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Overcoming immunosuppression in bone metastases

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ABSTRACT

Bone metastases are present in up to 70% of advanced prostate and breast cancers and occur at significant rates in a variety of other cancers. Bone metastases can be associated with significant morbidity. The establishment of bone metastasis activates several immunosuppressive mechanisms. Hence, understanding the tumor-bone microenvironment is crucial to inform the development of novel therapies. This review describes the current standard of care for patients with bone metastatic disease and novel treatment options targeting the microenvironment. Treatments reviewed include immunotherapies, cryoablation, and targeted therapies. Combinatorial treatment strategies including targeted therapies and immunotherapies show promise in pre-clinical and clinical studies to overcome the suppressive environment and improve treatment of bone metastases.

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1. Introduction

Prevention and effective treatment of bone metastatic disease can have a significant impact on the outcomes of patients with advanced malignancies. The burden of bone metastatic disease is demonstrated by autopsy studies identifying bone metastases in approximately 70% of breast and prostate cancer, 30–40% of non-small cell lung cancer (NSCLC), and 20–35% of thyroid and kidney cancer-related deaths (Weilbaecher et al., 2011). It has been estimated that greater than 50% of patients with bone metastases die within 3 years of diagnosis (Coleman, 2006). Furthermore, bone metastases are associated with skeletal-related events (SRE) including pathological fractures, spinal cord compression, and hypercalcemia, which severely compromise patient quality of life (QoL) (Clemons et al., 2012; Zustovich and Fabiani, 2014). Even though most patients have concomitant metastases in visceral organs and lymph nodes, there is a subset of patients with bone-predominant metastatic disease that may require a distinct treatment approach compared to, for instance, patients with only pulmonary metastases based on site-specific impact on disease prognosis and, possibly, distinct patterns of response to systemic therapies such as chemotherapy and immunotherapies. Therefore, advancing the understanding of mechanisms involved in the establishment of bone metastases can lead to the identification of therapeutic targets with meaningful implication in the management of these patients. This manuscript reviews the challenges in treating bone metastases and highlights emerging therapeutic strategies exploring the interface between the bone microenvironment and immune system with the ultimate goal of fostering the advancement of novel bone-directed therapies.

2. Bone tumor microenvironment

2.1. Bone metastatic niche

Tumor cells 'seed' the bone marrow in a multistep process (Fidler, 2003). Initially, circulating tumor cells (CTCs) create a pre-metastatic niche with the production of factors that render the bone microenvironment conducive to tumor dissemination (Wan et al., 2013). Disseminated tumor cells (DTCs) compete with "hematopoietic stem cell niche" in the bone marrow, thereby creating an "onco-niche" where they can proliferate or remain dormant. The bone marrow niche seems to protect DTCs from immune surveillance contributing to resistance to chemotherapy and post-treatment relapses by several mechanisms.

Bone marrow DTCs from breast cancer lose expression of Ki67 and overexpress ERBB2 that might play a role in resistance to chemotherapy. DTCs at distant sites found after chemotherapy also express cytokeratin heterodimers CK8/CK18 and CK8/CK19 known to inhibit major histocompatibility complex 1 (MHC 1) interactions with $CD8^+$ T cells, a crucial step in immune escape (Braun et al., 2000). To overcome natural killer (NK) cell cytotoxicity following loss of MHC, DTCs adopt a stem cell phenotype with reduced expression of NK cell receptor D (NKG2D) and MHC1 polypeptide-related sequence (MICA/MICB) (Mohme et al., 2017). Furthermore, DTCs home to the hematopoietic stem cell (HSC) niche, which is the most hypoxic area of bone marrow. It is known that increased expression of hypoxia induced factor (HIF1 α) in neoplastic cells enhances a disintegrin and metalloproteinase (ADAM10) which in turn cleaves MICA/MICB leading to suppression of antigen presentation and NK cell cytotoxicity (Pantel and Alix-Panabières, 2014). Therefore, the hypoxic environment of HSC niche in bone marrow contributes to immune escape, stem-like properties of DTCs, and promotes resistance to chemotherapy (Kang and Pantel, 2013).

2.2. Osteomimicry

It is well established that cancers like breast and prostate exhibit bone tropism and express bone associated genes and proteins, a phenomenon called "osteomimicry", which promotes their dissemination, survival, and proliferation in the bone (Rucci and Teti, 2010). Tumor cells homing to bone express molecules like osteonectin, cathepsin-K, and connexins that are usually expressed by osteoclasts and osteoblasts. Prostate cancer cells acquire an osteoblast-like phenotype by expressing bone sialoprotein and osteocalcin. RUNX2 is a transcription factor crucial for osteoblast differentiation and the expression of RUNX2 by cancer cells marks a key step in osteomimicry. The stem cell pathways Notch and Wnt were shown to be important for activation of hepatocyte growth factor (HGF) and its interaction with Met, another key pathway in osteomimicry (Jadaan et al., 2015). Breast cancer cells also express osteoclast activating factors like parathyroid hormone-related protein (PTHrP) and TNF-α to promote RANKL induced osteoclastogenesis (Kan et al., 2016). Together, the expression of these molecules promotes colonization to bone, confers a survival advantage and initiates the tumor-bone vicious cycle.

2.3. Tumor-bone vicious cycle

Bone is a significant site of metastatic disease because of its large surface area and high vascular supply. Tumor invasion to bone results in bone resorption and formation, a process induced by cancer cells and mediated by osteoblasts and osteoclasts (Bussard et al., 2008). Certain types of solid tumors metastasize to bone and induce osteolytic (bone destructive) or osteoblastic (bone formative) phenotypes. For example, metastases from prostate cancer frequently form osteoblastic lesions in contrast to the predominant osteolytic lesions associated with breast, lung and kidney cancers (Ortiz and Lin, 2012). Tumor-derived signaling mediators like WNT, bone morphogenic proteins (BMPs) and transforming growth factor-beta (TGF-β) stimulate osteoblast function by activating RUNX and activated transcription factor (ATF) signaling (Matsumoto and Abe, 2011; Westendorf et al., 2004; Xiao et al., 2005). Activated osteoblasts secrete receptor activator of nuclear factor kappa β (RANKL), which binds to its receptor RANK on osteoclast precursors and induces osteoclastogenesis through NF-kB, NFATc1 and C-JUN signaling (Li et al., 2000). During the process of resorption, bone cells and the mineralized bone matrix release TGF-β, IGF, and Ca^{2+} promoting tumor growth and release of osteolytic and osteoblastic factors like PTHrP, IL-6 and matrix metalloproteinases (MMPs) (Soki et al., 2012). Thus, a "vicious cycle" of tumor-induced bone disease is formed, wherein tumor modifies the bone microenvironment to support its own survival (Mundy, 2002).

2.4. Bone microenvironment – cellular and molecular mediators

The vast immune cell composition of bone marrow including lymphocytes and myeloid cells exhibit both anti-tumor and tumor-promoting effects on bone metastases

(Capietto and Faccio, 2014; D'Amico and Roato, 2015). During an antitumor response, dendritic cells present tumor specific antigens to activate $CD4^+$ T cells, which in turn activate $CD8^+$ T cells leading to the killing of antigen-positive tumor cells (Foss, 2002). In contrast, activated regulatory T cells (T-Regs) and T helper cells type 17 (Th 17 cells) cause a protumor response through immune suppression and RANKL mediated osteoclast differentiation (Kunzmann et al., 2009; Monteiro et al., 2013). Additionally, myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) suppress T-cell mediated anti-tumor responses through production of cytokines and angiogenic factors (Gabrilovich et al., 2012; Vasiliadou and Holen, 2013). In addition to the immune