IEO model: A novel concept describing the complete metastatic process in the liver microenvironment (Review)

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Abstract. Metastasis is a characteristic behavior of malignant tumor cells. It is determined by the mutual interaction between primary tumor cells and the state of the microenvironment at sites of metastasis, particularly the liver, bone, lungs and brain. In the present review, a novel pattern is defined and termed the IEO model (prI-, prE- and pOst-metastatic niche), for the hepatic metastatic microenvironment which characterizes the complete metastatic process. In the IEO model, the components of the hepatic metastatic niche, including the extracellular matrix, hepatocytes, mesenchymal cells, Kupffer cells, hepatic sinusoidal endothelial cells, hepatic stellate cells and immunocytes are continually remodelled by tumor cells to form various microenvironments during different stages of hepatic metastasis. The IEO model explains the plasticity of the hepatic microenvironment and provides novel insights into the role of different stages of the metastatic niche. This novel concept may provide a basis for advances in theoretical cancer research and for improvements in the complete course management of malignant tumors.

Contents

1. Introduction
2. Pri-metastatic niche
3. Pre-metastatic niche
4. Post-metastatic niche
5. Conclusion

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1. Introduction

Due to their specific anatomical structures and biological properties, the majority of the different types of digestive cancer first metastasise to the liver (1,2). The timing of, and the molecular determinants underlying the process of metastasis are largely unknown, and improving the ability to determine these factors has clinical significance (3). A number of studies (4-6) have reported that the metastatic microenvironment is altered before malignant cells metastasise to the liver or lung, forming the pre-metastatic niche. Furthermore, multiple clinical studies (7-10) have revealed that patients with cirrhosis or hepatitis exhibit a lower incidence of hepatic metastasis despite presenting with the same types of primary cancer. This indicates that the liver microenvironment may be modulated by primary liver disease influencing hepatic metastasis, and this altered microenvironment is defined as the pri-metastatic niche. After tumor cells migrate to the liver, parenchymal, immune and mesenchymal cells interact with the tumor cells to modify the cell state and local microenvironment (including cancer-associated fibroblasts and macrophages) to perform specific cancer-associated functions that promote tumor cells colonization, proliferation and evade immune defence, this is termed the post-metastatic niche (11-13). These three different niches are the major components of the IEO model (the pri-, pre- and post-metastatic niche), as described in Table I, explaining the hepatic metastatic niche throughout the complete process of tumor progression.

Hepatic metastasis is the primary form of metastasis in colorectal cancer (CRC) and is the leading cause of CRC-associated mortality worldwide (3,9). Colorectal liver metastasis (CRLM) occurs in >25% of patients diagnosed with primary CRC and 50% of patients during the whole course of the disease (2-5). Thus, it is important to understand the underlying mechanisms behind hepatic metastasis, and to develop measures to prevent or delay this process. According to the seed and soil theory, the process of metastasis can be stratified into two major phases (4). The first phase involves the migration of tumor cells from the primary tumor site to a targeted metastatic tissue, and the second phase involves cell proliferation at the site of metastasis (4). This theory emphasises the importance of the 'soil' or microenvironment during the process of metastasis (12). The liver microenvironment is comprised of numerous components, including hepatocytes, Kupffer cells

(KCs), hepatic sinusoidal endothelial cells (HSECs), hepatic stellate cells (HSCs), pit cells and the extracellular matrix (ECM) (11). The tumor-associated hepatic niche is regulated via two mechanisms; the tumor-associated microenvironment formed by the primary tumor lesions and the intrinsic microenvironment formed by liver disease (7,14,15). Specific stages include the recruitment of fibroblasts, migration of immune cells, matrix remodelling and the development of vascular networks (11). The metastatic cells pass through the portal vein system into the hepatic sinusoid, and the anchoring of the circulating tumor cells (CTCs) to the hepatic sinus, and its attached cells (HSECs, HSCs and KCs), affects invasion and proliferation (1,4). Additionally, blood flow in the hepatic sinusoids is regulated by the vasoconstrictive properties of HSCs that control the oxygen and nutrient supply (5,16). Fig. 1 provides an overview of the processes underlying pathological metastasis that form the basis of the IEO model, as described in detail in the following sections.

2. Pri-metastatic niche

The target organ, with its inherent microenvironment influenced by chronic or acute local disease states, may further affect the occurrence of cancer metastasis from primary tumors (5,7-9). The local microenvironment at the metastatic site forms the pri-metastatic niche. Various diseases affecting the liver (such as fatty liver, cirrhosis, liver steatosis, hepatitis B and C infection or acute liver injury) may affect the liver microenvironment and the incidence of hepatic metastasis (14,15,17). Accordingly, the pri-metastatic niche serves an important role in the process of hepatic metastasis.

A study of 5,092 autopsies of colorectal, breast or lung tumors indicated that the incidence of liver metastasis is 28.6% compared with non-cirrhosis cases, which is higher than the 4.5% observed in patients with cirrhosis (8). Liver metastasis from CRC is also infrequent in patients with cirrhosis (10%) compared with non-cirrhosis cases (25%), indicating that liver cirrhosis substantially reduces the rate of CRLM, perhaps due to the differential properties of the liver microenvironment (10). Moreover, a meta-analysis of data concerning 10,349 patients with CRC from 10 studies was performed to investigate the association between CRLM and local liver disease. Based on this meta-analysis, chronically diseased livers (fatty liver, cirrhosis or chronic hepatitis B and C virus infection) exhibited a pri-metastatic niche and a significantly lower incidence of CRLM (14). The mechanism may involve the remodelling of the inherent liver microenvironment components, including fibrosis and the hepatic sinus. Activated immune cells residing in the liver microenvironment of the diseased liver kill metastatic tumor cells that circulate in the bloodstream. During cirrhosis, KCs release pro-inflammatory cytokines to remodel the hepatic immune niche, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 (14). In an analysis of rats with cirrhosis, Song *et al* (15) revealed that KCs and CRC cells exhibited upregulated Fas/FasL protein expression, which induced cell apoptosis, and the apoptotic cancer cells are further targeted by infiltrating lymphocytes. Thus, while the activation of KCs in cirrhosis participates in tissue damage and fibrogenesis, it also exerts a protective effect by inhibiting the hepatic metastasis of colon cancer. Seitz (16) reported that liver cirrhosis is associated with high metalloproteinase inhibitor levels and decreased levels of lectins or lectin-binding sites. Patients with liver cirrhosis reduced blood flow from the portal vein that may decreases tumor cell migration to the liver, which may contribute to rare occurrences of liver metastasis. However, cytokine analysis of metastasis of pancreatic cancer to the liver has indicated that in the early phase of metastasis, pancreatic ductal cancer cells decrease IL-6/signal transducer and activator of transcription 3 signalling via a negative feedback loop to construct the microenvironment of liver fibrosis and attract bone marrow-derived cells, promoting pancreatic duct engraftment to the liver (18).

Patients with CRC infected with hepatitis B virus (HBV) or hepatitis C virus exhibit a lower incidence of metastasis (8.1%) and longer survival time compared with that in patients without infection (21.2%), although they may have a higher probability of developing liver cancer (19). HBV may affect liver-associated immunity and increase cytotoxic liver activity on metastatic cells mediated by T cells, KCs or TNF-α synthesized by liver cells (8,20,21). Metalloproteinase inhibitors, such as metalloproteinase tissue inhibitor-1, have also been isolated from myofibroblasts of diseased livers (cirrhosis and hepatitis) but less so from healthy livers. Disease livers with more TIMP1 may inhibit MMPs expression from tumor cells, and this may explain the lower incidence of metastasis observed in diseased livers (22,23). Furthermore, HBV activates cytotoxic T-cells and KCs, which have the potential to kill metastatic tumor cells when they pass the liver sinuses (24-26). Additionally, HBV may stimulate HBV specific T cells to increase the secretion of TNF-α (27).

Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease are major health issues associated with tumor cell metastasis to the liver (28). According to previous studies, high alcohol intake is associated with CRLM (29,30). Both KCs and hepatocytes are affected by alcohol, and high expression of lipopolysaccharides and pro-inflammatory cytokines, such as TNFα and IL-1β changes the hepatic niche and CRC metastasis (28). NAFLD has been used to demonstrate the higher metastatic burden in steatotic livers compared with that in normal livers. NAFLD is characterized by fat accumulation, which alters the local hepatic niche by stimulating triglyceride, recruiting inflammatory cells, increasing TNFα expression and disrupting the normal structure of ECM. These alterations of the liver microenvironment, including tumor-associated inflammatory cells and aberrant ECM structure may promote colonization of tumor cells and cancer progression with poor outcome (28-30). However, Karube *et al* (31) demonstrated that fat metabolism disorders inhibit tumor cell proliferation and angiogenesis to prevent tumor growth and reduce the likelihood of metastasis.

3. Pre-metastatic niche

As indicated in Fig. 2, prior to the establishment of metastatic lesions in the targeted organ, tumor-associated exosomes, CTCs, immune cells and chemokines affect the liver microenvironment, forming the pre-metastatic niche (4,6,11,32-34).

Tumor-derived exosomes are composed of proteins, mRNAs and microRNAs that regulate pre-metastatic niche formation and affect metastasis (35-37). In the metastatic

Table I. Characteristic stages of the IEO model in the hepatic metastatic environment.

Characteristics	Pri-metastatic niche	Pre-metastatic niche	Post-metastatic niche
Definition	Hepatic IME remodeled by the chronic or acute local diseases.	Hepatic TME altered by tumor-associated factors before tumor cells arrived.	Hepatic TME changed by tumor cells and their associated factors.
Bio-factors	Cirrhosis, hepatitis and fatty liver.	Exosomes, chemokines, immune cells and CTCs.	Tumor cells, exosomes, chemokines and immunocytes.
Tumor-associated	No	Yes	Yes
Metastasis-associated	Yes	Yes	Yes

IME, inherent microenvironment; TME, tumor microenvironment; CTCs, circulating tumor cells; IEO, pri-, pre- and post-metastatic niches.

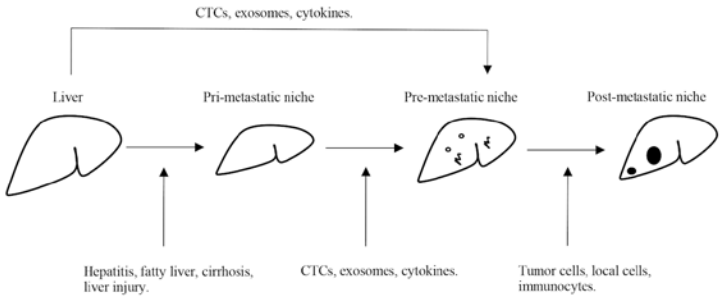

Figure 1. Different liver states in the IEO model. Hepatic disease (hepatitis, fatty liver and cirrhosis) may alter the normal liver microenvironment into the pri-metastatic niche, which is the primary hepatic niche prior to tumor cell migration to the liver. CTCs, immunocytes and their secretions, exosomes and chemokines remodel the hepatic microenvironment prior to pre-metastatic niche and the lesion co-adapts to the microenvironment along with the local hepatic cells to form the post-metastatic niche. CTCs, circulating tumor cells; IEO, prI-, prE- and pOst-metastatic niches.

process, exosomes also affect epithelial-mesenchymal transition, cancer stemness, apoptosis and metastatic angiogenesis via CXCR, integrins or the TGF-β signaling pathway (38-40). Wang *et al* (11) reported that CRC tumor-derived exosomes affect the hepatic niche and increase CXCR4 expression in stromal cells, thus creating a CXCR4-enriched microenvironment suitable for metastasis (11). In addition, pancreatic cancer cells release migration inhibitory factor-associated exosomes that induce TGF-β secretion, which results in the production of the glycoprotein fibronectin by HSCs, and the aggregation of bone marrow-derived cells to promote hepatic metastasis (33). Integrins in exosomes influence metastasis to specific organs and prepare the microenvironment for tumor cell arrival, such as integrin β5 in liver metastasis and integrin α6 in lung metastasis (41). In addition to tumor-associated exosomes, CTCs are also necessary elements for successful metastasis (18). CTCs circulate to the targeted metastatic organ, evade immune defence via TGF-β associated signaling pathways and platelet protection, arrive at the supportive niche and serve as latent tumor seeds in the niche, ultimately proliferating in the host tissue to form the metastatic lesion and altering the liver microenvironment (42,43). CTCs regulate the metastatic microenvironment via cytokine secretion, including TGF-β and IL-1. The perivascular space around the small blood vessels supports metastasis; it facilitates the proliferation of CTCs and hinders antitumor therapy (44,45). The cytokine signals secreted by the primary tumor may affect the microenvironment of distant organs and form a pre-metastasis niche prior to the arrival of CTCs (46,47). Physical contact between stromal cells and tumor cells, such as the claudin-2-mediated bridge between metastatic cancer cells and hepatocytes, induces c-Met signalling and hepatic metastasis in breast cancer (48). Hepatic sinusoids lined by endothelial cells and basal lamina gaps (49) may support the extravasation of CTCs and result in liver and bone metastasis (50,51). The major factors in anti-metastatic immunity are cytotoxic T and NK cells (52). Furthermore, the liver has a specific immune cell composition, characterised by abundant NK cells, which affects the susceptibility of the target organ to metastasis (4). Compared with levels in the normal mucosa, expression of the inflammatory mediator cyclo-oxygenase- is upregulated in CRC and to a greater extent in hepatic metastases (53), indicating that inflammation affects disease progression and may serve as a clinical indicator for malignant tumors (54). In HSECs, the vascular cell adhesion protein-1 blockade decreases microvascular formation of the hepatic metastatic lesion (53,54). CTCs, circulating free-DNA, miRNAs and exosomes may potentially be used for the development of critical assays for the early detection of metastasis in patients with CRC and as a therapeutic target.

4. Post-metastatic niche

After tumor cells metastasize to the liver, they interact with the liver niche and adapt to their new microenvironment, which is called the post-metastatic niche (Fig. 2). In the new and

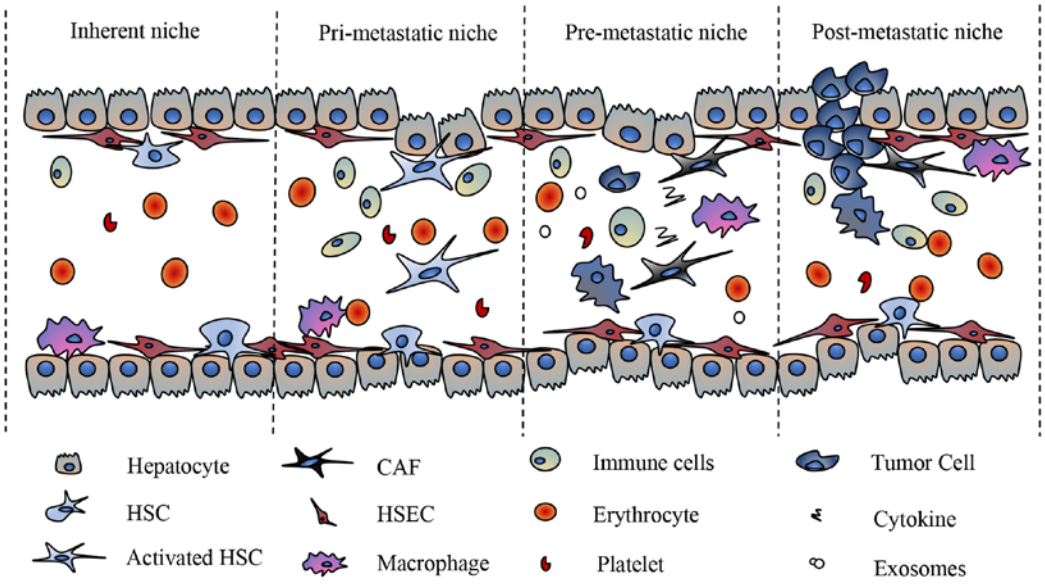

Figure 2. IEO model of the metastatic process in liver microenvironment. Microcirculation in hepatic sinusoid and hepatic local cells may be remoulded by the primary liver disease and the tumor-associated HSCs, macrophage and exosomes. CAF, cancer-associated fibroblasts; HSEC, hepatic sinusoidal endothelial cells; HSCs, hepatic stellate cells; IEO, prI-, prE- and pOst-metastatic niches.

challenging metastatic niche, newly established tumor cells must acquire the ability to survive immune cell attacks (55-58).

The interaction between the hepatic innate immune response and tumor cells is a double-edged sword for tumor metastasis (55,56). Although an initially effective defence can inhibit CTCs via the cytotoxic attack of KCs and NK cells (57), immune cells also promote tumor invasiveness and metastasis via various mechanisms, such as the activation of angiogenesis (55) and a pro-tumorigenic phenotype to promote tumor cell proliferation (56,58). Neutrophils or tumor-associated neutrophils exhibit high levels of plasticity in order to regulate the tumor microenvironment (59). They are also associated with the formation of the pancreatic liver metastatic microenvironment (60). The neutrophil subtype that infiltrates at the early phase of metastasis recruits macrophages and fibroblasts, and promotes the formation of metastatic lesions (61). Neutrophils promote tumor invasion (59), and tumor-associated neutrophils express immunosuppressive factors, such as TGF-β and FGF2 (62). CXCR2 protein expression in neutrophils during liver metastasis serves an important role in the early phase of tumor development and accelerates fibroblast anchoring to tumor cells in the hepatic sinus (60). Tumor-associated neutrophils may promote fibroblast growth factor 2 (FGF2), which is primarily expressed in and released from the ECM (12). The normalisation of microvessels in the tumor microenvironment is associated with FGF2 (63), which promotes vascular formation in liver metastases and induces an immune response in endothelial cells to recruit more immune cells (64). Tumor-infiltrating lymphocytes (TILs), an indicator of the anticancer immune response, influence cancer progression, metastasis and chemoresistance and are superior in the TNM classification as a predictor of survival in patients with digestive and lung cancer (65). A high number of TILs in the metastatic tumor is associated with improved clinical outcomes, overall response rates and chemotherapeutic outcomes (65). Moreover, patients with CRC exhibit reduced sensitivity to programmed cell death protein 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1), with the exception of patients with mismatch repair (MMR) genes deficiencies, such as MSH2, MSH6, MLH1 or PMS2 gene (66). The unique immune microenvironment in the liver forms a special immune tolerance type. The mechanism underlying immune tolerance involves the induction of surface immune suppression ligands of T cells and suppression of the immune receptor expression in liver cells and HSCs (65-67). The post-metastasis microenvironment may enhance immune cell infiltration and increase immunosuppression checkpoints so that sensitivity to PD-1/PD-L1 is greater in MMR-deficient CRC compared with that in MMR-proficient CRC (67). Additionally, decreased TGF-β protein expression levels in the post-metastatic niche may increase the activation of cytotoxic T cell-dependent processes and change MMR-proficient CRC cells to immune-hot cells (68). During metastasis, α-SMA-positive stromal cells present on the interstitial surface of the tumor, and the residual fibroblasts differentiate into myofibroblasts that express collagen in the periphery (69,70). According to microenvironmental change, three distinct growth patterns have been described in CRC adenocarcinoma liver metastases (69).

In the replacement growth pattern, the liver structure is preserved. In the pushing growth pattern, the hepatic lobules extend to one side and the liver stromal cells surround the metastatic lesion, and in the desmoplastic growth pattern, a fibrous ring separates the hepatic stromal tissue from the metastatic lesion (70). The survival and proliferation of cancer cells at the metastatic site is important for the establishment of metastatic tumors and the re-expression of E-cadherin on cancer cells at the metastatic site promotes proliferation in breast cancer (71). Further, if the hepatic sinus blood vessel is blocked by a large number of tumor cells and blood flow is obstructed, the inflammatory response of ischemia-reperfusion is initiated (72,73).

This may result in the release of nitric oxide (NO) and reactive oxygen species in local HSECs and KCs (72,73). The release of NO and interferon-γ by HSECs entering the hepatic sinus results in the upregulation of FasL, initiating apoptosis in 95% of metastatic tumor cells (74).

5. Conclusion

The liver is the most common site of metastasis for various types gastrointestinal cancers from the portal vein system (2-4,41-43). A deeper understanding of the process of metastasis and cancer recurrence may be beneficial for the identification of novel treatment strategies. A novel concept for the metastatic environment referred to as the IEO model (pri-, pre- and post-metastatic niche) to explain the key steps in metastasis has been described in the present review. The liver microenvironment is formed by invading tumor cells and the immune system. Local cells in the liver and tumor cells develop complex interaction networks and adaptions, which may either inhibit or promote tumor metastasis.

The IEO model provides novel insights into the prevention of tumor metastasis by identifying interventions targeting the liver microenvironment mediated by liver diseases. The model may be used to establish a comprehensive disease management system for the prevention and treatment of liver metastasis, from a microenvironmental perspective.

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Authors' contributions

LW contributed to the conception of the study, writing the manuscript and performing the literature search. YS, MY and WZ conducted analysis and revised the manuscript. XY performed analysis and the quality assessment of the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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