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Review Article

Review of the premetastatic niche in liver cancer bone metastases

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Abstract: Liver cancer bone metastasis, a severe complication of liver cancer, is a leading cause of cancer death in China, featuring poor prognosis, intractable pain, and impaired quality of life. At present, the research of liver tumor bone metastasis mostly focuses on the treatment means and biological behavior analysis of malignant liver cancer, but the construction of the microenvironment before liver tumor metastasis is rarely studied. Unpredictable tumor metastasis hinders early intervention, leading to low cure rates. Since proposed the "premetastatic niche" concept was proposed in 2009, it has offered a novel framework for explaining liver cancer bone metastasis, supplementing traditional theories (e.g., "soil theory", "seed theory") and becoming a research focus. Herein, we review the premetastatic niche theory's origin, induction factors, mechanisms, and advances in liver cancer bone metastasis. Premetastatic niche formation is mainly induced by two factors: primary tumor-derived soluble factors (TDSFs) and extracellular vesicles (EVs). TDSFs (e.g., LOX, G-CSF, CCL2) are secreted under hypoxia and inflammation, reaching target organs via blood to promote matrix remodeling, recruit BMDCs, and establish immunosuppression. EVs carry mRNA, microRNA, and integrins, modifying target cell biology to facilitate PMN formation (e.g., Src phosphorylation, proinflammatory factor upregulation). BMDCs - especially MDSCs, neutrophils, and macrophages - are core PMN components. They interact with resident cells (e.g., hepatic stellate cells, osteoblasts) to secrete growth factors and matrix proteins, remodeling the microenvironment for tumor colonization. Animal studies confirm key regulatory molecules: TIMP-1 induces liver niches via SDF-1 upregulation and Ly6G+ neutrophil recruitment; CXCR2 inhibition reduces metastasis by limiting BMDCs and boosting immunity. While premetastatic niche research in liver cancer bone metastasis remains preliminary, it holds promise for clinical prevention and diagnosis. Future studies should clarify its molecular mechanisms and validate findings in clinical samples, laying the groundwork for translating this theory to improve patient prognosis.

Keywords: Liver tumor, metastasis, pre-metastasis niche, clinical significance

Introduction

Bone metastasis from liver tumors, also known as malignant liver cancer in clinical practice, is one of the most common malignant tumors, and is the second largest cause of cancer death in China [1-3]. Liver tumors induce bone metastasis primarily through the following core pathways, which are supported by experimental evidence [1]: 1) Exosome-miRNA mediated pathway: Hepatoma cells secrete exosomes carrying miR-574-5p, which targets bone morphogenetic protein 2 (BMP2) to drive osteoclastogenesis. In vivo studies further confirm that these exosomes promote osteoclast differentiation and subsequent bone metastasis by regulating miR-574-3p expression. 2) RANKL/OPG imbalance pathway: Exosomes derived from Hep3B cells disrupt the balance between receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG)-specifically reducing OPG expression while increasing RANKL levels-thereby activating osteoclast differentiation, a key step for bone metastasis. 3) Classic pro-metastatic signaling pathways: Liver tumors secrete soluble factors such as transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF). These factors remotely regulate the bone microenvironment by enhancing vascular permeability, inducing angiogenesis, and mediating immunosuppression, collectively creating a favorable niche for metastatic colonization.

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In the early stage of liver cancer, there are fewer cancer metastases, but extra-liver metastasis will increase with the age of the patient. Bone was found to be a common site of liver cancer metastasis, accounting for 25.4% of sites [4]. The development of liver cancer to bone metastasis has a great influence on the treatment of patients, and has a poor prognosis, accompanied by different degrees of paroxysmal pain, which has an impact on the patient's life and psychology [5]. Therefore, early diagnosis and treatment of liver cancer bone metastasis can prevent bone fracture and even paralysis, which will also help the patient's quality of life and psychological state [6]. Clinical diagnosis and treatment of liver cancer in China is performed with liver ultrasound and serum methyl-fetal protein to monitor high-risk groups. In clinical practice, liver ultrasound examination, X-ray tomography, nuclear magnetic resonance imaging and other equipment are used to analyze the specific conditions of patients with liver cancer. With the improvement of computer technology, dynamically enhanced CT and multimodal MRI scanning are widely used in the analysis of the clinical impact on liver cancer due to there being no radiation impact and having a high imaging rate. Clinical treatment of liver cancer depends on the different development periods and the deterioration degree of the cancer. In the early stage of liver cancer, the surgical treatment of liver cancer resection or transplantation of liver tissue is used to eradicate the liver cancer, however, both surgical treatment methods need special attention on postoperative protection and daily life. Overall, the treatment method is relatively simple, although patients who develop to middle stage liver cancer generally require local ablation or carotid chemoembolization (TACE). Acupuncture and other traditional Chinese medicine therapies can improve the treatment effect and enhance patients' autoimmunity. For patients with advanced liver cancer, radiation therapy is generally used in the clinic, with the main aim being to relieve pain and inhibit the cancer cells from expanding the degree of metastasis, although the chance of treating liver cancer is low for this period [7]. However, because the metastasis of tumor cells is irregular and unpredictable, it is impossible to accurately predict the development of the disease in order to treat and prevent in advance, making the cure rate of liver cancer low. This microenvironment is conducive to cancer cell colonization and proliferation, and it is called the premetastatic niche or tumor microenvironment after colonization; having specific components, formation requirements, and regulatory mechanisms.

Notably, the microenvironmental characteristics of liver tumor bone metastasis play a crucial role in mediating the entire metastatic process [8]. The bone microenvironment, inherently characterized by a dynamic balance between osteoblastic bone formation and osteoclastic bone resorption, undergoes dramatic remodeling upon the arrival of liver cancer cells. This remodeling is driven by complex crosstalk between tumor cells, stromal cells (including osteoblasts, osteoclasts, and bone marrow stromal cells), immune cells (such as macrophages, T cells, and neutrophils), and the extracellular matrix (ECM) [9]. Liver cancer cells secrete a variety of cytokines and growth factors, such as parathyroid hormone-related protein (PTHrP), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs) [10]. These factors disrupt the normal bone remodeling balance: PTHrP, for instance, promotes osteoclast differentiation and activation by upregulating receptor activator of nuclear factor-κB ligand (RANKL) expression in osteoblasts, leading to increased bone resorption [8]. The released TGF-β from the resorbed bone matrix further stimulates tumor cells to secrete more PTHrP, forming a "vicious cycle" that accelerates bone destruction and tumor progression [9]. Additionally, the bone microenvironment exhibits immunosuppressive properties, with increased infiltration of regulatory T cells (Tregs) and M2-type macrophages that inhibit anti-tumor immune responses, creating a favorable "soil" for the colonization and proliferation of liver cancer cells [11].

In the context of tumor metastasis research, the concept of "pre-transfer" (or more precisely, the pre-metastatic stage) has emerged as a critical premise for understanding the formation of metastatic lesions. Based on previous studies, the pre-transfer stage refers to a period before the arrival of circulating tumor cells (CTCs) at distant target organs, during which the target organ microenvironment undergoes a series of pathological changes to form a spe-

cialized microenvironment that is conducive to the adhesion, survival, and colonization of subsequent CTCs. This stage is not a passive process but is actively "educated" and remodeled by primary tumor-derived factors, including exosomes, soluble cytokines, and bone marrow-derived cells (BMDCs). Primary liver cancer cells release exosomes carrying specific proteins, lipids, and nucleic acids (such as miRNAs and mRNAs), which are transported to the bone marrow through the circulatory system. These exosomes can be taken up by local stromal cells and BMDCs, inducing phenotypic and functional changes: for example, promoting the recruitment of BMDCs (such as myeloid-derived suppressor cells and macrophages) to the bone microenvironment, modifying the composition of the ECM, and regulating the expression of adhesion molecules and growth factors. These changes collectively transform the quiescent bone microenvironment into a pre-metastatic microenvironment with high receptivity to tumor cells, laying the foundation for the subsequent formation of bone metastases [8-12].

In 2009, Kanplan et al. first put forward the concept of the "premetastasis niche" [13], largely explaining the mechanism of liver cancer bone metastasis, not only in theory; therefore, the soil theory [14], seed transfer hydrodynamic theory [15] and metastasis waterfall theory [11], became a new direction of liver tumor tissue metastasis research and hot spot. This paper reviews the origin, induction cause and formation mechanism of the theory of the premetastasis niche in malignant liver cancer and discusses the clinical application and developmental prospect of bone metastasis from the premetastasis niche in liver tumors.

Origin and significance of the pre-transfer niche theory

Tumor cell metastasis is closely related to the treatment effect of liver cancer patients, and is an important monitoring index of later prognosis. Tumor cell bone metastasis has a negative effect on patients, even gradually developing into malignant tumors. Liver tumor bone metastasis symptoms begin with the spread of the primary tumor, finding suitable target organs and transferring to the target organs, involving multiple inducing factors, multiple tissue structures, and more complex steps of the pathological process. The tumor cell metastasis process can be divided into several main steps [16, 17]: cancer cells shedding from the primary tumor, local invasion, infiltration into blood vessels, avoiding the immune system in the circulation, escape from blood vessels, target organ proliferation, and metastatic focus formation. The study of early tumor metastasis is mostly focused on the primary tumor lesions and the molecular pathological changes in the early and middle stages of metastasis, while the metastasis steps such as target organ selection and the formation of metastatic sites in the late stage of metastasis are rarely studied. This study shows that the proliferation of the tumor cells scattered from the primary tumor finding the target organs has no predictable pattern, and the choice of the target organs cannot accurately explain the later stage of the tumor metastasis. However, the concept of a "pre-metastatic niche" proposed by Kanplan et al. can reasonably explain the physiological behavior of tumor cells after determining the target organs, that is, the soil microenvironment (niche) suitable for the colonization of free cancer cells for the reproduction of tumor cells. The concept of a premetastatic niche explains the cellular and molecular events induced by primary tumor-derived soluble factors and exosome induction of tumor cells before transferring to the target organs, including the recruitment of bonemarrow-derived-cells cells (BMDCs), the interaction of BMDCs with intrinsic cells, matrix soil remodeling, and the immunosuppressive microenvironment [18, 19]. The above behavior of microenvironment transformation is of great significance for the late tumor metastasis of target organ selection, tumor cell metastasis and metastasis formation, and it is also a key factor for the realization of tumor metastasis to the target organ. Tissue metastasis tendency is a prominent feature of solid tumor metastasis. However, given the association between target organ metastasis and primary tumor and metastases, and the simulated metastasis model construction and in vivo detection methods, the specific mechanism of target organ metastasis is not clear. The expression of tumor cells, genes, chemokine receptors, adhesion molecules [20-23], infiltrating tumor cells in the target organs, secretion of extracellular glycoproteins, such as tenascin C [24], and high expression of the target tissue matrix protein periostin, are all important factors affecting the tumor cell tar-

geted metastasis and its survival and reproduction in the target organs. The tumor premetastasis niche explains the molecular movement of the tumor cells before transfer to the target organs. According to the premetastasis niche theory, more and more soluble factors (such as LOX, LOXL2, etc.), and extrinsic contents (ITGαuβ5, ITGα6β4, ITGα6β1, etc.) have been found to be important for targeting specific organs [25-28], and it provides a new direction for liver tumor targeted metastasis.

Induction factors for formation of pretransfer niche formation

Primary tumor-secreted TDSFs play an important role in inducing the formation of premetastatic niches. Local hypoxia and inflammation are common prominent microenvironment characteristics of solid tumors. In order to adapt to the surrounding hypoxia and inflammatory environment, tumor cells generally undergo adaptive pathological changes, significantly enhance the malignant characteristics of tumor cells, and release TDSFs to induce the formation of a premetastasis niche in metastatic target organs [28, 29]. Local hypoxia can lead to the increased expression and secretion of primary tumor lysine oxidase family proteins (LOXs). Secreted LOXs reach distant target organs with blood circulation, promoting matrix remodeling of target organs [30]. In a mouse breast cancer model, LOX, LOXL2, and LOXL4 can not only catalyze the collagen crosslinking of lung tissue, but also mobilize BMDCs recruiting CD45+/CD11b+ to the lung tissue of the metastasis target organ [31, 32], promoting the formation of a premetastatic niche in lung tissue. Increased expression of the hypoxia-inducible factor-1 can also activate the CAIX/nuclear factor-B (nuclear factor-B, NF-B)/G-CSF signaling pathway, where primary tumors secrete G-CSF into the circulation, mobilize and recruit granulocyte myeloid-like inhibitory cells to reach the lung tissue, and induce premetastasis niches to form [33]. In mouse Lewis lung cancer and melanoma models, primary tumor-derived S100A8 and S100A9 induces serum amyloid A3 (serumamyloid3, SAA3) to recruit Mac + bone marrow cells; TLR-4 can act as a receptor for SAA3. SAA3 stimulates NF-B signaling and promotes the premetastasis niche to form [34, 35]. Tumor-derived chemokines also show importance in inducing premetastatic niche formation. In mouse breast cancer and melanoma models, the primary tumor-derived chemokine monocyte chemotactic protein 1/chemokine ligand CCL2, induce premetastatic niche formation by two mechanisms: (1) mobilize and recruit BMDCs, especially CD11b+, Ly6Cmed/Ly6G+ bone marrow cells and CD3-/NK1.1+ immune cells; (2) significantly reduce the number of natural killer cells (natural killer cell, NK) in the target organs, weakening their anti-tumor effect to facilitate metastasis formation of [36]. In colon cancer, the primary tumor-derived matrix metalloproteinase inhibitor-1 (TIMP-1) increases SDF-1 in liver tissue, mediates liver recruitment to neutrophils, and induces the formation of a liver premetastasis niche in target organs. In addition, some other TDSFs, such as transformed growth factor (transforming growth factor beta, TGF-β), tumor necrosis factor alpha (TNF-α) [37] and osteogenic N-calcadhesin (osteogenicN-cadherin) can also induce premetastasis niche formation in malignant tumors [38-40].

In conclusion, the primary tumor-derived TDSFs reach the metastatic target organs along with the blood circulation and form a premetastatic niche by promoting the infiltration of target organs by BMDCs and interacting with the intrinsic stromal cells of the target organ. In addition to primary tumors that secrete soluble cytokines and chemokines, tumor-derived extracellular vesicles (extracellular vesicles, EVs) also play a negligible role in inducing the formation of premetastatic niches. EVs carrying physiological or pathological mRNA, small RNA, microRNA, and proteins that interact with target cells in a receptor-ligand manner can alter the biological behavior of target cells not only through direct stimulation, but also by indirect means of transferring surface receptors to target cells. The secretion of large amounts of EVs by tumor cells does not only stay in the tumor stroma, but EVs also enter the blood circulation, reaching the distant target organs to play a more critical role in [41]. Tumor-derived extracellular membrane vesicles are mainly divided into exosomes and microvesicles. They can induce pretransfer niche formation in many ways, such as functioning by inhibiting immune cells [dendritic cells (DCs), NK, and T lymphocytes] in the target organs [42-45]. Pancreatic cancer cell-derived exosomes containing macrophage migration repressors are ingested by

liver Kupffer cells, resulting in increased secretion of TGF-β, and hepatic stellate cell fibronectin production, promoting liver recruitment of bone marrow-derived macrophages. Primary tumor-derived exosomes carry specific integrin molecules that are taken up by lung fibroblasts and epithelial cells [46], liver Kupffer cells, and brain epithelial cells, enabling Src phosphorylation and increasing the expression of the proinflammatory factor S100, inducing the formation of a premetastasis niche [47]. Exosomes can also alter the soil environment by changing the target organ cell stroma and by carrying various microRNA [48]. Breast cancer and cervical cancer cells contain angiogenic-related molecules, such as fibroblast growth factor, interleukin-8 (interleukin-8, IL-8). Angiopoietin can activate the phosphorylation of the intrinsic endothelial cell protein kinase B in the target organs, enable the target organs to form a microenvironment conducive to angiogenesis, and promote the proliferation and growth of tumor cells [49, 50]. In conclusion, the mechanism of primary tumor-derived exosomes and microvesicle-induced premetastatic niche formation is more complex than tumor-derived TDSFs, and has attracted high attention in recent years.

Cell fraction required for the formation of the pretransfer niche

The recruitment of BMDCs during the formation of different tumor premetastatic niches is generally considered as a common pathological alteration in the metastatic target organs. The recruited bone marrow-derived cells interact with the stromal cells of the target organs to produce various growth factors, integrins, chemokines, inflammatory mediators, pro-angiogenic molecules, reactive oxygen species and reactive nitrogen, causing tumor cell colonization and proliferation, angiogenesis, as well as immunosuppression [51].

Recently, an increasing number of BMDCs have been shown to be closely associated with premetastatic niche formation in malignant tumors. Among them, myeloid-derived suppressor cells (MDSCs) are one of the common cells of pre-metastasis niches. MDSCs are immunosuppressive bone marrow cells [52]. Their physiological function is to maintain the normal tissue environment when the system is damaged, including infection and trauma. Primary tumor-derived TDSFs and EVs can induce recruitment of MDSCs in target organs, promote tumor cell colonization growth, angiogenesis, disrupt immune surveillance mechanisms and promote metastogenesis. Gr-1+/CD11b+ MDSCs recruited to lung tissue express the chemokine ligand CCL9, which plays an important role in the TGF-signaling pathway, promoting tumor cell colonization and metastatic formation of [53]. In mouse breast cancer models, Gr-1+/CD11b+ MDSCs stimulate the release of lung tissue proinflammatory factors and MMP-9, making lung tissue matrix and vascular remodeling more suitable for tumor cell adhesion and proliferation, and thus conducive to metastasis. TDSFs generated by pancreatic cancer mobilize and recruit bone marrow-derived transfer-related macrophages to reach the liver, and macrophages secrete granulal protein to activate hepatic stellate cells (hepatic stellate cell, HSC) [54], transform them to myofibroblasts, secrete periostein, promote collagen deposition and cross-linking, and make the liver matrix “soil” more suitable for CTCs colonization and growth [55]. Neutrophils are also one of the common cells of the premetastasis niche. In a murine breast cancer model, cancer cell secretion of G-CSF increases lung tissue to recruit neutrophils, which express metastasis-associated proteins such as Bv8, MMP-9, S100A8, S100A9, promote the formation of a lung premetastasis niche, and facilitates CTCs overflow vessels, colonization and metastasis [56]. In addition, MDSCs in the pre-transfer niches can also disrupt immune surveillance to promote the colonization and growth of CTCs, such as interfering with the function of the antigen presentation of DCs [57], affecting T cell activation, M1 macrophage polarization, and inhibition of cytotoxic in NK cells [58]. In addition to the recruited bone marrow-derived cells, some other cells in the target organ tissue, interacting with BMDCs, are also involved in the construction of tumor premetastasis niche.

In colon malignancies, HSCs can promote the formation of a liver premetastatic niche. HSCs differentiate from a static state to myofibroblasts in pretransfer niches, expressing laminin and extending pseudopodia to interact with vascular endothelial cells to promote angiogenesis [59]. HSCs can also secrete large amounts of cytokines such as IL-1a, VEGF, and TGF-α to promote metastasis and development [60]. Osteoblasts play an important role in bone ECM

remodeling and tumor bone metastasis. Under the action of TDSFs such as SICAM1, microRNA expression is altered in osteoblasts, inhibiting osteoblast differentiation and promoting bone metastasis formation [61]. Endothelial cells also play an important role in the formation of pretransfer niches. The production of ANG-2, adhesion molecules, and chemokines in the endothelial cells in the target organs can promote the recruitment of CCR + Tie2-macrophages, and induce the production of the inflammatory environment and angiogenesis [62]. VEGF induces prostaglandin E2 in mouse lung microvascular endothelial cells and promotes adhesion in breast cancer cells. Furthermore [63], Treg cells can cluster in premetastatic niches and play similar roles in MDSCs, such as inhibiting tumor-associated antigen presentation, or interfering with cytotoxic T cell function [64], playing a metastasis-promoting function.

Advances in the establishment of premetastatic niches in an animal model of liver tumor bone metastasis

Premetastasis niche formation is the rate-limiting step in the final realization of metastasis, and although premetastasis niches are continuously identified in multiple tumor animal models, digestive system tumor evidence is still relatively scarce. TIMP-1 is a primary tumor-derived soluble factor. Previous studies found TIMP-1 to be associated with metastasis in colon cancer patients, and Seubert et al. [65] confirmed the relationship between TIMP-1 and the formation of a liver premetastasis niche. In a mouse colon cancer model, elevated TIMP-1 in the serum induced migration of colon cancer cells to the liver. In situ tumor-derived TIMP-1 enables the liver premetastasis niche to form signature molecules such as SDF-1, FN1, TGF-1, Upa, S100A8, etc. In a research study, it was found that Ly6G+ neutrophils recruited to the liver were significantly increased compared with a control group. However, after SDF-1/CXCR4 inhibitor intervention, Ly6G+ neutrophils and colonized tumor cells were significantly reduced. This indicates that increased TIMP-1 in the serum causes increased SDF-1 expression in the liver, and CXCR4+/Ly6G+ neutrophils were recruited to reach the liver, promoting liver premetastasis niche formation. However, the above changes were not detected in mouse lungs. The targeting of liver metastasis in colon cancer was shown in a study done by Zhang et al. [66] who found that in a rat colon cancer model, CD133+ was recruited to the liver, and the rat's had increased HUHPCs, which induced premetastatic niche formation and promoted the colonization of circulating tumor cells to form metastatic sites.

Hoshino et al. [67] found that integrins carried by primary tumor-derived exosomes are important for metastasis targeting in pancreatic and breast cancer. Pancreatic cancer-derived exosomes containing integrin v 5 are ingested by liver Kupffer cells to promote the production of S100 pro-inflammatory factor family proteins, forming a microenvironment suitable for tumor cell survival in the liver; while breast cancer-derived integrin 64 was ingested by fibroblasts and endothelial cells in lung tissue, also promoting the release of inflammatory factors and lung metastasis in breast cancer. The above findings not only explain the different targeting of metastasis of different types of malignant tumors, but also provide the possibility of exosomes containing different integrin subtypes as early diagnosis and intervention targets of tumor metastasis, showing potential clinical applications. Jung et al. [68] found that CD44v6 and exosomes cooperate in promoting the infiltration of lymph nodes and the formation of lung premetastasis niches in pancreatic cancer models. By significantly reducing CD44v4-v7 in knockout rats, and injecting cell culture supernatants containing CD44v6 and exosome into the rats, this promoted lymph node and lung premetastasis niche formation, thus promoting colonization of CD44v4-v7 knockout cells.

Steele et al. [69] reported that the incidence of liver metastasis was significantly reduced in an animal model of pancreatic ductal adenocarcinoma when they knocked down the chemokine receptor CXCR2. It was noted that CXCR2 expression was inversely associated with survival in patients with pancreatic ductal cancer. Neutrophils and MDSCs of Ly6G+ expressing CXCR2 macrophages were mobilized and recruited to the liver, increasing CXCR2 in the liver, promoting premetastasis niche formation. While inhibition of CXCR2 expression increased CD3+ T cell infiltration in liver tissue, enhanced immune surveillance function, and inhibited metastasis formation. In addition, the joint use of CXCR2 inhibitors with chemotherapeutic drugs or other targeted drugs can increase the efficacy of chemotherapeutic dr-

Table 1. Multivariate Logistic regression analysis of risk factors for bone metastasis in patients with liver cancer

Factor	β	OR (95% CI)	X^2	P
CEA	0.005	1.005 (1.001-1.010)	4.911	0.027
CA153	0.043	1.044 (1.005-1.084)	4.875	0.027
ALP	0.002	1.002 (0.999-1.006)	1.269	0.260
TC	0.202	1.223 (0.694-2.157)	0.485	0.486
Calcium	5.353	211.192 (2.066-21 589.601)	5.141	0.023

Notes: β: Coefficient of regression; OR: Odds ratio; CI: Confidence interval; CEA: Carcinoembryonic antigen; CA153: Carbohydrate antigen 153; ALP: Alkaline phosphatase; TC: Total cholesterol.

ugs and targeted drugs and they show good clinical application value. Park et al. [70] found that in a nude mouse model of primary hepatocellular carcinoma (hepatocellular carcinoma, HCC), transcription factor FoxM1b expression increased the upregulation of LOX and LOXX2 expression, induced the formation of the lung premetastatic niche and promoted metatogenesis. Wong et al. found that in a rat HCC model, LOXL2 can induce migration of BMDCs to the lungs by remodeling the extracellular matrix [71], participating in premetastasis niche formation, thus inducing the occurrence of lung metastasis [72]. The study of Otto et al. confirmed the existence of a premetastasis niche in esophageal cancer and proposed its potential diagnostic and therapeutic value. However, the application of premetastasis niche formation still needs the validation and support of large-scale clinical specimens [73].

Dong Qingyuan et al. [74], at the first affiliated hospital of Nanchang University, studied 1,134 patients with liver cancer. Using their clinical data and a regression equation principle for liver cancer bone metastasis including pathogenic factors, found the most common metastasis sites to include the spine, ribs and pelvis, and thoracic spine, accounting for 45.83%. Data is shown in the regression equation analysis **Table 1**.

Kanda et al. [75] found that elevated tumor biomarkers in liver cancer patients may indicate extrahepatic metastasis. In this study, AFP was not found to be a risk factor for bone metastasis in HCC because of limitations in AFP prediction for HCC metastasis. Not all HCCs secrete AFP, with about 30% of patients having normal AFP [76]. Therefore, more accurate indicators are needed to predict HCC bone metastasis.

Wang Y et al. explored the intricate landscape of the pre-metastatic niche, emphasizing the roles of tumor-derived secreted factors, extracellular vesicles, and circulating tumor cells in shaping this niche. This work elaborated on the temporal mechanisms, including epithelial-mesenchymal transition, immunosuppression, extracellular matrix remodeling, metabolic reprogramming, vascular permeability, and angiogenesis [77]. Notably, stromal and immune cell populations synergistically sustain the structurally sophisticated bone niches, yet their homeostasis is disrupted when distant primary tumors and metastatic lesions are present. Investigating the bone niches that support metastatic dissemination through innovative technologies offers promising prospects for preventing bone-resident and bone-mediated metastasis [78]. Relevant experimental evidence [79] has confirmed that Hep3B hepatoma cells can promote osteoclast differentiation of RANKL-induced Raw264.7 cells through exosome secretion, which is accompanied by reduced osteoprotegerin (OPG) expression and elevated receptor activator of nuclear factor-κB ligand (RANKL) levels. Functional studies on exosomes isolated from Hep3B cells further verified their capacity to induce osteoclast differentiation, and the underlying mechanism involves exosomal miR-574-5p targeting bone morphogenetic protein 2 (BMP2) to drive osteoclastogenesis. In vivo experiments additionally demonstrated that Hep3B-derived exosomes facilitate osteoclast differentiation and subsequent bone metastasis by regulating miR-574-3p expression [79].

Conclusion

In summary, the study of bone metastasis premetastasis niche formation of liver tumors is immature. The formation and mechanism of action of premetastasis niches needs further investigation. However, understanding the premetastasis niche is conducive to the clinical prevention and diagnosis of the further deterioration of liver cancer. Because the mechanism of action is not clear, diagnostics cannot be used in clinical treatment, but application in clinical treatment has great development pros-

pects. In addition, the existence of premetastapstatic niches will have an impact on the treatment process, as well as how primary tumors will be confirmed in clinical studies. We plan to conduct further research on the mechanism of action of pre-metastatic niches in bone metastasis from hepatocellular carcinoma.

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Disclosure of conflict of interest

None.

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