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Effect of MicroRNA on Tumor Microenvironment During Bone Metastasis in Breast Cancer

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Abstract: One of the most prevalent types of cancer worldwide is breast cancer (BC), with hundreds of thousands of women dying from BC each year. Among them, bone metastasis which occurs frequently in the advanced stage of BC is the main cause of death in BC patients, and MicroRNA is involved in this process and significantly changes the tumor micro environment (TME). In current clinical treatments, some therapies are used to inhibit bone metastasis in BC, and it has been proposed that microRNA is crucial to the development of BC. However, these studies can only improve the patients' quality of life or detect the period of BC, lack of practical therapeutic significance. In this paper, TME in BC bone metastasis is analyzed to explore the relationship between microRNA and BC, and to obtain MicroRNA's function in altering TME during BC bone metastasis. This provides a new idea and reference for controlling the phenotype and symptoms of BC by regulating the expression level of Micro RNA in the future, but there is no effective method to accurately deliver Micro RNA to the human body, and future research can focus on this region.

Keywords: Breast cancer, tumor microenvironment, microRNA, bone metastasis.

1. Introduction

One of the most prevalent malignancies worldwide is breast cancer (BC), which claimed the lives of 685,000 people in 2020, according to statistics, and this number will grow to 1,000,000 by 2040. Although the overall survival rate of BC patients has improved with the advancement of medical technology, the primary cause of BC death is still tumor cell metastasis. Bone metastasis is a major form of tumor cell metastasis. There is no cure for bone metastases and it can cause bone-related symptoms such as spinal cord compression, discomfort, and hyperglycaemia, which degrade the patient's quality of lives [1]. At the same time, the median survival time of patients with BC due to complications caused by bone metastases was less than that of patients without any related complications [2]. Therefore, exploring the mechanisms underlying bone metastasis is essential for the treatment of BC.

Bone metastasis is caused by the spread of original cancer cells in the bone microenvironment. The micro-environment in which cancer cells live is significantly different from that of normal cancer cells micro-environment, which is highly vascularized, and the presence of osteocyte (osteoblasts, osteoclasts) and additional cells attached in the marrow (such as immune cells) interact with cancer cells [3]. Interestingly, cancer cells do not begin to metastasize immediately after entering the bone but remain dormant or hyperproliferative for a long time until their reactivation mechanism is

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stimulated by a adventitious signal. As long as tumor cells started to proliferate, they first undergo non-detectable micrometastasis and then develop into noticeable metastasis [4]. Currently there are two major therapy method for bone metastasis: systemic therapies, such as chemotherapy and endocrine therapy, to alleviate the rate of cancer cell proliferation; Bone-targeting therapy, such as bisphosphonates and denosumab, to inhibit bone destruction caused by cancer. However, these are palliative care to improve the patients' quality of life, so new treatments and diagnostic measures need to be studied to prevent bone metastasis.

MicroRNAs (miRs) are defined as small, non-coding RNAs that eliminating mRNA and limiting mRNA translation to control gene expression, a process thought to play a significant part in a number of biochemical processes, such as cell differentiation, proliferation, apoptosis, and carcinogenesis. Consequently, miRNAs are thought to have enormous potential in clinical treatment and have been used as specific biomarkers for therapeutic targets and certain diseases. According to reports, certain miRNAs can be essential in the progression of BC and can promote the proliferation of cancer cells and promote bone metastasis, for example miR-16 levels in patients' serum with BC bone metastases is higher than normal [5].

This review emphasize that tumor microenvironment is able to regulate bone metastases in BC through adjusting its cellular components. Furthermore, by means of analyzing the clinical effect of secretory miRNAs in adjusting tumors and their microenvironment during BC bone metastasis, the curative potential of miRNAs also come under observation .

2. Bone metastasis process in BC

2.1. Intraosseous microenvironment

The intraosseous microenvironment is a complex system consisting of endothelial cells, osteocytes (osteoblasts, osteoclasts, etc.), other stromal cells (fibroblasts, adipocytes, etc.). There are indications that these cells are derived from normal cells but alter throughout the growth of tumor. For instance, multiple solid tumors grow with varying degrees of stromal cell dissemination and extracellular matrix deposition, a phenomenon known as describable hyperplasia [6]. The proliferation and metastasis of tumor cells become feasible as a result of tumor tissue remodeling. This remodeling also leads to increased interstitial fluid pressure, hindering delivery of drug to its destination during treatment. In BC, fibroblasts (CAFs) contribute to these responses in a variety of ways.

2.2. The specific process of bone metastasis

It involves a series of consecutive processes to establish metastatic disease, including separation of tumor cells from the primary tumor, intravenous and blood circulation, followed by the external canal of the secondary organ, adjustment to the new surroundings, and eventual spread and constitution of external metastasis. Bone metastasis in BC is predominantly osteolytic and characterized by local bone degradation due to increased osteoclast activity [7]. The approach of bone metastasis is a systematic multi-step cascade of reactions, which is divided into marrow colonization, quiescence/survival of current tumor cells, regeneration of dormant cells, and invasive metastasis after cells develop into proliferating cells.

In bone metastasis of BC, sporadic BC cell attached to marrow arrive in a heterogeneous microenvironment consisting of various cell types from hematopoietic or mesenchymal stem cells (HSCs or MSCs, respectively). In short, osteoblasts from MSCs and osteoclasts from HSCs preserve bone intensity by utilizing tightly balanced recasting circulation [8]. The close interaction between cells and diffuse tumor cells is required for the occurrence of bone metastasis. The homing, dormancy, and colonization of tumor cells at secondary sites are believed to be adjusted by the tumor support environment. These provide a favorable environment for the survival of cancer cells.

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3. MicroRNAs and BC

The relevance of microRNAs to cancer pathogenesis is slowly becoming known, including BC. These research advances are related to the progress of disease research and the analysis of clinical outcomes. Using traditional miRNA analysis matrices, many research teams have analyzed familiar miRNAs that are dysregulated in cancer, miRNAs particular aim at tumor subtypes, miRNAs associated with bone metastasis, and miRNAs associated with disease recurrence [9,10].

MiRNAs are usually around 20 nucleotides in length. Introns, exons and endo-exon junctions are combined as the majority of anthropic miRNAs. There are various steps in the miRNA biosynthesis process.In the nucleus, the primary transcription product of the miRNA gene, pre-miRNA(approximately 300-1,000 bases in length), is cleaved by Rnasell-Drosha enzyme into the hairpin structure precursor miRNA (pre-miRNA), approximately 70-90 bases in length. After preliminary shearing, the pre-miRNA is transported from the nucleus to the cytoplasm under the action of the transporter esportin-5. Then, another RNaselll - Dicer enzyme is further cleaved to produce mature miRNA (mature miRNA), which is about 20-24nt long. Mature mirnas, together with other proteins, form the RISC (RNA-induced silencing complex), which causes target mRNA degradation or translation.

Numerous biological processes could be mediated by miRNAs, including proliferation, stress response, inflammation, cell cytoactive, apoptosis, and more, which are all essential for tumor formation. Accumulating experiments intimate that aberrant expression of miRNAs may have therapeutic usefulness, particularly in triple-negative breast cancer (TNBC) that lacks prognostic indicators and potential clinical targets. Over 3,000 miRNAs correlated with the tumor genesis, growth and metastasis have been identified so far. Similar to lncRNAs, miRNAs fall into two groups: oncogenic miRNAs and inhibitor miRNAs. Table 1 summarizes the target of certain miRNAs and their role in TNBC [11-13].

Table 1: Certain microRNAs that play a crucial part in BC disease progression

miRNA	Function	Target
miR-10b	Initiation of BC infiltration and metastasis	HoxD10
miR-17-92	Positive modulator of migration, invasion and transfer	CDK1, CDK2
miR-21	Positive modulator of BC cell growth, invasion, and metastasis	PDCD4, MMP, MARCS、RHOB, TPM1
miR-23b/27b	Promotes the growth of BC Inhibits the metastasis of BC cells	Nischarin (NISCH) PAK2 kinase
miR-31	Inhibits cancer cell invasion and abduction	Integrin α5, radixin, RhoA
miR-34a/c	Inhibits prostate stem cells and metastatic tumor growth and regeneration	CD44, c-myc , Notch4, Fra-1
miR-101	Inhibits the growth and invasion of BC	EZH2, Stathmin1
miR-125b	Inhibits the metastasis of BC cells	IGFBP2, PITPNC1
miR-127,-129,-222,-223	Reduces BC cell proliferation	CXCL12
miR-141	Suppresses osteoclast activity to prevent osteolytic damage	Mitf, Calcr
miR-143,-145	Inhibit migration, invasion, and transfer	HEF1
miR-146	Reduces tumor growth, invasion, metastasis, and angiogenesis,	EGF, RMMP2

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Table 1: (continued).

miR-155	Promote invasion and inhibit transmission	TCF4,Rho4
miR-196	Inhibits BC migration and metastasis	Hoxc8
miR-200	Inhibits the invasion of BC	ZEB1, Sip1, Sec23
miR-203	Inhibits cancer cell EMT, invasion and motility	ZEB2, Bmi, Survivin, Smad4
miR-204,-211,-379	Inhibits TGF-induced IL11 production	IL-11
miR-205	Inhibits EMT and metastasis	ErbB3, VEGF, ZEB1, ZEB2、kinase C
miR-218	Promotes bone mimicry of bone metastatic BC cells	Sost, TOB1
miR-219	Inhibits osteolytic bone disease by attenuating osteoclast activity	Traf6
miR-225	Inhibits tumor initiation, migration, invasion, and metastatic colonization	Sox4, TenascinC

4. Role of micro RNA in BC bone metastasis

4.1. Electromagnetic (EMT)

In recent years, EMT has been recognized as the main mechanism of BC cell migration and invasion, and has drawn massive attention. Research has indicate that that miRNAs are involved in EMT process.

According to previous research, miR-125b is suppressed in TNBC cells and leading to lower expression level, which is associated with poor prognosis, chemical resistance, as well as reduction on cell migration and invasion. Hong et al. (2016) discovered that mitotic activator protein kinase kinase 7 (MAP2K7) is a novel target of miR-125b, and its knockdown can avoid EMT in TNBC cells [14].

MiR-20a level in human BC has been elevated, especially in TNBC, according to the Cancer Genome Atlas Program (TCGA) data.

Liu et al. demonstrated that miR-20a can promote tumor initiation and growth, showing the oncogenic function of miRNAs during breast tumor formation [15]. Electron cadrine (CDH1) promotes the formation of adhesion junctions and the establishment of a polarized cell monolayer, the loss of which is a fundamental event in EMT.

De et al. reported a link between miR-20a and EMT, and they found that in TNBC cells (MDA-MB-231), HSA-miR-20a can regulate important downstream key markers such as CDH1, N-cadrin, and fibrodesmin by altering the Twist-1 mRNA expression. In addition, the analysis confirmed that miR-20a can abolish transforming growth factor-β (TGF-β) by inhibiting the expression of TGF-β receptor 2 (TGFBR2), thereby inhibiting MET [16].

4.2. Migration, invasion and transfer

Numerous investigations have demonstrated that miRNAs play an essential part in cell migration, invasion, and metastasis in TNBC.

For instance, miR-21, an oncogene, was discovered that got high level expression in BC patients compared to healthy controls. Liu et al. demonstrated that in TNBC cells, miR-21 and lncRNA AWPPH can can upregulate each other. Studies also revealed that miR-21 binds to the 3' UTR of

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LZTFL1 (leucine zipper transcription factor-like 1) to promote BC cell proliferation and metastasis. Fang et al. found that suppressing miR-21 expression can induce cell apoptosis while decreasing the TNBC proliferation, viability, and invasiveness of the cell line (MDA-MB-468). According to these findings, miR-21 has the possibility of being an innovative and prospective biomarker for the diagnosis and evaluation standard of TNBC.

Inhibitor miRNAs also play an important role in TNBC. Compared with healthy controls, miR-199a-5p in the plasma of TNBC patients is less; cell proliferation can be reduced by transfection of miR-199a-5p mimicry agent into mammary cells. miR-199a-5p possesses an suppressive impact on tumors in TNBC, and its overexpression hinders cell proliferation, invasion, and migration by altering gene expression associated with EMT, such as CDH1 and ZEB1, which is attributed to EMT [17].

5. Challenges and concerns

MiRNAs serve as crucial modulators of bone metastasis progression in BC, with correspondent functions in situ regulation of BC metastatic according to diverse levels of miRNAs. When miRNAs interact with bone-resident cells, their differentiation and activity will be influenced. Indeed, the alternation of spectacular miRNAs content in BC cells during bone metastasis will affect BC cell migration, proliferation, drug-resistance as well as stem-like phenotypes to promote adaptability and seeding of BC cells in bone.

In addition, BC-derived miRNA circulation can alter and remodel the bone marrow microenvironment over long period, increasing its resistance to the proliferation of diffuse cancer cells, and then diffuse cancer cells in the bone marrow can directly interact with bone cells to modify their biological functions, which helps maintenance of cancer cell growth.

6. Conclusion

By analyzing the tumor microenvironment in BC bone metastasis, this paper explores the effect of microRNA on BC, obtains the specific role of microRNA in BC bone metastasis, and acknowledges the impact of the tumor microenvironment in BC bone metastasis. Given how crucial miRNAs are to bone metastasis, it is recommended to reduce miRNA expression levels in metastatic BC cells in order to rescue their expression levels, or inhibit their expression levels, or regulate circulating miRNA expression levels. It has been proven that manipulation of even one miRNA has the potential to alter the phenotype of BC cells or alter their impact on the skeletal microenvironment. Even though these innovative technologies are quite successful, an efficient delivery system for miRNA therapy in healing BC is still a long way off. In addition, miRNAs can be utilized as diagnostic and prognostic strategies in clinical treatment to detect early recurrence or response to specific treatments because of miRNA's stability in biological liquid systems and simple detectability. These are all difficult and hot spots in future research, which deserve attention and in-depth research.

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