, case fatality rate remains relatively constant at 15–20% [83].

Diagnosis: In patients at risk for SOS, the diagnosis can often be made based on the presence of painful hepatomegaly, weight gain, and hyperbilirubinemia, but with careful exclusion of other causes of these signs and symptoms. The diagnosis can be supported in unclear cases by Doppler ultrasound, transjugular liver biopsy, and wedged hepatic venous pressure gradient.

Prognosis: High elevations of ALT, higher portal pressure, and multiorgan failure are predictive of a poor prognosis [83]. For patients who develop SOS due to cyclophosphamide-containing regimens, outcome can be predicted based on bilirubin level and weight gain using published graphs [90].

Prevention: The highest risk patients are those with underlying liver disease, previous myeloablative regimens, and previous evidence of SOS. Regimens that have not been linked to SOS and could be considered in these high-risk patients are the myeloablative regimen fludarabine with targeted busulfan [91, 92] or the nonmyeloablative regimen of fludarabine plus low-dose TBI [93]. If high-risk patients are to be treated with cyclophosphamide–TBI or busulfan–cyclophosphamide, regimens may need to be modified. Lower doses or personalized dosing of cyclophosphamide [94, 95], TBI doses below 12 Gy, or administration of intravenous busulfan after rather than before cyclophosphamide [96] may reduce the risk of SOS. As mentioned earlier, a longer interval between myeloablative regimens and gemtuzumab-ozogamicin decreases the risk for SOS. The risk of SOS from gemtuzumab-ozogamicin is also decreased when a reduced-intensity regimen is used for the hematopoietic cell transplantation, although the risk is still dependent on

interval between modalities [97]. Gemtuzumab-ozogamicin has a low incidence of SOS when given alone vs. the higher risk of the combination with 6-thioguanine [97], a drug that also causes SOS when used as a single drug [98–100]. In prospective studies, prophylaxis with heparin, ursodeoxycholic acid, or antithrombin III did not prevent fatal SOS [69]. Various other proposed prophylactic strategies still need to be tested in randomized controlled studies.

Treatment: Treatment of SOS requires pain management and management of fluid overload with diuretics, paracentesis, hemofiltration, or hemodialysis. Defibrotide, a single-stranded polydeoxyribonucleotide, has been used extensively for SOS, but has never been studied in a randomized controlled trial. Liver transplantation should only be considered if the disease that necessitated the chemo-irradiation has a favorable prognosis.

Radiation-Induced Liver Disease (RILD)

RILD occurs in patients who undergo irradiation for primary or metastatic cancer in the liver. Given the radiosensitivity of endothelial cells and the general resemblance to SOS, RILD is assumed to be due to endothelial damage, but it is not known whether this is mainly a venous or a sinusoidal injury. The lesion has not been reproduced in experimental animals.

RILD is a syndrome of anicteric ascites, hepatomegaly, and abnormal liver tests which develops 2 weeks to 4 months after hepatic irradiation in excess of 30–35 Gy. The risk of developing RILD is dependent on the irradiated liver volume and hepatic functional reserve.

Histological features are sinusoidal hemorrhage and congestion, fibrotic veno-occlusive lesions of the central vein but also occasionally of the intermediate size portal veins, and centrilobular atrophy [101–103]. Portal to central bridging fibrosis and persistent fibrotic veno-occlusive lesions of the central veins may be seen months to years later [103]. Ultrastructurally, fibrin has been identified in central venules, but there are no thrombi of fibrin or platelets [102].

The clinical features of RILD are painful hepatomegaly, weight gain, and ascites. Liver tests show normal bilirubin, alkaline phosphatase elevations that are 3–10 times the upper limit of normal, and modest AST and ALT elevations. Most patients recover over 3–5 months, but some progress to chronic liver disease. A small fraction of patients who develop progressive fibrosis with jaundice, refractory ascites, and coagulopathy have a poor prognosis [103].

Although there are similarities between SOS and RILD, these are distinct syndromes. Clinically, SOS is accompanied by hyperbilirubinemia and patients with RILD usually have normal bilirubin levels. The chronic course of RILD resembles the course of pyrrolizidine alkaloid-induced SOS with often greatly delayed onset and a course of months and sometimes years, whereas SOS related to myeloablative regimens occurs within 2–4 weeks of the insult and resolves within weeks to months. On histology, there is centrilobular atrophy but no necrosis in RILD and occasional veno-occlusive lesions can be in the portal veins, whereas the classic lesion of SOS includes centrilobular necrosis and does not involve the portal veins. Ultrastructurally, fibrin is present in the central venules of RILD, but fibrin is absent on ultrastructural studies of SOS.

Heterogeneous Liver Perfusion

Historically, diffuse nodular regenerative hyperplasia, partial nodular transformation, idiopathic noncirrhotic intrahepatic portal hypertension, and incomplete septal cirrhosis were described as distinct forms of liver pathology. However, the current consensus holds that these lesions are a single entity with a common etiology, i.e., uneven perfusion of the liver, that result in a spectrum of pathological lesions and clinical manifestations [104–107]. More than one of these pathological lesions may be found in some patients, supporting the concept that these lesions are a spectrum of responses due to a shared etiology [105]. These lesions of heterogeneous liver perfusion occur, by definition, in the absence of cirrhosis or of

chronic liver disease that might cause cirrhosis. The circulatory impairment may be either at the level of the portal vein or the sinusoid, the latter justifying the inclusion of these lesions in this chapter.

It should be stated that it is still an unproven working hypothesis, albeit a widely accepted one, that these lesions are due to heterogeneous perfusion. The hypothesis, first described for nodular regenerative hyperplasia [107], is that impaired regional perfusion of the liver leads to atrophy with apoptotic or atrophic hepatocytes [108] and reactive hyperplasia in adjacent areas with preserved blood flow. The original concept was that impaired perfusion was due to obstructive portal vasculopathy [107] and was subsequently revised to include impaired flow at the level of the sinusoid. A recent study suggests that impairment of flow at the level of the sinusoid may account for a significant proportion of cases [104]. The hypothesis of heterogeneous perfusion is based on histopathological observations, but has never been tested experimentally. Mice with inducible inactivation of Notch1 develop nodular regenerative hyperplasia without vascular obliteration, although ultrastructural studies of the sinusoids were not performed, which would have definitively ruled out abnormalities at the sinusoidal level [109].

Risk factors for lesions with heterogeneous liver perfusion include collagen vascular diseases, clotting disorders, myelo- and lymphoproliferative diseases, immunological disorders, and a variety of drugs and toxins (Table 2.4). For many of the predisposing factors it is apparent how the venous or sinusoidal circulation would be impaired, but for others it is unclear. Inflammation of the hepatic artery in collagen vascular diseases or immune complex diseases may extend to adjacent portal veins [110, 111]. Prothrombotic disorders may cause thrombosis at the level of either the venous or sinusoidal circulation [104]. Azathioprine and myeloablative regimens may damage LSEC [66, 73]. It is noteworthy that there is significant overlap between causes of SOS (see Table 2.3), lesions with heterogeneous liver perfusion (see Table 2.4), and peliosis hepatis (see Table 2.6), supporting the

Table 2.4 Conditions leading to lesions of heterogeneous liver perfusion

Collagen vascular diseases
Rheumatoid arthritis
Scleroderma
Systemic lupus erythematosus
Polyarteritis nodosa
Glomerulonephritis
Hematological diseases
Polycythemia vera
Essential thrombocythemia
Agnogenic myeloid metaplasia
Chronic myeloid leukemia
Hodgkin's disease
Non-Hodgkin's lymphoma
Multiple myeloma
Primary hypogammaglobulinemia
Immunological disorders
Cryoglobulinemia
Antiphospholipid syndrome
Myasthenia gravis
HIV/AIDS
Drugs and toxins
Anabolic steroids
Azathioprine
Myeloablative conditioning regimens
Oral contraceptives
Oxaliplatin
Thoratrast
Toxic oil syndrome
6-Thioguanine

concept that the LSEC may be a common target of some of these risk factors.

The common clinical syndrome manifested by these lesions is noncirrhotic portal hypertension. The presentation can vary from asymptomatic disease diagnosed only at autopsy to decompensated liver disease. Symptomatic patients may present with variceal bleeding or splenomegaly. Liver test abnormalities may include changes in prothrombin time, alkaline phosphatase, bilirubin, AST, and ALT [105]. Two large autopsy series found a prevalence of diffuse nodular regenerative hyperplasia of around 2.5% [106, 107]. Given that diffuse nodular regenerative hyperplasia is a relatively uncommon clinical diagnosis, this demonstrates that most cases of diffuse nodular regenerative hyperplasia are

Table 2.5 Lesions due to heterogeneous liver perfusion [105]

Liver lesions	Histology
Diffuse nodular regenerative hyperplasia	Monoacinar nodules consisting of hyperplastic hepatocytes diffusely distributed throughout the liver without a surrounding fibrous septum
Partial nodular transformation	Multiple nodules consisting of hyperplastic hepatocytes, several centimeters in diameter, involving several portal tracts, located in perihilar region
Incomplete septal cirrhosis	Large, diffusely distributed nodules, surrounded by incomplete slender fibrotic septa; septa extend from periportal or perivenular fibrosis; abnormal spacing between portal tracts and between portal tracts and central veins
Idiopathic noncirrhotic intrahepatic portal hypertension	No nodules; portal tracts are fibrotic, thin fibrotic septa may be present, when present, bridging fibrosis is subcapsular; sinusoidal dilatation is common

asymptomatic. Morphology of lesions attributed to heterogeneous perfusion of the liver is described in Table 2.5.

The liver lesions require no therapy, but the predisposing factor may require treatment. Portal hypertension is treated with the conventional approaches. A requirement for liver transplantation has been reported, but is rare.

Peliosis Hepatis

In peliosis hepatis, blood-filled cystic lesions are distributed irregularly throughout the hepatic parenchyma. The peliotic cavities range in size from less than 1 mm to several centimeters. Peliosis is most common in the liver, but also occurs in the spleen, abdominal lymph nodes, and bone marrow.

Table 2.6 lists the hematological disorders, drugs and toxins, and immunological and infectious diseases that predispose to peliosis. Historically, peliosis hepatis was found at autopsy in patients with chronic wasting illnesses, in particular tuberculosis and cancer. In patients with acquired immunodeficiency syndrome (AIDS), infection with *Bartonella henselae* or *Bartonella quintana* may cause peliosis as well as bacillary angiomatosis. One might therefore speculate that, analogous to AIDS, *Bartonella* sp. may play a role in some of the other predisposing factors with associated immunosuppression, such as tuberculosis, cancer, malnutrition, and glucocorticoid therapy.

The initial histological change in peliosis is sinusoidal dilatation and this progresses to formation

Table 2.6 Conditions associated with peliosis hepatis

Hematological diseases
Myeloproliferative diseases
Lymphoma
Macroglobulinemia
Multiple myeloma
Leukemia
Drugs and toxins
Anabolic steroids
Arsenic
Azathioprine
Oral contraceptives
Oxaliplatin
6-Thioguanine
Thoratrast
Vinyl chloride
Immunological/infectious disorders
AIDS/bartonella infection
Tuberculosis

of cavities without sinusoidal endothelial cells [112, 113]. Later in the course of the disease, the peliotic cavities may reendothelialize. Peliosis due to *Bartonella* species most clearly demonstrates that the lesion is initiated by damage to LSEC. Electron microscopy studies demonstrate the presence of *Bartonella* bacilli in LSEC of peliotic lesions [114] and disruption of the LSEC lining [112]. As described in the section on lesions of heterogeneous liver perfusion, several of the drugs listed in Table 2.6 have also been linked to the other disorders that target LSEC (see Tables 2.3 and 2.4). More strikingly, there are case reports of patients treated with azathioprine who were found to have all three lesions, SOS, diffuse nodular regenerative hyperplasia,

and peliosis, in their liver. Other predisposing factors listed in Table 2.6 cause peliosis through an as yet undefined mechanism.

Peliosis hepatis is usually asymptomatic, but patients may present with portal hypertension, ascites, cholestasis, or liver failure. Rupture of a peliotic cavity may lead to a hepatic hematoma or an intraperitoneal hemorrhage that may rapidly progress to shock and death. Peliosis may regress if the precipitating cause is withdrawn or resolves.

Conclusions

LSEC have a number of important functions and may be the initiating target of a number of vascular liver diseases. The difficulty in isolating these cells has limited the number of laboratories that have studied LSEC. As more investigators turn their attention to this fascinating cell, we are likely to uncover pathology related to their dysfunction in chronic liver disease and aging and to discover more diseases in which LSEC injury places a role.

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