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REVIEW

Inflammatory networks cultivate cancer cell metastasis to the liver

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ABSTRACT

The liver is the most frequent site of metastatic spread in malignancies that arise from the digestive system, including pancreatic ductal adenocarcinoma (PDAC). Metastasis to the liver is a major cause of morbidity and mortality in cancer patients, yet mechanisms that govern this process remain poorly understood. Until recently, liver tropism of metastasis was believed to be driven by mechanical factors that direct the passive flow of circulating cancer cells to the liver. However, emerging evidence now shows that liver metastasis is a dynamic process that is, at least in part, dependent on the formation of a "pro-metastatic niche". Key features of this niche are myeloid cells and fibrosis that support cancer cell colonization and growth. Inflammatory responses that are mounted early during primary tumor development are critical for the recruitment of myeloid cells and the deposition of extracellular matrix (ECM) proteins within the liver. Intriguingly, the inflammatory processes that direct the formation of a pro-metastatic niche share remarkable resemblance to mechanisms of liver injury and regeneration, suggesting that cancer co-opts physiological liver functions to support metastasis. Therefore, therapeutic strategies that target key elements of liver inflammation that form the basis of a pro-metastatic niche may lead to effective treatments for metastatic cancer.

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Metastasis is the most common cause of morbidity and mortality in cancer patients. This is especially evident in gastrointestinal (GI) malignancies, which most commonly spread to the liver. Apart from focal or isolated disease that can be surgically resected, metastatic disease typically portends a grim prognosis. In PDAC, for example, combination chemotherapies have improved the median overall survival by up to 5 months [1,2], but the 5-year overall survival rate remains at 3% [3]. Furthermore, immune checkpoint blockade [4–6], cancer vaccines [7,8], and chimeric antigen receptor (CAR)-modified T cell therapies [9,10] have not provided a major clinical benefit to patients with metastatic PDAC. High mortality in PDAC is, at least in part, attributable to the propensity of cancer cells to spread to the liver early in the disease, even when the primary tumor is small [11,12]. In addition to GI malignancies, cancers that arise from many non-GI organs, including the breast, ovary, lung, and skin, frequently metastasize to the liver. The presence of liver metastases is associated with worse outcomes in patients [13] and reduced response to immunotherapies [14]. Thus, metastatic disease, particularly liver metastasis, poses a significant barrier to effective cancer therapies.

Mechanisms that determine the spread of cancer cells to the liver are now starting to be elucidated. In PDAC, metastatic lesions in the liver are believed to emerge from primary tumor cells that acquire distinct genetic mutations [15]. While these lesions typically harbor identical driver gene mutations [16], liver lesions show a heterogeneous response to cancer treatments [17]. Even across different patients, PDAC has limited heterogeneity in mutations, but patients display varying patterns of metastases and disease behavior [18]. Together, these results suggest that the metastatic behavior of cancer cells is likely determined by both tumor-intrinsic as well as tumor-extrinsic factors. Therefore, understanding mechanisms that direct the spread of cancer cells to the liver and reversal of this process may lead to effective therapies for metastatic cancers. In this Review, we discuss key determinants of liver metastasis, with a focus on cancer cell-extrinsic mechanisms that form the basis of liver tropism of metastasis.

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Mechanical determinants of liver metastasis

Metastatic spread of cancer cells is a multi-step process. The traditional model of cancer metastasis delineates a linear process in which primary cancer cells grow and invades their surrounding vasculature. Single cancer cells or aggregates then detach from the primary tumor, enter the circulation, and eventually become embedded in the capillary beds of a distant organ, including the liver. Here, cancer cells undergo extravasation, invade into the distant organ parenchyma, and proliferate. For metastases to form, all steps must be fulfilled, and each step may be rate-limiting [19]. Unique architectural features of the liver have long been believed to enable pooling and seeding of circulating tumor cells. For example, in contrast to many organs in the body, the liver has a dual blood supply. The portal vein, which drains most digestive organs, including the pancreas and colon, provides 60–70% of hepatic blood flow, while the hepatic artery supplies the remaining blood flow. Within the liver, these vessels further ramify through 17 to 20 orders of branches, and this extensive vascular network is believed to function as a "mechanical trap" that captures circulating tumor cells within the liver [20] (Figure 1).

Blood supplies to the liver are especially pertinent to the spread of GI malignancies, since the portal vein serves as a direct conduit between many digestive organs and the liver. In patients with PDAC, for example, circulating tumor cells are detected in all portal vein blood samples, whereas less than 25% of peripheral blood samples contain tumor cells [21]. Similarly, patients with colorectal carcinoma (CRC) display a higher number of circulating cancer cells in the mesenteric vein, which drains to the portal vein, compared to the peripheral vein [22]. These findings support the notion that the liver may capture cancer cells that are released into the circulation by the primary tumor. The fenestrated endothelial layer of the liver sinusoids is also believed to facilitate the invasion of cancer cells into the parenchyma. Compared to other organs in the body, the duration of tumor cell extravasation is typically shorter in the liver due to unique structural and migratory properties of liver endothelial cells. In a mouse

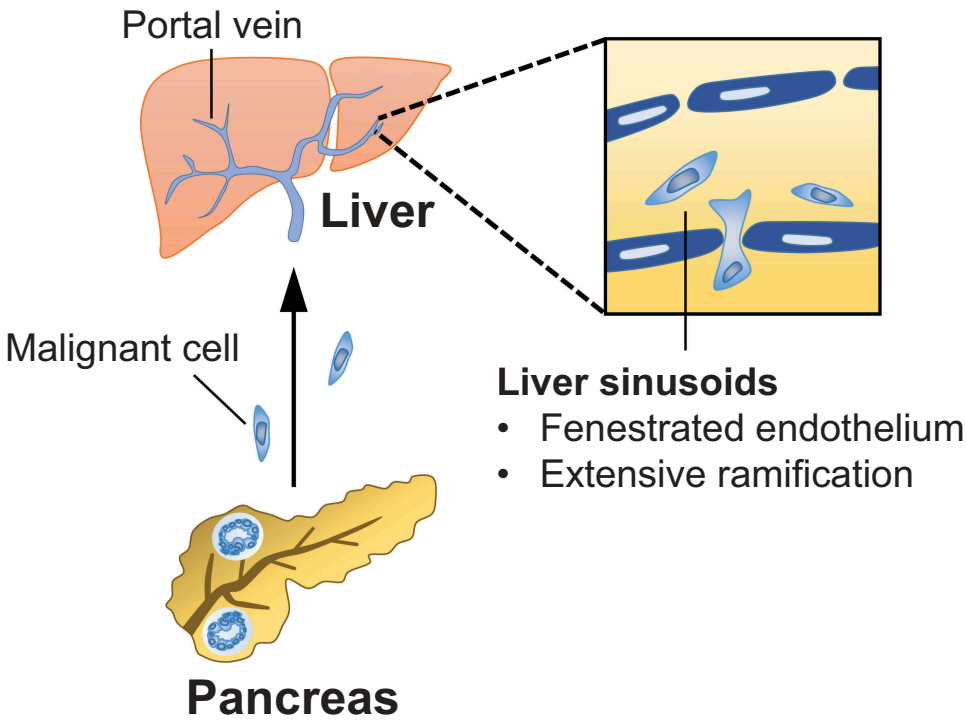

Figure 1. Mechanical determinants of liver metastasis. Primary cancer cells that are released into the circulation drain to the liver via the portal vein. The extensive vascular network and fenestrated endothelial layer of the liver sinusoids act as a mechanical trap that capture circulating tumor cells.

model of metastasis, liver endothelial cells were found to migrate and directly engage tumor cells that are dislodged within the liver sinsoids [23]. Mediated by cytoplasmic projections on liver endothelial cells, this interaction facilitates extravasation of tumor cells into the liver parenchyma. Taken together, liver tropism of metastasis is, at least in part, determined by distinct anatomic structures of the liver.

Immunological determinants of liver metastasis

While metastatic spread of cancer may depend on structural features of the liver, metastatic tropism is a complex process that cannot be described using mechanical rationale alone. The liver is a frequent site of cancer spread in many malignancies, including those that arise from organs without a direct vascular connection to the liver. For example, liver metastases are detected in 14% and 9% of patients with breast and ovarian cancers, respectively [13]. This observation was first made by Stephen Paget in 1889, when he described that breast cancer and malignancies of the female reproductive tract metastasize to the liver at a much higher frequency than to the spleen, though both organs are vascular in nature [24]. Based on this observation, Paget posited that metastasis requires a proper "soil" that nurtures the growth of "seeds" (i.e. tumor cells). Another finding supportive of the "seed and soil" hypothesis is that metastasis is a remarkably inefficient process. Previous studies showed that primary tumors may shed more than a million cells per gram of tissue, but less than 0.1% of these cells form metastatic lesions [25–27]. Even though disseminated tumor cells may become dislodged in distant organs, their presence is insufficient to predict the subsequent development of metastases [28]. Moreover, these studies demonstrated that metastases preferentially occur in the liver, suggesting the liver provides a fertile environment (i.e. pro-metastatic niche) for circulating tumor cells to seed and grow.

The molecular and cellular basis of a pro-metastatic niche in the liver is an active area of investigation. The formation of a pro-metastatic niche is initiated by molecules that are released by the primary tumor, including exosomes [29,30], tissue inhibitor of metalloproteinases-1 (TIMP1) [31,32], and interleukin 6 (IL-6) [33]. Exosomes are small membrane vesicles (30–150 nm in size) that contain biomolecules derived from cancer cells, including proteins and nucleic acids [34]. In contrast, TIMP1 and IL-6 are proteins secreted by malignant cells and stromal cells that reside within the primary tumor [31–33]. Even though these molecules are biologically distinct, they all converge on inflammatory responses that induce myeloid cell accumulation and fibrosis within the liver, and these changes in concert create a pro-metastatic niche (Figure 2). Liver-resident cells, including Kupffer cells, hepatic stellate cells (HSCs), and hepatocytes, are critical determinants of this process. Below, we discuss in detail mechanisms by which tumor-derived exosomes, TIMP1, and IL-6 initiate the establishment of a pro-metastatic niche in the liver.

A role for exosomes in directing liver tropism of metastasis was first described by David Lyden and colleagues [29]. Their study showed that macrophage migration inhibitory factor (MIF)-positive exosomes are released into the circulation by primary cancer cells. Exosomes are subsequently phagocytosed by Kupffer cells, which are liver-resident macrophages whose primary function is to bind and internalize pathogens and associated molecules [35]. Kupffer cells in turn produce transforming growth factor β (TGF-β) that induces HSCs to deposit fibronectin within the liver. Much akin to a role for fibronectin in recruiting myeloid cells into the lung [36], fibronectin in the liver enhances the recruitment of F4/80$^+$ myeloid cells that promote cancer cell seeding and growth. Disruption of this signaling cascade via depletion of MIF from exosomes or blockade of TGF-β receptor inhibits liver metastasis. In a follow up study, exosomes that direct the spread of cancer cells to the liver were also shown to express the integrin $\alpha_v\beta_5$, which is distinct from exosomes that direct metastasis to other organs, including the brain and lung [30]. Once phagocytosed by Kupffer cells, $\alpha_v\beta_5$-expressing exosomes induce the expression of pro-inflammatory S100 proteins, which recruit myeloid cells into the liver. Collectively, these studies identified myeloid cell accumulation and fibrosis as key elements of a pro-metastatic niche.

TIMP1 is another factor that has been proposed by Achim Krüger and colleagues to initiate the

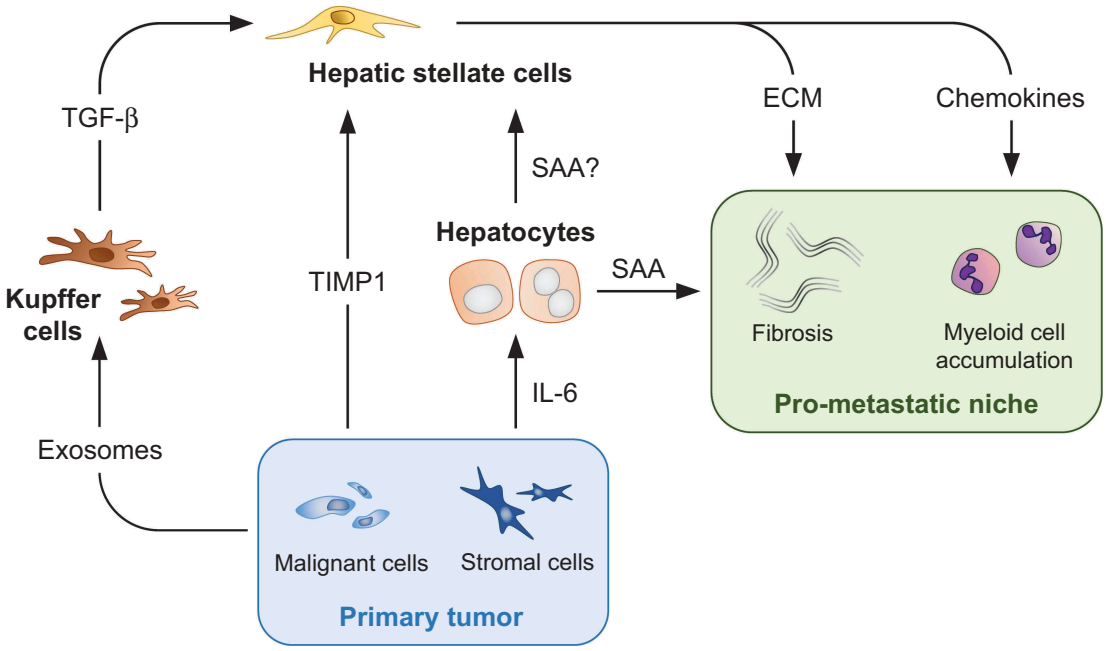

Figure 2. Immunological determinants of liver metastasis. Malignant cells and stromal cells that reside within the primary tumor release factors that engage liver-resident cells, including Kupffer cells, hepatocytes, and hepatic stellate cells. Inflammatory responses mounted by these cells induce myeloid cell accumulation and fibrosis, which form the basis of a pro-metastatic niche in the liver. ECM, extracellular matrix; IL-6, interleukin 6; SAA, serum amyloid A; TGF-β, transforming growth factor β; TIMP1, tissue inhibitor of metalloproteinases-1.

formation of a pro-metastatic niche in the liver [31,32]. Associated with poor prognosis in patients with metastatic cancer, TIMP1 is secreted into the circulation by tumor cells starting in early stages of primary tumorigenesis. Once in the liver, TIMP1 binds its receptor CD63 on HSCs, and this engagement induces the activation of HSCs via phosphatidylinositol 3-kinase (PI3K). Activated HSCs express α-smooth muscle actin (α-SMA) and desmin, in essence becoming myofibroblasts that induce fibrogenesis in the liver [37]. Activated HSCs also secrete chemokine (C-X-C motif) ligand 12 (CXCL12), which in turn, recruits $Ly6G^+$ myeloid cells into the liver in a chemokine (C-X-C motif) receptor 4 (CXCR4)-dependent manner. Autocrine production of TIMP1 by activated HSCs further reinforces the formation of a pro-metastatic niche in the liver by propagating a positive feedback loop. Studies also showed that genetic ablation of *Timp1* or its receptor *Cd63* prevents activation of HSCs and subsequent myeloid cell accumulation [31,32]. Without these cellular changes, metastatic seeding of pancreatic cancer cells within the liver is inhibited. These results, along with previous studies on exosomes, identify liver inflammation as a key driver of metastasis.

In addition to Kupffer cells and HSCs, hepatocytes play a major role in directing liver tropism of metastasis. Previously, claudin-2 that is expressed on the surface of hepatocytes was shown to enhance liver metastasis by facilitating adhesion between circulating tumor cells and hepatocytes [38]. Our recent work also highlights the importance of hepatocytes in inducing the formation of a pro-metastatic niche in the liver [33]. Early during pancreatic cancer development in mice, stromal cells that reside within the primary tumor release IL-6 into the circulation. IL-6 drains to the liver through the portal vein and subsequently activates signal transducer and activator of transcription 3 (STAT3) signaling in hepatocytes. In turn, hepatocytes produce acute phase reactants serum amyloid A1 and A2 (referred to collectively as SAA). Overexpression of SAA by hepatocytes also occurs in patients with PDAC, and many patients with locally advanced and metastatic disease have elevated levels of circulating SAA compared to healthy individuals. Our results are

consistent with a previous study demonstrating an association between increased circulating levels of acute-phase reactants and pancreatic cancer development [39]. We also found that high levels of circulating SAA correlate with worse outcomes in patients with metastatic PDAC. Intriguingly, overexpression of SAA by hepatocytes occurs in patients with metastatic CRC, suggesting that SAA may regulate liver metastasis across various malignancies.

Our study further showed that SAA is critical for the deposition of fibronectin and collagen within the liver. SAA also induces the expression of myeloid chemoattractants, including S100 proteins and chemokine (C-C motif) ligand 6 (CCL6). Through these functions, SAA engenders the accumulation of $F4/80^+$ and $Ly6G^+$ myeloid cells and liver fibrosis, which in concert establish a pro-metastatic niche. Genetic ablation or blockade of any component of IL-6 – STAT3 – SAA signaling effectively prevents this process and inhibits liver metastasis. In addition, even though SAA released by hepatocytes enters the systemic circulation, the SAA-mediated formation of a pro-metastatic niche is specific to the liver, and genetic ablation of *Saa* has no bearing on lung metastasis. Based on this result, cellular targets of SAA are most likely liver-resident cells that have the capacity to either directly or indirectly recruit myeloid cells and induce fibrotic changes in the liver. Identification of such liver-resident cells is an area of active investigation in our laboratory. One promising target is HSCs, which produce chemokines and promote fibrosis in the liver upon stimulation by SAA [40]. In summary, SAA released by hepatocytes in response to IL-6 derived from stromal cells within the primary tumor orchestrates liver metastasis.

Even after a pro-metastatic niche in the liver is fully formed and metastasis has already occurred, myeloid cells and the fibrotic microenvironment of the liver continue to have a major role in supporting liver metastasis. Consistent with studies showing that tumor cells release chemotactic factors to recruit myeloid cells [41,42], metastatic tumor cells attract pro-tumorigenic myeloid cells to the liver. A recent study showed that myeloid cells associated with these tumor cells secrete granulin, which activates HSCs to differentiate into myofibroblasts [43]. Myofibroblasts then release periostin, an ECM component that sustains a fibrotic microenvironment needed for the proliferation of metastatic tumor cells. In the same study, inhibition of granulin halted the growth of metastatic lesions and, by doing so, prevented metastasis to the liver. Myeloid cell accumulation and fibrotic changes continue as metastatic lesions grow, and these lesions ultimately mirror the microenvironment of the primary tumor [44]. Thus, myeloid cells and fibrosis are critical determinants of liver metastasis and are essential to all stages of this process.

Myeloid cell recruitment and ECM alterations are key features of pro-metastatic niches in other organs as well, such as the lung [34,45]. Much akin to the formation of a pro-metastatic niche in the liver, molecules released from the primary tumor initiate cellular and stromal alterations in the lung. For instance, the hypoxic microenvironment of the primary tumor drives tumor cells to secrete lysyl oxidase (LOX), which enhances the capacity of tumor cells to migrate and invade into distant organs [46]. LOX that is released into the circulation also crosslinks collagen fibers and creates within the lung a fibrotic microenvironment that induces the recruitment of $CD11b^+$ myeloid cells [47]. These cells then further modify ECM components in the lung to facilitate cancer cell seeding and growth. Interestingly, LOX-mediated fibrosis also enhances metastatic colonization of the liver in a model of breast cancer [48], suggesting that LOX may be fundamental to pro-metastatic niche formation not only in the lung, but also the liver.

Primary tumor cells may also release into the circulation exosomal RNAs, which engage Toll-like receptor (TLR) 3 in lung epithelial cells [49]. As a result, lung epithelial cells express chemokines that promote myeloid cell accumulation within the lung. Activation of TLR3 in lung epithelial cells is also associated with fibronectin deposition, and, together with myeloid cell accumulation, these changes establish a pro-metastatic niche in the lung. Versicans are yet another tumor-derived molecule that has been implicated in driving the metastatic spread of cancer cells to the lung [50]. Upon engaging TLR2 on myeloid cells, versicans induce myeloid cells to produce tumor-necrosis factor α (TNF-α) that creates

a pro-inflammatory milieu hospitable for metastatic growth. Future studies should further explore roles for these tumor-derived molecules in regulating the spread of cancer cells to the liver and crosstalks that may exist between processes that establish a pro-metastatic niche in various distant organs.

Common themes in liver regeneration and metastasis

Solid malignancies, including PDAC and CRC, are described to be in a perpetual state of "wound healing" because of pervasive immune cell infiltration and fibrosis that are typically associated with tissue repair [51]. Central to this principle is the notion that physiological processes that are beneficial to our health may in another context be co-opted for tumorigenesis. We find that this principle applies not only to primary tumor development but also to processes that direct liver metastasis. This is particularly relevant to IL-6 – STAT3 signaling in hepatocytes. While this signaling is critical for the formation of a pro-metastatic niche in the liver, IL-6 – STAT3 signaling is also important for coordinating liver repair and regeneration after injury [52]. In mouse models of liver injury, including partial hepatectomy [53], sclerosing cholangitis [54,55], and steatohepatitis [56], IL-6 – STAT3 signaling protects hepatocytes from apoptosis and is required for their proliferation. Genetic ablation of either *Il-6* or *Stat3* predisposes the liver to tissue necrosis and metabolic derangements that eventually lead to liver failure.

Comparable to myeloid cell accumulation that occurs within the liver early during primary tumor development, liver injury engenders robust recruitment of myeloid cells into the liver, especially in response to trauma or infection [57–59]. Liver injury induces hepatocytes to produce acute phase reactants, which facilitate elimination of pathogens and tissue repair to restore homeostasis. SAA is a major acute phase reactant whose circulating levels may increase by more than a 1,000-fold in response to inflammatory stimuli [60]. Evolutionarily conserved in mammals [61,62] and other vertebrate species [63], SAA is believed to be an archetypal acute phase reactant. In addition to serving as an opsonin for bacteria [64], SAA binds a range of structurally distinct receptors that are expressed on the surface of myeloid cells and fibroblasts, including TLR2, TLR4, and formyl peptide receptor 2 (FPR2). Through these interactions, SAA induces the expression of pro-inflammatory cytokines and migration of myeloid cells [65]. Within the liver, myeloid cells attenuate inflammatory responses mediated by other innate immune cells and T cells to minimize liver damage while supporting tissue repair [57–59].

Another molecule that serves a key determinant of both liver metastasis and regeneration is CXCL12 [66]. Following liver injury, HSCs and liver sinusoidal endothelial cells release CXCL12, which in turn mobilizes bone marrow-derived mesenchymal stem cells [67]. Upon engraftment into the liver, these cells transdifferentiate into hepatocyte-like cells to facilitate liver regeneration. A balanced interplay between CXCL12 and its receptors CXCR4 and CXCR7 is believed to promote liver regeneration while minimizing liver injury [68]. In addition to promoting liver regeneration, CXCL12 supports the progression of hepatocellular carcinoma (HCC). CXCL12 is expressed early during the invasion of HCC and remains upregulated throughout the invasion process [69]. Produced primarily by liver cells that are located adjacent to HCC [70], CXCL12 recruits pro-tumorigenic Gr-1^{+} myeloid cells and activates HSCs to induce liver fibrosis [71]. Taken together, molecules that mediate the formation of a pro-metastatic niche in the liver have major roles in liver metastasis as well as liver regeneration.

ECM alterations that follow liver injury also resemble the deposition of ECM proteins that occurs during the establishment of a pro-metastatic niche in the liver. Recovery of liver injury requires coordinated ECM remodeling to ensure proper restoration of liver tissue. In response to injury, the liver shows increased deposition of ECM proteins, including fibronectin and collagen, and alterations in non-structural proteins [72,73]. Together, these changes increase liver stiffness, which is believed to promote the migration and proliferation of bone marrow-derived cells necessary for liver regeneration [74,75]. In addition, fibronectin that is deposited within the liver in response to injury improves the survival of hepatocytes [76] and promotes liver sinusoid repair by enhancing the adhesion of

liver sinusoidal endothelial cells to injured tissues [77]. Fibronectin also prevents the liver from becoming excessively fibrotic by regulating the availability of TGF-β to HSCs, thereby ensuring optimal levels of fibrosis necessary for liver repair [78]. Hence, even though the formation of a pro-metastatic niche and liver regeneration are biologically distinct, parallels can be draw in that both processes depend on myeloid cell accumulation and ECM remodeling. Interestingly, these changes are also observed in the liver of female mice after weaning, providing potential rationale for the higher frequency of liver metastases in women with postpartum breast cancer [79]. Collectively, these parallels suggest that cancer usurps physiological liver functions to promote the spread of tumor cells to the liver.

Therapeutic strategies and future directions

In describing liver tropism of metastasis in 1889, Paget stated that "he who turns over the records of cases of cancer is only a ploughman, but his observation of the properties of the soil may also be helpful [24]." Recent studies are beginning to provide insight on mechanisms underlying the formation of a fertile "soil" that supports cancer cell colonization and growth in the liver. Based on these studies, hepatocytes, HSCs, and Kupffer cells have emerged as key liver-resident cells that orchestrate myeloid cell accumulation and fibrosis. Therefore, therapeutic strategies that target specific molecular and cellular components of the liver pro-metastatic niche may prevent liver metastasis and, by doing so, significantly improve patient outcomes. For instance, hepatocyte-mediated formation of a pro-metastatic niche in the liver presents multiple opportunities for therapeutic intervention [80]. Given that IL-6 initiates pro-metastatic niche formation, antibodies that target IL-6 or IL-6 receptor (IL-6R) offer an effective means to prevent liver metastasis. In addition, molecules that target components of IL-6 – STAT3 signaling, including Janus kinase 1/2 (JAK1/2) and STAT3 inhibitors, provide an approach to inhibit metastasis with high specificities. Other molecules that drive the formation of a pro-metastatic niche in the liver, including TGF-β, may also be targeted using small molecules [29].

Apart from antibody- and small molecule-based therapies, nanoparticles that enable liver-specific expression of antibody-like proteins (so-called "traps") that bind specific molecules offer an alternative means to inhibit the formation of a pro-metastatic niche. In a recent study, CXCL12 traps were utilized to prevent the recruitment of myeloid cells and seeding of $CXCR4^{+}$ cancer cells within the liver [81]. Similar strategies may be applied to neutralize key chemoattractants that have been implicated in pro-metastatic niche formation, including SAA and S100 proteins. Therapeutic agents that can reverse liver fibrosis may also be used in conjunction with modalities that inhibit myeloid cell recruitment to further prevent liver metastasis. CD40 agonists [82,83] as well as focal adhesion kinase (FAK) inhibitors [84,85] are promising therapeutic agents that may be used to reverse ECM deposition within the liver. In general, strategies that target the pro-metastatic niche in the liver may be combined with conventional chemo- and radiation therapies. However, one must exercise caution because some cancer treatments, including anti-vascular endothelial growth factor (VEGF) therapy [86], are known to induce liver fibrosis and may counteract therapies designed to prevent the formation of a pro-metastatic niche in the liver. Medications that are prescribed for common chronic conditions, such as diabetes, may also accelerate tumor metastasis [87]. Therefore, additional studies are needed to determine optimal cancer treatment regimens that can effectively tackle the primary cancer as well as metastatic disease in the liver.

Future studies should also focus on understanding the impact of liver pro-metastatic niche on adaptive immune responses against the primary tumor and metastatic lesions. The fact that patients with liver metastases respond less to immunotherapies [14] suggests that the formation of a pro-metastatic niche in the liver may suppress local as well as systemic T cells responses against tumor cells. Supportive of this idea is the capacity of SAA to regulate T cell migration [88], which may impact T cell infiltration into tumor tissue and subsequent interactions between T cells and tumor cells. Myeloid cells are also an important determinant of cancer dormancy [89], and therapeutic strategies that target myeloid cells in the liver may alter recognition and elimination of tumor cells by

T cells. Together, additional studies on mechanisms that direct the formation of a pro-metastatic niche and its impact on anti-tumor immune responses may lead to effective therapies for cancer.

Disclosure statement

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