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Review

Osteoclast–osteoblast communication

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ABSTRACT

Cells in osteoclast and osteoblast lineages communicate with each other through cell–cell contact, diffusible paracrine factors and cell–bone matrix interaction. Osteoclast–osteoblast communication occurs in a basic multicellular unit (BMU) at the initiation, transition and termination phases of bone remodeling. At the initiation phase, hematopoietic precursors are recruited to the BMU. These precursors express cell surface receptors including c-Fms, RANK and costimulatory molecules, such as osteoclast-associated receptor (OSCAR), and differentiate into osteoclasts following cell–cell contact with osteoblasts, which express ligands. Subsequently, the transition from bone resorption to formation is mediated by osteoclast-derived 'coupling factors', which direct the differentiation and activation of osteoblasts in resorbed lacunae to refill it with new bone. Bidirectional signaling generated by interaction between ephrinB2 on osteoclasts and EphB4 on osteoblast precursors facilitates the transition. Such interaction is likely to occur between osteoclasts and lining cells in the bone remodeling compartment (BRC). At the termination phase, bone remodeling is completed by osteoblastic bone formation and mineralization of bone matrix. Here, we describe molecular communication between osteoclasts and osteoblasts at distinct phases of bone remodeling.

The skeletal system functions and maintains itself based on communication between cells of diverse origins such as osteoclasts and osteoblasts [1,2]. Osteoclasts are derived from hematopoietic stem cells and share precursors with macrophages, whereas cells of the osteoblast lineage such as stromal cells, bone lining cells, osteoprogenitors, preosteoblasts, osteoblasts and osteocytes are derived from mesenchymal stem cells, which also differentiate into fibroblasts, chondrocytes, myoblasts and adipocytes. Osteoclast–osteoblast interactions occur at various stages of differentiation. Around 1997, several laboratories identified the essential osteoclastogenic ligand RANKL (also called TRANCE), a transmembrane glycoprotein belonging to the tumor necrosis factor (TNF)-α[1] superfamily and produced as a trimer by stromal cells. Osteoclast precursors, on the other hand, express RANK, the receptor for RANKL. Prior to identification of RANKL, generation of osteoclasts by co-culturing hematopoietic precursors with stromal cells such as calvarial osteoblasts demonstrated the existence of osteoclast differentiation factor (ODF) [3] or stromal osteoclast-forming activity (SOFA), both of which turned out to be RANKL (reviewed in [4]). Since identification of the gene encoding RANKL, a cocktail of soluble forms of RANKL and macrophage colony-stimulating factor (M-CSF, also known as CSF-1) has been used to generate osteoclast-like cells *in vitro* in the absence of osteoblasts, simplifying analysis of osteoclast differentiation. Besides RANK–RANKL interactions, several molecules mediate communication between osteoclast and osteoblast lineages, and their functions are not limited to triggering osteoclast differentiation. Most notably, osteoclast–osteoblast interaction contributes to coupling of bone resorption and formation. In this review, we discuss osteoclast–osteoblast interactions and describe molecules expressed in distinct phases of bone remodeling.

Osteoclast–osteoblast communication

There are at least three modes of osteoclast–osteoblast communication. Osteoclasts and osteoblasts can make direct contact, allowing membrane-bound ligands and receptors to interact and

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[1] *Abbreviations used:* BMU, basic multicellular unit; OSCAR, osteoclast-associated receptor; BRC, bone remodeling compartment; TNF, tumor necrosis factor; ODF, osteoclast differentiation factor; SOFA, stromal osteoclast-forming activity; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; MCP, monocyte chemoattractant protein; IL, interleukin; PTH, parathyroid hormone; SDF, stromal cell-derived factor; NFAT, nuclear factor of activated T cells; NO, nitric oxide; PTHrP, parathyroid hormone-related peptide; PKA, protein kinase A; OPG, osteoprotegerin; LPS, lipopolysaccharide; Ig, immunoglobulin; PIR, paired immunoglobulin-like receptor; ICAM, intercellular adhesion molecule; RGD, arginine-glycine-aspartic acid; TGF, transforming growth factor; BMP, bone morphogenetic protein; IGF, insulin-like growth factor; ARO, autosomal recessive osteopetrosis; TRAP, tartrate-resistant acid phosphatase; TRIP, TGF-β receptor-interacting protein; S1P, sphingosine 1-phosphate; mim, myb induced myeloid protein; PDGF, platelet-derived growth factor; HGF, hepatocyte growth factor; LRP, low-density lipoprotein receptor-related protein; OCIL, osteoclast inhibitory lectin; SLF, steel factor; GPI, glycosyl-phosphatidyl inositol; ROK, Rho-kinase; TCF, T-cell factor; LEF, lymphocyte enhancer factor; EBF, early B-cell factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

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initiate intracellular signaling. They can also form gap junctions allowing passage of small water-soluble molecules between the two cell types. Communication can also occur through diffusible paracrine factors, such as growth factors, cytokines, chemokines and other small molecules secreted by either cell type and acting on the other via diffusion. Finally, during bone resorption, osteoclasts may liberate growth factors and other molecules deposited by osteoblasts in bone matrix [5].

Cell culture experiments can distinguish between communication dependent on cell–cell contact and on diffusible factors. For example, osteoblasts fixed with paraformaldehyde can stimulate differentiation of hematopoietic precursors cocultured on these cells, demonstrating direct cell–cell contact [6]. By contrast, a role for a paracrine factor can be demonstrated if that factor crosses a synthetic membrane with a relatively small pore size separating cells in a Transwell plate. These kinds of experiments have demonstrated that hematopoietic precursors differentiate into osteoclasts following direct contact with osteoblasts.

In *in vitro* co-culture systems, osteoclasts differentiate underneath the sheet of osteoblasts and on top of the plastic dishes. In addition, mature multinucleated osteoclasts transmigrate through layers of cells, and transmigration activity is sensitive to inhibitors of c-src and matrix metalloproteinases (MMPs) [7]. Osteoclasts recognize the bone surface, especially collagens and minerals, and form the sealing zone and actin ring, while on a plastic surface osteoclasts do not form proper actin rings [8]. Some researchers use dentine or bovine bone slices with *in vitro*-generated resorption lacunae to analyze the potential regulatory effect of resorption lacunae on osteoblastic bone formation. Collectively, accumulating evidence indicates that all three modes of communication—direct, paracrine, and cell–bone matrix—regulate bone remodeling.

Three phases of bone remodeling

In bone remodeling, bone resorption by osteoclasts is followed by osteoblastic bone formation, so that resorbed lacunae are filled to the original level by osteoblasts. Bone remodeling has been described as a "bone remodeling cycle" consisting of activation, resorption, reversal, and formation phases [9]. However, in terms of osteoclast–osteoblast communication, it may be more convenient to view bone remodeling as occurring in three phases: initiation, transition, and termination of remodeling (Fig. 1). The directions of major communication are opposite between initiation and transition phases: from osteoblasts to osteoclast precursors in initiation, and from osteoclasts to osteoblast precursors (or bidirectionally) in transition. The initiation phase includes recruitment of osteoclast precursors, differentiation and activation of osteoclasts, and maintenance of bone resorption. Osteoclastic bone resorption lasts about three weeks in human bone. The transition phase is a period when osteoclastic bone resorption is inhibited, osteoclasts undergo apoptosis, and osteoblasts are recruited and differentiate. The resorbed surface is prepared for bone formation that follows ("reversal" of bone resorption into formation [10–13]) in the transition phase. The termination phase includes new bone (osteoid) formation, mineralization and entry into quiescence. The termination phase is much longer than the initiation phase since osteoblastic bone formation, which lasts about three months in humans, is a much slower process than osteoclastic bone resorption. During the termination phase, osteoclastic differentiation is apparently inhibited.

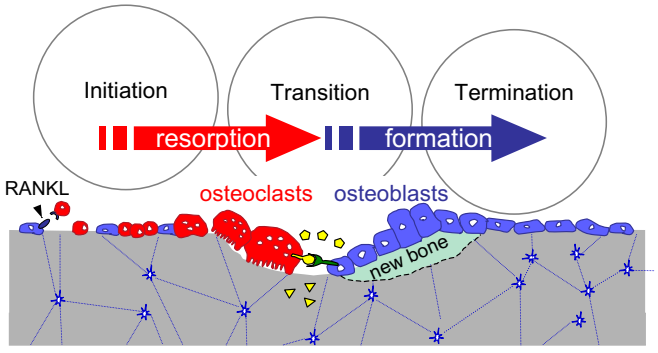

Fig. 1. Three-phase model of bone remodeling. Cells in osteoclast (red) and osteoblast (blue) lineages are shown. Osteocytes (star-shaped) and canaliculi (blue lines) are also shown in bone (gray). Initiation starts with recruitment of hematopoietic precursors. Osteoclast differentiation is induced by osteoblast lineage cells expressing osteoclastogenic ligands such as RANKL. Osteoclasts become multinucleated and resorb bone. Transition is marked by switching from bone resorption to formation via coupling factors, possibly including diffusible factors (yellow pentagons), membrane bound molecules (yellow lollipops), and factors embedded in bone matrix (yellow triangles). The termination phase ensures that the resorbed lacuna is refilled due to the bone-forming activity of osteoblasts, and osteoblasts flatten to form a layer of lining cells over new bone.

Initiation phase

Osteoclast–osteoblast communication occurs in the BMU, a site for bone remodeling generated asynchronously at various places in the skeleton. Initiation of osteoclastogenesis largely depends on interaction between osteoclast precursors and cells in the osteoblast lineage. Bone lining cells, which express RANKL and stimulate RANK on osteoclast precursors, are flat and not bone-forming, while osteoblasts are round or cuboidal, and actively form osteoid. Osteoblasts produce M-CSF, which is required for survival of cells in the macrophage–osteoclast lineage [14,15]. M-CSF also controls cell migration and cytoskeletal reorganization in macrophages and osteoclasts, both of which express c-Fms, the tyrosine kinase receptor for M-CSF [16].

Recruitment by chemokines

How do osteoclast precursors find a specific bone surface to differentiate on? And to what extent do cells in the osteoblast lineage determine positioning of circulating osteoclast precursors onto bone surface? Bone remodeling takes place in response to different stimuli, including generation of bone microcracks, loss of mechanical loading, low blood calcium, alterations in hormones and cytokines. It is possible that recruitment of osteoclast precursors *per se* is rate limiting.

Chemokines are chemotactic cytokines stimulating recruitment of monocytes and other leukocytes, and they are likely to be secreted by stromal cells or bone lining cells to recruit osteoclast precursors. Monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) is produced by osteoblasts and is a candidate recruiter of osteoclast precursors [17,18]. While inflammatory cytokines such as TNF-α and Interleukin (IL)-1β induce MCP-1 expression in osteoblasts, MCP-1 is expressed in osteoblasts even in the absence of inflammation, such as during tooth eruption [17] and in response to parathyroid hormone (PTH) [18]. In osteoclast precursors, expression of MCP-1 receptors is induced by RANKL [19], suggesting that osteoblasts can enhance MCP-1-dependent recruitment through RANKL. Besides MCP-1, stromal cell-derived factor (SDF-1, also known as CXCL12) is thought to recruit osteoclast precursors [18]. SDF-1 is a chemokine produced by bone vascular endothelial and marrow stromal cells, which binds to osteoclast precursors expressing the chemokine receptor CXCR4 and induces MMP-9 expression [20,21]. Interestingly, proteolytic activity of mature CXCR4-positive osteoclasts promotes mobilization of hematopoietic progenitors by degrading SDF-1 and osteopontin in endosteum regions in response to stress [22].