Journal of Bone Oncology 2 (2013) 47–57

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Review Article

The role of the bone microenvironment in skeletal metastasis

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ARTICLE INFO

Article history:
Received 25 October 2012
Received in revised form
22 November 2012
Accepted 22 November 2012
Available online 11 December 2012

Keywords:
Bone metastasis
Cancer
Bone microenvironment
Bone remodelling

ABSTRACT

The bone microenvironment provides a fertile soil for cancer cells. It is therefore not surprising that the skeleton is a frequent site of cancer metastasis. It is believed that reciprocal interactions between tumour and bone cells, known as the "vicious cycle of bone metastasis" support the establishment and orchestrate the expansion of malignant cancers in bone. While the full range of molecular mechanisms of cancer metastasis to bone remain to be elucidated, recent research has deepened our understanding of the cell-mediated processes that may be involved in cancer cell survival and growth in bone. This review aims to address the importance of the bone microenvironment in skeletal cancer metastasis and discusses potential therapeutic implications of novel insights.

1. Introduction

Bone metastases are a major cause of cancer-related pain and can result in pathological fractures, paralysis and life-threatening hypercalcaemia. Less than 20% of patients survive for five years after the discovery of bone metastasis [1–4]. In other types of cancers, such as liver and lung malignancies, the incidence of bone metastasis has increased in recent years, possibly due to the effect of improved treatment regimens on life expectancy [5,6].

Metastasis of tumour cells to bone depends on a complex cascade of events which includes the detachment of individual cancer cells from the primary tumour site; invasion into the vasculature; migration and adherence to distant capillaries within the bone; extravasation and initial survival within the new environment; proliferation to micrometastases; recruitment of blood supply to the tumour for further expansion; and invasion beyond the adjacent tissues [3,4,7]. The ability of cancer cells to survive and expand in the bone marrow cavity has long been based on the "seed and soil" theory: In 1889, Sir James Paget proposed that bone acts as a fertile environment ('soil') for cancer cell ('seed') colonization and growth [8]. Many years later, Mundy and colleagues greatly broadened our understanding of the mechanisms that govern the growth of bone metastases by developing a concept widely known as the "vicious cycle" [7,9–11]. This theory elegantly explains how cancer metastases, once established in bone, modify their immediate environment to support their own survival and growth. Thus, tumour-derived factors such as parathyroid hormone-related protein (PTHrP) up-regulate the expression of Receptor Activator of Nuclear Factor KB Ligand (RANKL) by cells of the osteoblast lineage (i.e., osteoblast precursors, osteoblasts and osteocytes). RANKL then binds to the Receptor Activator of Nuclear Factor KB (RANK) on osteoclasts and osteoclast precursors to increase osteoclast recruitment and formation, and to activate bone resorption. Accelerated bone resorption then triggers the release of growth factors embedded in the bone matrix, which in turn act on cancer cells to promote their further growth [7,10,12] (Fig. 1). This model has been extremely useful in elucidating some of the mechanisms that support and maintain established cancer metastases in bone. It is, however, less clear how individual cancer cells survive and proliferate within the bone environment at the very early stages of colonisation, i.e., before reaching a critical mass that allows them to manipulate resident bone cells in a significant way. We would therefore predict that additional mechanisms are at work at the early stages of bone metastases that involve more direct signalling pathways than those described by the classical vicious pathway.

Numerous animal studies have demonstrated beyond doubt that effective inhibition of osteoclastogenesis or osteoclast function significantly reduces metastatic tumour growth in bone [13–20]. Likewise, clinical trials in patients with non-metastatic or metastatic cancers established that treatment with "anti-resorptive" agents such as bisphosphonates or the anti-RANKL antibody,

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2212-1374/$ - see front matter
http://dx.doi.org/10.1016/j.jbo.2012.11.002

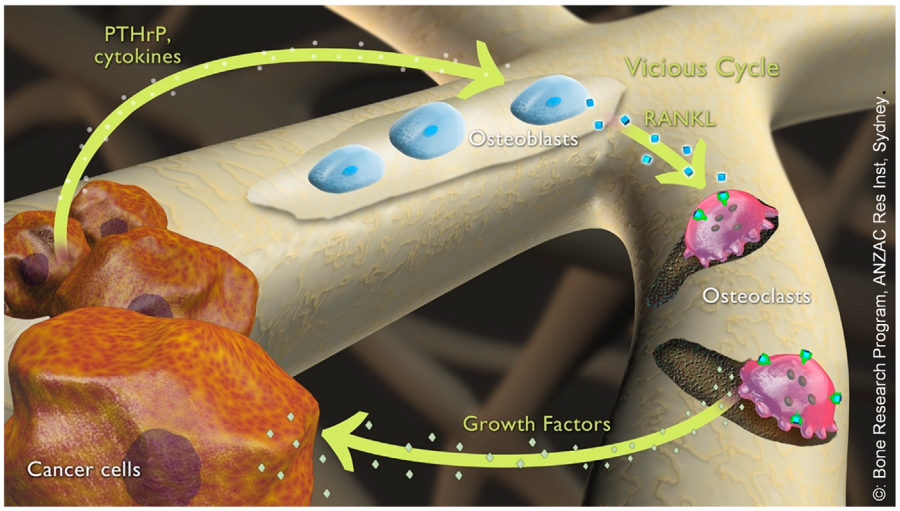

Fig. 1. Schematic representation of the 'vicious cycle'. Up-regulation of RANKL in bone cells and subsequent osteoclast activation is driven primarily by tumour-derived factors such as PTHrP and IL-6. Accelerated bone resorption then triggers the release of growth factors from the degraded bone matrix, which in turn promote further tumour growth.

denosumab, resulted in significant reductions in the incidence, progress or complications of bone metastases [21–23]. Despite these significant developments, complications of bone metastases still occur in up to 50% of patients even whilst receiving anti-resorptive therapy [1,4], indicating that there are still significant unmet needs in the prevention and treatment of metastatic bone disease.

2. Types of bone metastasis

Bone metastases have generally been characterized as osteolytic or osteoblastic based on their radiographic appearance [1]. Osteolytic lesions are caused by increased osteoclast activity accompanied by a concomitant absolute or relative decrease in osteoblast number or activity. This results in net bone resorption [7,24] with little or no associated bone repair. In contrast, osteoblastic lesions are characterized by abnormal bone formation around tumour cell foci, but this typically also co-exists with increased osteoclast activity. Thus, both types of cancer metastasis to bone are characterised by significantly accelerated bone resorption with the radiographic appearance depending on the concurrent levels of bone formation. These tumour-induced changes in bone metabolism can clinically be identified and monitored through the measurement of bone turnover markers, which correlate with both tumour burden and therapy-induced reductions in skeletal related events [1,25–35]. Thus, the classification of metastatic bone lesions into osteolytic and osteoblastic represent no less than the two extremes of a continuum in which the normal bone remodelling process becomes dysfunctional. Furthermore, patients can present with both osteolytic and osteoblastic lesions, and in fact, many bone metastases are mixed in nature, containing both lytic and blastic elements [12]. For example, breast cancer predominantly causes osteolytic metastases but at least 20% of patients present with mixed osteolytic-osteosclerotic lesions [2]. Conversely, prostate cancer presents mostly with osteoblastic lesions although a concurrent increase in bone resorption invariably occurs [2,4,36]. In patients with advanced bone metastases, high circulating levels of bone resorption markers, such as the aminoterminal telopeptide of type I collagen (NTX), were seen regardless of whether the lesions were radiographically lytic, blastic or "mixed" [30,37,38]. This indicates that all types of bone metastases contain an element of osteoclast activation, and this has been confirmed histologically. The role of osteoclasts in the spectrum of metastatic bone lesions is also supported by the fact that anti-resorptive therapy effectively reduces skeletal related events independent of whether there is predominantly lytic or blastic metastatic bone disease [23,39,40].

Within the bone microenvironment, the establishment of a tumour thus results in a disruption of the normally well-coordinated coupling of osteoblast and osteoclast functions. The resulting abnormal and accelerated bone remodelling then offers a fertile soil for further tumour expansion. Therefore, when it comes to the understanding of the mechanisms that enable cancers to grow in bone, the role of the bone microenvironment and its manipulation by the cancer cannot be underestimated.

3. The bone microenvironment

The term 'bone microenvironment' attempts to describe a complex structural and biological system which contains both haematopoietic and mesenchymal cells of multiple lineages, a sinusoidal blood supply, the bone marrow stroma and the bone extracellular matrix. In the context of skeletal cancer metastases, the bone matrix serves as a rich source of growth factors, while a number of different cells types inside, or recruited to the bone marrow cavity function to orchestrate the bone-tumour interactions. The cells within the bone microenvironment include resident bone cells (osteoclasts, osteoblasts and osteocytes) as well as various other cell types such as myeloid and immune cells, platelets, bone marrow endothelial and haematopoietic cells and bone marrow-derived mesenchymal stem cells, all of which may engage with the metastatic process to varying degrees.

3.1. Role of the bone matrix

Over the past 30 years it has become apparent that the bone matrix is extremely rich in growth factors. Many of these, including TGFβ, IGFs, FGFs, PDGF and BMPs not only promote the growth of metastatic cancer cells in bone, but also increase the production and release of cytokines and other bone resorbing factors from tumour cells [1,41]. Growth factors released by the bone matrix are able to change the phenotype of tumour cells to cause more aggressive metastatic lesions [3,7]. To again use Paget's analogy: The bone 'soil' is 'fertilized' by matrix-derived growth factors to