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Review Article

Anti-RANKL therapy for bone tumours: Basic, pre-clinical and clinical evidences

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ABSTRACT

Bone remodelling is related to coordinated phases of bone resorption and bone apposition allowing the maintenance of bone integrity, the phosphocalcic homoeostasis all along the life and consequently the bone adaptation to mechanical constraints or/and to endocrine fluctuations. Unfortunately, bone is a frequent site of tumour development originated from bone cell lineages (primary bone tumours: bone sarcomas) or from nonosseous origins (bone metastases: carcinomas). These tumour cells disrupt the balance between osteoblast and osteoclast activities resulting in a disturbed bone remodelling weakening the bone tissue, in a strongly altered bone microenvironment and consequently facilitating the tumour growth. At the early stage of tumour development, osteoclast differentiation and recruitment of mature osteoclasts are strongly activated resulting in a strong bone matrix degradation and release of numerous growth factors initially stored into this organic/calcified matrix. In turn these soluble factors stimulate the proliferation of tumour cells and exacerbate their migration and their ability to initiate metastases. Because Receptor Activator of NFκB Ligand (RANKL) is absolutely required for in vivo osteoclastogenesis, its role in the bone tumour growth has been immediately pointed out and has consequently allowed the development of new targeted therapies of these malignant diseases. The present review summarises the role of RANKL in the bone tumour microenvironment, the most recent pre-clinical and clinical evidences of its targeting in bone metastases and bone sarcomas. The following sections position RANKL targeted therapy among the other anti-resorptive therapies available and underline the future directions which are currently under investigations.

1. Introduction

Bone is a very dynamic tissue resulting from coordinated phases of formation and resorption called bone remodelling. Additional to its role in phosphocalcic homoeostasis, bone remodelling process is necessary for bone growth, for renewal of cellular and extracellular matrix components to adapt bone organisation to the various biological and mechanical constraints [1–3]. Bone remodelling then leads to the renewal of around 10% of total bone mass each year in human. This metabolic process is based on a molecular crosstalk occurring between osteoblasts involved in bone apposition and osteoclasts specialized in bone resorption. Osteoclasts are multi-nucleated cells that originated from hematopoietic stem cells [4–6] whereas osteoblasts are derived from bone marrow mesenchymal stem cells [3,7,8]. Osteoblasts control osteoclast differentiation and activation through a very complex network of soluble factors which act in combination with various hormones produced by endocrine system even if contacts between both cell types also strongly contribute to full activation of osteoclasts [9,10]. Reciprocity between osteoblasts and osteoclasts can be observed as shown by bidirectional signalling limiting osteoclast activities and stimulating osteoblast differentiation [11].

Bone remodelling can be dysregulated by oncologic events originated from bone cells (primary bone tumours: osteosarcoma, chondrosarcoma, Ewing's sarcoma, etc.) or from nonosseous origins (bone metastases). Large series revealed that around 0.2% of all neoplasms are bone sarcomas and two new primary bone tumours arise per 100,000 persons a year [12]. Bone tissue is then the most frequent site of their first relapse and consequently, the incidence of bone metastases is relatively high and is dependent on the cancer cell types (i.e. in 70–80% of patients with breast or prostate cancer, in 40% of patients with lung metastases or with kidney cancer). Bone

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metastases are frequently associated with numerous clinical complications named skeletal-related events (SREs) and have a strong deleterious impact on the quality of life. SREs include pathological fractures or spinal cord compression and exacerbated bone pains. All bone tumours disrupt the equilibrium between bone apposition and bone resorption leading to the first stop of the tumour development to an osteolytic process followed or not by bone forming lesions. Soluble mediators stored initially into the bone matrix contribute in turn to stimulate the tumour growth and to maintain the vicious cycle between bone and tumour cells [13]. The loss of equilibrium between bone formation and degradation combined with an osteomimetism behaviour of cancer cells (cancer cells acquire bone-like properties) explains the diversity of histological features (osteolytic or bone forming tumours) of bone metastases [14]. Additionally, the modulation of bone micro-environment ("niche" concept) by cancer cells is beneficial for their proliferation and also contributes to the drug resistance patterns [15].

In the late 1990s, two research groups in Japan and in USA have identified a truncated TNF receptor-like molecule (named OPG for osteoprotegerin, TNFRSF11B) inducing marked osteopetrosis phenotype when overexpressed in transgenic mice [16,17]. One year later, RANKL (Receptor Activator of Nuclear Factor kB Ligand or TNFSF11) has been identified as a ligand for OPG [18,19]. In a few years, OPG/RANKL couple became the principal system regulating osteoclastogenesis and bone resorption and has impressively stimulated the development of OPG/RANKL targeting agents for the treatment of osteolytic disorders in oncologic contexts or not competing with bisphosphonates, a well admitted drug class for the treatment of bone loss [13,19–23].

In all bone cancers, a strong relationship between tumour cells and bone micro-environment has been then clearly established, facilitating the tumour development and/or the metastatic process. These specific communication pathways have strongly stimulated the research and development programs to design new drugs to treat oncologic bone diseases and have led specifically to the development of therapies targeting RANKL. The present review summarises the most recent progresses in the treatment of bone cancers based on RANKL targeting and underlines the future directions which are currently under pre-clinical investigations.

2. OPG, RANK and RANKL are key protagonists controlling osteoclast biology and bone remodelling

The critical function of OPG in osteoclastogenesis has been initially revealed by the osteopetrotic phenotype of mice overexpressing it [18,19]. In contrast, OPG deficient mice exhibit osteoporotic phenotype which is totally reversed by administration of recombinant OPG [24]. RANKL has been identified as the main ligand of OPG known to bind RANK (TNFRSF11A), a transmembrane receptor of the TNFR

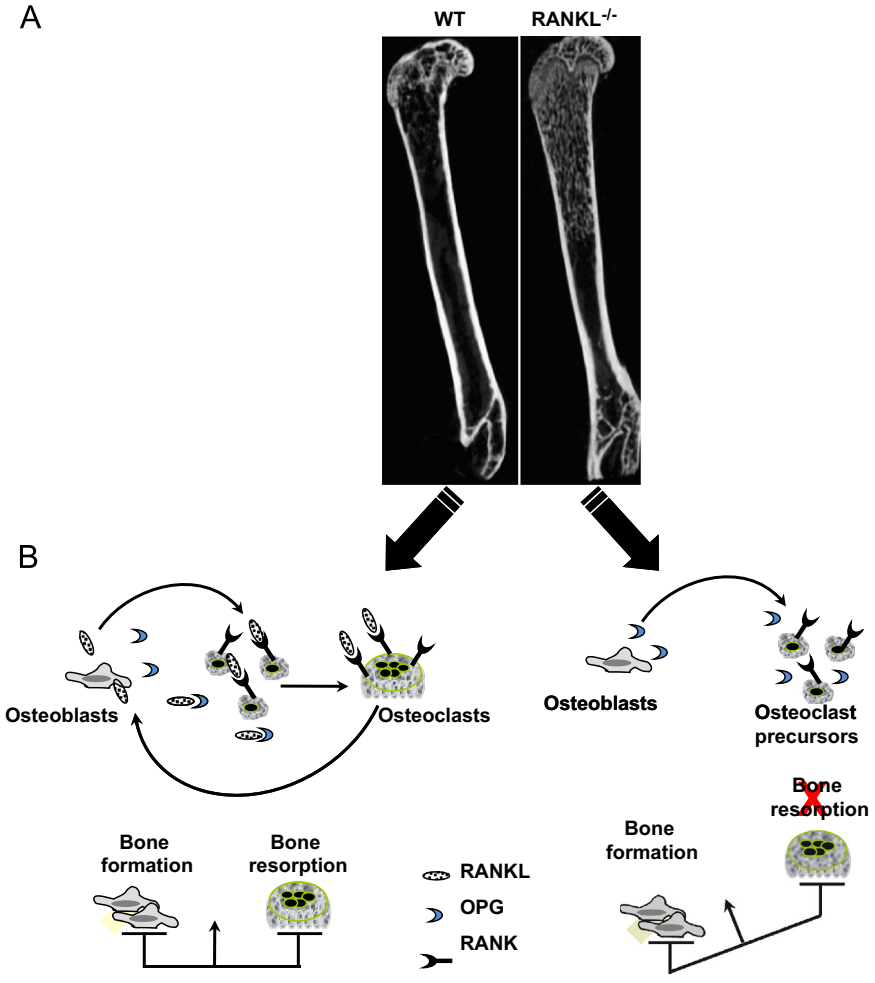

Fig. 1. *RANKL is absolutely required for osteoclast differentiation in vivo as revealed by the bone phenotype exhibited by RANKL knockout mice.* (A) Osteopetrotic phenotype exhibited by RANKL knockout ($RANKL^{-/-}$) compared to wild type (WT) C57BL6 mice analysed by μCT (skyscan 1076). (B) Osteoblasts produced RANKL (membrane and soluble forms) which binds to membrane RANK expressed by osteoclast precursors, OPG synthesised by osteoblasts acts as a decoy receptor, blocks the RANKL/RANK interactions and then inhibits bone resorption. The lack of RANKL results in a disturbed bone remodelling characterised by an excessive bone formation and a reduced bone resorption compared to the control mice.