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

Katie L. Owen, Belinda S. Parker*

Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Victoria, Australia

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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

* Corresponding author at: LIMS1, La Trobe University, Melbourne, VIC, 3086, Australia.
E-mail address: Belinda.Parker@latrobe.edu.au (B.S. Parker).

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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 cooperation 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

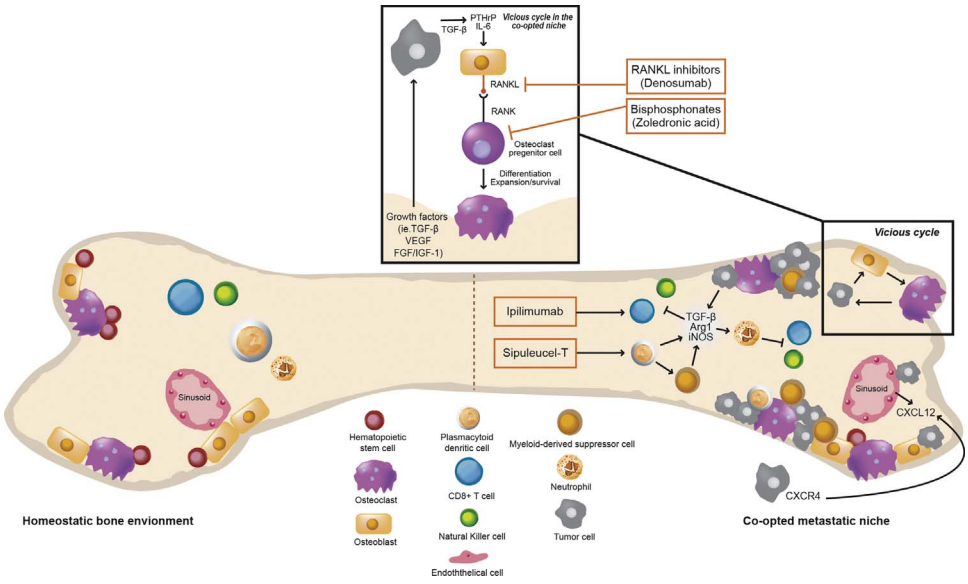

Fig. 1. Bone offers a unique environment for co-option by disseminated tumor cells. Homeostatic remodeling of the bone extracellular matrix (ECM) to maintain hematopoietic and structural integrity relies on crosstalk with immune populations that develop within or are recruited to the bone microenvironment. Competent co-option by tumor cells that express preferential tropism for bone is initiated by successful recruitment and attachment, facilitated in part by chemokine gradients (CXCR4/CXCL12) and bone endothelial expression of adhesions molecules. Tumor progression is subsequently influenced by a 'vicious cycle' of bone degradation and tumor growth, facilitated by tumor cell induction of osteoblast-mediated osteoclastogenesis that culminates in bone resorption and release of growth factors and minerals from the ECM that furthers metastatic growth. The vicious cycle is the primary target for current therapy (RANKL inhibitors/bisphosphonates) in patients with advanced bone-metastatic disease. Tumor cells also induce immune suppression through the release of factors that promote immune suppressive cell expansion and inhibition of effector cells, that ultimately creates a permissive milieu that supports metastatic growth. Therapies that stimulate immune cells (such as Ipilimumab and Sipuleucel-T) are an alternative therapeutic approach to altering the course of tumor progression in bone.

of their bone remodeling counterparts, osteoclasts (Ren et al., 2015). In addition to their supporting role in HSC maintenance and expansion, mature osteoblasts have long been implicated in DTC homing (Calvi et al., 2003). It is well established that the migration of breast and prostate DTCs to bone involves the exploitation of stromal cell production of trophic factors that establish and maintain a gradient toward which tumor cells expressing complimentary chemokines are directed (Patel et al., 2012; Gartrell et al., 2015). One mutual exchange subsists on tumor cell expression of chemokine (C-X-C motif) receptor 4 (CXCR4), which selectively binds to the ligand CXCL12 (also known as SDF-1) expressed by osteoblasts and other resident cells of the perivascular niche (Busillo and Benovic, 2007; Gladson and Welch, 2010; Moll and Ransohoff, 2010). Overexpression of CXCR4 in patient-derived tumors and murine models of prostate and breast cancer has been observed and increased CXCR4 primary tumor expression has been described as a predictor of bone relapse in a breast cancer patient cohort (Chinni et al., 2006; Gravina et al., 2015; Mukherjee and Zhao, 2013; Sacanna et al., 2011; Sun et al., 2003). While ongoing clinical trials are currently exploring the effectiveness with which CXCR4 inhibitors (such as Plerixafor) impact myeloma, limited pre-clinical studies have demonstrated that in vivo blockade of the CXCR4/CXCL12 axis using CXCR4 antagonists, including CTCE-9908, is sufficient to reduce bone metastatic burden in breast and prostate cancer models (Gravina et al., 2015; Ramsey and McAlpine, 2013; Richert et al., 2009; Sun et al., 2005). However, a longitudinal study showed that single-agent CTCE-9908 therapy was only effective in slowing tumor progression and was not sufficient to decrease prostate-derived bone metastasis, while others have reported that CXCR4 blockade significantly increased DTCs in bone in prostate cancer, due to the proposed displacement of HSCs into circulation (Gravina et al., 2015; Shiozawa et al., 2011). Therefore, it remains unclear as to whether targeting this pathway therapeutically would help or hinder attempts to eschew DTC colonization. Beyond its potential role in osteotropism, osteoblast-derived CXCL12 has also been implicated in DTC localization, with the highest expression of CXCL12 observed at the epiphyseal plate of the metaphysis in long bones – a region densely populated with mature osteoblasts and one of the most commonly co-opted locations in bone-metastatic cancers (Schneider et al., 2005; Sun et al., 2005; Wang et al., 2014). Consequently, stromal CXCL12 expression has been targeted therapeutically in mice bearing bone metastatic tumors with promising results, however the impact of CXCL12 blockade on bone physiology independent of DTC colonization in immunocompetent systems has not been examined (Roccaro et al., 2014; Sun et al., 2005).

Perhaps the most well explored function of osteoblasts is the deposition of bone, vital to the maintenance of cytoskeletal architecture and structural integrity. Bone remodeling is a tightly regulated yet asynchronous process mediated by both osteoblasts, which drive bone formation, and osteoclasts that induce resorption through the lysis of mineralized bone (Croucher et al., 2016). Osteoblast activity is reliant on a multitude of local and systemic stimulatory factors, many of which are also produced at high levels by DTCs. Endothelin-1 (ET-1), overexpressed in bone-metastatic tumor cells, has been shown to skew bone remodeling toward unregulated bone production by stimulating osteoblast mitogenesis through stromal cell suppression of Dickkoph-1 (DKK-1) and promoting osteoclast apoptosis (Guise et al., 2003). However targeting ET-1 as a single agent has yielded conflicting outcomes in xenograft models, and a phase III clinical trial investigating the efficacy of the ET-1 antagonist Atrasentan in metastatic prostate cancer reported no difference in bone-metastatic progression between treated and untreated groups (Carducci et al., 2007; Guise et al., 2003; Keller and Brown, 2004). Yet, underscoring the importance of strategic delivery, ET-1 inhibition may hold promise in patients at risk of recurrence, as DKK-1 expression has been associated with DTC quiescence in bone (Casimiro et al., 2009; Linde et al., 2016). Several bone morphogenic proteins (BMPs) have also been implicated in increased bone growth adjacent to metastatic lesions through their induction of osteoblast differentiation (Jin et al., 2011). Multiple reports of altered BMP expression and activity, particularly BMP4 and 7, across different prostate and breast bone-metastatic cell lines and clinically derived patient samples during progression to bone highlight the potential role of BMPs in the temporal development of bone metastases (Jin et al., 2011; Keller and Brown, 2004; Morrissey et al., 2010a; Mundy, 2002). In fact, Cao et al. (2014) reported that overexpression of BMP4 in a metastatic breast cancer model significantly decreased tumor burden through modulation of innate immune suppressive mechanisms. Yet, a lack of consensus on the effect of specific BMPs, of which 13 have been classified, has undermined efforts to establish BMPs as a clinically relevant target (Cho et al., 2016; Morrissey et al., 2010b; Suva et al., 2011; Ye et al., 2009).

2.3. Beyond the vicious cycle

Structurally related to BMPs, transforming growth factor (TGF)-β is perhaps one of the important mediators of osteogenesis and one of the

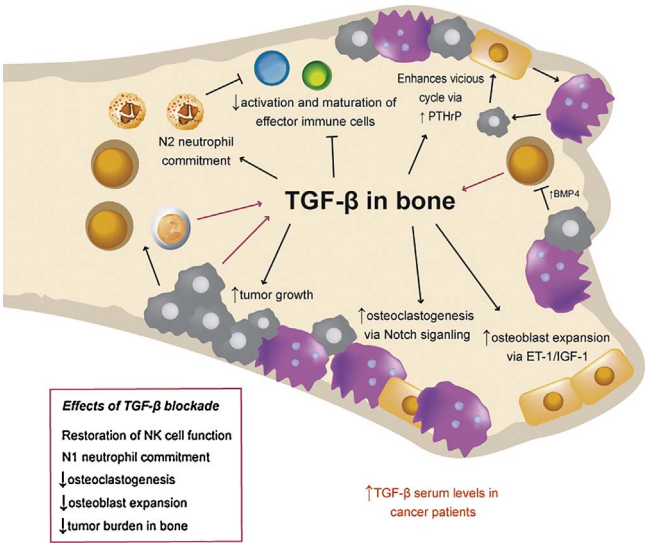

Fig. 2. Transforming growth factor (TGF)-β has emerged as a central cytokine in bone-metastatic progression and high serum levels have been associated with poor prognosis in bone-metastatic patients. Produced ubiquitously in the co-opted niche, TGF-β is a chief regulator of osteoimmunity, increasing both osteolytic and osteoblastic activity that destabilizes homeostatic bone remodeling while simultaneously enhancing tumor cell growth. This, in turn, promotes immunosuppression, further augmented by direct immune modulation by TGF-β on plastic populations, such as neutrophils. Therapeutic blockade of TGF-β has been effective in reducing tumor burden in bone by promoting antitumor immune activity and inhibiting errant bone destruction.

only identified bone mitogenic cytokines known to induce both osteoblastic and osteoclastic genes, thus regulating bone formation as well as resorption (Kveiborg et al., 2001; Suva et al., 2011; Yin et al., 2003; Fig. 2). TGF-β promotes osteoblast proliferation and differentiation by inducing ET-1 transcription and upregulating stromal insulin growth factor (IGF)-1 (Jin et al., 2011). The latter is reported to be highly expressed in bone metastases derived from both prostate and breast cancers, along with its respective receptor, suggesting possible paracrine and endocrine promotion of tumor cell growth concurrent to osteoblast activation (Christopoulos et al., 2015; Hiraga et al., 2012). The opposing function of TGF-β to promote osteoclastogenesis is regulated by the induction of Jagged1, involved in Notch signaling – a pathway heavily linked to bone metastasis and patient relapse in breast cancer – as well as parathyroid hormone-related protein (PTHrP) and several stromal-derived cytokines, including interleukin(IL)-11 (Esposito and Kang, 2014; Sethi and Kang, 2011a,b). In a somewhat convoluted process, TGF-β mediates bone resorption via the upregulation of tumor-derived or stromal PTHrP, which in turn induces osteoblast production of RANKL (receptor activator of nuclear factor κB ligand) that binds to its respective receptor RANK, expressed on hematopoietic osteoclast precursors (Jin et al., 2011; Roodman, 2004). Binding initiates a signaling cascade that culminates in osteoclast maturation. Mature osteoclasts then facilitate bone degradation. Tumor-derived TGF-β is central to the proposed concept of a vicious cycle, in which active tumor cells in the HSC niche induce PTHrP-mediated production of RANKL to promote osteoclast activation and subsequent bone resorption, consequently releasing an abundance of bone-stored growth factors that enhance tumor cell proliferation and further promote osteolytic activity (Abe et al., 2004; Mundy, 2002). Yet other endogenous and tumor-derived factors in the co-opted bone metastatic niche, including cathepsin K, IL-8 and IKKβ, have been shown to stimulate RANKL-independent osteolysis (Bendre et al., 2005; Clarke, 2008; D'Amico and Roato, 2015; Otero et al., 2010). The ability of tumor cells to circumvent RANKL-dependent osteolysis likely contributes to the failure of RANKL inhibitors, including Denosumab, to increase progression-free survival in advanced breast and prostate cancer patients, despite the effectiveness with which they have been shown to delay onset of skeletal-related events (Aragon-Ching, 2011; Fizazi et al., 2011; Gnant et al., 2015; Smith et al., 2015; Snedecor et al., 2013). Similar findings have been reported from clinical trials investigating the benefit of bisphosphonates, such as Zoledronic acid, which specifically target osteoclast progenitor development, to treat and prevent bone metastases (Simos et al., 2013; Wirth et al., 2015).

Taken together, the targeting of isolated interactions between tumor and bone resident cells to deter the establishment or progression of DTCs in bone has not proven adequate to reverse or inhibit bone metastasis in advanced disease, however identification of predictive markers for disease progression that may facilitate more timely delivery of therapies targeting bone resident populations may increase the efficacy of theses agents. While this underlines the relevance of exploring combinatorial approaches to better manage such a dynamic and multifaceted disease, it has also prompted investigators to look beyond the skeletal system.

3. Innate osteoimmunity and automimicry: shaping metastatic progression in the co-opted niche

The last decade has seen a surge in interest in the link between bone and the immune system – a logical progression given that the HSC niche provides a common point of origin for both bone and immune cells. Multiple lines of evidence support the contribution of immune cells to bone homeostasis and have exposed critical mechanisms of crosstalk between skeletal and immune systems that may be exploited by DTCs to gain a foothold in bone and progress. It is well-established that adaptive immune cells, including $CD4^+$ and $CD8^+$ T cell subsets, play a crucial role in mediating antitumor immunity in both primary and metastatic disease (Galon et al., 2013, 2006; Qin and Blankenstein, 2000; Roato, 2013; Slaney et al., 2013). In fact, $CD8^+$ T cells in bone have been evidenced to modulate tumor progression independent of the functional and biological status of osteoclasts in the co-opted niche, which supports the requirement for targeting multiple pathways to combat bone metastasis over osteoclast-targeted therapies alone (Zhang et al., 2011). Innate immune populations, including natural killer (NK) cells, have also been exposed as key contributors to tumor-directed immune surveillance however, as is the case for many immune cell lineages, their specific role in bone physiology and in the bone metastatic niche has been understudied and has therefore not translated into the development of robust innate-immune targeted therapies (Smyth et al., 2000; Zhao et al., 2012). Unfortunately, the field of osteoimmunology in the context of bone metastasis has been marred by a lack of syngeneic murine models that reliably metastasize to bone (Rosol et al., 2011). Therefore, much of what we know about tumor and innate immune cell interactions in bone has come to light using in vitro systems that fail to recapitulate the complexity of the bone microenvironment, or has been extrapolated from immunocompromised models. Despite this, accumulating evidence has revealed a critical role for innate immune cells in the regulation of DTCs in the bone microenvironment.

3.1. Tumor suppression

Involved in nonspecific elimination of DTCs via the production of interferon (IFN)- γ, release of cytolytic granules or TRAIL/FASL-induced apoptosis, mature NK cells represent approximately 12% of circulating lymphocytes, yet comprise as little as 1% of the lymphocyte population in bone – the primary site of NK cell development (Farag and Caligiuri, 2006). The effector function exerted by mature NK cells is contingent on a fine balance between inhibitory (including NKG2A and Ly49A in mice or KIR-L and CECAM-1 in humans) and activating receptors (including NKG2D, NKp46, NKp30 in mice and humans) present on NK cells, and their total engagement with respective ligands expressed on targeted or transformed cells (Waldhauer and Steinle, 2008). The nonspecific nature of NK cell immunosurveillance permits elimination of DTCs that have evaded adaptive immune recognition by

downregulating expression of membrane major histocompatibility complex class I (MHC-I), which normally serves to engage $CD8^+$ T cell receptors to induce cytolytic activity – a fundamental feature of the missing self paradigm (Desbois et al., 2012; Kärre, 2002). Additional stimuli critical to NK cell detection of tumor cells independent of MHC dysregulation is tumor cell upregulation of stress ligands, which are recognized by NK cell activating receptors (Pende et al., 2002). Stress ligands have been shown to be highly expressed during the early stages breast and prostate cancer in both the primary tumor and circulating cells, and have been associated with decreased patient relapse in breast cancer (de Kruijf et al., 2012; Liu et al., 2013; Pasero et al., 2015; Roberti et al., 2012). Differentiation of common lymphoid progenitors into functional NK cells in vivo relies on bone endothelial and monocyte production of IL-15, which interacts with the IL-2 receptor on NK cell precursors in the absence of its cognate ligand IL-2, reportedly absent in bone marrow, while NK cell expansion requires priming by co-stimulatory tyrosine kinases ligands flt-3 and c-kit supplementary to IL-15 (Farag and Caligiuri, 2006; Mrozek et al., 1996; Saeed and Revell, 2001). Interestingly IL-15 has also been shown to directly induce osteoclastogenesis in normal bone and has been implicated in non-cancer related pathological bone loss (Ogata et al., 1999). However, TGF-β, in addition to it's contribution to RANKL-dependent bone remodeling and suppression of $CD8^+$ T cell expansion and effector function, has been demonstrated to downregulate both IL-15R and IL-2R expression, which may negate IL-15 mediated osteoclast activation in favor of other osteolytic pathways (Lucas et al., 2006; Sanjabi et al., 2009). Conversely, TGF-β has been evidenced to inhibit NK cell activation and proliferation by antagonizing IL-15-dependent NK cell maturation and expression of both NKp30 and NKG2D, which may have major implications for NK cell-mediated tumor cell elimination in bone (Richards et al., 2006; Wilson et al., 2011). In fact, high serum TGF-β in cancer patients, which correlates with systemic immunosuppression, has been associated with poor patient outcome (Lee et al., 2004). We have previously demonstrated that NK cells are essential to the suppression of breast cancer metastasis to bone using the 4T1.2 immunocompetent model, when tumor-intrinsic type I IFN signaling is intact – type I IFN being a critical mediator of NK cell activation and effector function (Bidwell et al., 2012; Heidemann et al., 1986; Swann et al., 2007). Furthermore, in type I IFN deficient hosts, we have shown that adoptive transfer of activated NK cells reduced tumor burden in the spines of mice bearing 4T1 orthotopic tumors (Rautela et al., 2015). Expression of NKp30 and NKp46 on circulating NK cells has also been associated with significantly increased patient survival in metastatic-prostate cancer and therapeutically activated NK cells were shown to exclusively abrogate bone metastasis in a neuroblastoma model (Lode et al., 1998; Pasero et al., 2015). While the immunosuppressive action of TGF-β, frequently elevated in bone-metastatic cancer patients, has been strongly attributed to the phenotypical and functional alterations that diminish the potential antitumor activity of NK cells, it has been evidenced that TGF-β does not impact IL-15 mediated NK cell survival (Lee et al., 2004; Wilson et al., 2011). Furthermore, inhibition of TGF-β has been demonstrated to restore NK cell dependent antitumor activity (Wilson et al., 2011). That NK cell suppression in the tumor microenvironment is reversible offers therapeutic opportunity to target TGF-β signaling to enhance innate antitumor immunity. In fact, numerous clinical trials utilizing TGF-β inhibitors in various cancer settings have reported favourable patient outcomes, lending further weight to TGF-β antagonism as a feasible therapeutic adjuvant (Neuzillet et al., 2015). It has also been demonstrated that targeted disruption of TGF-β signaling can deter the development of breast-derived bone metastases in 4T1 tumor bearing mice, however the impact of TGF-β blockade on osteoimmunological regulation was not reported (Biswas et al., 2011). While little remains known about the direct effect of TGF-β inhibition on NK cell mediation of bone metastasis, it presents a promising area of future investigation, particularly in conjunction with alternative therapeutic strategies demonstrated to enhance NK cell functionality, such as type I IFN-inducers.

3.2. Tumor progression and automimicry

Interestingly, NK cells derived from tumor-bearing mice and transferred into immunocompetent animals have been shown to take on the phenotypical and functional characteristics of myeloid derived suppressor cells (MDSCs) in the presence of MDSC stimulating factors, such as granulocyte macrophage colony stimulating factor (GM-CSF) – a phenomenon that was suppressed in the presence of exogenous IL-2, a potent activator of NK cells, or in NK cells derived from naïve animals (Park et al., 2013). While this adds a further level of complexity to an already furtive innate population, it also emphasizes how cell plasticity in the tumor microenvironment can be exploited by DTCs to create a milieu that supports progression through reciprocation.

More traditionally, however, MDSCs encompass a heterogeneous population of distinctly immunosuppressive immature myeloid cells (iMC) that comprise up to 30% of bone marrow cells (Sawant et al., 2013). In the absence of malignancy, inflammation or infection, iMCs leave the bone marrow and undergo differentiation into macrophages, dendritic cells (DCs) and granulocytes in peripheral organs, however interaction with tumor cells drives iMC conversion to MDSCs and tumor-associated macrophages (TAMs) (Goedegebuure, 2013). Macrophages have been shown to influence both tumorigenesis and visceral metastasis, as well as bone homeostatic processes in non-pathological states however, their role in bone-specific metastatic progression is both conflicting and poorly defined (Ruffell and Coussens, 2015; Sinder et al., 2015; Sousa and Määttä, 2016). While MDSCs have also been underexplored in the context of bone metastasis, they have been demonstrated to be inextricably linked to osteoimmunological bi-regulation of tumor growth. Tumor secreted factors, including tumor necrosis factor (TNF)-α, GM-CSF, IL-6 and nitric oxide synthase (iNOS), have been shown to facilitate MDSC expansion and accumulation in the bone-metastatic niche (Capietto and Faccio, 2014; Cook et al., 2014; Law et al., 2017). In turn, MDSCs have been evidenced to drive metastatic progression both directly, via the secretion of pro-tumorigenic factors, including vascular endothelial growth factor (VEGF) and TGF-β (Fig. 2), and indirectly, through Arginase (Arg)-1 and iNOS-mediated impairment of NK and T cell reactivity, expansion of regulatory T cells (Treg), stimulation of TGF-β-induced innate immune suppression and induction of TGF-β/PTHrP-mediated RANKL-dependent bone resorption that accelerates the vicious cycle (OuYang et al., 2015; Sawant et al., 2013). Furthermore, MDSC are central contributors to IL-17 production in bone, which has recently been evidenced to induce RANKL-dependent osteoclastogenesis independent of PTHrP (Lee, 2013). Upregulation of circulating MDSCs has been reported in advanced metastatic prostate cancer patients, in addition to several other cancers (Condamine et al., 2015; Mehra et al., 2016). We have previously demonstrated elevated MDSC accumulation in immunocompetent mice bearing 4T1.2 bone-metastatic lesions, while MDSCs were significantly decreased in mice inoculated with bone-metastatic 4T1.2 cells with constitutive interferon regulatory factor (IRF) 7 expression – a key driver of type I IFN signaling, previously associated with decreased MDSC immunosuppressive function (Bidwell et al., 2012; Parker et al., 2016). In support of this, Cao et al. (2014) reported a significant decrease in peripheral MDSCs in mice bearing bone-metastatic tumors that constitutively expressed BMP4, a demonstrated inhibitor of protumorigenic cytokines, which correlated with decreased tumor burden in bone. Interestingly, it has been demonstrated that MDSCs derived from bone metastases in both 4T1 and 4T1.2 tumor-bearing mice are capable of differentiation into functional osteoclasts both in vitro and in vivo (Edgington-Mitchell et al., 2015; Sawant et al., 2013). While this appears logical, given that MDSCs are osteoclast progenitors, Sawant et al. (2013) reported that this observation was restricted to MDSCs isolated from bone-metastatic lesions compared to visceral metastases, which underscores the importance of

osteoimmunological crosstalk with tumor cells as a critical regulator of MDSC conversion. Moreover, it highlights the capacity of tumor cells to modulate the differentiation potential of cells in bone – an observation that underpins the concept of osteomimicry.

Given the perceived importance of bone marrow MDSCs in tumor progression, numerous pre-clinical studies and clinical trials have explored therapeutic modulation of MDSC immunosuppression and expansion to inhibit tumor growth (Najjar and Finke, 2013; Umansky and Sevko, 2013). To date, the chemotherapeutic Gemcitabine has been shown to decrease both circulating MDSCs and tumor burden in bone in the 4T1 model, while Cox-2 inhibitors, which counter the suppressive function of MDSCs by blocking iNOS signaling and production of Arg-1, have been associated with decreased risk of bone metastasis in breast cancer (Sawant et al., 2013; Valsecchi et al., 2009). While few studies have explored the impact of MDSC-targeted agents in metastatic disease, one stimulating avenue of investigation is the utilization of all-*trans*-retinoic acid (ATRA), a nuclear retinoid receptor agonist and metabolite of vitamin A. ATRA promotes MDSC differentiation into mature myeloid cells, including DCs, ultimately exchanging their immunosuppressive function for one that may be manipulated to promote immunoreactivity in the metastatic niche, and has been demonstrated to restore the cytotoxic function of $CD8^+$ T cells in metastatic renal cell carcinoma by driving MDSCs into a differentiated state (Kusmartsev et al., 2008; Wesolowski et al., 2013).

Dendritic cells provide as a critical link between innate and adaptive immunity due to their capacity as antigen-presenting cells (APCs) to induce T cell activation and prime $CD8^+$ T cell subsets through batf3-dependent signaling, and ability to modulate NK cell cytotoxic responses through IL-12 delivery (Borg et al., 2004; Capietto and Faccio, 2014; Spranger et al., 2017). Divided into both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) subsets, oncoimmunological research has chiefly focused on delineating the role of pDCs in the tumor microenvironment. Recent identification of third $CD11c^+B220^+NK1.1^+$ Gr^- DC subset in both the spleen and bone marrow of mice, characterized as IFN-γ producing killer dendritic cells (IKDC) and shown to lyse tumor cells through both NKG2D and TRAIL-dependent pathways, has also generated considerable interest in the oncoimmunology field given that it is the first population of cells discovered to possess killing, $CD8^+$ T cell priming and classical APC abilities (Chan et al., 2006; Himoudi et al., 2008; Taieb et al., 2006). However IKDC have been relatively underexplored in the context of metastatic disease and as yet no human homolog, with the possible exception of γδ T cells, has been reliably identified (Anderson et al., 2012). Numerous studies have observed a positive correlation between mature pDC infiltration and overall patient survival, as well as metastasis-free survival, in several immunogenic cancers with reduced or absent affinity for bone, which has been largely attributed to the intrinsic ability of mature pDCs to stimulate T cell responses (Ma et al., 2013). However in bone-metastatic disease derived from low-immunogenic tumors, such as breast and prostate, infiltrating pDCs are largely immature, lacking antigen-processing machinery and susceptible to factors prevalent in the bone-metastatic niche that engender an immune suppressive phenotype (Ma et al., 2013). Interestingly, human bone-metastatic prostate cancer cells have been demonstrated to actively inhibit the maturation of DC precursors (Aalamian et al., 2001). In line with this observation, increases in infiltrating pDCs have been detected in bone metastatic lesions in breast cancer, where they have been proposed to promote tumor progression through the release of TGF-β, Arg-1, indoleamine-2,3-dioxgenase (IDO) and IL-6 and induce a Th2-skewed immunosuppressive response (Sawant and Ponnazhagan, 2013). Bone marrow pDCs have also been demonstrated to express high levels of RANKL and programmed death receptor ligand 1 (PD-L1) to stimulate osteoclastogenesis and deactivate $CD8^+$ T cells respectively, reinforcing their role as osteoimmune regulators central to bone-metastatic progression (Anjubault et al., 2012; Gajewski et al., 2013a,b). Moreover, while DCs are capable of producing type I IFNs at high concentrations, intratumoral pDCs derived from triple-negative breast cancer patients were shown to exhibit impaired IFN-α production, which may further the suppressive function of pDCs in bone (Sisirak et al., 2012). While limited studies have investigated the impact of pDCs on bone metastasis, depletion of pDCs in mice bearing 4T1 tumors was demonstrated to significantly reduce tumor burden in bone as well as osteoclast density, which was associated with decreased bone destruction (Sawant et al., 2012). Inhibition of pDC was also associated with polarization toward a Th1 immune response and restoration of $CD8^+$ T cell function and IFN-γ production, previously suppressed in the presence of bone marrow pDC (Sawant et al., 2012). Cumulative evidence supporting the role of DCs in tumor progression initiated the development the first FDA approved DC targeted therapy for metastatic prostate cancer patients, Sipuleucil-T, in which autologous DCs from the patient are pulsed with prostatic acid phosphatase antigen, ubiquitously expressed in prostate cancer cells, and activated to become mature APCs *ex vivo* then re-introduced to the patient as a vaccine to induce a specific antitumor immune response (Kang et al., 2016). To date, Sipuleucil-T remains the only autologous DC targeted therapy to provide significant survival benefit to patients with advanced castrate-resistant prostate cancer, however numerous other agents are undergoing clinical trial to combat metastasis and tumor recurrence, and as such DC-targeted therapies represent an exciting area of immunotherapeutic development (Ahmed and Bae, 2014).

Like pDCs, the function of neutrophils may be subject to immunosculpting by tumor cells in the co-opted niche. Controversy surrounding the contribution of neutrophils to tumor progression and metastasis lies in their ability to both promote and inhibit DTC expansion, depending on the environmental cues they receive and further compounded by their ability to switch between states of polarization. Granot et al. (2011) demonstrated that neutrophil depletion significantly increased pulmonary metastases in mice bearing 4T1 tumors and that neutrophils from breast and melanoma tumor-bearing animals displayed greater cytotoxic activity against tumors cells through a process of entrainment that directed them toward an antitumor N1 phenotype. It has also been evidenced that differential tumor cell expression of FAS ligand was a critical determinant in the generation of N1 neutrophils that could effectively mediate lung metastatic outgrowth in a melanoma model (Chen et al., 2003). In contrast, endogenous TGF-β and prolonged exposure to G-CSF, both highly accessible in bone, have been evidenced to commit neutrophils to an immunosuppressive, protumorigenic N2 phenotype, while TGF-β inhibition was shown to adequately potentiate neutrophil activation and subsequent antitumor activity by converting neutrophils back to N1 status (Casbon et al., 2015; Fridlender and Albelda, 2012). Given the association between TGF-β and cancer progression, it is not surprising that in numerous cancers, including breast and prostate, increased neutrophil to lymphocyte ratios have been associated with both poor patient outcome and impaired therapeutic response (Treffers et al., 2016). Moreover, in bone-metastatic patients, high circulating neutrophils significantly correlated with decreased patient survival and were suggested to be an independent predictor of postoperative recurrence and progression (Wang et al., 2011). Interestingly, high serum IL-17 has also been reported in bone-metastatic patients as well as bone metastatic lesions, which is central to neutrophil expansion and egress from bone marrow into circulation – as such, high circulating numbers of neutrophils may more adequately reflect increasing tumor burden and immunosuppression in bone, as both MDSC and tumor cells are significant producers of IL-17 (Coffelt et al., 2016; D'Amico and Roato, 2015). In bone, neutrophils have been shown to induce bone resorption through RANKL-dependent osteoclastogenesis and osteoblast retraction, which may contribute to the expansion of bone-metastatic DTCs (Allaeys et al., 2011; Mori et al., 2013). Additionally, tumor-infiltrating neutrophils (TANs) have been associated with enhanced angiogenesis and invasive potential through secretion of matrix metalloproteinase 9 (MMP9), cathepsin-G and VEGF and play a central role in mediating

tumor cell–cell interaction through the establishment and maintenance of CXCR2/IL-8 gradients (Bekes et al., 2011; Treffers et al., 2016). N2 neutrophils have also been shown capable of exerting immune suppression through the production of Arg-1 and reactive oxygen species (ROS) to inhibit T cell receptor expression, function and survival, similar to both MDSCs and pDCc (reviewed in Kalyan and Kabelitz, 2014; Pillay et al., 2013). However the precise mechanisms that underpin neutrophil modulation of metastatic progression are complex, highly transmutational and remain relatively unmapped. As such, neutrophil targeted therapies are lacking and those under investigation are currently restricted to mediating neutrophil trafficking via CXCR2 inhibition and facilitated adhesion of tumor cells in the metastatic niche, in addition to IL-17 blockade (Coffelt et al., 2016).

A wide body of evidence supports the role of other innate immune cells along with adaptive cells in regulating tumor progression and metastasis. However, with the exception of Ogiya et al. (2016) who found that metastatic bone-infiltrating $CD8^+$ and $CD4^+$ T cells are significantly lower than in matched primary tumors in breast cancer patients and Bidwell et al. (2012), who reported a significant increase in MDSCs in the bone metastases of 4T1.2 tumor-bearing mice compared to matched primary tumors, few studies have profiled the immune infiltrate in bone metastatic lesions during the different stages of DTC colonization and outgrowth. As such, the immune landscape of bone metastases is still poorly understood, which has compromised our ability to effectively manipulate the immune system in a targeted and effective manner to overcome tumor progression in bone. One feature common to many innate immune populations is their capacity to assume either anti- or protumorigenic roles, depending on the microenvironmental signals they receive, which further compounds population-targeted therapies. The tumor-inherent changes that contribute to osteoimmune sculpting have only recently begun to be explored, however striking evidence has underlined the importance of bone-specific tumor cell alterations that may significantly impact the temporal development of bone metastasis. Consequently, further exploration of tumor-intrinsic modulation in the co-opted niche is also required to provide a more complete understanding of metastatic outgrowth in bone.

4. Tumor-intrinsic modulation of osteoimmunity: how tumor cells make their bed and thrive in it

Bone has largely been acknowledged as an immune-privileged site, therefore the skew toward a pro-tumorigenic phenotype may be augmented by a fundamental subdual of immune activation and inflammatory mediators, which functions to maintain resident stem cells – a state exploited by DTCs to promote immune exclusion and further suppression (Fujisaki et al., 2011; Mercier et al., 2014). One tumor-inherent mechanism proposed to modulate the osteoimmune milieu is differential production of type I IFN (Fig. 3). Type I IFNs, including IFN-α and -β, are a family of tightly regulated cytokines known to exert a range of immunomodulatory effects across many different cells types that contribute to immune moderation by promoting priming, activation and subsequent repression of innate and adaptive immune cell populations (Edwards et al., 1985; Fuertes et al., 2013; Thornley et al., 2007, Parker et al., 2016). Type I IFNs have also been shown to negatively regulate osteoclastogenesis by suppressing RANKL-dependent activation of c-FOS signaling, to prevent errant bone resorption (Takayanagi et al., 2002). Production of type I IFN in response to type I IFN-dependent activation of a JAK-STAT signaling cascade, is primarily mediated by cytoplasmic IRF9, which binds to a STAT1/STAT2 heterodimer to form the IFN-stimulated gene (ISG) factor 3 (ISGF3) complex that undergoes subsequent nuclear translocation to bind the IFN-stimulated response element (ISRE). Binding induces a multitude of IFN-stimulated genes (ISGs), one of which is IRF7 that drives transcription of type I IFN genes (Fu et al., 1990; Varedi, 2005). Early studies demonstrated that constitutive tumor cell expression of IFN-β

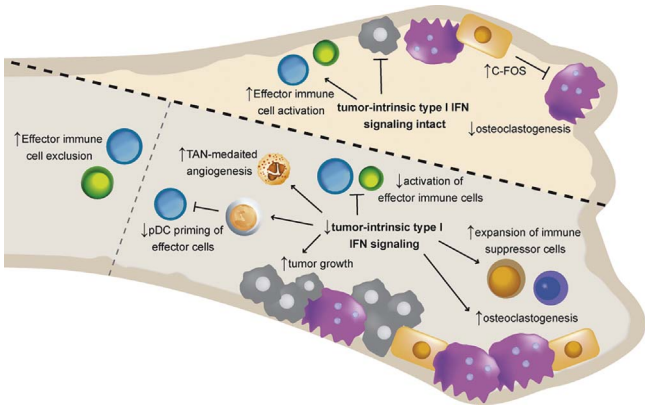

Fig. 3. Dysregulation of type I IFN is a critical mediator of bone-specific tumor progression. A known regulator of antitumor immunosurveillance and bone homeostasis, the loss of type I IFN signaling in overt metastatic lesions has widespread implications. These include downregulation of immune cell activation, inhibition of innate-immune priming of cytotoxic cells, increased angiogenesis and degradation of bone and ineffective homing of circulating immune cells (immune exclusion), all of which facilitate metastatic progression.

could inhibit growth and metastasis in vivo through increased activation of NK cells and enhanced clearance by macrophages (Dong et al., 1999). It was also demonstrated that IFN-α was critical to NK-mediated activation and early elimination of melanoma and Lewis lung cell carcinoma cells and could prevent outgrowth in a murine model of sarcoma via hematopoietic cell activation (Dunn et al., 2005; Swann et al., 2007). More recently, type I IFNs were shown to be required for DC-mediated rejection of transplanted tumors via enhanced cross-presentation of antigen to $CD8^+$ T cells and that impaired IFN-α signaling by intratumoral pDCs promoted breast cancer progression through the expansion of immunosuppressive $Foxp3^+$ Tregs in the tumor microenvironment (Diamond et al., 2011; Sisirak et al., 2013). Loss of systemic type I IFN signaling (IFNAR −/- mice) has also been associated with a significant increase in metastasis to bone in 66cl4 and 4T1 breast cancers models, with decreased tumor burden in bone in wild type animals with intact type IFN signaling associated with significant increases in NK cell activation and IFN-γ production (Rautela et al., 2015). However, perhaps most importantly, dysfunctional tumor-intrinsic type I IFN signaling has been shown to mediate metastasis to bone. Bidwell et al. (2012) demonstrated that Irf7, along with 208 prospective Irf7 targeted genes, were significantly downregulated in tumor cells derived from spine metastases of 4T1.2 tumor-bearing mice compared to primary tumors. Furthermore, constitutive expression of Irf7 in 4T1.2 tumor cells significantly decreased metastasis to bone compared to controls and significantly prolonged survival, suggesting that enforced type I IFN expression in tumor cells could suppress the formation of overt metastases (Bidwell et al., 2012). Furthermore, this observation only pertained to the formation of bone-metastatic lesions, as primary tumor growth was unaffected by Irf7 expression, suggesting that the mechanisms regulating tumor cell expansion are site-specific. The clinical relevance of this finding was demonstrated through the analysis of Irf7 signatures in breast cancer patient cohort, in which it was evidenced that Irf7 expression was suppressed in bone metastases relative to the primary tumor (Bidwell et al., 2012). Moreover, low Irf7 signature expression in the primary tumor was shown to correlate with decreased bone-metastasis-free survival time, indicating that Irf7 could be further explored as a predictive marker of breast cancer progression (Bidwell et al., 2012). Such an association was also reported in an independent study by Touati et al. (2017), in which a high Irf7 signature prior to neo-adjuvant chemotherapy was associated with reduced incidence of bone as the initial site of recurrence in invasive breast cancer patients. In bone, the consequences of suppressed tumor-intrinsic type I IFN signaling are potentially vast. Loss of IFN-β has been demonstrated

to drive TAN-mediated angiogenesis during early metastatic colonization – a critical determinant of DTC expansion (Fridlender and Albelda, 2012). Loss of type I IFN signaling in the bone metastatic niche may also impact the survival and function of effector immune cells and promote the expansion of immunosuppressive populations. Moreover, it may indirectly inhibit the recruitment and infiltration of activated effector cells to bone-metastatic lesions and suppress priming of resident effector cells tumor site, which has major implications for immunotherapies aimed at T cell activation. To put it simply, if activated effector cells are localized to the tumor site at a critical window of time, activation becomes redundant. Furthermore, tumor-intrinsic downregulation of type I IFN may encourage bone resorption by destabilizing bone homeostatic mechanisms that moderate osteoclast activation, thereby directly contributing to the vicious cycle of bone destruction and tumor cell growth. Such findings have divulged the importance of further investigating tumor-intrinsic alterations that occur within the bone microenvironment and how these changes shape osteoimmune responses during the temporal development of bone metastases to better stratify patient selection and immunotherapeutic practices. It also highlights the potential of application of type I IFN inducers to overcome the consequences of tumor-intrinsic suppression of type I IFN signaling in bone to enhance the effectiveness of both conventional and immune-based therapeutics.

5. Conclusion

Homeostatic mechanisms dictate that bone undergoes a continual remodeling process that results in the mobilization of factors and nutrients to create a fertile 'soil' that not only supports the survival and growth of DTCs that preferentially 'seed' within regions rich in protumorigenic factors – a concept first proposed Steven Paget (1889) over a century ago – but also contributes to osteoimmune modulation. Co-option of the bone to create a unique metastatic niche relies on a continually evolving exchange between tumor and host cells that drives tumor cell adaption, encourages osteomimicry and exploits the plasticity of both skeletal and immune cells to maintain a favourable and ultimately fatal cascade of events. Increased understanding of both endogenous and tumor-intrinsic mechanisms that underpin tumor progression in bone, from dormancy to the evolution of overt metastases, and the acknowledgement that progression must be explored in an open system permissive of the osteoimmune relationship with DTCs, is critical to devising more effective therapeutic strategies that target the interplay between bone co-option and immune suppression to prevent formation of overt metastases. Critical to such prevention will be the validation of biomarkers that can accurately predict the risk of bone metastasis or allow for very early detection of micrometastases that have reached a congenial soil. Improvements in such studies will no doubt be accelerated by multidisciplinary studies combining osteobiology and osteommunology.

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