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# Tumour Microenvironment and Metastasis

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## Abstract

In recent years, cancer is more and more severe harm to the health of people in the world. Although tumour diagnosis and therapy have made some progresses, there is little improvement in overall. One of the main reasons is that the pathogenesis of cancer metastasis is still enigmatic. Cancer development and metastasis are a complicated process that depends on the antigenic properties of cancer cells and a favoured environment in organs. Cancer cells metastasis causes more than 90% cancer death in the lungs, liver, brain, and bone, and a primary tumour causes less than 10% death. Therefore, understanding the process of cancer metastasis is essential, and it is convenient to deal with the problem of cancer metastasis and reduce cancer-related thrombosis. It has shown that tumour microenvironment plays a significant role in cancer progression. A variety of carcinoma-associated fibroblasts, and tumour-related macrophages play expanding and critical functions in sustaining cell proliferation, evading growth suppressors, promoting survival, activating invasion and metastasis, and reprogramming energy metabolism, but the purpose of each constituent remains unknown. This chapter will focus on discussing the role of the microenvironment on tumour invasion and metastasis to improve molecular diagnostics and therapeutics.

**Keywords:** cancer, metastasis, tumorigenesis, migration, invasion, tumour microenvironment, exosomes, autophagy, BMPs

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## 1. Introduction

Cancer cells can be distant metastasis at the late stage, and they can cause damage and injury to the body of the patients. Breast cancer is a common clinical malignancy; it can metastasis to liver, bone, brain, lung and pleural metastasis, as follows. 1. Metastasis to the liver: Experts point out that the rate of breast cancer liver metastasis is 10%, the metastatic pathway has

directly reached the liver through blood and lymphatic channel. There was no damage to the liver in the early stage. The liver function was normal. Liver volume could be enlarged. The condition of the patients deteriorated rapidly and died within a few months in the latter period. 2. Metastasis to bone: Bone metastases account for secondary blood metastasis of breast cancer. Common metastases places are vertebrae, ribs and pelvis. Bone metastases mainly encroach on the red bone marrow; the X-ray examination shows that it leads to irregular bone destruction, similar to the alteration of the insect specimen; some show double changes in osteoclast and osteogenesis. 3. Metastasis to brain: Brain metastases are rare, accounting for 5% of the metastatic cases of breast cancer, which can be divided into two types: meningeal metastasis and brain parenchymal metastasis. Brain metastases can cause brain oedema or brain swelling, the symptoms of increased intracranial pressure appear such as a headache, vomiting, visual impairment, convulsions and even coma. 4. Metastasis to lung and pleural: Lung and pleura are the most common metastatic sites of breast cancer. Lung metastases are often nodular and tend to be distributed in the peripheral lung field. The principal factors affecting the metastasis of breast cancer are the following factors.

## **2. Carcinoma-associated fibroblasts (CAFs) in the tumour microenvironment**

Breast cancer mammary matrix fibroblasts can be regulated by the heat shock protein 1 [heat shock factor 1 (HSF1)] and promote the malignancy of a tumour, it indicates that CAFs may be activated before epithelial transformation [1]. CAFs are linked to the size of primary breast cancer. CAFs are triggered by the paracrine effect of various growth factors, cytokines and hormones, which can promote the proliferation of cancer cells. A large number of studies have reported that growth factors and their downstream signalling pathways produced by CAFs have a role in tumour cell survival, proliferation and cell cycle progression. At the same time, tumour cells can induce CAFs to synthesise growth factors and cytokines, and then form a positive feedback pathway to encourage tumour development. Studies have confirmed that CAFs secreted CXCL12 is linked to breast cancer cell surface homologous receptor CXCR4, promoting breast cancer cell growth [2]. HGF derived from CAFs can be bind to the C Met receptor and activate downstream signal proteins, such as tyrosine kinase, RAS/RAF/ERK, PI3K/AKT, and promote the proliferation of breast cancer cells [3]. In the co-culture of bone marrow stromal cells and breast cancer cells, CAFs phenotype can be obtained, and the growth and aggregation of tumour cells are promoted by increasing the ratio of RANKL/OPG in breast cancer cells [4]. Besides, CAFs may be a significant source of local oestrogen. Cancer-associated aromatase can be written in CAFs, resulting in increased oestrogen production and tumour cell proliferation [5]. Also, distant metastasis is a significant cause of breast cancer death. Metastasis is an ongoing multistage process, including the invasion and growth of tumour cells, ECM degradation, tumour cells infiltrating into the blood and lymphatic systems, and the formation of metastatic clones in distant organs. CAFs activation can affect the invasiveness of breast cancer cells. Studies have demonstrated that CAFs can promote the invasive phenotype of breast ductal [6].

### 3. Tumour-related macrophages (TAMs) in the tumour microenvironment

TAMs promote tumour cell proliferation and survival with expression and secretion of a large number of factors, such as epidermal growth factor, platelet source growth factor, transform growth factor- $\beta$ 1, liver cell growth factor, etc. In vitro, macrophages and tumour cells were co-cultured, the former can significantly promote the growth of the latter by high secretion of the above factors. The tumour cell growth and development were slowed down or even stopped mice knock out their macrophages, which confirmed the role of macrophages in promoting tumour growth. The results of genetic studies in mice showed that the low rate of tumour growth and low metastasis was strictly related to the smaller number of TAMs. The researchers established the CSF-1 spontaneous breast cancer mouse model to find tumour proliferation. Growth rate and lung metastasis rate were lower than those of the wild-type CSF-1 [7].

Three steps can summarise the role of TAMs in tumour invasion and metastasis: The tumour cells adhere to the extracellular matrix components to release protein hydrolase to degrade extracellular matrix and induce invasion migration with chemokines. The cancer cells are free of charge in the primary lesion after proliferation and adhere to the basement membrane. The enormous number of matrix proteases released by them will have a destructive effect on the extracellular matrix and basement membrane, and then invade the lymphatic vessels or blood vessels to cause damage to the tissue and form a metastatic focus. TAMs secrete a large number of proteolytic enzymes for tumour invasion and metastasis. For example, matrix metalloproteinases, include gelatinase-2, collagen enzyme-1, matrix degradation enzyme-3 and more than 20 kinds of proteins; these TMMPs enzymes can degrade the extracellular matrix and degrade the fibrous collagen. The researchers to establish a breast cancer mouse model and find that lung metastasis decreased the loss of systemic macrophages, indicating that tumour metastasis was affected by TAMs and that macrophages existed in the early stages of lesions, invasion and rupture of the basement membrane. And its proteolytic enzyme expression is increased (such as Cathepsin B), indicating that TAMs are also engaged when tumour cells are in normal tissues around them [8]. Studies have demonstrated that together with tumour cells and macrophages, the latter enhances the dynamic properties of the former by using the form of MMP and TNF- $\alpha$  [9]. The tissue structure and basement membrane can be hit by MMP expression, thus promoting tumour cell growth, diffusion and metastasis. MMP in invasive tumours is generally provided by TAMs [10]. TAMs are synergistic with stomatal tumour cells and epithelial cells to promote tumour metastasis [11]. The destruction of the basement membrane is TAMs, and the proteolytic activity of protease B in the local tissue is increased, indicating that TAMs affect the tumour cells to invade the normal tissues around the tissue [12, 13]. The study showed that TAMs in different tumour tissues synthesised a series of urokinase (urokinase, uPA) involved in tumour invasion, invasion, extracellular matrix degradation and tumour angiogenesis [14]. By separating TAMs from breast cancer cells, it was found that TGF- $\beta$ 1 could stimulate the transcription of uPA in TAMs and enhance the stability of uPA Mrna. In addition, TAMs secrete cathepsin to promote tumour development by the expression of cathepsin B, cathepsin D and cathepsin L in breast cancer [15].

#### 4. Exosomes in the tumour microenvironment

The 'seed' cells are situated in the primary site of a tumour. They regulate the 'soil' microenvironment of the target organs so that the scattered 'seed' cells can adapt to the new 'soil' and still survive. In the process of the formation of pre-metastatic niche, exosomes play an essential role in raising the chemokine receptor, changing the expression of cell adhesion molecules and creating an immunosuppressive microenvironment. CHEN and others analyse the proteomics in the serum of patients with colon cancer and normal human serum, they found that the expression of 36 exosomes proteins in colon cancer patients was up-regulated [16]. WANG and others found that a tumour could transfer to the liver by the animal model of subcutaneous colon cancer cells HT-29 in nude mice. The exosomes were secreted by HT-29 cells can collect and express chemokine C-X-C primitives on target organs by CXCR4 [chemokine (C-X-C motif) receptor 4, CXCR4] matrix cells to the tumour cells in this process. The organisation's transfer provides favourable conditions [17]. ZHOU and others found that miR-105 was carried in the exosomes secreted by breast cancer cells, which can specifically lead to the down-regulation of the tight connexin ZO-1 expression in endothelial cells and destroy the vascular endothelial barrier, which plays an important role in the early stage of microenvironment formation [18].

Exosomes promote the development of inflammatory response and create a pure metastatic microenvironment conducive to tumour metastasis. COSTA-SILVA and others found that the exosomes derived from pancreatic cancer cells expressed high expression of macrophage migration inhibitory factor [macrophage migration inhibitory factor (MIF)], and after absorption of these exosomes, the liver macrophages (Kupffer cells) secreted a significant amount of TGF beta, and TGF beta promoted the formation of immunosuppressive microenvironment and thus promoted EMT and blood. The TGF beta secreted by liver macrophages activates the hepatic stellate cells, up-regulated the expression of fibronectin, and then raises bone marrow-derived macrophages in the liver and prepares the microenvironment for the arrival of the tumour cells. The exosomes derived from chronic lymphocytic leukaemia, carrying protein molecules and miRNA can promote the transformation of matrix cells into a tumour-related fibroblasts, release inflammatory response factors, and form a microenvironment to tumour growth [19]. The miRNA (miR-21 and miR-29a) carried by the exosomes can combine the Toll-like receptor [Toll-like receptors (TLRs)] of the immune cells, resulting in the nuclear factor-kappa B [nuclear factor kappa B (NF-kappa)]. The release of tumour necrosis factor-alpha (TNF-alpha) and IL-6, the activation of the inflammatory response factor to encourage the proliferation and metastasis [20, 21]. Exosomes not only provides a suitable growth environment for migrating tumour cells but also mediates tumour-specific organ metastasis. Hoshino et al. research a variety of exosomes secreted by separate metastatic tumour organs [22]. It is found that these exosomes priorities are combined with their respective present points of receptor cells. The exosomes mediate the tumour's organ-specific transfer through the exosomes related and activate the Src phosphorylation pathway of the receptor cells to up-regulation the gene expression of S100 in order to promote the growth of tumour cells [23].

## 5. Autophagy associated with cancer metastasis

Autophagy inhibits metastasis of tumour cells by inducing anti-inflammatory effects and lysates can cause inflammation in the surrounding tissues, Degenhardt et al. have proved that the microenvironment of an inflammatory tumour may lead to invasion and metastasis of tumour cells [24]. At the initial stage of primary tumour metastasis, signal stimulation is needed to promote migration and invasion. Tumour cells get into the systemic circulation through vascular infiltration [25]. Hypoxia and oxidative stress usually affect solid tumours, which can lead to cell necrosis and inflammatory reaction and inflammatory cells infiltrate. Although some inflammatory cells, such as cytotoxic T cells and natural killer cells can antitumour immune responses and influence metastasis of tumour. Importantly, inflammatory mediators such as macrophages infiltration are often associated with poor clinical prognosis [25–27]. The PyMT (polyoma middle T) transgenic model of breast cancer metastasis has proved that macrophage infiltration in primary tumours is required for invasion and metastasis [28]. Degenhardt and others find that autophagy can indirectly inhibit the inflammatory response on the metastatic promoter site, by raising the survival rate of tumour cells under hypoxia and metabolic stress [29]. Also, autophagy can also regulate the inflammatory response directly by controlling the release of immunoregulatory factors such as the release of high mobility group protein 1 [high mobility group box protein 1 (HMGB1)]. Once HMGB1 is released, it will activate dendritic cells through the Toll-like receptor–4 (Toll-like) of these cells to play a role in inducing cells to produce potent antitumour immune responses that kill tumour cells and prevent their metastasis [30]. More interestingly, high levels of autophagy could be induced during cell death in malignant glioma cells treated with mycin, resulting in a substantial release of HMGB1 from the dead cells [30, 31].

## 6. Hypoxia-regulated genes implicated in cancer metastasis

The effect of hypoxia on tumour immunity is another essential influence factor. Under the condition of hypoxia, tumour cells can secrete a variety of immunosuppressive factors, transforming growth factor beta (transforming growth factor-beta) is one of the most critical factors. TGF-beta can make tumour cells acquire immune escape function through the following ways: (1) Inhibit the proliferation of cytotoxic T cells and the expression of cytotoxin genes, which makes T cells unable to play an antitumour effect and induces the production of CD4 + CD25+ regulatory T cells with immunosuppressive function. (2) Inhibit the expression of antigen-presenting molecules, conciliatory factors and chemokine receptors to prevent the dendritic cells from functioning normally and make dendritic cells unable to deliver tumour antigens to T cells [32–35]. (3) Inhibit the activation of natural killer (NK) cells and reduces the expression of multiple surface receptors in NK cells so that they cannot identify and dissolve tumour cells [36]. In addition, hypoxia can also directly activate myeloid-derived suppressor cells (MDSCs), dendritic cells, and programmed cell death receptor ligand 1 [programmed cell death-ligand 1 (PD-L1)] through HIF-1 alpha, which can reduce the expression of MDSCs secreting interleukin -6 and interleukin -10 p to promote activation in T cells [37–39].

## 7. BMPs effect on tumour microenvironment, migration and invasion

BMPs belong to the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily and were initially identified as obstetrician cytokines that can promote bone and cartilage formation *in vivo*. Recently, BMPs have turned out to be involved in the regulation of tumorigenesis, development and bone metastases, they have been shown to be involved in the regulation of tumour development and bone metastasis. Clement et al. find BMP2 can enhance the migration and invasion of breast cancer cells, those cells with high expression of BMP2 showed more cell migration than GFP and blank control group. Katsuno et al. find that BMP2 promotes the invasion and migration of MDA-MB-231 through BMPs/SMAD pathway, and the two BMPs receptors play an equally important role. Lack of anyone receptor affects the signalling process [40]. BMP2 can promote oestrogen receptor positive MCF7 to invade migration *in vivo* and *in vitro* [41]. Scherberich et al. research show that BMP2 enhances the tumour invasion by regulating the expression of skeleton protein M in the tumour microenvironment. BMP2 induces the expression of skeleton protein M by p38 MAPK and JNK signalling pathway. BMP2 can also promote the invasion and migration of breast cancer by up-regulation the ID1 expression [42]. BMP-4 increases the invasion and migration of breast cancer cell by CCN6, which has been shown directly antagonise the BMP-4 mediated invasiveness and metastases *in vitro* and *in vivo* to. Fibroblasts stimulated with BMP-4 enhanced the MCF-7 cell invasion, and these effects were inhibited by DMH1. BMP-4 increased the expression of MMP-3 and IL-6 in conditioned medium from treated mammary fibroblasts, suggesting BMP-4 can impact the tumour microenvironment to promote breast cancer invasion [43]. The latest research has found that BMP6 can inhibit the growth and migration of breast cancer cells. Takahashi finds that BMP6 and estradiol co-work can inhibit the proliferation of MCF-7 cells through p38 MAPK cell signalling, however, it will not play a role only BMP6 exists [24]. Yang et al. also find that BMP6 down-regulates the expression of miR-192 to inhibit the transcription of ZEB1, and the decrease of miR-21 expression to impede the migration ability of MDA-MB-231 and BMP6 could also reduce the proliferation ability of MDA-MB-231 cells [25]. Zeisberg et al. find that TGF-beta can reduce the expression of E-adhering to renal epithelial cells, but BMP7 can increase the expression of E-adhering. Buijs et al. Point out that BMP7 can induce the activity of E-adhering to breast cancer cells and reduce invasiveness. Therefore, BMP7 can induce the expression of E-adhering in normal epithelial cells and maintain the stability of epithelial cells, loss of BMP7 gene will decrease of the expression of E- adhering to lead the epithelial cells to the stomatal cells in the evolution of the tumour [44]. Alamo finds that BMP7 stimulates the growth of two breast cancer cell lines and inhibits the proliferation of four breast cancer cell lines. Exogenous BMP7 can significantly enhance the migration of MDA-MB-231 *in vitro*. The causes of these two differences are not yet clear, Ye Lin has found that the expression of BMP10 in breast cancer is reduced. It can inhibit the invasion and migration of MDA-MB-231 through the BMPs/SMAD pathway and suggests that BMP10 can serve as a target for molecular therapy of breast cancer [45].

## 8. BMPs and bone metastasis

There are comparatively few studies on the role of BMPs in bone metastasis of breast cancer. Recently, it has been noted that BMPs is involved in the process of breast cancer bone

metastasis. BMP has been involved in the development of bone metastases in up-regulating or down-regulating the corresponding regulatory factors in breast cancer cells. BMPs can increase the expression of Osteoblast bone saliva protein BSP. BSP is related to the formation of new bone, so it can connect to the process of breast cancer with bone metastasis. Runx2 similar to BSP is that the target gene of BMP, which is closely linked to the osteolytic metastasis of breast cancer [46].

The overexpression of BMP7 or exogenous BMP7 can significantly reduce the formation of bone metastasis by reducing the expression of romantic, increasing the expression of E-cadherin and reversing the EMT in the animal model of mouse breast cancer bone metastases. In contrast, additional studies found BMPs could increase the invasion of a tumour and the ability of bone metastases and the active SMAD1/5/8 was detected in primary and metastatic tumours [47].

In conclusion, BMPs involves the growth and invasion of breast cancer. Different types of BMPs have different roles in the same breast cancer cell line, even if the same kind of BMPs has different effects on various breast cancer cell lines. It is believed that this mechanism will be clarified with the research. BMP9 can inhibit the growth of breast cancer cells in vitro and in vivo, BMP-9 is also involved in the inhibition of tumour growth in bone by down-regulation of connective tissue growth factor(CTGF).

## 9. Conclusions

It has shown that tumour microenvironment plays an essential role in cancer progression. The more recent studies have demonstrated hypoxic and autophagy in both primary tumours and metastases, contributing to angiogenesis, invasion, BMPs can inhibit or promote the growth of breast cancer by different signalling pathway. It detects a promising therapeutic value for BMPs in the management of metastases by influencing the propensity to disseminate to and survive in the bone microenvironment.

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