Osteoblast Dysfunction

Subjects: Others

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Osteoblasts (Ob) originate from mesenchymal cells, secrete matrix proteins and promote mineralization during the bone modelling and restructuring process. Ob are unable to function as a single cell, in fact they function in a group of cells and the functional unit made up of Ob and the bone produced is called bone multicellular units (BMU). The mineralized skeleton is the support for human body and is a fundamental store of calcium, phosphate, participating also to the basic-acid homeostasis.

bone sclerosis melorheostosis bone metabolism osteoblasts osteocondensation

1. Introduction

Sclerosing bone diseases are a heterogeneous group of skeletal alterations that share the process of impaired bone ossification. They are mostly rare diseases that are usually classified in hereditary and non-hereditary bone diseases. Hereditary sclerosing bone diseases are caused by genetic alterations resulting in increased bone formation and are represented by osteopetrosis, osteopoikilosis, pyknodysostosis, progressive diaphyseal dysplasia, osteopathia striata, hereditary multiple diaphyseal sclerosis andhyperostosis corticalis generalisata. Non-hereditary sclerosing bone diseases include intramedullary osteosclerosis, melorheostosis, Paget disease of bone, Erdheim-Chester disease, myelofibrosis and sickle cell disease. The diagnostic process of these conditions is often challenging. The resulting osteocondensation seen in imaging may be the final stage of an impaired process of stem cells differentiation which is in turn the consequence of altered levels of soluble growth factors. The basic laboratory tests in the diagnostic process of osteocondensation should include blood count, erythrocyte sedimentation rate, protid electrophoresis, transaminases, serum creatinine, calcium, bone alkaline phosphatases (bALP) and prostate specific antigen (PSA). Histology may also be required in order to exclude the diagnosis of hematological neoplasms. Impaired levels of soluble factors influencing osteoblast (Ob) metabolism such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) or bone morphogenetic protein (BMP) or alterations of intracellular pathways such as Wnt signaling, Mitogen-activated protein kinase (MAPK) signaling, Receptor activator of NF-κB (RANK)/ RANK ligand (RANKL)/ Osteoprotegerin (OPG) pathway have been described in this group of diseases. Ob metastases showed peculiar mechanisms inducing osteosclerosis such as cross-talk between cancer cells and Ob. The aim of this review is to describe the main clinical features in non-hereditary sclerosing bone diseases and to review the existing evidence concerning the Ob dysfunction involved in the physiopathological mechanism of these disorders.

2. Osteoblast Physiology

Osteoblasts (Ob) originate from mesenchymal cells, secrete matrix proteins and promote mineralization during the bone modelling and restructuring process [1]. Ob are unable to function as a single cell, in fact they function in a group of cells and the functional unit made up of Ob and the bone produced is called bone multicellular units (BMU). The mineralized skeleton is the support for human body and is a fundamental store of calcium, phosphate, participating also to the basic-acid homeostasis [2]. Osteoclasts are the counterpart of Ob, being mainly involved in the bone resorption process. RANK is expressed on the surface of osteoclasts while RANKL, a trans-membrane protein produced in stromal cells and Ob, enhances the activation and differentiation of osteoclast by binding to RANK. OPG is secreted by Ob and stromal stem cells and prevents excessive bone resorption from skeleton by binding to RANKL and preventing the interaction with RANK [3]. Although RANK/RANKL pathway is mostly considered to be a key factor in the activation of osteoclasts, Sugamori et al. [4] demonstrated that RANKL-binding peptides WP9QY and OP3-4 may stimulate Ob proliferation and vesicular RANK secreted by the maturing osteoclasts; binding osteoblastic RANKL, they promote bone formation by triggering RANKL reverse signaling [5]. Ob proliferation and migration is influenced by soluble factors such as FGF, PDGF, BMP, parathyroid hormone (PTH), insulin-like growth factor (IGF), and the Wnt family of proteins. FGF stimulates Ob proliferation [6] and leads to a decreased apoptosis [7]; it has been known that PDGF increases both migration and proliferation in Ob [8]. MAPK or MAP kinase is a protein kinase that plays a leading role in the regulation of complex cell functions such as differentiation, proliferation or apoptosis [9]. Extracellular signal regulated kinase 1 and 2 (ERK 1/2) are members of MAPKs, which are activated by a kinase called MAPK/ERK kinase (MEK) in response to growth stimuli. It has been shown that FGF and PDGF activate ERK and consequently define Ob proliferation [10], although the precise mechanisms of this activation are not known. Kyono et al. [11] displayed that FGF2 upregulates genes involved in osteocyte differentiation in a MAPK dependent manner. Wnt proteins bind to surface receptors on mesenchymal cells such as Frizzled and LRP5, triggering the activation and nuclear translocation of the transcription factor β-catenin, which in turn defines the transcription of genes involved in Ob differentiation [12]. Dysregulation of these bone homeostasis control may be involved in the pathogenesis of bone sclerosing diseases. Constitutive activation of β-catenin has been linked to the pathogenesis of osteopetrosis, a disease included among hereditary sclerosing bone dysplasias [13].

3. Osteoblastic Metastasis

Prostate cancer (PCa) is the prototype of cancer with a predilection for generating osteoblastic metastases. The disordered bone architecture of bone metastases defines a structural weakness prone to fracture [14]. Since patients with metastatic bone prostate cancer have a relatively long survival [15], skeletal complications such as bone pain, hypercalcemia, impaired mobility, spinal cord compression may occur [16]. The genesis of osteoblastic metastases is a complex cascade of events involving both Ob and metastatic cells. A factor that may play a role in the development of osteoblastic PCa metastases is MDA-BF-1, a 45-kDa secreted form of the growth factor receptor ErbB3 expressed in PCa cells from metastatic bone lesions, but not in liver or lung metastases or in localized PCa cells [17]. Further evidence is needed to confirm a cause-and-effect relationship between the development of osteogenic metastases and the serum level of this factor. In vivo studies have shown that paracrine BMP signaling-mediated osteogenesis supports PCa progression in bone, since inhibition of the paracrine BMP4

decreases PCa tumor growth [18]. There is growing evidence that impaired osteoblastic function may be due to interaction with PCa, which secrete osteoblastic factors and induce Ob proliferation. PCa-118b is a patient-derived xenograft (PDX) generated from osteoblastic bone lesions [19], showing an increased expression of soluble factors belonging to the BMP/TGFβ and FGF family [20][21]. Wnt 7b is also highly expressed in PCa cells, thus promoting the development of osteoblastic lesions [22]. Growing evidence supports the role that endocellular vesicles (EV) may have in favoring the proliferation of PCa. PCa derived EV trains Ob towards a pro-tumorigenic cell type, creating a favourable niche for tumor growth [23]. Osteomimicry is a striking strategy adopted by PCa; in fact, they are able to express bone matrix proteins and interfere with the crosstalk of the bone cells [24], leading to an increased survival and proliferation of tumor cells. In vitro studies have shown that microRNA-141-3p contained in the exosomes from MDA PCa cells 2b is transferred to the Ob, promoting their activity and increasing OPG expression. Ob activity is significantly affected by changes in miR-141-3p levels. In vivo studies confirmed the important role played by microRNA in the genesis of bone metastases. In fact, intravenous injection of miR-141.3p mimic exosomes in mice develops apparent osteoblastic bone metastases at 4 weeks after injection [25]. The expression of VEGF by C4-2B PCa cells may also contribute to Ob proliferation in metastases, by linking VEGF receptor on the surface of Ob [26]. After a diagnosis of bone metastases, treatment is designed as a palliative and aims to reduce symptoms related to bone diseases such as fractures, pain or hypercalcemia [27]. Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate which selectively bind the hydroxyapatite binding sites on bony surfaces, especially on surfaces undergoing active resorption. Then they are internalized in osteoclasts leading to the disruption of bone resorption [28]. Intravenous infusion of pamidronate has been shown to relieve skeletal pain in both lytic and sclerotic bone metastases [29]. Evidence of the anti-cancer effect was observed in breast cancer cells [30] and a meta-analysis showed disease-free survival benefits and a 15% improvement in overall survival [31]. Denosumab is a human monoclonal antibody that inhibits the activity of RANKL and osteoclasts; is injected subcutaneously in metastatic bone disease every 4 weeks and shows similar side effects to bisphosphonates such as osteonecrosis of the jaw, nausea, diarrhea and weakness [32]. Canabozantinib is a multikinase inhibitor targeting VEGFR2, MET, KIT, and mutationally activated RET. This therapy showed improvements in disease-free survival in patients with advanced PCa [33].

4. Paget Disease of the Bone

Paget disease of the bone (PDB) is a metabolic bone disorder characterized by an unbalanced turnover of bone tissue affecting one or more bones. Bone pain is the most common symptom and typically worsens at rest or during the night. In a series of cases, deafness was evaluated in 7.9% of the patients [34]. Entrapment of the cranial nerves in their foramina, a characteristic facial deformity known as “leontiasis ossea” and the involvement of the jawbones can also be observed. The bALP levels are increased in these patients, reflecting disease activity and being useful for follow-up, while the serum calcium titer is usually normal. The differential diagnosis includes bone metastases, osteopetrosis and McCune Albright syndrome. First line therapy of PDB is mainly supportive and involves the use of bisphosphonates, in order to inhibit osteoclast activity.

Focal bone changes are characterized by hypertrophic and giant osteoclast clusters containing up to 100 nuclei, while normal osteoclasts show up to 20 nuclei [35]. Ob hyperactivity is considered to be secondary to osteoclasts overactivation. A possible link between these two bone cell subtypes could be identified in sphingosine-1-phosphate (S1P), a sphingolipid involved in the production of RANKL in the Ob and in Ob differentiation [36]. Nagata et al. [37] showed higher S1P expression in osteoclasts of patients with PDB compared with normal donors. This sphingolipid defines an overexpression of the S1P receptor-3 on the surface of Ob in patients with PDB, which was higher than in healthy controls. Ob do not change morphologically, but their accelerated activity induces the formation of a disordered and woven lamellar bone resulting in weak tissue with a higher risk of stress fracture. A role played by the measles virus (MV) in PDB etiopathogenesis has been speculated since the 1970s, in fact sequences of MV messenger RNA (mRNA) have been observed in up to 90% of osteoclasts and other mononuclear cells in Pagetic bone samples. Pagetic osteoclasts expressing the MVNP (measle virus nucleocapsid protein) gene enhance the synthesis of soluble factors that induce osteoclast differentiation as well as the proliferation of Ob precursors and the constitutive expression of RANKL, which is a cornerstone in osteoclasts proliferation [38]. Bisphosphonates such as zoledronic acid or pamidronate represent the mainstay of the treatment, which is necessary in case of clinical manifestations such as pain, increased bALP serum levels or hypercalcemia, while asymptomatic patients do not require any treatment [39].

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