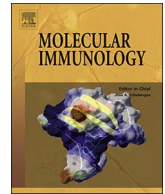


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## Beyond the vicious cycle: The role of innate osteoimmunity, automimicry and tumor-inherent changes in dictating bone metastasis

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### ABSTRACT

Bone metastasis is a fatal consequence of a subset of solid malignancies that fail to respond to conventional therapies. While a myriad of factors contribute to osteotropism and disseminated cell survival and outgrowth in bone, efforts to inhibit tumor cell growth in the bone-metastatic niche have largely relied on measures that disrupt the bi-directional interactions between bone resident and tumor cells. However, the targeting of isolated stromal interactions has proven ineffective to date in inhibiting bone-metastatic progression and patient mortality. Osteoimmune regulation is now emerging as a critical determinant of metastatic growth in the bone microenvironment. While this has highlighted the importance of innate immune populations in dictating the temporal development of overt bone metastases, the osteoimmunological processes that underpin tumor cell progression in bone remain severely underexplored. Along with tumor-intrinsic alterations that occur specifically within the bone microenvironment, innate osteoimmunological crosstalk poses an exciting area of future discovery and therapeutic development. Here we review current knowledge of the unique exchange that occurs between bone resident cells, innate immune populations and tumor cells that leads to the establishment of a tumor-permissive milieu.

### 1. Introduction

Bone metastasis is a debilitating and ultimately fatal consequence of a number of malignancies that become treatment refractory, including breast and prostate cancer. In solid malignancy, early intervention is largely focused on debulking or eradicating the primary tumor via surgical, chemical or hormonal means. Yet, inevitably, approximately 8–10% of breast and prostate cancer patients go on to develop bone metastases despite conventional therapies (Nørgaard et al., 2010; Sathiakumar et al., 2012; Wong and Pavlakis, 2011). Once diagnosed, treatment of bone metastatic lesions relies on chemotherapy, radiotherapy or blocking interactions between bone resident and tumor cells to alleviate painful bone destruction and delay tumor progression (El-Amm and Aragon-Ching, 2013; Gomez-Veiga et al., 2013; Shibata et al., 2016). However, management is palliative rather than curative, and the targeting of bone remodeling pathways using agents that promote osteoclast dysfunction and apoptosis have not proven adequate to inhibit metastatic outgrowth (Dearnaley et al., 2009; Rosen et al., 2003; Van Acker et al., 2016). Combined with the lack of molecular targets and consensual predictive signatures in high-risk patients, the failure of conventional therapies to abrogate disease once colonization of bone is initiated emphasizes the requirement for deeper exploration into

alternative modalities to predict or preclude bone metastatic events. Improved awareness of osteoimmunological regulation of metastatic progression coupled to the recent success of the immunotherapy Ipilimumab in extending patient survival in metastatic melanoma has led to a new wave of immune-based therapies designed to supersede or enhance conventional treatments (Hodi et al., 2010; Kaminski et al., 2003). Yet, the jury is still out on the efficacy of immunomodulatory agents to negatively regulate tumor progression in bone due to paradoxical outcomes. As such, continued efforts to deconvolute the temporal development of bone metastasis within the boundaries of host-tumor interaction, which extends to immune regulation and tumor-driven events, is requisite to developing more effective means through which to target bone metastasis.

Establishment of a secondary tumor following the dissemination of cancer cells from the primary site is a complex and dynamic process suggested to occur early during tumorigenesis (Eyles et al., 2010; Pantel and Brakenhoff, 2004; Van der Toom et al., 2016; Wan et al., 2013). The cascade of events that culminate in metastatic outgrowth in a distant organ rely on early tumor cell resistance to anoikis during intravasation and circulatory migration, stimulation of angiogenesis within the metastatic niche and competent co-option at the secondary site to sustain disseminated tumor cell (DTC) growth and persistence

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amid resident cells (Eckhardt et al., 2012; Patel et al., 2012; Sethi and Kang, 2011a,b). In bone, DTC co-option of the hematopoietic stem cell (HSC) niche is augmented by factors suggested to both modulate tumor cell dormancy and drive subsequent outgrowth (Jung et al., 2012; Kim et al., 2013). Dormancy, in which DTC expansion is restricted by tumor-driven or microenvironmentally-induced mechanisms, has been proposed to underpin the long latency that often accompanies breast and prostate cancer recurrence and may confer tumor cell resistance to conventional therapeutics that target actively mitogenic cells (Aguirre-Ghiso, 2007; Karrison et al., 1999; Khoon, 2015; Osisami and Keller, 2013). However, poor mechanistic understanding of the signals that induce, maintain and promote outgrowth from dormancy in bone has compounded efforts to gain comprehensive insight into the early events that culminate in the formation of macrometastases. Yet, perhaps the most critical determining factor in successful metastatic progression is the ability of tumor cells to exploit and subsequently impede immune surveillance mechanisms demonstrated to effectively control cancer initiation and progression (Bidwell et al., 2012; Capietto and Faccio, 2014; Esposito and Kang, 2014a; Rautela et al., 2015; Suva et al., 2011; Zhang et al., 2011).

One emerging prospect in the treatment and prevention of bone metastasis stems from our increased understanding of immune cell regulation of tumor progression. Immunosurveillance pertains to the capacity of autologous immune cell populations to mediate or eliminate transformed cells – a process frequently marred by the acquired or inherent capacity of DTCs to evade immune regulatory mechanisms (Burnet, 1957; Dunn et al., 2006, 2004). The evident success of immune-based therapies to induce durable immune responses in patients with advanced hormone-refractory disease has sparked initiation of numerous clinical trials to evaluate the potential of immunotherapies in a bone metastatic setting (Lu et al., 2017; Maia and Hansen, 2017; Sharma and Allison, 2015; Spellman and Tang, 2016). The majority of therapies under scrutiny are T cell activating, such as Ipilimumab and Sipuleucel-T, and rely on intact and readily mobilized adaptive immune cell populations coupled to high tumor cell immunogenicity to elicit an effective antitumor response. To date, results have been underwhelming, conferring no significant survival benefit or decrease in tumor burden in patients bearing bone-metastatic lesions, with the exception of melanoma (Beer et al., 2017; Hodi et al., 2010; Kwon et al., 2014; Miles et al., 2011; Ylitalo et al., 2016). The inadequacy of modern immunotherapeutics to abrogate bone metastasis is a likely consequence of tumor-induced tolerance, and the low immunogenicity of bone metastatic lesions and the primary tumors from which they arise, however studies that adequately address this in the bone-metastatic setting are lacking (reviewed in Gajewski et al., 2013a,b; Spranger and Gajewski, 2015). The contribution of innate immune regulation of metastasis has also been largely ignored in the development of immune-based therapies currently in the spotlight. Several elegant studies utilizing immunocompetent animal models of bone metastasis have revealed a crucial role for innate immune populations as key regulators of metastatic outgrowth in bone (Capietto and Faccio, 2014; Lode et al., 1998; Pasero et al., 2015; Rautela et al., 2015). Coupled to the fact that innate immune cells are heavily intertwined in normal bone-homeostatic processes, there may be a requirement for innate immune stimulation to enhance current therapeutic regimens (Charles and Nakamura, 2014; Zhao et al., 2012). Additional studies have also implicated direct tumor-intrinsic modulation of immunosurveillance mechanisms as a critical driver of bone-specific metastasis, yet this is an area well underexplored in osteoimmune oncology (Bidwell et al., 2012; Touati et al., 2017). In this review, we summarize the impact of the bone microenvironment on metastatic progression, and explore the influence of innate immune cells on of tumor growth and how tumor-inherent changes alter the course of tumor progression in bone via immunomodulatory means – all of which must be taken into consideration to devise more effective and sustainable strategies to treat or inhibit formation of overt metastases in bone (Fig. 1).

## 2. The bone microenvironment: congeniality, attraction and mutual exchange

Comprised of both perivascular and HSC compartments that sustain both hematopoiesis and osteoequilibrium, bone is rich repository for factors that support and enhance cellular growth, survival and functionality (Hauschka et al., 1986; Pluijm et al., 2001). The fertile milieu bone provides is a critical determinant of persistence and expansion in arrested DTCs (Roodman, 2004). However, DTC presentation in bone does not always lead to the formation of macrometastases. This implies that DTCs that preferentially migrate to bone must exhibit inherent or acquired biological characteristics that predispose them to successful engagement and prosperity in this unique secondary system, including the capacity to overcome dormancy. Indeed it has been demonstrated that only a percentage of bone-derived DTCs identified as non-proliferative in prostate and breast cancer patients were capable of expansion in vitro and that the proliferative potential of isolated cells correlated with disease progression (Solakoglu et al., 2002). Furthermore, it has been evidenced that several osteogenic molecules such as osteonectin, osteoglycan, biglycan and osteopontin are expressed in prostate and breast epithelial cells, from which carcinomas arise (Berquin et al., 2005; Inman and Shore, 2003). Yet, while the specific molecular and phenotypical traits of certain solid malignancies may play a role in organ tropism, the remarkable capacity of DTCs to thrive within the bone microenvironment is largely governed by stromal co-operation and the propensity for transformed cells to adapt within a continually evolving niche. In fact, the majority of research into elucidating bone-metastatic mechanisms has focused on the interaction between tumor and bone resident cells such as endothelial cells, osteoblasts, osteoclasts and their stem cell progenitors.

### 2.1. Adhesion and conveyance

Endothelial cells of the bone perivascular niche that surround sinusoidal networks modulate leukocyte trafficking and have been implicated in both DTC adhesion and regulation of dormancy during early tumor cell colonization. In fact, prostate-derived DTCs have been shown to preferentially bind to bone endothelial cells rather than endothelium from other organs or the bone extracellular matrix (Cooper et al., 2000; Lehr and Pienta, 1998; Romanov et al., 2004). Bone endothelial cells mediate DTC attachment and conduction via constitutive expression of adhesion molecules, including VCAM1 and E-selectin, which engage with ligands such as  $\alpha_4\beta_1$  integrin, PSGL1, and CD44, upregulated on bone-metastatic breast and prostate cancer cells (Dimitroff et al., 2005; Lehr and Pienta, 1998; McFarlane et al., 2015). Similarly, the interaction between galectin-3 on endothelial cells and Thomsen-Friedenreich glycoantigen (TF-Ag) on prostate-derived DTC has been demonstrated to mediate bone metastasis, which could be effectively inhibited using a TF-Ag mimetic in mice (Glinskii et al., 2012). Beyond adhesion, endothelial cells have also been shown to modulate DTC quiescence following extravasation into bone via thrombospondin-1-induced cell cycle arrest in a metastatic breast cancer model (Ghajar et al., 2014). While this suggests a potential role for endothelial cells in regulating tumor cell proliferation, numerous studies exploring endothelial cell-mediated dormancy have failed to provide evidence that identified quiescent cells are capable of reactivation and subsequent formation of overt metastases (Ghajar et al., 2014; Jung et al., 2012). Yet perhaps the most intriguing role of endothelial cells as a driver of bone-metastatic progression is their recently confirmed ability to undergo conversion to osteoblasts when associated with bone metastatic tumor cells (Lin et al., 2017).

### 2.2. Homing and establishment

Descended from mesenchymal stem cells (MSCs), osteoblasts are perhaps the most well-described population in bone, with the exception

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