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Research Progress of Oncostatin M in Microenvironment Regulation and Metastasis of Breast Cancer

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Abstract: Oncostatin M (OSM), a cytokine belonging to the interleukin-6 family, plays a crucial role in modulating the breast cancer microenvironment and facilitating metastasis. It influences tumor cells directly, as well as immune cells, stromal cells, and vascular endothelial cells indirectly, thereby creating a complex interactive network that enhances tumor invasion and spread. The high expression of OSM in breast cancer is positively correlated with tumor grade, stage and metastasis, and enhances the invasion ability and chemotherapy resistance of tumor cells by activating JAK/STAT3 and PI3K/AKT signal pathways. In addition, OSM induced tumor-associated macrophages (TAMs) to polarize to M2 type, weakened the function of CD8^+T cells, promoted the proliferation of myeloid-derived suppressor cells (MDSCs), and inhibited the anti-tumor immune response. At the same time, it activates cancer-associated fibroblasts (CAFs) and promotes angiogenesis, supporting the formation of tumor matrix and metastasis niches. OSM signals are cross-regulated with multiple channels, forming a transfer-promoting loop. Clinical studies have shown that the high expression of OSM is related to the shortened survival period of patients, and intervention studies have verified its function of promoting metastasis. Nevertheless, the exact mechanism of OSM in breast cancer needs to be further explored, especially its potential as a therapeutic target and its application prospect as an inhibitor or antagonist, which provides a direction for future research.

1. Introduction

Breast cancer is one of the most prevalent malignancies in women worldwide, characterized by high incidence and mortality rates. Despite significant advancements in its diagnosis and treatment in recent years, metastasis remains the primary cause of death among patients. The Tumor Microenvironment (TME) plays a critical role in the initiation, progression, and spread of breast cancer. Comprising tumor cells, stromal cells, immune cells, vascular endothelial cells, and the extracellular matrix, the TME functions as a dynamic and complex ecosystem. These components communicate through intricate signaling networks, collectively influencing tumor behavior and disease outcomes [1].

Oncostatin M (OSM) is a multifunctional cytokine, belonging to the interleukin -6(IL-6) family. OSM mainly activates JAK/STAT, MAPK and PI3K/AKT by binding to OSM receptor (OSMR) or gp130 receptor complex on the cell surface, and participates in regulating cell proliferation, differentiation, inflammatory response and immune response [2]. In recent years, more and more studies show that OSM plays an important role in many malignant tumors, especially in breast cancer. OSM can not only directly affect the growth and survival of tumor cells, but also promote the invasion and metastasis of tumors by remodeling TME [3].

However, the precise mechanisms by which OSM regulates the breast cancer microenvironment and promotes metastasis remain incompletely understood. Investigating the role and underlying molecular pathways of OSM in the tumor microenvironment is crucial for elucidating the molecular basis of breast cancer metastasis and identifying novel therapeutic targets. This review aims to provide a comprehensive overview of recent advances in OSM research related to breast cancer microenvironment regulation and metastatic progression. It will emphasize how OSM influences tumor invasion and spread by modulating various TME components and assess its potential as a therapeutic target.

2. Regulatory mechanism of OSM in breast cancer microenvironment

OSM directly acts on tumor cells and indirectly regulates immune cells, stromal cells and vascular endothelial cells in the microenvironment, forming a complex regulatory network and promoting the invasion and metastasis of breast cancer.

2.1. Direct effect of OSM on tumor cells

OSM influences the growth, migration, and invasive capacity of breast cancer cells through autocrine or paracrine signaling. Elevated OSM expression in breast tumor tissues is associated with higher tumor grades, advanced disease stages, and increased metastasis (Table 1). In vitro studies demonstrate that exogenous OSM markedly boosts the migratory potential of various breast cancer cell lines, including MDA-MB-231 and MCF-7. However, this effect can be diminished through genetic knockout or neutralization with specific antibodies [4–5]. The mechanism of OSM mainly involves activating JAK/STAT3 signaling pathway, up-regulating MMP-2/9 and EMT-related factors Vimentin and Snail, thus promoting tumor cell invasion; At the same time, it can also improve the survival rate of tumor cells and increase their resistance to chemotherapy drugs through PI3K/AKT pathway.

Table 1 Correlation between expression of OSM in breast cancer and clinical features

Research index	High OSM expression group vs. low OSM expression group	P value
Tumor stage (III/IV)	Significantly higher than that of stage I/II (65% vs.28%) [6]	<0.01
Lymph node metastasis	The positive rate was higher (72% vs.41%) [7]	<0.01
HER2 state	The expression of OSM in HER2 positive patients increased by 2.3 times [8]	<0.05

2.2. Regulation of OSM on tumor-associated immune cells

OSM plays a key role in the regulation of tumor-associated immune cells, inhibiting anti-tumor immune response and promoting immune escape by reshaping tumor immune microenvironment. Specifically, OSM can induce tumor-associated macrophages (TAMs) to polarize to immunosuppressive M2 type, increase the proportion of CD163^+ cells, and inhibit the activity of T cells by secreting IL-10, TGF-β and up-regulating the expression of PD-L1.

OSM also directly weakens the killing function of CD8^+ T cells, reduces their ability to secrete Granzyme B and IFN-γ, and inhibits the expression of T cell activation-related genes through STAT3 pathway [9]. At the same time, OSM can promote the recruitment and expansion of myeloid-derived inhibitory cells (MDSCs), and further inhibit the anti-tumor immune response by activating STAT3 to up-regulate the expression of immunosuppressive molecules such as IDO1 and ARG1.

2.3. Regulation of OSM on matrix and angiogenesis

OSM regulates the formation of tumor matrix and metastasis niche by activating cancer-associated fibroblasts (CAFs) and promoting angiogenesis. It can induce CAFs to secrete extracellular matrix protein, promote ECM remodeling through TGF-β/SMAD pathway, up-regulate the expression of VEGF and MMPs, enhance the proliferation and migration of vascular endothelial cells, and thus promote tumor metastasis. In vivo experiments also confirmed that neutralizing OSM can significantly reduce the microvessel density of breast cancer transplanted tumor [10].

2.4. Integration and cross-regulation of OSM signal path

OSM exerts biological effects through the signaling pathway mediated by its receptor complex (OSMR/gp130), including the synergistic effect with JAK/STAT3 and NF-κB pathways, regulating the expression of EMT-related genes and inflammatory factors, and forming a positive feedback loop to promote metastasis; OSM also interacts with TGF-β pathway, enhances TGF-β-induced epithelial-mesenchymal transition (EMT), and amplifies TGF-β' s fibrogenic effect by up-regulating TGF-β receptor II(TGFBR2) [11]. These interactions jointly promote the development and metastasis of tumors.

3. Correlation between OSM and breast cancer metastasis

Recent studies have confirmed that OSM can significantly promote breast cancer metastasis by regulating the dynamic interaction between tumor cells and microenvironment. The clinical cohort analysis showed that the expression level of OSM in metastatic breast cancer tissues was significantly higher than that in primary lesions. The immunohistochemical score of metastatic lesions was 3.8 ± 0.6 vs. 1.2 ± 0.4 in primary lesions, $p<0.001$ [12]. And its high expression was significantly correlated with shortened overall survival (HR=2.31, 95% CI 1.76-3.04) [13]. Mechanism research shows that OSM can drive the transfer through the following multi-dimensional effects (Table 2).

Table 2 Function dimension and verification method of OSM-driven transfer

Action dimension	Key mechanism	Functional verification method
Tumor cell EMT	Activate STAT3/Snail axis, down-regulate E-cadherin and up-regulate N-cadherin	3D sphere invasion experiment and qRT-PCR verification
Matrix remodeling	Inducing CAFs to secrete TGF-β and MMP9, collagen deposition increased by 5.2 times [14]	Mass spectrometry and Masson staining.
Immunosuppression	Up-regulating the expression of PD-L1 (2.8 times) and promoting the infiltration of Treg cells (CD4+FoxP3+ cells increased by 37%) [15]	Flow cytometry and immunofluorescence co-localization
Angiogenesis	Up-regulation of VEGF-C promotes lymphangiogenesis (microvessel density increases by 2.5 times) [16]	In vitro lumen formation experiment

At the level of molecular mechanism, OSM signals show significant cross-pathway integration characteristics. In vitro experiments show that OSM pretreatment can increase the sensitivity of

MCF-7 cells to TGF-β by 4.3 times, and this synergistic effect comes from OSM-mediated epigenetic regulation of TGF-Br2. ChIP-qPCR shows that the modification level of H3K4me3 increases by 2.8 times [17]. Notably, single cell sequencing data revealed that there was significant spatial co-location between OSM+ macrophage subsets and EMT tumor cells in the microenvironment before metastasis ($P < 0.0001$), suggesting that OSM from microenvironment cells may play a key role [18].

The intervention study further verified the function of OSM in promoting metastasis. In the orthotopic transplantation model of mice, OSMR knockout can reduce the number of lung metastatic nodules by 72% [19], and combined with JAK inhibitor ruxolitinib can completely block OSM-induced STAT3 phosphorylation and reduce the Western blot signal by 95%.

4. Controversy and future direction

OSM, a multifunctional cytokine belonging to the interleukin -6 family, has attracted increasing attention in the regulation and metastasis of breast cancer microenvironment. Although some studies have shown that OSM has the ability to inhibit the proliferation of tumor cells, more and more evidence shows that it may accelerate the progress of tumor by promoting angiogenesis and metastasis, showing its dual role in breast cancer. In addition, the exact mechanism of how OSM promotes cancer development by reprogramming immune and non-immune cells in TME is not clear. Therefore, although the potential of OSM as a therapeutic target has been widely discussed, its specific clinical application strategy still needs further study to clarify its real value and feasibility.

Future research should focus on the in-depth analysis of the interaction between OSM and its receptor OSMRβ and its influence on breast cancer cell behavior and microenvironment, especially its role and regulatory mechanism in different subtypes of breast cancer. In addition, it is also an important direction to explore the potential of OSM inhibitors or OSMRβ antagonists as therapeutic targets and evaluate the efficacy of these drugs combined with existing treatment methods. Studying the specific mechanism of OSM promoting the migration and metastasis of breast cancer cells by inducing EMT will help to further understand its role in tumor progression and develop new therapeutic strategies.

The research progress of OSM in microenvironment regulation and metastasis of breast cancer shows its complexity and duality. Future research needs to solve the current controversy and explore the possibility of OSM as a potential therapeutic target. By deeply understanding the mechanism of OSM in the development of breast cancer, it is expected to provide new strategies for the precise treatment of breast cancer.

5. Conclusion

Studies on OSM's role in regulating the breast cancer microenvironment and promoting metastasis reveal that it exerts diverse effects on tumor cells, immune cells, stromal cells, and vascular endothelial cells through both direct and indirect pathways. OSM enhances the migratory and invasive capabilities of breast cancer cells, induces EMT, and increases resistance to chemotherapeutic agents. Moreover, it suppresses anti-tumor immunity by driving macrophage polarization toward the M2 phenotype, while also facilitating tumor spread through the activation of CAFs and stimulation of angiogenesis. Clinical studies have confirmed that the high expression of OSM is significantly related to the poor prognosis of breast cancer, including late tumor stage, high lymph node metastasis rate and shortened overall survival of patients. Interventional studies also show that blocking OSM signaling pathway can significantly reduce tumor metastasis, suggesting its potential as a potential therapeutic target. Although some studies have shown that OSM may

have the ability to inhibit the proliferation of tumor cells in some cases, more and more evidence supports its important role in promoting the progress of breast cancer. Future research should continue to deeply analyze the interaction between OSM and its receptor and its overall impact on the cell behavior and microenvironment of breast cancer, so as to clarify its specific application value in the treatment of breast cancer.

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