Journal of Bone Oncology 5 (2016) 112–116

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Research Paper

Vascular niches for disseminated tumour cells in bone

Anjali P. Kusumbe [a,b]

[a] Kennedy Institute of Rheumatology, University of Oxford, Roosevelt Drive, Headington, Oxford OX3 7FY, UK
[b] Max-Planck-Institute for Molecular Biomedicine and University of Münster, D–48149 Münster, Germany

ARTICLE INFO

Article history:
Received 4 January 2016
Received in revised form
21 April 2016
Accepted 22 April 2016
Available online 21 July 2016

Keywords:
Endothelial cells
Metastasis
Dormancy
Disseminated tumour cells
Angiogenesis

ABSTRACT

The vasculature of the skeletal system regulates osteogenesis and hematopoiesis, in addition to its primary function as a transportation network. Recent studies suggest that the vasculature in bone regulates multiple steps involved in the metastatic cascade. Matrix and growth factor abundant vascular microenvironments in bone not only provide a fertile soil for the metastatic growth but also support the dormancy of Disseminated Tumour Cells (DTCs). Interestingly, vasculature also seems to direct the reactivation of dormant DTCs. Targeting such early steps of bone metastasis by directing therapies against vascular niches can lead to the development of effective therapeutic strategies that delay or even prevent the metastatic relapse. However, this would require a detailed understanding of the regulatory mechanisms that govern the interaction between endothelial cells and DTCs in the early stages of bone metastasis. This review aims to highlight the importance of vascular niches and outline their newly identified roles during bone metastasis.

1. Introduction

The skeleton is the most prevalent site of metastasis for several cancer types. Skeletal metastasis is associated with a reduced quality of life owing to prolonged pain, poor therapeutic success and low survival rate [1,2]. The initial stages that underpin this poor outcome is laid by the extravasation and lodging of circulating tumour cells in the bone marrow microenvironment, a process that in most patients precedes the primary tumour detection. Disseminated tumour cells (DTCs) may survive within the bone marrow microenvironment in the state of dormancy (cell cycle arrest) for very long periods. While a subset of patients develop detectable metastases as late as two-to-three decades post primary tumour detection, others show no signs of relapse despite the detection of DTCs in bone postmortem [2–4]. Such clinical evidence argue in favor of targeting DTCs within the bone microenvironment, rather than targeting the initial steps of tumour cell extravasation and dissemination. Designing strategies to target DTCs within the bone marrow microenvironment is likely to facilitate the development of therapeutic regimes that delay or prevent metastatic relapse. However, this requires fundamental understanding of the mechanisms that lead to dormancy and subsequent reactivation of cancer cells. Existing therapeutic strategies target and slow down progression in the late stage of the disease; but these therapies are not curative [1–4]. Despite its tremendous impact on the therapeutic outcome, our understanding of the early stage (survival, quiescence, migration and proliferation of cancer cells in bone) of the disease remains poor. Multiple lines of evidence demonstrate that tumour cells are regulated in a non-cell-autonomous manner. Notably, recent findings highlight the important roles of the microenvironment in determining the fate of DTCs [5,6].

Extensive vascularization of the skeletal tissue suggests the importance of blood vessels in regulating its physiological functions. Endothelium, the innermost cellular layer of blood vessels forms a central component of the bone marrow vascular microenvironment [7]. Recent evidence support that a pivotal role is played by the vascular niche during the early stages of bone metastasis [5]. During the later stages of the disease, blood vessels enhance the metastatic outgrowth by mediating the delivery of oxygen, nutrients and growth factors. This implies that altering the vascular microenvironment of DTCs during the early stages of metastasis can lead to the elimination of DTCs; thereby preventing the relapse, while targeting the vasculature at the later stages can slow down the metastatic growth. This review highlights the significance of vascular niches during skeletal metastases and discusses the potential therapeutic interventions for targeting the vascular niche.

E-mail addresses: anjali.kusumbe@mpi-muenster.mpg.de, anjali.kusumbe@kennedy.ox.ac.uk

http://dx.doi.org/10.1016/j.jbo.2016.04.003

2. Properties of the bone vasculature

Organ specificity of the vasculature and heterogeneity among vascular beds has been suggested to guide the differential extravasation of tumour cells to various organs. Therefore, understanding the morphological, cellular, molecular and functional properties of the bone vasculature is critical for deciphering the role of the vascular niche during skeletal metastases [8]. Like vascular beds in other organs, endothelial cells in the skeletal system are also organized as a widespread hierarchical network of blood vessels that perform multiple functions. Apart from being a transport network, blood vessels in the skeletal system provide inductive signals to regulate skeletal development, homeostasis and remodeling [7]. Emerging studies reveal that the vasculature of the skeletal system plays crucial roles in osteogenesis (bone formation) and haematopoiesis through direct cellular interactions and paracrine (angiocrine) signalling pathways [9–11]. Haematopoietic Stem Cells (HSCs) are frequently detected within vascular microenvironments, which involve different vessel subtypes comprising of both endothelial and perivascular cells. Specific vascular microenvironments are required to support HSC homing, self-renewal and quiescence [10]. The skeletal vascular microenvironment is thus often denoted as the "bone-marrow vascular niche". Consequently, there has been a tremendous interest in understanding the structural and functional properties of the skeletal endothelium. However, the progress has been hampered by the lack of understanding of the precise organization of the vasculature. Bone vasculature is vaguely defined as a network of sinusoids and arterioles. The discontinuous and fenestrated sinusoidal endothelium constitutes the predominant vascular surface in the skeletal system [12]. We have recently unravelled the fundamental aspects of the basic hierarchical organization of bone arteries, capillaries and veins. We found that the molecular signature, metabolic activity and functional properties vary between metaphysis and diaphysis blood vessels. In addition, we have identified and characterized a distinct capillary and endothelial cell subpopulations, one of which (termed type H) plays critical roles in the regulation of osteoprogenitor cells and thereby bone formation [9,11].

Different vessel subtypes have distinct functional roles in the vertebrate skeletal system. Veins drain the sinusoids and type H capillaries, while arteries deliver oxygen-rich blood and terminate into the type H capillaries. Columnar type H capillaries oriented towards the growth plate are characterized by high expression of markers CD31 and Endomucin and are physically connected to distal arterioles in the metaphysis and endosteum of long bone (Fig. 1). Type H capillaries are surrounded by bone-forming osteoprogenitor cells and release pro-osteogenic growth factors. In contrast, type L ($CD31^{lo}$ $Endomucin^{lo}$) blood vessels, which correspond to the highly branched network of sinusoidal endothelium of the bone marrow cavity, are not directly connected to arterioles and lack association with bone forming osteoprogenitor cells [9,11]. Such unique properties of the bone vasculature combined with its heterogeneous nature and expression of growth factors suggest the existence of distinct microenvironments in bone which may support the early events during skeletal metastasis and can also accelerate disease progression in the late stage.

3. Dissemination-permissive characteristics of the BM vascular niche

Sinusoids (type L capillaries) are the most abundant blood vessels in bone and widely distributed throughout the bone marrow cavity [8]. Sinusoids in bone are discontinuous single layer of endothelial cells devoid of pericytes. Due to the absence of a consistent vessel wall and low level expression of tight junction molecules, sinusoidal endothelium is highly permeable in nature [8]. Additionally, the sinusoidal wall is specialized to facilitate easy two-way trafficking of hematopoietic cells [8]. These characteristics of bone sinusoids are known to expedite invasion, extravasation and docking of circulating tumour cells within the bone

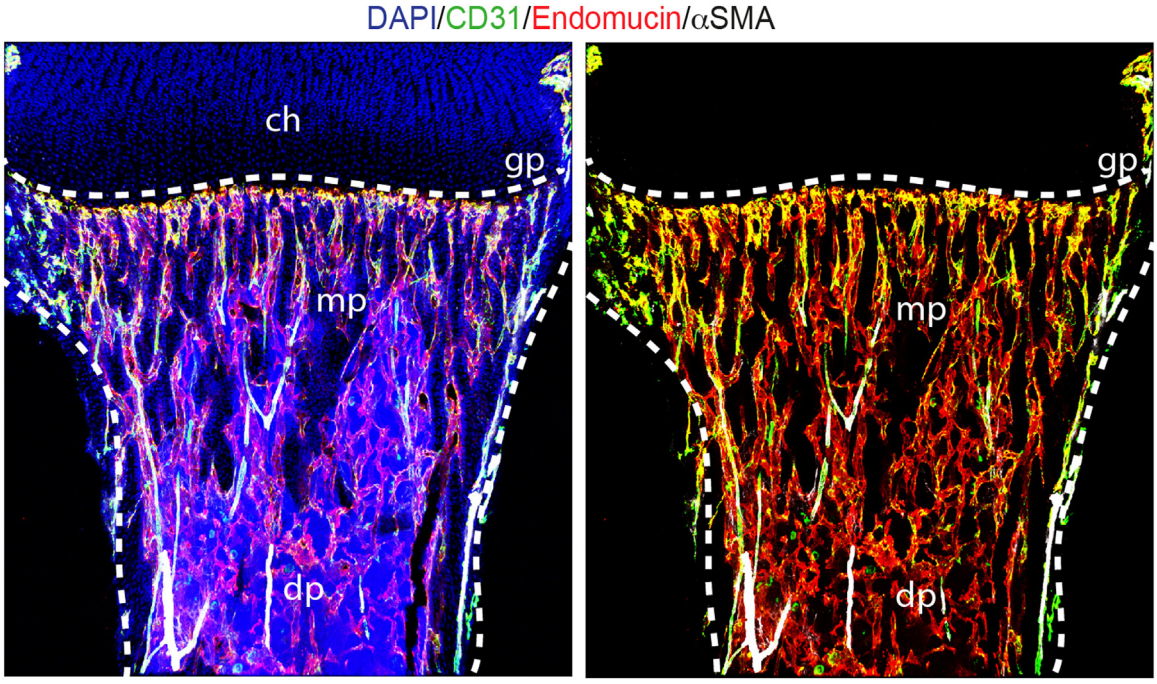

Fig. 1. Organization of blood vessels in bone. Tile scan confocal images showing metaphysis (mp) and diaphysis (dp) regions of the mouse long bone (tibia) immunostained for CD31 (green), Endomucin (red) and α-SMA (white). Linear $CD31^{hi}$/$Endomucin^{hi}$ type H blood vessels are abundant in the metaphysis while a highly branched network of sinusoidal endothelium (type L) forms the predominant vascular surface in the diaphysis. $CD31^{hi}$ (green) $Endomucin^{-}$ arteries with α-SMA^{+} coverage are directly connecting to type H capillaries but not to type L blood vessels. Dashed lines mark the growth plate (gp) and compact bone. Chondrocytes; ch. Nuclei are stained with DAPI (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)