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*Review Article*

# The role of liver sinusoidal endothelial cells in cancer liver metastasis

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**Abstract:** Liver sinusoidal endothelial cells (LSECs) are the gatekeeper cells in the liver, contributing critical roles in liver physiological and pathological changes. Factors such as dietary macronutrients, toxins, and aging impact LSEC fenestration. Defenestration of LSECs changes their phenotype and function. Under liver injury, capillarized LSECs promote hepatic stellate cells (HSCs) activation and fibrogenesis, while decapillarized LSECs protect the activation of HSCs and liver injury. The expression of chemokines, such as CXCL9 and CXCL16, changes and impacts the infiltration of immune cells in the liver during disease progression, including hepatocellular carcinoma (HCC). As the largest solid organ, liver is one of the most favorable organs into where tumor cells metastasize. The increased interaction and adhesion of circulating tumor cells (CTCs) with LSECs in the local microenvironment and LSEC-induced tolerance of immunity promote cancer liver metastasis. Several strategies can be applied to target LSEC to modulate their function to prevent cancer liver metastasis, including gut microbiota modulation, microRNA therapy, and medical treatment. Delivery of different treatment agents with nanoparticles may promote precise target treatment. Overall, targeting LSECs is a potential strategy for treatment of early liver diseases and prevention of cancer liver metastasis.

**Keywords:** LSECs, liver, cancer metastasis, treatment, gut microbiota

## Introduction

Liver sinusoidal endothelial cells (LSECs) line in hepatic sinusoids and play critical roles in liver physiological homeostasis and pathogenesis [1, 2]. As the gatekeeper cells, LSECs interact with circulating blood macromolecules, pathogens, and toxic agents [3, 4]. They are fenestrated endothelial cells featured by the presence of transcellular pores [5, 6]. The fenestrated LSECs inhibit hepatic fibrogenesis by maintaining hepatic stellate cells (HSCs) quiescence (**Figure 1A**), whereas capillarized/defenestrated LSECs precede liver fibrosis [7, 8]. Besides, fenestrated LSECs can reverse the activated HSCs to the quiescent stage by the production of nitric oxide (NO) with the stimulation of vascular endothelial growth factor (VEGF) [9]. Moreover, LSECs can protect the liver from damage [10] and are primary mediators for hepatic immune tolerance [11], which is mediated by the products such as programmed death-ligand 1 (PD-L1) [12, 13].

Cancer metastasis accounts for a large proportion of cancer deaths [14], at least for solid tumors [15]. Liver is the largest solid organ in human body, and it is one of the most sites where other cancers metastasize (**Figure 1B**), such as colorectal cancer [16], pancreatic cancer [17], breast cancer [18], renal cell carcinoma [19], and lung cancer [20]. The colonization of circulating tumor cells (CTCs) in the liver leads to cancer liver metastasis [21, 22]. LSEC capillarization plays a pivotal role in liver cancer development and cancer liver metastasis. For example, the phenotype and function of microvascular endothelial cells from human liver cancer tissue (HLCECs) are different from LSECs in healthy human liver [23]. The expression of intercellular-adhesion molecule 1 (ICAM-1) was decreased in HLCECs compared with LSECs, while productions of tumor necrosis factor receptor (TNFR) p75, αvβ3 and αvβ5 integrins were increased. Those changes increased human hepatocellular carcinoma BEL-7402 cell

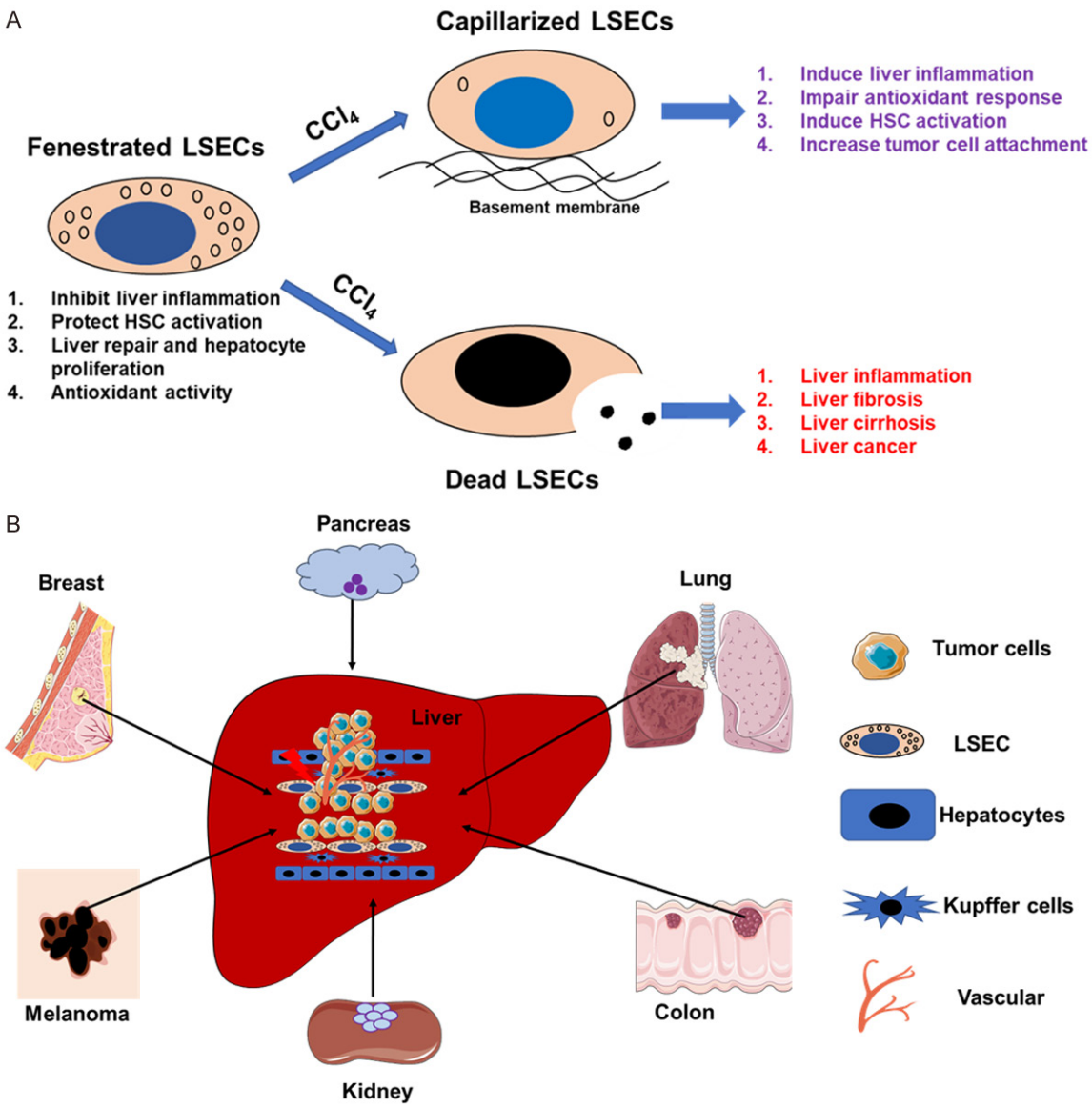


**Figure 1.** LSECs play critical roles in liver diseases and cancer liver metastasis. A. The function of liver sinusoidal endothelial cells (LSECs) in liver diseases. Fenestrated LSECs inhibit liver inflammation and HSC activation, promote liver repair and hepatocyte proliferation, and have antioxidant activity. In contrast, capillarized or defenestrated LSECs caused by factors such as $CCl_4$, can induce liver inflammation and promote HSC activation and tumor growth, and have low antioxidant activity. Furthermore, LSEC death can promote liver inflammation, fibrosis, cirrhosis, and final liver cancer. B. The different tumors with liver metastasis. Liver is the largest solid organ in the body, which is one of the most common places different cancers metastasize into, such as breast cancer, pancreatic cancer, lung cancer, colorectal cancer, renal cell carcinoma, and melanoma. LSECs are the liver gatekeeper cells and first interact with circulating tumor cells (CTCs) in the liver site. Therefore, LSECs play critical roles in cancer liver metastasis via interacting with CTCs and creating a microenvironment for cancer cell growth.

adherence on HLCECs than LSECs, but decreased leukocyte adherence on HLCECs compared to LSECs, resulting in cancer development.

In this review, the phenotype switching of LSECs under different microenvironments is firstly introduced. Then, the roles of LSECs in liver inflammation, fibrosis, and regeneration are reviewed. The LSEC-derived important factors that mediate cancer liver metastasis are highlighted. Finally, potential treatment options targeted on LSECs to prevent cancer liver metastasis are discussed.

### Phenotype switching

Many factors, including aging [24], diet [25], drugs and toxins [26], can lead to the change of LSEC fenestration, which is accompanied by the progression of chronic liver disease (**Figure 1**). Alteration of LSEC phenotype results in defenestration or capillarization and formation of the basement membrane, which promotes HSC activation and results in liver fibrosis [27]. In the progression of carbon tetrachloride ($CCl_4$)-induced fibrotic liver, Notch signaling was activated to induce LSEC dedifferentiation, evidenced by the loss of transcellular pores and buildup of basement membrane [28]. Meanwhile, Notch activation attenuated the secretion of hepatocyte mitogens in LSECs such as hepatocyte growth factor (HGF), resulting in the impaired proliferation of hepatocytes and liver regeneration. Another study showed that DLL4, a ligand of the Notch signaling pathway, was also overexpressed in the LSECs of human and $CCl_4$-induced murine fibrotic livers, while *in vivo* silencing DLL4 ameliorated LSEC capillarization and $CCl_4$-induced murine liver fibrosis [29].

Liver X receptor alpha (LXRα) also plays a crucial role in LSEC capillarization. LSEC capillarization was exacerbated in LXRα-deficient mice with the treatment of $CCl_4$, as evidenced by the overexpression of CD34, loss of fenestrae, and formation of continuous basement membrane [30]. In addition, $CCl_4$-induced inflammation and collagen deposition were markedly aggravated in LXRα-deficient mice. In contrast, LXR agonist maintained freshly isolated LSECs fenestration at *in vitro* culture for 3 days. The mechanistic study showed that the function of LXRα on LSEC fenestration is mediated by Hedgehog-regulated gene signaling.

Pathogens such as viruses and bacteria also impact LSEC phenotype change. In the setting of hepatitis C virus (HCV) infection, LSEC underwent a morphological change that is correlated with hepatic damage and liver fibrogenesis [5]. However, the expression of phenotype markers of LSEC was maintained in HCV-infected liver, such as CD32, CD31, and caveolin-1. Endotoxin (lipopolysaccharide, LPS) and pyocyanin from Gram-negative bacterium *Pseudomonas aeruginosa* can induce loss of LSEC porosity and cause subsequent immune tolerance to bacterial toxins, which is a factor causing hyperlipidemia of sepsis [31].

### Role of LSECs in liver homeostasis and pathogenesis

*LSECs in inflammation*

A proinflammatory phenotype of LSEC is shown in mouse NAFLD progression. The expression of ICAM-1, E-selection, platelet endothelial cell adhesion molecule-1 (PECAM-1 or CD31) was increased in the early stage of high-fat diet (HFD)-induced NAFLD, and the expression of prostaglandin-endoperoxide synthase 2 or cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), NADPH oxidase *2* (*Nox2*), and release of prostaglandins ($PGE_2$ and $PGF_{2\alpha}$) was elevated in the late stage of NAFLD [32]. In $CCl_4$ or partial inferior vena cava ligation induced murine liver fibrosis model, increased expression C-C motif chemokine ligand 2 ($CCL_2$) was shown in injured LSECs, causing the accumulation of recruited macrophages that was reduced in LSEC-specific p300-deficiency mice [33]. Molecular mechanism study showed that p300 interacts with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and bromodomain-containing protein 4 (BRD4) to increase $CCL_2$ expression in LSECs. Treatment with long-chain fatty acids palmitic acid (PA) and oleic acid (OA) downregulated expression of chemokines (e.g., $CCL_2$) in primary mouse LSECs and LSEC cell line TSEC cells, in a mitogen-activated protein kinase (MAPK)-dependent pathway [34]. Meanwhile, this treatment inhibited the TSEC-mediated migration of CD-$11b^{+}Ly6C^{high}$ monocytes. Feeding an ethanol-containing diet for 4 weeks induced more severe hepatic injury in endothelial cell-specific STAT3 knockout mice than wild-type control groups [35], accompanying a large amount of apoptotic sinusoidal endothelial cells (SECs).

Viral infection can modulate the expression of proinflammatory cytokines in LSECs. Infection of mouse hepatitis virus type 3 (MHV3) virulent strains increased LSECs to release proinflammatory cytokines (e.g., TNF-α) and reduced anti-inflammatory genes (e.g., IL-10) by activating TLR2 compared to infection induced by attenuated strains [36], resulting in more severe hepatitis.

*LSECs in liver fibrosis*

Freshly isolated LSECs (decapillarized form) from healthy rat livers can protect HSC activation as evidenced by reduced alpha-smooth muscle actin (α-SMA) production, whereas capillarized LSECs isolated from rats with thioacetamide-induced cirrhotic livers showed an opposite effect on HSC activation [9]. The paracrine production of VEGF from hepatocytes and HSCs mediated the fenestration of LSECs via stimulating NO production [37]. Therefore, co-culturing with LSECs plus VEGF can revert the activated HSCs to the quiescent stage through VEGF-stimulated NO production.

Some important genes modulate LSEC function during liver fibrosis. For example, Gata4 deficiency in LSECs ($Gata4^{LSEC\text{-}KO}$) of adult mice resulted in perisinusoidal liver fibrosis through modulating Myc-mediated production of HSC activating cytokine PDGFB (platelet-derived growth factor subunit B) [38]. $Gata4^{LSEC\text{-}KO}$ mice also showed increased perisinusoidal liver fibrosis compared to wild-type mice. Moreover, GATA4-positive LSECs were decreased in human cirrhotic liver. Another study showed that Gata4 was significantly downregulated in Bmp9 gene knockout (Bmp9-KO) mice compared with wild-type mice, accompanying the development of liver perisinusoidal fibrosis and LSEC defenestration [39]. The expression of Delta-like ligand 4 (DLL4) in the Notch signaling pathway was upregulated in LSECs from fibrotic livers of $CCl_4$-treated mice and human patients [29]. In addition, DLL4-targeting siRNA treatment prevented LSEC capillarization and ameliorated $CCl_4$-induced liver fibrosis in mice.

LSEC autophagy also plays a critical role in NASH and liver fibrosis. Autophagy was defective in LSECs from NASH patients compared to LSECs from non-NASH or steatosis patients [40]. Also, LSEC autophagy deficiency promoted liver inflammation, cell apoptosis, and perisinusoidal fibrosis in mice when fed a HFD.

Manipulation of LSEC function and differentiation can alter the severity of liver fibrosis. In the $CCl_4$-induced mouse fibrotic liver, LSEC dysfunction-induced hepatic sinusoidal angiogenesis is associated with liver fibrosis. Treatment with curcumol can inhibit LSEC-mediated angiogenesis via regulating the Hedgehog signaling pathway and production of hypoxia-inducible factor-1α (HIF-1α) to ameliorate liver fibrosis [41]. Restoration of LSEC differentiated phenotype in high fat glucose-fructose diet (HFGFD)-fed rat post-statin treatment was associated with regression of HSC activation, decrease of portal hypertension, improvement of NASH features [42].

*LSECs in metabolism*

LSECs play a critical role in nutrient transport, including lipids and lipoproteins. In chronic liver disease, such as nonalcoholic fatty liver disease (NAFLD), LSEC injury can cause accumulation of lipids in the liver [43]. Moreover, lipid metabolites impact LSEC phenotype and function. A combined lipid supplement or oleic acid (OA) alone plus VEGF-containing medium enhanced the viability and proliferation of cultured primary rat LSECs and maintained their differentiation over 3 days [44]. The important signaling pathway implicated in lipid or OA function is early protein kinase B (PKB/Akt) signaling followed by extracellular signal-regulated kinase (ERK) signaling.

Sphingosine 1-phosphate (S1P) as a bioactive sphingolipid metabolite can enhance tumor growth, resistance to chemotherapy, and metastasis. It also modulates anticancer immune response, inflammation, and angiogenesis [45]. S1P can promote LSEC proliferation by activating Akt and extracellular signal-related kinase pathways, and inhibited LSEC apoptosis by modulating cell death signaling genes, such as Bcl-2, Bax, and cleaved caspase-3 [46]. S1P is an important regulator for endothelial integrity and immune response. It induces IL-6 and VEGF production in LSECs [46]. The serum concentration of S1P was markedly reduced in patients with advanced stages of liver disease [47], functioning as an indicator of organ failure and early mortality.

*LSECs in liver regeneration*

Revascularization is of critical importance in liver regeneration [48]. LSEC proliferation was shown in the rest of liver tissue of mice post-partial hepatectomy compared to sham-operated mice [49], as evidenced by the increased expression of lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1). The expression of Prospero homeobox protein 1 (PROX1) was also detected an increase in liver sections. On

day 7 post-partial hepatectomy, co-localization of LYVE1 and PROX1 was shown in LSECs. Another study showed that LSEC proliferation was significantly attenuated in RBP-J knockout mice after partial hepatectomy, as evidenced by reduced VEGFR2-positive cells [50], which resulted in decreased proliferation and increased apoptosis of hepatocytes. The production of angiopoietin-2 (Ang2) in LSECs changed dynamically at different stages of liver regeneration [51]. In the early stage, the expression of Ang2 in LSECs was decreased post-partial hepatectomy together with a decrease of transforming growth factor-β1 (TGF-β1) expression, resulting in hepatocyte proliferation. In the later phase, the production of Ang2 activated angiogenesis via enhancing the expression of vascular endothelial growth factor receptor 2 (VEGFR2) in LSECs [51].

HGF expressed in LSEC progenitor cells promotes liver regeneration, but mature LSECs lose their ability to express HGF. After partial hepatectomy in rats, except liver LSEC progenitor cells, bone marrow (BM)-derived LSEC progenitor cells can migrate to the liver and become fenestrated LSECs [52]. These BM-derived LSEC progenitor cells express a higher amount of HGF than liver resident LSEC progenitors to stimulate liver regeneration. Liver-specific HGF deficiency in LSECs can result in necrotic damage and delay of liver regeneration post partial hepatectomy. The molecular mechanistic study showed that Hgf/c-Met mediates downregulation of Deptor in hepatocytes, which controls hepatocyte proliferation and sensitivity to hepatectomy-induced necrosis [53].

*Other functions*

LSECs not only can promote the proliferation and differentiation of hematopoietic stem cells, but support *in vitro* survival, self-renewal, undifferentiated growth, and differentiation of murine embryonic stem cell line CGR8 cells [54]. Furthermore, LSECs play a critical role in hepatic immunity with the ability to clear pathogens. For example, rat LSECs can uptake GFP-labelled *Enterobacteria* phage T4 and effectively degrade it in the lysosomal compartment [55]. In contrast, other hepatic cells such as liver resident Kupffer cells can protect the damage of LSECs from injury [12].

**LSECs in HCC and cancer liver metastasis**

*The role of LSEC in HCC*

Tumor cell adherence on vessel cells of the metastatic site is the first step of metastasis. In ischemia condition, the adhesion of platelets to LSECs is markedly increased, which facilitates the adhesion of tumor cells with LSECs, resulting in tumor metastasis [56]. The *in vivo* adhesion of platelets to LSECs is dramatically increased in mice after partial hepatectomy compared to sham-operated mice [57]. Furthermore, the interaction between platelets and LSECs induces IL-6 secretion in LSECs to stimulate HGF secretion in HSCs, resulting in the proliferation of hepatocytes.

Co-culture of human colorectal cancer cell line HT-29 cells with primary isolated mouse LSECs markedly increased the expression of adherent genes in adherent HT-29 cells [58], such as DGCR8 (DiGeorge Syndrome Critical Region Gene 8) and EFEMP1 (EGF containing fibulin extracellular matrix protein 1), whereas some anti-adherent genes were overexpressed in nonadherent HT-29 cells, including ITPKC (Inositol-Trisphosphate 3-Kinase C).

LSEC transdifferentiation is a major pathogenic phenomenon in HCC progression. For instance, LSEC marker proteins stabilin-1, stabilin-2, LYVE-1, and CD32b were lost in the murine and human HCC tumor tissues [59]. Besides, loss in expression of stabilin-2 in peri-tumor liver tissue of human HCC patients was significantly predictive of a longer survival [59].

Oncogenic yes-associated protein (YAP) is also accompanied by the development and progression of liver cancer. LSECs were gradually replaced by continuous endothelial cells in the liver vascular niche during the development of YAPS127A mutation-induced tumor via the Hgf/c-Met signaling pathway [60].

*LSECs in immune tolerance and surveillance*

The secreted IL-10 in LSECs or Kupffer cells in response to LPS in portal vein blood, can suppress the expression of MHC class II and costimulatory molecules CD80 and CD86 on LSECs, as well as mannose receptor activity to inhibit LSEC-mediated T cell activation [61, 62]. Unlike conventional antigen-presenting cell

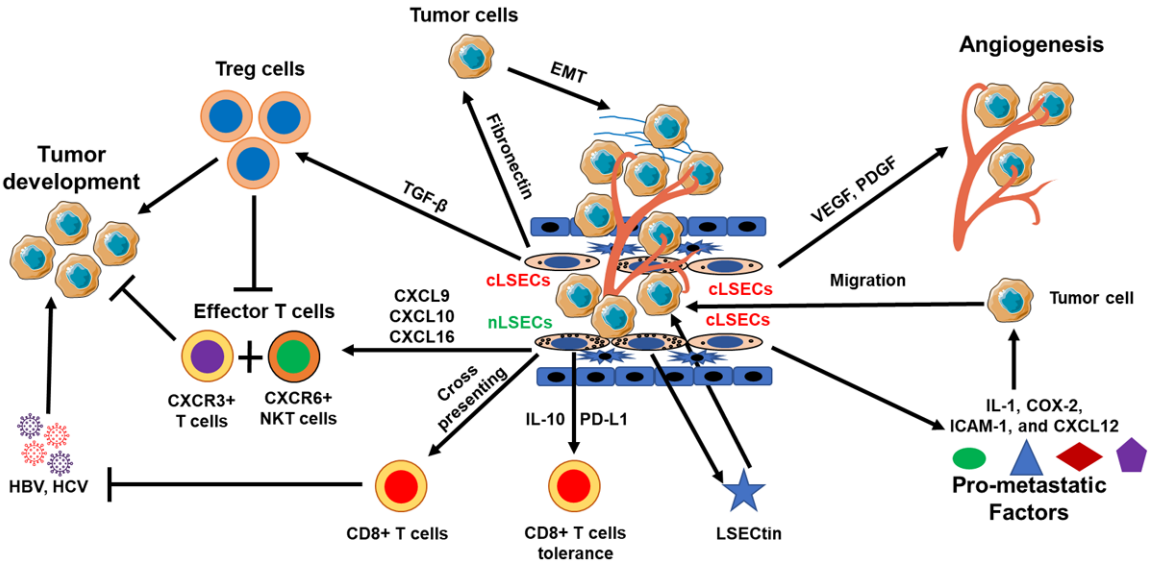


**Figure 2.** LSECs orchestrate the immune microenvironment during cancer liver metastasis. Normal LSECs (nLSECs) can cross-present antigens to $CD8^+$ T cells to inhibit viral infection, which may induce liver cancer development. In addition, nLSECs can also secrete CXCL9, CXCL10, and CXCL16 to chemoattract $CXCR3^+$ T cells and $CXCR6^+$ NKT cells to prevent tumor development. Injury LSECs or cancer-activated LSECs (cLSECs) can secrete TGF-β to enhance the proliferation of Treg cells, which can inhibit the effector T cell function and result in cancer development. LSEC-derived extra domain A (EDA) of fibronectin promotes cancer cell liver colonization via inducing epithelial-mesenchymal transition (EMT). Moreover, sLSECs express angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor-B (PDGF) to promote angiogenesis. The secretion of LSECtin and other pro-metastatic cytokine and chemokines help to induce migration of tumor cells and cause cancer liver metastasis.

(APC) dendritic cells (DCs), non-conventional APC LSECs can inhibit interferon-γ (IFN-γ) and IL-17 secretion from Th1 and Th17 effector $CD4^+$ T cells, mediated by IL-10 and PD-L1 [63]. Furthermore, LSECs are the major cells that mediate TGF-β-dependent conversion of $Foxp3^-$ cells into $Foxp3^+$ Tregs in the liver, and those Tregs are functional suppressor cells *in vitro* and *in vivo* [13]. LSECs function as APCs can cross-present MHC class I molecules from HSCs to $CD8^+$ T cells to play an important role in immune surveillance during viral infection [64]. In addition, recruitment of immune cells is importantly crucial in immune surveillance during liver diseases. For example, in the concanavalin A-induced hepatitis murine model, the expression of chemokines CXCL9 and CXCL10 in LSECs mediated hepatic accumulation of $CXCR3^+$ $CD4^+$ T cells during liver inflammation [65]. Besides, LSECs can transfer internalized chemokines perivascularly to enhance T cell migration. CXCL16, the ligand of CXCR6, is expressed on LSECs [66]. Gut microbiota-mediated alteration of bile acid components can impact the CXCL16 expression in LSECs, which results in the accumulation of $CXCR6^+$ NKT cells to inhibit tumor growth [67]. Moreover, LSEC-derived extra domain A of fibronectin (EDA) can promote the metastatic ability of colorectal cancer (CRC) cells via inducing an epithelial-mesenchymal transition (EMT) [68]. The tumor cell-activated LSECs increased the expression of Mannose receptor (ManR) and increased prometastatic factors including IL-1, ICAM-1, and cyclooxygenase-2. Those LSECs had an immunosuppressive effect on hepatic sinusoidal lymphocytes to decrease their anti-tumor effect [69]. Finally, LSECs can also secrete other angiogenic factors such as platelet-derived growth factor (PDGF) except the above-mentioned angiopoietins, resulting in activation of angiogenic phenotype of HSCs and growth of sinusoidal vascular structure [70]. Those molecular functions in LSECs are summarized in **Figure 2**.

*Important molecules in LSECs during cancer liver metastasis*

*CXCL12:* The CXC chemokine receptor (CXCR) 4 expressed on tumor cells has been shown to be implicated in cancer metastasis [71-73], with the interaction of its ligand CXCL12 that is frequently expressed at the site of metastasis.

This metastatic effect was inhibited with the treatment of anti-CXCL12 antibody. In the liver, the metastasis of CXCR4-expressed murine melanoma B16 cells was associated with an increased expression of CXCL12 in LSEC microenvironments [74]. Furthermore, treatment of CXCR4-B16 cells with CXCL12 increased their proliferation, migration, and adhesion to LSECs, while treatment CXCR4 receptor antagonist AMD3100 (Plerixafor) inhibited the migrating effect induced by CXCL12.

*ICAM-1:* Coculture of colorectal cancer cell line C26 cells and LSECs increased ICAM-1 secretion compared to each monoculture. ICAM-1 blockade in the LSECs decreased the adhesion of cancer cells and their transmigration through LSEC monolayers *in vitro* and *in vivo*. *In vitro,* pre-stimulated tumor cells with soluble ICAM-1 increased 35% of the liver colonization area than metastatic area induced by untreated tumor cells. Meanwhile, blockade of the ligand of ICAM-1, the β2 integrin lymphocyte function-associated antigen (LFA)-1, reduced tumor burden and antigenicity, evidenced by a reduction of $CD31^+$ cells. These results suggest that ICAM-1 in LSECs mediates CRC liver metastasis and is a potential target for preventing colorectal cancer liver metastasis [75]. Anti-ICAM1 antibody treatment significantly inhibited tumor cell adhesion to hepatic endothelial cells (HEC) in wild-type mice, which was mediated by Notch signaling [76]. In addition, C-type lectins produced by LSECs (LSECtin) can enhance the liver metastasis of colon cancer cell line LS174T and LoVo cells, as well as primary colon cancer cells in mice (**Figure 2**), as reduction of cancer liver metastasis was shown in LSECtin knockdown mice [77].

*TLRs:* LSECs respond to different TLR ligands, including producing TNF-α in response to TLR1 to -4, -6, -8, and -9 ligands, producing IL-6 in response to TLR3 and TLR4 ligands, and producing IFN-β in response to TLR3 ligand [78]. Activating TLR4 modulates angiogenesis in murine liver fibrosis models induced by $CCL_4$ or bile duct ligation (BDL), and myeloid differentiation protein 88 (MyD88) signaling is involved in this function [79]. *In vitro* stimulation of LSECs with TLR1/2 ligand (palmitoyl-3-cysteine-serine-lysine-4; P3C) activated virus-specific $CD8^+$ T cells partially through IL-12 production, but not TLR3 ligand poly (I:C) or TLR4 ligand LPS [80]. Therefore, TLR-mediated functional change of LSECs can impact cancer liver metastasis.

*KLF5:* Overexpression of Krüppel-like factor 5 (KLF5) is shown in many different cancers, including non-small cell lung cancer (NSCLC) [81], CRC [82], breast cancer [83], and pancreatic cancer [84], which predicts a poor prognosis for cancer patients. High KLF5 expression is also associated with CRC liver metastasis [82]. At these studies, molecular investigation shows that KLF5 plays a pivotal role in the control of the cell cycle by modulating genes such as E2F1 and cyclin D1. Another study demonstrates that KLF5 can not only modulate cell proliferation of laryngeal cancer human epithelial type 2 (Hep-2) cells, but also can impact their migration, invasion, and epithelial-mesenchymal transition (EMT) via inhibiting NF-κB pathway [85]. The expression of KLF5 has a positive correlation with the progression of cervical squamous cell carcinoma by activating the expression of tumor necrosis factor receptor superfamily member 11a (TNFRSF11a) [86]. Meanwhile, altering KLF5 expression is positively associated with the change of TNFRSF-11a expression. Moreover, an *in vivo* study showed that functional deplete of TNFRSF11a suppresses tumor genesis and liver metastasis. TNFAIP2, a tumor necrosis factor-α (TNFα)-induced gene, is another direct KLF5 targeting gene, which regulates breast cancer cell proliferation, migration, and invasion through two small GTPases Rac1 and Cdc42 [87].

*microRNAs:* The expression of microRNAs also impacts cancer development. With the analysis of microRNAs from LSECs either isolated from livers with colorectal cancer metastasis or healthy controls, microRNA-20a was downregulated in tumor-activated LSECs compared to control LSECs [88]. Additionally, its targeted proteins, such as E2F1 and Rho GTPase-activating protein 1 (ARHGAP1), were also downregulated. Moreover, transfection of exogenous microRNA-20a can prevent tumor-activated LSEC migration.

*CYP1B1:* Deficiency of cytochrome P450 1B1 ($Cyp1b1^{-/-}$) LSECs showed limited fenestration and decreased levels of VEGF and BMP6, and they were significantly more apoptotic, proliferated at a faster rate, and were less adherent and more migratory [89]. Furthermore,

Cyp1b1$^{-/-}$ LSEC expressed lower levels of inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1/$CCL_2$) and TNF-α, impacting anticancer immune response in liver microenvironment.

*PD-L1:* Programmed cell death protein (PD-1)/PD-L1 axis plays a vital role in cancer immunotherapy [90]. Cancer cells express PD-L1 or PD-L2 that binds with its ligand PD-1 on T cells to induce immune tolerance, causing reduction of antitumor effect of T cells in the tumor microenvironment. PD-L1 expressed by LSECs plays a pivotal role in maintaining liver immune tolerance by interacting PD-1 on T cells [91, 92]. Injection of circulating carcinoembryonic antigen (CEA) from CRC cells resulted in CEA-specific $CD8^+$ T cells mediated LSECs in a PD-L1 dependent manner, but those antigen-specific $CD8^+$ T cells lost the tumoricidal effect on CEA-expressing cancer cells [93]. In addition to PD-L1, LSECs also express other inhibitory or immunoregulatory molecules such as Fas ligand, LSECtin, and IL-10 to regulate the function of T cells [94]. Overexpression of PD-L1 in LSECs interferes with the tumor cytotoxic T cell function.

*STAT3:* Activating STAT3 in murine endothelial MS-1 cells *in vitro* with tumor cell-conditioned media increased the expression of cell adhesion molecules, including E-selectin and P-selectin, which was also shown in pre-metastatic lungs of tumor-bearing mice *in vivo* [95]. STAT3-knockdown in endothelial cells reduced the metastasis of Lewis lung carcinoma (LLC) cells in experimental and spontaneous metastasis murine models *in vivo* (**Table 1**). Hence, inhibition of STAT3 LSEC expression might reduce the potential cancer liver metastasis.

*Therapeutic approaches for targeting LSEC in liver cancer*

Liver is one the most cites where other cancers metastasize (**Figure 1B**). As discussed above, LSECs play critical roles in cancer liver metastasis. Many different strategies can be applied to modulate LSEC phenotype or function to inhibit cancer liver metastasis (**Figure 3**) as discussed below.

*Gut microbiota-mediated therapy*

Gut microbiota has been shown to play important roles in various diseases [96, 97], including liver disease. In the gut-liver axis, LSECs are first exposed to gut microbiota-derived metabolites and products. Macronutrient intake impacts the fenestration of LSECs [98]. For instance, dietary fat intake impacts the number of pores (fenestration), and protein and carbohydrate intake influence the size of pores (fenestration diameter) [98]. Synbiotic supplementation can modulate ethanol-induced gut dysbiosis to attenuate hepatocyte injury and improve liver endothelial barrier integrity to protect against LSEC damage [99]. Manipulation of gut microbiota can reduce LSEC injury and decrease the change of primary cancer development and cancer liver metastasis.

*MicroRNAs-mediated therapy*

Chronic alcohol consumption induced higher mRNA expression of endothelin-1 (ET-1), HIF-1α, and inflammatory cytochemokines in LSECs compared with LSECs from control rats, resulting in liver inflammation and cirrhosis [100]. With the analysis of miRNAs involved in ethanol-mediated gene expression, both miR-135 and miR-199 were shown to impact HIF-1α mRNA expression in rat and human LSECs, while only miR-199 affected ET-1 mRNA expression in rat LSECs. In human endothelial cells (HMEC-1), miR-199 mediated HIF-1α and ET-1 mRNA expression. Sinusoidal obstruction syndrome (SOS) is a liver injury associated with clinical chemotherapy-induced damage LSECs. Serum miRNAs were increased within a day when the damage of LSECs in male Sprague-Dawley rats induced by oral treatment of monocrotaline. Among them, miR-21-5p and miR-511-3p in serum increased in response to LSEC damage, which may serve as an early diagnostic biomarker for SOS [101]. Studies have shown that treatment with microRNA-20a delivered by nanoparticles to LSECs significantly decreases colon cancer liver metastasis in mice, and inhibits activated LSEC migration into a metastatic site [88].

*Nanoparticles*

Liver as an immunologic tolerance organ is a common site for cancer metastasis through blood circulation [102]. LSECs play an essential role in liver immunologic tolerance [103, 104]. Treatment with melittin nanoparticles (α-melittin-NPs) suppressed the metastasis of injected tumor cells (murine melanoma cell line

**Table 1.** The role of LSEC in primary and metastatic liver cancer

| Cancer | Target | Function | References |
|---|---|---|---|
| Melanoma and colorectal carcinoma | Notch signaling | Anti-ICAM1 antibody treatment significantly inhibited tumor cell adhesion to hepatic endothelial cells (HEC) in wild-type mice, which was associated with Notch signaling | [76] |
| Melanoma | CXCR4/CXCL12 axis | The metastasis of CXCR4-expressed murine melanoma B16 cells was associated with an increased expression of CXCL12 in LSEC microenvironments | [74] |
| Colon cancer | CXCR4/CXCL12 axis | The CXCR4/CXCL12 axis was involved in the formation of intrasplenic injection of colon cancer cells induced hepatic metastasis in nude Balb/c mice | [108] |
| Liver cancer | CXCR6/CXCL16 axis | Gut microbiota-mediated alteration of bile acid components can impact the CXCL16 expression in LSECs, resulted in the accumulation of $CXCR6^+$ NKT cells to inhibit tumor growth | [67] |
| Colorectal cancer (CRC) | Intercellular Adhesion Molecule 1 (ICAM-1) | ICAM-1 blockade in the LSECs decreased the adhesion of cancer cells and their transmigration through LSEC monolayers *in vitro* and *in vivo*. *In vitro,* pre-stimulated tumor cells with soluble ICAM-1 increased 35% of liver colonization area than metastatic area induced by the untreated tumor cells | [75] |
| Colorectal cancer (CRC) | MicroRNA-20a | The microRNA-20a and its targeted proteins, such as E2F1 and Rho GTPase-activating protein 1 (ARHGAP1), were downregulated in LSECs from the liver with colorectal cancer metastasis compared to that in LSECs from a healthy liver | [88] |
| Colorectal carcinoma (CRC) | PD-L1 | Injection of circulating carcinoembryonic antigen (CEA) from colorectal carcinoma (CRC) cells resulted in CEA-specific CD8 T cells mediated LSECs in a PD-L1 dependent manner, but those antigen-specific CD8 T cells lost the tumoricidal effect on CEA-expressing cancer cells | [93] |
| Lewis lung carcinoma (LLC) | STAT3 | Activating STAT3 in murine endothelial MS-1 cells *in vitro* with tumor cell-conditioned media increased the expression of cell adhesion molecules, including E-selectin and P-selectin, which was also shown in pre-metastatic lungs of tumor-bearing mice *in vivo*. STAT3-knockdown in endothelial cells (ECs) reduced the metastasis of LLC cells in experimental and spontaneous metastasis murine models *in vivo* | [95] |

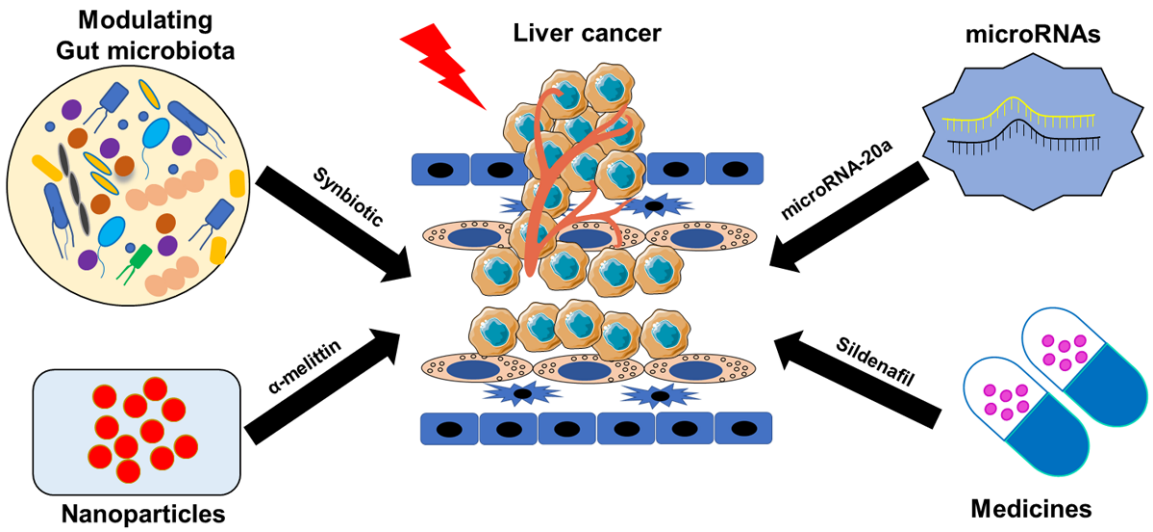


**Figure 3.** The therapeutic strategies of targeting LSECs to prevent cancer liver metastasis. Gut microbiota, microRNAs, and therapeutic medicines plus nanoparticle delivery are potential treatment options for targeting LSECs to prevent cancer liver metastasis or to cure secondary liver cancer.

B16F10 in C57BL/6 mice, mammary carcinoma cell line 4T-1, and colon carcinoma cell line CT26 cells in BALB/c mice) from the spleen into the liver, prolonging the survival time of tumor-bearing mice [105]. A functional study showed that α-melittin-NP increases the expression levels of cytokines and chemokines, such as IL-1α, CXCL9 (MIG), CXCL10 (IP-10), CXCL13 (BLC), $CCL_3$ (MIP-1α), CXCL1 (KC), $CCL_4$ (MIP-1β), and $CCL_5$ (RANTES) than the control treatment.

*Drugs*

Some medicines such as beraprost sodium (BPS) can suppress monocrotaline (MCT)-induced sinusoidal obstruction syndrome in mice [106]. BPS treatment significantly reduced the number of extravasated platelet aggregation and the expression of plasminogen activator inhibitor but increased the expression of endothelial nitric oxide synthase (eNOS), which can reduce the chance of cancer cell liver residence. A similar effect was also shown in the intraperitoneal administration of recombinant human soluble thrombomodulin [107]. As above-described, the axis of CXCR4/CXCL12 in cancer liver metastasis, treatment with low-molecular-weight heparin (LMWH), a common drug for venous thromboembolism, inhibited the CXCL12-stimulated proliferation, adhesion, and colony formation of CXCR4-expressed human colon cancer HCT-116 cells [108]. In addition, LMWH significantly inhibited the development of metastatic liver cancer induced by intrasplenic injection of colon cancer cells in nude Balb/c mice and downregulated CXCL12 expression in LSECs.

Furthermore, LSEC fenestration is markedly reduced with increasing age in mice. Treatment with different pharmaceutical agents including cytochalasin 7-ketocholesterol, sildenafil, amlodipine, simvastatin, 2, 5-dimethoxy-4-iodoamphetamine (DOI), bosentan, TNF-related apoptosis-inducing ligand (TRAIL), or nicotinamide mononucleotide (NMN), showed that fenestration is regulated in both NO-dependent and independent pathways, and age-induced defenestration can be reversed pharmacologically [109].

## Summary

LSECs have critical defense roles in the development and progression of liver diseases, including liver inflammation, fibrosis, cirrhosis, and liver cancer. The morphological and phenotypic changes impact the function of LSECs in liver disease, including immune surveillance against pathogens and tumor growth. Restoration of fenestration of LSEC protects liver inflammation and injury, which could be a strategy for liver fibrosis treatment. LSEC expressed molecules such as ICAM-1 and KLF5 are involved in cancer liver metastasis. Targeting these molecules via gut microbiota, microR-

NAs, and nanoparticles mediated therapies or other medicines are future therapeutic options. Preclinical and clinical studies are waited to explore the key genes involved in LSEC and cancer cell interaction.

## Disclosure of conflict of interest

None.

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