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Review Article

The role of biomarkers in the management of bone-homing malignancies

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ABSTRACT

Bone represents a common site of metastasis from several solid tumours, including breast, prostate and lung malignancies. The onset of bone metastases (BM) is associated not only with serious skeletal complications, but also shortened overall survival, owing to the lack of curative treatment options for late-stage cancer.

Despite the diagnostic advances, BM detection often occurs in the symptomatic stage, underlining the need for novel strategies aimed at the early identification of high-risk patients. To this purpose, both bone turnover and tumour-derived markers are being investigated for their potential diagnostic, prognostic and predictive roles.

In this review, we summarize the pathogenesis of BM in breast, prostate and lung tumours, while exploring the current research focused on the identification and clinical validation of BM biomarkers.

1. Introduction

Bone metastases (BM) represent a frequent incurable complication of several malignancies, owing to specific interactions between cancer cells and the bone microenvironment that make it suitable for tumour cell implantation and growth [1]. Indeed, approximately 70% of patients suffering from advanced breast or prostate malignancies develop BM during the course of the disease [2,3], with or without disease at other sites, while skeletal involvement characterizes approximately 30–40% of lung cancer (LC) patients [4].

Depending on the primary tumour, BM may exhibit a prevalent osteolytic or osteoblastic pattern, although in most cases a mixed radiological appearance is detected. Early-stage skeletal lesions are usually not detectable by current diagnostic tools, and their sensitivity and specificity are further limited when disease progression is slow and mimics non-malignant conditions. Moreover, the radiological appearance of BM may vary over time, both spontaneously and following anti-resorptive and anti-cancer treatments, and this ultimately complicates their monitoring [5].

As a consequence, BM are often not diagnosed until symptoms occur, leading to a significant impairment of patients' quality of life; furthermore, late BM diagnosis increases the risk of skeletal related events (SREs) that include hypercalcemia, pathological fractures, spinal cord injury and unremitting pain requiring radiotherapy and/or surgery. Moreover, the occurrence of one SRE increases the risk of further SREs and significantly impairs overall survival [6].

Physiologically, a delicate balance exists between bone resorption and osteogenesis, with dysregulation evident during the evolution of BM [1]. Since bone turnover releases specific molecules in blood and urine [7], several attempts have been made to associate variations in those markers (bone turnover markers, BTM) with BM onset and progression. In particular, BTM have been extensively investigated for their potential as diagnostic tools and to provide prognostic information, as well as to monitor treatment response [7]. At present, the high inter- and intra-individual variability still represents a limitation to their routine use.

Abbreviations: BM, bone metastases; SREs, skeletal related events; BTM, bone turnover markers; P1NP and P1CP, N and C terminal pro-peptides of type 1 collagen; BALP, bone specific alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase type 5b; NTX and CTX, N- and C- telopeptides of type 1 collagen; RANK, receptor activator of nuclear factor kB; RANK-L, RANK-ligand; OPG, osteoprotegerin; TNF, tumour necrosis factor; IL, interleukin; M-CSF, macrophage colony stimulating factor; PTH, parathyroid hormone; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; BMDC, bone marrow derived cells; EMT, epithelial to mesenchymal transition; CXCR, C–X–C motif chemokine receptor; CXCL, C–X–C motif chemokine ligand; SDF-1, stromal cell-derived factor 1; CaSR, calcium sensing receptor; BC, breast cancer; DTC, disseminated tumour cells; PTH-rP, PTH related protein; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PC, prostate cancer; BMPs, bone morphogenetic proteins; FGF, fibroblast growth factor; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; HR, hormone receptor; IL-1R, IL-1 receptor; ZNF217, zinc-finger protein 217; MAF, v-maf avian musculo-aponeurotic fibrosarcoma oncogene homolog; miRNA, micro RNA; TRAF3, TNF receptor associated factor 3; BSP, bone sialoprotein; CCL2, chemokine C-C ligand 2; CAPG, macrophage-capping protein; GIPC1, PDZ domain–containing protein member 1; PSA, prostate specific antigen; PDGFRα, PDGF receptor α; shRNA, short hairpin RNA; CTC, circulating tumour cells; LC, lung cancer; NSCLC, non-small cell LC; PYD, pyridinoline; DPD, deoxypyridinoline; uNTX, urinary NTX; β-CTX, CTX β isomer; 1CTP, cross-linked carboxy-terminal telopeptide of type 1 collagen; sBALP, serum BALP; BTA, bone-targeting agents

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Additionally, novel tumour-derived markers are being explored that predict the risk of development of BM and potentially identify responders to adjuvant bone-targeted treatments [8,9]. This may lead to intensified follow-up in selected patients as well as personalized adjuvant therapies, with the purpose to inhibit the onset of BM, which represent a non-curable condition.

Here, we will summarize the current view on BM pathogenesis in solid tumours, while exploring the recent advances in the BM biomarker field, focusing on breast, prostate and lung malignancies.

2. Methods

We first conducted an extensive research among previous international literature by using the PubMed database and key words such as "cancer osteotropism", "bone metastasis biomarkers" and "bone turnover markers", associated with "breast", "prostate" or "lung cancer". Then, we reviewed the references of relevant papers published in English between 1997 and 2017. Conference abstracts and papers were identified by reviewing the websites of relevant international oncology meetings.

2.1. Physiological bone turnover

Bone turnover is the result of the opposing activities of osteoblasts and osteoclasts (Fig. 1). The former have a mesenchymal origin and are deputed to osteogenesis. They first synthesize pro-collagen, whose cleavage at N- and C-terminals produces type 1 collagen and P1NP/P1CP pro-peptides, respectively; these fragments are released into the bloodstream and undergo hepatic clearance [5,10]. Then, osteoblasts secrete bone specific alkaline phosphatase (BALP) which hydrolyses pyrophosphate, a physiological inhibitor of bone matrix maturation, releasing inorganic phosphate [11]. Some osteoblasts are trapped in the newly formed matrix and become osteocytes, namely dendritic cells that commute mechanical stimuli into biochemical response, that in turn regulates bone turnover [12].

Osteoclasts are multinucleated bone-resorbing cells derived from the monocyte/macrophage lineage. Their erosive activity is based on the secretion of H^+ ions and lytic enzymes, such as proteases and the tartrate-resistant acid phosphatase type 5b (TRACP-5b). Proteases degrade type 1 collagen, thereby releasing N- and C-terminal fragments (NTX and CTX, respectively) that are detectable in both blood and urine [13,14].

Several factors contribute to the regulation of bone turnover, including the receptor activator of nuclear factor kB-ligand (RANK-L)/RANK/osteoprotegerin (OPG) axis. RANK-L belongs to the tumour necrosis factor (TNF) cytokine superfamily and is produced by osteoblasts and stromal cells. RANK-L stimulates osteoclast differentiation and maturation by interacting with its receptor RANK, expressed by pre-osteoclasts; excessive bone resorption is prevented by OPG, an osteoblast-derived soluble decoy receptor for RANK-L. A number of pro-osteoclastogenic (e.g. interleukin-1, IL-1; IL-6; macrophage colony stimulating factor, M-CSF) and anti-osteoclastogenic (e.g. IL-4, IL-18 and interferon-β) cytokines contribute to regulate the balance between bone resorption and osteogenesis [15], together with the hormones involved in calcium homeostasis. Indeed, vitamin D on one hand enhances bone resorption to increase calcium bioavailability, while on the other regulates the synthesis of bone matrix component such as osteocalcin, osteopontin and BALP. Parathyroid hormone (PTH) and calcitonin exert mutually opposite effects, with the former stimulating bone resorption and the latter enhancing osteogenesis [13].

Both estrogens and androgens have a predominant anabolic effect on the skeleton. Estrogens increase osteoblast number and activity, while inhibiting osteoclast maturation. Androgens exert not only direct effects on the growth plate, but also indirect regulatory activity, since they are converted to estradiol through the aromatization process [16].

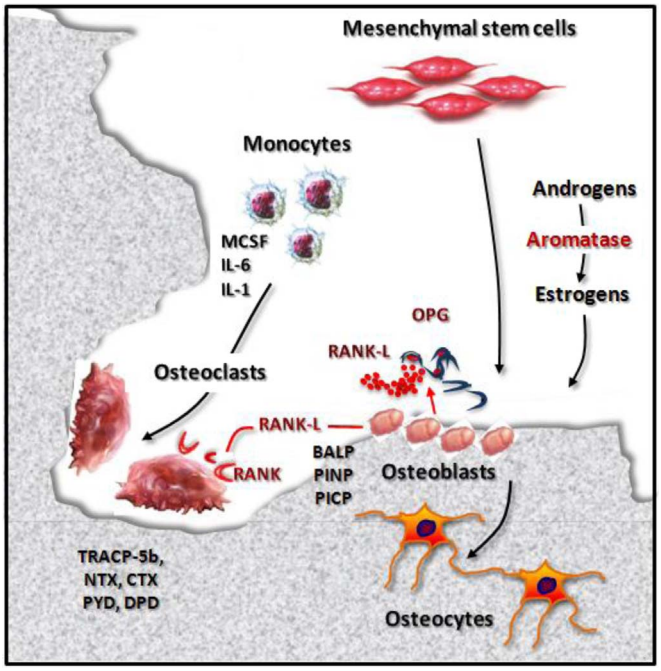

Fig. 1. Physiological bone turnover. Bone turnover physiologically results from the opposite activities of osteoclasts and osteoblasts. The former derive from the monocyte/macrophage lineage and exert a bone resorptive function, through the secretion of H^+ ions and enzymes, such as TRACP-5b. Osteoclastogenesis is enhanced by pro-osteoclastogenic cytokines (e.g. M-CSF, IL-6, IL-1). During bone erosion, type 1 collagen undergoes proteolytic cleavage which results in the release of degradation peptides (NTX, CTX, PYD, DPD), that are measurable in blood and urine. Conversely, osteoblasts have a mesenchymal origin and are deputed to osteogenesis. In particular, they synthesize pro-collagen whose cleavage at N- and C-terminals produces type 1 collagen, P1NP and P1CP peptides. Osteoblasts secrete also BALP which is necessary for the mineralization of bone matrix. Some osteoblasts become osteocytes, namely dendritic cells acting as mechano-transducers. Bone turnover is regulated by the RANK-L/RANK/OPG axis. Indeed, osteoblasts and stromal cells release RANK-L that, by binding its receptor RANK expressed by pre-osteoclasts, promotes their differentiation in osteoclasts. OPG partially inhibits this process, in order to prevent excessive bone resorption. Similarly, sex hormones exert a predominant anabolic effect. Adapted from D'Oronzo et al. 2015 [95]. Abbreviations: bone alkaline phosphatase (BALP), C-terminal fragment (CTX), deoxypyridinoline (DPD), interleukin-1 (IL-1), interleukin-6 (IL-6), macrophage colony stimulating factor (M-CSF), N-terminal fragment (NTX), osteoprotegerin (OPG). pro-collagen type 1 C-terminal propeptide (P1CP), pro-collagen type 1 N-terminal propeptide (P1NP), pyridinoline (PYD), receptor activator of nuclear factor kB (RANK), receptor activator of nuclear factor kB-ligand (RANK-L), tartrate-resistant acid phosphatase type 5b (TRACP-5b).

2.2. The metastatic process and the bone microenvironment

The development of metastasis has been traditionally interpreted as the consequence of a late-stage detachment of cancer cells from the primary site, their subsequent intravasation into blood and lymphatic vessels and extravasation in distant organs. This process was considered stochastic and merely mechanical, with the first site reached by cancer cells regarded as the most likely metastatic site, due to tumour cell entrapment in small sized vessels [17]. In this context, the cells capable of escaping host immune response would first develop micrometastases and then macrometastases in months or even years, depending on the balance between tumour dormancy and proliferation [18].

More recently, the primary tumour has turned out capable to release exosomes, growth factors (e.g. transforming growth factor-β, TGF-β; vascular endothelial growth factor, VEGF; placental growth factor, PlGF) and cytokines (e.g. TNF-α) that are able to recruit bone marrow derived cells (BMDC). BMDC increase vascular permeability, promote the extracellular matrix remodeling and modulate immune suppression to create the pre-metastatic niches, providing suitable microenvironments for cancer cell nesting and survival [19] (Fig. 2).

Additionally, epithelial cancer cells undergo a morphological and