Proceedings of Anticancer Research, 2024, Volume 8, Issue 4
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Research Progress on the Bone Metastasis Mechanism of Prostate Cancer and Bone-Targeted Drugs

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Abstract: Prostate cancer is a common male malignant tumor, and bone metastasis is one of the common complications in the late stage of prostate cancer. The mechanism of prostate cancer bone metastasis is a complex process involving multiple factors and steps. In recent years, with in-depth research on the mechanism of prostate cancer bone metastasis and the development of new drugs, important progress has been made in the treatment of prostate cancer bone metastasis. Based on this, this article introduces the mechanism of prostate cancer bone metastasis and the research progress of several bone-targeted drugs to provide reference and inspiration for future research.

Keywords: Prostate cancer; Bone metastasis; Mechanism; Bone targeting drugs; Cancer cell

Online publication: August 13, 2024

1. Introduction

As a malignant tumor, the incidence rate of prostate cancer has increased year by year in recent years [1,2]. For this large group of people, bone metastasis has become an important factor affecting their survival. The incidence of bone metastasis in patients with prostate cancer is generally high. According to statistics, the incidence of bone metastasis in patients with advanced prostate cancer is as high as 90% [3,4]. Once bone metastasis occurs, the patient's quality of life and life expectancy will be seriously affected [5]. Therefore, it is of great significance to study the mechanism of prostate cancer bone metastasis and find effective treatments. Many studies have shown that the interaction between prostate cancer cells and bone matrix is one of the important causes of bone metastasis. Treatment methods for prostate cancer bone metastasis usually include

chemotherapy, radiotherapy, surgery, etc., but the treatment effect is still limited. Bone-targeted drugs are a new type of treatment method that has attracted much attention due to their advantages of strong targeting and low side effects [6]. At present, some bone-targeting drugs such as radium-233, strontium-89, and bisphosphonates have gradually been proven to achieve good clinical results in the treatment of prostate cancer bone metastasis.

2. Mechanism of prostate cancer bone metastasis

2.1. Colonization

Colonization of prostate cancer cells in bone is the first step in prostate cancer bone metastasis. Colonization refers to the process in which cancer cells enter the bone through the blood circulation or lymphatic vessels and survive and proliferate in the bone matrix. Research generally agrees that a variety of factors influence this process. Some studies believe that certain components in the bone matrix can promote the adhesion and proliferation of prostate cancer cells. For example, CXCL12 in the bone matrix can bind to CXCR4 expressed by prostate cancer cells, promote cell adhesion and proliferation, and migrate to the bone marrow [7,8]. In addition, some growth factors (such as insulin-like growth factor, fibroblast growth factor) and cytokines, such as interleukin-6 (IF-6) [9], tumor necrosis factor-alpha (TNF-α), prostate-specific antigen (PSA), free prostate-specific antigen (fPSA), and interleukin 17A (IF-17A) can also stimulate the proliferation and migration of prostate cancer cells, thus promoting the colonization process [10]. These factors are expressed in blood circulation and bone matrix and can affect the growth and metastasis of tumor cells. Of course, more studies have shown that the colonization of prostate cancer cells in bone is promoted by cytokines synthesized in bone matrix release and bone turnover [11,12].

2.2. Dormancy

After colonization, prostate cancer cells often enter a dormant state to adapt to their new environment and avoid immune system attack. Cancer cells in a dormant state no longer proliferate but remain in a “dormant” state, waiting for the right time to activate again. Although the dormant cancer cells appear to have been cured, this state can still contribute to cancer recurrence, so this stage should also be highly valued [13]. During the dormancy process, the roles of some molecules and signaling pathways are very important. Research by He Ziqiu *et al.* [14] believes that activation of the Wnt signaling pathway can reduce the degradation of β-catenin and promote the dormancy and proliferation of cancer cells. Liao Zhuangwen *et al.* [15] found that alkaloids may inhibit the epithelial-mesenchymal transition of PC-3 cells by inhibiting the Wnt/β-catenin/Snail signaling pathway.

Prostate cancer cells avoid immune system attack while in a dormant state. Immune escape means that tumor cells evade or inhibit the recognition and attack of the immune system through various mechanisms, thereby growing and metastasizing in the body [16]. Tumor cells can evade immune attack by expressing immunosuppressive molecules, producing immunosuppressive factors, or inhibiting the activation and function of immune cells through other mechanisms. For example, Zhou Rubao *et al*. [17] co-cultured PC-3 cells overexpressing miR-335-5p with NK-92MI cells and found that the levels of TNF-α and IFN-γ in the cell supernatant were significantly increased. This means that overexpression of miR-335-5p can kill PC-3 cells by promoting the release of TNF-α and IFN-γ from NK-92MI cells, thereby inhibiting immune escape. Huang Lin *et al.* [18] believe that the PD-1/PD-L1 pathway plays an important role in inducing effector T cell apoptosis, inhibiting T cell activation, and inhibiting the body’s anti-tumor immune response and tumor immune escape.

2.3. Reactivation

When certain signals stimulate dormant cancer cells, they reactivate and begin to proliferate. These stimulating

factors may include cell adhesion molecules, hypoxic bone microenvironment, RAI14 [19], etc. The reactivated cancer cells begin to proliferate and produce more cancer cells through cell division. In this process, cancer cells' genome instability and immune evasion ability are key factors.

2.4. Proliferation

As cancer cells proliferate, surrounding bone tissue is destroyed and resorbed. This process involves the action of some osteoclasts and osteoblasts. Osteoclasts can break down the organic components and minerals in the bone matrix, while osteoblasts can synthesize new bone tissue to repair the damaged bone matrix [20]. This dynamic balance of destruction and repair will continue for some time until a relatively stable microenvironment is formed. In this microenvironment, cancer cells survive and continue to proliferate.

3. Research on targeted drugs for prostate cancer bone metastasis

3.1. Radionuclides

3.1.1. Radium-223

Radium-223 is a potential prostate cancer bone metastasis-targeting drug. It is a radioactive isotope that emits alpha particles with high energy and penetrating ability, killing cancer cells and inhibiting their growth [20]. The targeting properties of radium-223 enable radiation therapy to target tumor cells directly while reducing damage to surrounding normal tissue. For patients with prostate cancer bone metastasis, radium-223 can precisely target tumor cells in the bones and relieve pain and other related symptoms [21]. As a radioactive substance, the use of radium-223 often brings concerns. However, a study showed that the ambient gamma radiation dose caused by ^{223}Ra injection to treat bone mCRPC is relatively low, and no special external radiation protection measures are required [22].

3.1.2. Strontium-89

Strontium-89 is also a targeted drug used to treat bone metastases from prostate cancer. It is also a radioactive isotope that emits beta particles, killing cancer cells and inhibiting their growth. In preclinical studies, strontium-89 has shown significant therapeutic effects against prostate cancer bone metastases. For example, to help patients suppress pain. Hong Liwei [23] found in the study that the observation group treated with strontium chloride [^{89}Sr] injection had an overall higher effective lesion treatment rate than the control group, and the patient's body pain improved more significantly. Shan Yangang's study [24] also believed that ^{89}Sr can significantly alleviate patients' clinical symptoms and achieve satisfactory results in the treatment of patients with prostate bone metastasis.

3.2. Bisphosphonate drugs

Bisphosphonates are targeted drugs commonly used to treat prostate cancer bone metastases. It is a synthetic compound [25] that can combine with hydroxyapatite crystals in bones to inhibit the growth and metastasis of tumor cells in bones. Bisphosphonates can inhibit osteoclast activity on the surface of tumor cells and reduce bone destruction and resorption [26]. At the same time, it can also inhibit the combination of tumor cells and bone matrix and reduce the adhesion ability of tumor cells, thereby inhibiting the growth and metastasis of tumors in bones. Miao Zhixiong *et al*. [27] compared the changes in various indicators before and one year after treatment with 99-technetium-methylene diphosphate in 76 patients with prostate cancer bone metastases. They found that 99-technetium-methylene diphosphate can promote bone proliferation, inhibit bone resorption, increase bone density, and prevent osteoporosis. The research by Zhang Qifeng *et al.* [28] also confirmed this. Liu Yongjiang *et al.* [29] studied that bisphosphonate drugs have a positive effect on reducing pain in patients with prostate cancer bone metastasis and rarely increase other side effects except nausea. Most notably, bisphosphonate drugs have

broad prospects in treating prostate cancer bone metastasis.

4. Conclusion

With the continuous development of science and technology and the continuous advancement of new drug research and development, the treatment methods for prostate cancer bone metastasis will become more and more abundant and effective. Bone-targeted drugs will also become one of the important means of treating prostate cancer bone metastasis in the future. In addition, with a deeper understanding of the bone metastasis mechanism of prostate cancer, it will be possible to discover more therapeutic targets and breakthroughs in the development of new drugs. At the same time, it is also necessary to pay attention to the progress of clinical trials and the effects of actual application to ensure the safety and effectiveness of new drugs. We look forward to achieving a more precise, safe, and effective method to treat prostate cancer bone metastasis in the near future, bringing patients better quality of life and longer survival.

Funding

Traditional Chinese Medicine and Integrated Traditional Chinese and Western Medicine Research Project of Tianjin Municipal Administration of Traditional Chinese Medicine (2021106); Beijing-Tianjin-Hebei Traditional Chinese Medicine Collaborative Development Specialty Alliance Construction Project (First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Qingxian County Traditional Chinese Medicine Hospital).

Disclosure statement

The authors declare no conflict of interest.

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