Pharmacology & Therapeutics 141 (2014) 222–233

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: B. Teicher

Targeting tumor–stromal interactions in bone metastasis

Mark Esposito, Yibin Kang *

Department of Molecular Biology, Princeton University, Princeton, NJ 08544, United States

ARTICLE INFO

Keywords:
Bone metastasis
Metastatic niche
Tumor dormancy
Osteoclast inhibitors
Tumor–stromal interactions
Immune surveillance

ABSTRACT

Bone metastasis is a frequent occurrence in late stage solid tumors, including breast cancers, prostate or lung. However, the causes for this proclivity have only recently been elucidated. Significant progress has been made in the past decade toward understanding the molecular underpinnings of bone metastasis, and much of this research reveals a crucial role of the host stroma in each step of the metastatic cascade. Tumor–stromal interactions are crucial in engineering a pre-metastatic niche, accommodating metastatic seeding, and establishing the vicious cycle of bone metastasis. Current treatments in bone metastasis focus on latter steps of the metastatic cascade, with most treatments targeting the process of bone remodeling; however, emerging research identifies many other candidates as promising targets. Host stromal cells including platelets and endothelial cells are important in the early steps of metastatic homing, attachment and extravasation while a variety of immune cells, parenchymal cells and mesenchymal cells of the bone marrow are important in the establishment of overt, immune-suppressed metastatic lesions. Many participants during these steps have been identified and functionally validated. Significant contributors include integrins, ($\alpha_v\beta_3$, $\alpha_2\beta_1$, $\alpha_4\beta_1$), TGFβ family members, bone resident proteins (BSP, OPG, SPARC, OPN), RANKL, and PTHrP. In this review, we will discuss the contribution of host stromal cells to pre-metastatic niche conditioning, seeding, dormancy, bone-remodeling, immune regulation, and chemotherapeutic shielding in bone metastasis. Research exploring these interactions between bone metastases and stromal cells has yielded many therapeutic targets, and we will discuss both the current and future therapeutic avenues in treating bone metastasis.

Contents

1. Introduction

Metastasis to the bone is one of the most common and devastating complications in patients with advanced cancers of the breast, prostate or lung. Also manifests in other cancers (thyroid, renal cell, colon, esophageal or rectum), bone metastasis is a pathological process notable for the ability of tumor cells to exploit endogenous stromal environments and coerce other host cell types into cooperation. Despite

Abbreviations: CTC, circulating tumor cell; DC, dendritic cell; DTC, disseminated tumor cell; HSC, hematopoietic stem cell; MSC, mesenchymal stem cell; NK, natural killer; T_{reg}, regulatory T cell.

* Corresponding author at: Department of Molecular Biology, LTL255, Washington Road, Princeton University, Princeton, NJ 08544, United States. Tel.: 609 258 8834; fax: 609 258 2340.
E-mail address: ykang@princeton.edu (Y. Kang).

0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.10.006

gross morphological differences between the bone and the soft tissues from which bone metastases originate, the underlying molecular interactions between disseminated tumor cells (DTCs) and bone tissues make bone a particularly attractive niche for the growth of metastatic lesions. Lending credence to this idea, many of the genes associated with breast cancer metastasis to bone are surface interaction proteins or secreted growth factors, demonstrating that mechanisms extrinsic to the tumor cells are paramount to metastatic progression (Kang et al., 2003). From instructing the pre-metastatic niche to establishing a vicious cycle of bone remodeling and tumor growth, tumor–stromal interactions are crucial to metastatic expansion in bone. Although this tumor–stromal relationship endows resistance to many conventional therapeutic approaches, exploiting the crosstalk between tumor cells and the bone stromal compartment may provide an effective mean to thwart cancer metastasis to bone.

Myriad evidence has emerged within the last decade which indicates the need to target early tumor–stromal interactions (pre-metastatic niche conditioning, seeding and dormancy) to best treat bone metastasis. Current treatments target overt, established metastases and the symptoms associated with increased bone remodeling (Roodman, 2004; Weilbaecher et al., 2011; Ell & Kang, 2012). Meanwhile, recent research implicates multiple novel therapeutic opportunities within the priming of the pre-metastatic niche, metastatic seeding, micrometastatic dormancy and immune surveillance (Sipkins et al., 2005; Catena et al., 2010) (Table 1). Knowledge regarding the later steps of metastasis, such as bone-remodeling and the establishment of an immune-suppressive environment, has also advanced in recent years and future treatments may strive to transform overt metastasis into a chronic, treatable condition. Furthermore, select patients are receptive to current immune-modulatory therapies, yet the factors that govern a positive response are unknown and require further research to elucidate.

2. Educating the bone: forming the pre-metastatic niche

The discovery that primary tumor cells are able to instruct the adaptation of foreign sites for future colonization represents a paradigmatic shift in cancer research. Rather than a stochastic process through which a certain proportion of CTCs is able to colonize sites of distant metastasis, the ability of the primary tumor to influence future routes of metastasis both supports Stephen Paget's well established seed and soil hypothesis (Paget, 1989), and presents new opportunities for therapeutic intervention. Considerable evidence points to the formation of perivascular pre-metastatic niches in the lung by bone-derived cells such as Toll-like receptor 4^+ ($TLR4^+$) myeloid cells or vascular endothelial growth factor receptor-1^+ ($VEGFR^+$) hematopoietic progenitor cells (Kaplan et al., 2005; Hiratsuka et al., 2008). Similar mechanisms are observed in liver metastasis as cytokine secretions from metastatic cells rapidly upregulate intercellular adhesion molecules in the liver and allow for enhanced adherence (Khatib et al., 1999). Evidence also exists for the presence of pre-metastatic conditioning in bone marrow (Kelly et al., 2005; Peinado et al., 2012), however the results of many studies suggest that the bone already possesses many features ideal for fostering metastatic colonization.

Peinado and colleagues recently demonstrated the ability of tumor-derived exosomes, or small lipid coated vesicles containing tumor-derived proteins, to educate bone marrow derived cells, thus facilitating metastasis to the bone or lung in a melanoma model (Peinado et al., 2012). This conditioning was attributed to increased Met signaling in bone marrow stromal cells. Likewise, inhibition of the hepatocyte growth factor (HGF) receptor (c-MET) interaction has shown promise in weakening the migratory phenotype of breast cancer metastatic cells, and in vivo administration of Tivantinib is able to significantly delay bone metastatic progression (Previdi et al., 2011). Changes in bone marrow structural components have also been observed (Fig. 1), as Heparanase (HPSE) secreted by primary tumors increases bone degradation in the absence of metastatic lesions (Kelly et al., 2005).

Understanding the role of mesenchymal stem cells (MSCs) in tumor–stromal interaction has become an important field of study (Koh & Kang, 2012). Patients with advanced lung or breast cancer, but without bone metastasis, exhibit changes in MSC plasticity which predispose the bone toward enhanced osteolysis (Fernandez Vallone et al., 2013). This predisposition was accompanied by altered serum levels of Dickkopf 1 (DKK1), an inhibitor of osteoblast differentiation, reflecting perturbations in bone marrow homeostasis prior to metastatic seeding (Fernandez Vallone et al., 2013).

Contrary to the hypothesis of pre-metastatic conditioning, the existence of sites permissive for tumor engraftment in healthy mice has also been established. Work by Sipkins et al. utilized in vivo imaging to show that both leukemic cells and hematopoietic stem cells (HSCs) home to discrete bone marrow sites expressing stromal-derived

Table 1
Current and potential therapeutics targeting tumor-stromal interactions in bone metastasis.

Therapeutic target	Mechanism	Agent	Reference
FDA-approved therapies			
Prenylation	Osteolysis inhibitor	Zoledronic acid	Rosen et al., 2001
RANKL	Osteoclastogenesis inhibitor	Denosumab	Fizazi et al., 2009
CTLA4	Cytotoxic T cell activator	Ipilimumab	Hodi et al., 2010
Cytotoxic cells	NK cell activator	Interleukin 2	Rosenberg et al., 1994
Potential therapies			
EGFR	Osteoclastogenesis inhibitor	Gefitinib	Normanno et al., 2005
PD1	Immunosuppression antagonist	CT-011	Dulos et al., 2012
CD137	Immunosuppression antagonist	BMS-663513	Simeone & Ascierto, 2012
Gal3	CTC attachment ligand mimic	Lactulose-L-leucine	Heimburg et al., 2006
c-MET	Pre-metastatic conditioning inhibitor	Tivantinib	Previdi et al., 2011
CXCR4	Homing and dormancy inhibitor	AMD3100	Shiozawa et al., 2011
CCL2	Homing and growth antagonist	Carlumab	Loberg et al., 2007
ET1	Osteogenesis antagonist	Atrasentan	Yin et al., 2003
Metastatic cells	Suppressive pathway activator	Interferon 7	Bidwell et al., 2012
PSA+ cells	PSA based vaccine	PROSTVAC-VF	Kantoff et al., 2010
VWF	Platelet shielding inhibitor	ARC1779	Karpatkin et al., 1988
β_3-Integrin	Seeding and growth antagonist	RGD-mimetic/mAb	Matsuura et al., 1996
Cathepsin B	Osteolysis inhibitor	CA-074	Withana et al., 2012
c-FMS	Osteoclastogenesis inhibitor	Ki-20227	Ohno et al., 2006
SRC	Proliferation inhibitor	Dasatinib	(Zhang et al., 2009)
Cathepsin K	Osteolysis inhibitor	Odanacatib	Le Gall et al., 2007
TGFβ	Osteoclastogenesis inhibitor	Ki26894, SD-208, LY2109761	(Ehata et al., 2007; Korpal et al., 2009; Mohammad et al., 2011)