

BONE BIOLOGY, OSTEOIMMUNOLOGY AND RHEUMATIC DISEASES

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Abstract. *Osteoimmunology (OI) is a relatively new field in medicine, improving our understanding of the pathogenesis of the rheumatic diseases. OI focuses on the relationship and interaction between the immune and the musculoskeletal systems, observing these processes in three main aspects: regulating the bone resorption by the immune system, the impact of inflammation on the bone formation, the role of bone and bone marrow as a depot for immune cells. Changes in the bone architecture may be due to the activation of the immune system. Proinflammatory cytokines leading in the pathogenesis of the inflammatory joint disease are potent activators of nuclear factor- κ B receptor activator (RANKL) expression and thus promote the osteoclast differentiation. This link explains why therapy whose target are the cytokines, especially TNF inhibition, is very effective in delaying structural damage in rheumatic diseases. Knowledge of these mechanisms would allow better use of medical therapies to reduce skeletal damage.*

Key words: osteoimmunology, immune system, musculoskeletal system, proinflammatory cytokines

BONE BIOLOGY

The main functions of the bones of the human skeleton are to ensure the strength and mobility of the body, to protect the internal organs and last but not least, the bone tissue performs an important metabolic function [16]. The bone consists of two main parts:

- Organic part – bone cells and organic matrix (collagen type I and non-collagenous proteins);
- Inorganic part – inorganic mineral salts deposited in the matrix.

The main component of the organic fraction of the bone (about 90%) is a matrix of collagen type I, and the rest are collagen type III and V and non-collagen proteins (proteoglycans, osteonectin, osteocalcin, etc.). Osteocalcin (OC) is a polypeptide, as its level in the serum can serve as a marker for bone construction [1, 2]. The main inorganic component of the bone that mineralizes the collagen is hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. There are 4 types of bone cells:

- Osteoblast (OB) – a mononuclear cell derived from a mesenchymal stem cell. Its main function is the synthesis of type I collagen and other matrix proteins, as well as metalloproteinases. It is responsible for the subsequent mineralization of the bone matrix, secreting sialoprotein, along with growth factors, osteocalcin and alkaline phosphatase. Several signaling pathways are involved in the differentiation of OB – Wnt signaling pathway, BMPs (bone morphogenic proteins), integrins, vitamin D and parathyroid hor-

mone (PTH) are also important. The activation of the Wnt pathway directs the mesenchymal stem cell to the development of osteoblast precursors [16]. Wnt and PTH inhibit while BMS can induce the apoptosis (programmed cell death) of the OB. After participating in the process of bone formation, 60-70% of the OB die by apoptosis as the rest of them become cover bone-lining cells or osteocytes.

- Osteocytes (OC) – the osteocytes are cells deep in the matrix, connected to each other by canaliculi. They are 90% of all bone cells and play the role of mechanical receptors. They send signals to the OB and the osteoclasts by the surface and thus participate in the process of bone remodeling. They die with the aging of the human body, which results in a loss of sensitivity to microdamages and, consequently, more difficult bone regeneration.

- Osteoclast (OCL) – large, multinucleated, monocyte-derived cells, extremely mobile. They secrete bone matrix resorbing enzymes, express nuclear factor- κ B (RANK) receptor activator. Glucocorticoids (GC) are a class of drugs that rapidly induce bone resorption by inhibiting osteoclast apoptosis.

- Bone-lining cells – Some OBs lose their bone-synthesizing capacity and become cover cells. They respond to mechanical and hormonal signals by producing metalloproteinases that resorb the bone. They can turn back into OB and locally build new bone, a process called modeling.

The bone remodeling is a process of resorption performed by the osteoclasts, followed by the construction of new bone by the osteoblasts. About 10%

of the skeleton is remodeled in 1 year. This cycle lasts about 180 days, of which 14-20 days are for the bone resorption and 160 days are for the bone formation, including the bone mineralization. The systemic regulation of this process is performed by the parathyroid hormone (PTH), calcitriol, sex and growth hormones and GC. The purpose of the remodeling is to adapt to mechanical impacts and repair the microfractures in the bone.

Many growth factors, produced by the bone or circulating towards it are critical to skeletal development and function: IGF1 and 2 (insulin-like growth factors), BMPs (bone morphogenetic proteins), TGF β (transforming growth factor β), FGFs (Fibroblast growth factors), VEGFs (vascular endothelial growth factors), PDGFs (Platelet derived growth factors), FGF-23 (Fibroblast growth factors). These factors can act in a paracrine and an autocrine way [3].

OSTEOIMMUNOLOGY

Osteoimmunology (OI) is a relatively new field in medicine that studies the interaction between the immune system and the bone skeleton, contributing significantly to the understanding of the joint destructive process in the rheumatoid arthritis and other arthropathies. OI also provides answers to the questions related to the reduction of the structural damage to the joints when conducting specific anti-rheumatic therapy [14].

The concept of OI is based on observations revealing that the T-lymphocytes are the key participant in the bone loss as they activate the differentiation of the bone-resorbing osteoclast cells [14]. OI focuses on the relationship and interaction between the immune and musculoskeletal systems as changes in the bone architecture may be due to activation of the immune system [4]. It considers these processes in 3 main aspects:

- Regulation of bone resorption by the immune system;
- Influence of inflammation on the bone formation;
- The role of bone and bone marrow as a depot for immune cells

BONE RESORPTION MEDIATED BY PROINFLAMMATORY CYTOKINES

In rheumatic diseases, systemic and local bone loss expose the close interaction between the immune system and bone, leading to an increase in the osteoclast activity and a consequent increase in the bone resorption [13]. The most common

rheumatic diseases are the inflammatory and the degenerative joint diseases. Their clinical manifestation is determined by the presence of joint inflammation, which is the main trigger of the subsequent processes. The combination of chronic immune activation and damage to the musculoskeletal tissue is a hallmark of the rheumatic diseases [13]. Rheumatoid arthritis (RA) and the group of spondyloarthropathies (SpA) are the most common inflammatory rheumatic diseases, affecting various joints and leading to their destruction. RA is considered as a prototype of destructive inflammatory arthritis with bone loss. In SpA, inflammation of the axial skeleton and enthesitis are observed, which lead not only to bone destruction but also to extra-articular pathological bone formation [13].

At the heart of the pathogenesis of RA is the immune dysregulation with activation of proinflammatory cytokines (interleukins) – IL-1, 2, 6, 10 and TNF α . The granulation tissue (pannus) formed by this autoimmune inflammation „creeps“ from the synovium to the articular cartilage and subchondral bone, with the subsequent formation of erosions. In psoriatic arthritis (PsA) and ankylosing spondylitis (AC), diseases of the SpA group, cytokines that are leading in the pathogenesis are IL-17, 12, 23 and TNF α , and the pathomorphological features are ankylosis, periostitis and syndesmophytes. In osteoarthritis (a degenerative joint disease) the main morphological features are marginal osteophytes and subchondral osteosclerosis and in it also leads the bone formation. The main participants in the bone damage are the osteoclasts, which are responsible for the bone erosions in patients with inflammatory rheumatic diseases. Their formation is controlled by a regulatory triad – nuclear factor- κ B receptor activator (RANK), its ligand RANKL and osteoprotegerin receptor (OPG), also known as osteoclastogenesis inhibitory factor. OPG binds to RANKL, making RANK-RANKL interaction difficult. The activation of RANK on the osteoclast mononuclear precursors initiates a transcriptional cascade culminating in osteoclast differentiation and activation [13]. The important factors for the osteoclast differentiation are also key regulators of the immune response – such as NF- κ B and nuclear factor of activated T cells.

The expressed on the surface of the osteoclast precursor RANK interacts with RANKL and forms a RANK-RANKL complex, which sets off a cascade of processes involving activation of the Wnt signaling pathway, leading to stimulation of the maturation, differentiation and activation of the osteoclasts and inhibits their apoptosis. The regulation is carried out

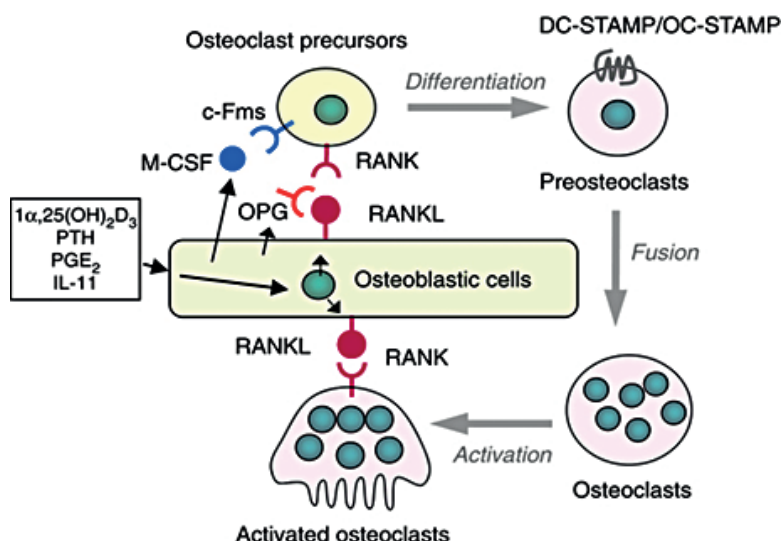


Fig. 1. RANK- RANKL signaling pathway for osteoclast activation

in two directions – activation and suppression of the process:

- Osteoprotegerin blocks this interaction and is a physiological regulator of the bone resorption.
- Pro-inflammatory cytokines, PTH, GC increase the expression of RANKL and thus activate bone resorption.
- Activated T cells produce RANKL, which activates OCL, which is not followed by activation of OB therefore bone construction did not follow – this is the so-called pathological remodeling.

Pro-inflammatory cytokines such as TNF and interleukin (IL) -1, IL-6 and IL-17 are potent activators of RANKL expression and thus also improve osteoclast differentiation. This association between proinflammatory cytokines and osteoclast formation most likely explains why cytokine-targeted therapy, especially TNF blockade, is very effective in delaying the structural damage in rheumatic diseases. On the other hand, TNF inhibits osteogenesis by enhancing the expression of Dickkopf-1 (DKK1) protein, which negatively regulates the Wnt signaling pathway. Wnt proteins are also involved in the regulation of osteoclastogenesis, as they increase OPG expression and block the formation of osteoclasts. Low levels of Wnt activity lead to low bone formation and high bone resorption, while high levels of Wnt activity increase bone formation and simultaneously block bone resorption. Wnt inhibitors, like DKK1, are expressed in the synovial tissue of RA patients, suggesting suppression of the bone formation [14].

RANKL expression is high in the synovial tissue of patients with peripheral joint disease RA, psoriatic arthritis and SpA. It has been shown through direct and indirect mechanisms in patients with arthritis

that T cells underlie the pathogenesis of bone loss [14]. Another group of cells in the arthritic joints are responsible for bone destruction and these are the synovial fibroblasts. They express RANKL under the action of interleukin-17 (IL-17), produced by T helper (Th) 17 cells [14]. That's why IL-17A activates the osteoclast precursors and increases the bone resorption.

Osteoclasts, as bone-specialized macrophages, are the only cells capable of degrading the bone matrix and thus participate in the process of modeling and remodeling of the bone. OCLs are present in the synovium in RA and PsA [8, 9]. OCL precursors commute in the arthritic joint and cytokines stimulate their differentiation. The RANKL-RANK

interaction is an induction for the OCL by NF- κ B and a family of transcription factors. In the synovium, T cells 1 and 17 and fibroblast-like synoviocytes are activated [5, 6]. This process has been repeatedly observed and described in RA with a negative effect on the juxta-articular bone mass (osteoporosis and erosions). Other potential inducers of RANKL are the proinflammatory cytokines: TNF α , IL-1, 6, 17, VEGF (vascular endothelial growth factor). This association between proinflammatory cytokines and osteoclast formation explains why cytokine-targeted therapy delays structural damage in RA. In addition to the local bone loss in RA, a higher incidence of systemic osteoporosis (OP) is known, where apart from the standard risk factors, also important are the hypodynamia, persistent low-grade inflammation, and glucocorticoid therapy [17]. Thus, the concept is clearly established that the inflammation is an independent risk factor for osteoporosis, respectively for increased fracture risk [8].

The predominant process of bone formation observed in ankylosing spondylitis (AC) is an interesting aspect of the rheumatic diseases. Recent observations support the fact that bone formation is suppressed by inflammation. Interestingly, TNF-alpha inhibits bone formation by enhancing the expression of Dickkopf-1 protein, which negatively regulates the Wnt pathway. Wnt-proteins stimulate the differentiation of OB, enhance the expression of OPG, which blocks the formation of OCL. PsA, AS, OA and metabolic arthropathies are characterized by juxta-articular and intervertebral bone spurs. These lesions are based on new bone formation. Anti-TNFs do not affect the formation of osteophytes/syndesmophytes

for the reasons described above. The target areas for osteophyte formation are the juxta-articular areas of the periosteum near the articular cartilage, the edges of the vertebral bodies and the places where the tendons attach to the bone. These places are rich of fibrocartilage, which is thought to be the tissue for osteophyte formation [9].

Osteo-immune interactions play an important role in other areas of the human body. The bone is a hematopoietic organ that provides a microenvironment for the maintenance and mobilization of hematopoietic stem cells (HSCs), as well as a site for an early B-cell differentiation and guiding the long-lived plasma cells that play a role in the sustentation of the autoimmune diseases [3] and the resistance to the immunosuppressive therapy. A new concept is that mesenchymal cells and HSCs form a unique niche in the bone marrow, which is regulated by the local environment, by signals from long distances, hormones [11]. OBs are required for the formation of HSCs, and OB-development is regulated by the OCLs [12]. These and other similar discoveries underlie the understanding that the bone is a dynamic, biologically active tissue.

CONCLUSION

Inflammation is the main mechanism involved in the bone loss in the inflammatory rheumatic diseases. Proinflammatory cytokines increase the osteoclast activation and the subsequent bone resorption. Therefore, treatment with cytokine blockers has been shown to improve bone remodeling.

Osteoimmunology significantly improves our understanding of the pathogenesis of rheumatic diseases, especially the rheumatoid arthritis. The interactions between the immune activity and the skeletal system at the molecular level largely explain why inflammatory diseases are also associated with bone loss. Knowledge of these mechanisms would allow better use of drug therapies to effectively reduce skeletal damage.

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