Osteokines in Rheumatoid Arthritis

Subjects: Rheumatology

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Osteokines are secreted by bone cells that possess effects locally in bones and systemically in other tissues and organs. They have endocrine, autocrine, and paracrine actions. In bones, osteocytes and osteoblasts are responsible for the secretion of osteokines through stimulation of several events, such as the mechanical stress from physical exercise. Osteokines exert healthy effects in increasing post-contraction glucose uptake in muscles through an insulin-dependent mechanism, influencing muscle contractility and mitochondrial biogenesis in the interior of muscle cells, reversing the decline in muscle function through the aging process, controlling phosphate homeostasis, influencing free fatty acids oxidation to produce energy, and mediating the transport of glucose transporters-4 (GLUT-4) from the cytoplasm to cell membranes. Among unhealthy effects, some osteokines can lead to the destruction and suppression of ectopic calcification of bones in addition to dysregulations in energy and phosphate homeostasis.

Keywords: Rheumatoid arthritis ; Osteoprotegerin ; Osteokines

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic and autoimmune disease that affects approximately 1% of the world's population. Being characterized mainly by persistent articular inflammation, this condition affects the synovial membranes of the joints, leading to joint destruction, loss of functions, and osteoarticular disabilities. In the disease's progression, bone and cartilage are destroyed, which brings deformities to the patients [1][2][3]. Although RA is prevalent worldwide, its incidence is higher among women when compared to men, with an incident ratio of about two or three women to one man, respectively.

The physiopathology of RA is still not fully understood. However, many cells have been implicated in its development. In RA, the joint damage is driven principally due to the activity of proliferative synovial tissue fibroblasts, which are accompanied by neutrophils, monocytes, and T and B lymphocytes trafficking into the articular synovium. These cells are mainly pro-inflammatory, secreting many pro-inflammatory cytokines into the articular cavities [1][2].

Besides inflammation, oxidative stress (OS) also plays an essential role in the pathogenesis and progress of RA impairments. The excessive production of free radicals causes the oxidation of many different molecules in the human body, including articular. These events seem to be positive and extensively associated with augmented inflammation and accelerated joint destruction [3][4]. Due to its complex systemic definition, RA can also be associated with extra-articular manifestations, such as cardiologic, hepatic, pulmonary, digestive, ocular, dermatological, and neurological [5].

2. Osteoprotegerin

Osteoprotegerin (OPG) is a soluble glycoprotein, a tumor necrosis factor receptor superfamily member. OPG is secreted by several cell types, such as osteoblasts, peripheral blood lymphocytes, endothelial cells, and vascular smooth muscle cells, and presents an important role in metabolism, being inversely proportional to adiposity and obesity. Inhibition of bone resorption is its most evident effect [6][7][8][9].

Osteoblasts secrete RANKL, directly proportional to the inflammatory marker CRP and promoted by inflammatory cytokines. RANKL binds to its receptor, nuclear factor κB receptor activator (RANK) on osteoclasts and monocytic osteoclast precursor cells, resulting in a stimulation of osteoclastic bone loss. The RANK link with RANKL is the main factor of bone destruction in inflammatory arthritis [7][10][11][12][13].

OPG has a protective effect on bone destruction and negatively regulates osteoclastogenesis by preventing RANK-RANKL binding by associating with RANKL, inhibiting osteoclast differentiation and activation, and increasing osteoclast apoptosis. As RANKL and OPG are the ultimate effectors of osteoclastogenesis, the ratio of RANKL to OPG in the bone marrow microenvironment is a key determinant of the rate of osteoclastic bone resorption. The balance between RANKL

and OPG determines the degree of proliferation and osteoclast activity and reflects local bone loss around joints caused by inflammation. A low OPG/RANKL ratio is present in patients with RA compared to healthy patients and is associated with increased radiographic damage and joint and bone destruction in RA. In this sense, the RANKL/OPG relationship plays an essential role in regulating bone homeostasis in RA, and changes in this relationship may be a protective mechanism against accelerated bone loss in RA [6][7][8][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25].

Several previous studies have investigated the relationship between OPG level and RA, with conflicting results. Some showed that RA patients had a higher OPG level than healthy controls, suggesting that elevated OPG levels may be a factor associated with RA. However, other studies have reported a decrease in OPG levels in RA patients, and some have demonstrated no difference in OPG indices compared to healthy RA patients and controls. Low levels of OPG in synovial fluid showed faster disease progression towards joint and bone destruction. Age, stage of the disease, and several other factors influence the levels of OPG, justifying such discrepant results between studies. Furthermore, autoantibodies to osteoprotegerin are associated with increased bone resorption in RA, with OPG antibody-positive patients having longer disease duration and activity and higher levels of bone resorption markers [22][23][26][27][28].

Significantly, OPG concentrations have been associated with the presence and the severity of coronary artery disease and predict future cardiovascular events, presenting an atherosclerotic role along with the inflammation characteristic of RA. Therefore, OPG highlights the potential implication of this molecule in the increased risk of CVD observed in patients with inflammatory arthritis. High amounts of OPG can be found in the arterial wall. Such a finding may suggest that endothelial cells may be significant contributors to the circulating pool of OPG in patients with RA [22][25][26].

Furthermore, it is interesting to highlight the crosstalk between several pro-inflammatory cytokines and OPG. Some of them regulate the expression of RANKL and OPG, including TNF-α and interleukins IL-1 and IL-6, which can decrease serum levels of OPG. All these factors are present in patients with RA, leading to a high prevalence of osteoporosis. On the other hand, other studies claim that TNF-α could increase the level of OPG or reduce it and induce osteoclast differentiation, increasing RANK/RANKL expression and resulting in osteoporosis [22][26][29][30].

3. Osteocalcin

Osteocalcin (OCN) is a bone-derived hormone that is synthesized and secreted by osteoblasts and then activated by osteoclasts during bone resorption. It is a key factor responsible for the mineralization of the extracellular matrix, and its serum levels increase dramatically during this process, being used clinically as a marker of osteoblastic bone formation [31][32][33][34][35].

Serum OCN can enter distant cells to regulate IR, glucose homeostasis, and brain function. Its uncarboxylated and subcarboxylated forms (ucOCN) increase insulin sensitivity and secretion by directly stimulating the pancreas. It promotes the uptake of glucose and free fatty acids (FFA) by skeletal muscle and stimulates catabolism in skeletal muscle, increasing after physical activity and decreasing with aging. OCN levels are inversely associated with BMI, IR, C-reactive protein (CRP), and body fat mass. Its absence makes the brain smaller and less developed, particularly the hippocampus, and generates anxiety and compromises memory. At the same time, its presence would be effective against age-related cognitive decline and valuable in the acute stress response by inhibiting the parasympathetic system. Thus, serum OCN can enter distant cells to regulate IR, glucose homeostasis, and brain function, with anti-inflammatory and beneficial activity. On the other hand, some studies also claim that OCN can recruit osteoclasts and potentiate their chemotaxis and inhibit osteoblast activity, contributing to osteoclastogenesis and leading to osteoporosis [31][33][34][35][36][37].

During high disease activity in RA, specifically in acute RA, there is a decrease in bone formation markers, including osteocalcin. Its levels tend to be lower compared to healthy volunteers. Therefore, lower levels of this osteokine in acute phase RA patients can associate highly with bone destruction and articular changes [12][24].

4. Osteopontin

Osteopontin (OPN) participates as a member of the small integrin-binding ligand (SIBLING) family of cellular matrix proteins. It was first identified in the bone matrix but was later discovered in almost all tissues. This organokine is an extracellular matrix glycoprotein present in the extracellular fluid surrounding the sites of mineralized tissue and bone remodeling. It is a substance strongly expressed in bone and released into body fluids, mainly secreted by osteoblasts. It is an important component of some events, playing an essential role in inflammation and bone metabolism. It acts as a pro-inflammatory mediator stimulating proliferation, migration, and adhesion of several cells and being an autocrine and paracrine factor. Its phosphorylated form is known to increase the number of macrophages and osteoclasts. In bone

metabolism, its role is to promote the adhesion of osteoclasts to the mineralized matrix, regulating bone resorption and formation, being a substantial factor for cell adhesion and migration, and acting in the neuroendocrine regulation of bone mass. The absence of OPN can block OCN expression and the induction of mineralization. With aging, the expression of OPN in the bone marrow stroma is reduced. OPN is closely related to the development of many bone-related diseases, including RA [12][26][29][32][33][38].

Serum and synovial fluid OPN was significantly higher in RA patients compared to healthy patients and is correlated with markers of bone resorption in RA patients, and their high levels are directly proportional to serum levels of CRP, chemo-monocyte attractant 1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β) on monocytes, interleukin-17 (IL-17), and other inflammatory cytokines including TNF-α and IL-1, IL-6, and IL -8. By binding to T cells, in addition to promoting the differentiation of Th1-type cells and increasing cellular immunity, OPN can, at the same time, inhibit Th2-type cells and humoral immune function. The imbalance of Th1/Th2 cells and the levels of secreted cytokines trigger events that lead to chronic inflammation and cartilage and bone destruction. Thus, OPN plays a crucial role in the pathogenesis and progression of RA by affecting the balance of Th1/Th2 cells and also inducing the differentiation of Th17 lymphocytes, affecting IL-17 levels and generating an inflammatory response, with its effects being more pronounced in their phosphorylated form [12][18][26][29][32][33][38][39].

OPN promotes osteoclast-mediated bone resorption by binding to its receptor, αvβ3 integrin, during arthritis. The binding of OPN to these cell surface receptors stimulates cell adhesion, cell migration, and other specific cell signaling functions, where OPN binds to fibronectin to activate FLS with B cells, stimulating the latter to produce inflammatory cytokines. It was also previously reported that it modulates tissue fibrosis by promoting TGF-β activation and fibronectin expression. Therefore, OPN acts as an important mediator in the maintenance of RA, as it activates synovial macrophages and fibroblasts, which stimulate cartilage and bone matrix degradation by secreting matrix MPPs and pro-inflammatory cytokines such as IL-6 and TNF-α in addition to stimulating fibrosis [29][32][33][38][39][40].

5. Sclerostin

Sclerostin, the product of the SOST gene, is a secreted glycoprotein expressed primarily in osteocytes and chondrocytes and acts as a negative regulator of bone homeostasis by inhibiting bone formation by osteoblasts and stimulating osteoclast formation. It is an organokine that affects the activity of bone morphogenetic proteins (BMPs) and is an inhibitor of the Wnt/β-catenin metabolic pathway in bone cells. Although sclerostin is as an osteocyte-specific protein, recent studies have shown that several additional cell types express SOST and can produce the sclerostin protein, such as osteoclasts, chondrocytes, and in tissues such as the kidney, heart, and liver [29][41][42][43].

Sclerostin is a key protein that inhibits osteoblast activity and represents a crucial link between osteoblasts and the mechanosensory capacity of osteocytes, as the absence of charge leads to increased sclerostin expression and bone loss. Osteocytes produce sclerostin by modulating the TGF-β-dependent pathway in response to mechanical loads. Mechanical loads directly stimulate osteoblasts and mainly decrease the synthesis of cytoplasmic signaling molecules in osteocytes that are needed for the upregulation of SOST gene expression. Consequently, sclerostin production is reduced, which indirectly stimulates osteogenesis, with the loss of sclerostin generating a high bone mass phenotype [21][44].

TNF-α induces sclerostin expression in osteocytes and FLS in RA, which increases osteoclast formation. Furthermore, sclerostin blocked TNF-α-induced inflammatory activity, suggesting a protective role of sclerostin in chronic inflammation. Sclerostin plays an important role in osteocyte–osteoblast signaling. When incorporated into the bone matrix, osteoblasts transform into osteocytes and increase sclerostin expression. Cytoplasmic extensions then transfer it to osteoblasts located on the surface of bone trabeculae. Furthermore, as sclerostin increases RANKL mRNA expression and reduces OPG, activation of NF-κB occurs, which further activates genes necessary for osteoclast differentiation. In healthy bone, osteocytes balance osteolysis and osteogenesis by controlling sclerostin secretion. Thus, as previously described, intracellular signal transduction regulates the development, proliferation, differentiation, migration, and apoptosis of osteoblasts. SOST inhibits the Wnt signaling pathway. This pathway is an essential stimulus for osteoblastogenesis, matrix mineralization, and OPG levels and inhibits apoptosis and osteoclastogenesis, which are essential in cartilage and bone homeostasis. Inhibiting the Wnt pathway by SOST involves activating caspases and pro-inflammatory cytokines produced by the synovial membrane, increasing bone resorption, and stimulating soluble antagonists of the canonical Wnt/βcatenin signaling pathway with subsequent inhibition of proliferation, maturation, and differentiation of osteoblast progenitors. Sclerostin can also antagonize BMP signaling directly by inhibiting BMP-7 secretion, leading to intracellular retention and proteasomal degradation of BMP-7, and blocking BMP signaling selectively in osteocytes that simultaneously synthesize sclerostin and BMP-7 proteins [29][32][41][42][43].

Some researchers have found elevated serum levels of sclerostin in patients with RA, and these levels are even higher in those patients with RA and osteoporosis. Increased serum levels of SOST indicate poor prognosis and resistance to treatment in these patients. Therefore, RA is characterized by reduced Wnt signaling. Given the importance of Wnt signaling in maintaining cartilage homeostasis, understanding the role of sclerostin is of great interest. Bone loss, erosion, and systemic osteoporosis with an increased risk of fractures are seen mainly in RA. Therefore, sclerostin inhibition is a powerful tool for improving bone repair in inflammatory arthritis [29][32][41][42][43].

6. Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMPs) belong to the TGF-β superfamily and have a wide range of effects on different cell types. Such proteins are potent regulators of cell proliferation, differentiation, and apoptosis. BMP signaling plays a vital role in osteoblastic and joint differentiation and induces bone formation by some components [17][34][36][41][45].

A chondroprotective role for different BMPs has long been proposed based on different in vitro experiments. Recently, greater attention has been given to BMP-7, also named osteogenic protein-1 (OP1), as a chondroprotective factor, which can be used as a medication for fractures. Its levels decrease with aging and are TNF-α-induced in addition to being increased in RA patients compared to healthy controls. BMP-2 indirectly decreases bone resorption by inhibiting the expression of IL-34, an inflammatory and osteoclastogenesis-stimulating cytokine, in synovial fibroblasts, thus contributing to antagonizing inflammation and bone erosions in RA. Osteoblasts highly expressed BMP-3 at sites of bone erosion, and its expression is induced by TNF-α, inhibiting osteoblast formation and function. BMP-4 and BMP-5 expression is significantly decreased in synovial tissue of RA patients compared to healthy controls and may be partially responsible for reduced bone formation at sites of bone erosion [40][45][46][47][48].

7. Osteonectin (Acidic and Cysteine-Rich Secreted Protein, SPARC)

Osteonectin, or acidic and cysteine-rich secreted protein (SPARC), is a multifaceted matricellular protein involved in normal and pathological tissue remodeling. SPARC is a multifunctional regulator of soft tissue cells and has diverse biological effects, including controlling the spread, proliferation, migration, and synthesis of soft tissue cell-matrix proteins and binding to collagens and directly regulating their assembly. SPARC is highly expressed in normal tissues in bones, teeth, eyes, and at sites of wound repair and tissue remodeling [18][27][49][50][51].

SPARC is critical in supporting bone remodeling and maintaining bone mass. Furthermore, it can facilitate extracellular matrix degradation by stimulating the synthesis of MMPs in the superficial zone of arthritic cartilage. At the same time, in the middle and deep zones, SPARC can regulate chondrocyte proliferation, promote matrix synthesis, and improve mineralization due to its ability to bind collagen and hydroxyapatite, exerting an anti-inflammatory response, inhibiting the NF-kβ pathway, and having increased levels after exercise. Therefore, since it is produced in both zones, SPARC has dual roles in the resorption and regeneration of arthritic cartilage. The abnormal synthesis and degradation of SPARC can be attributed to cartilage and bone destruction, and when expressed by endothelial cells in the synovium during vascular remodeling, it releases a series of bioactive peptides that could regulate angiogenesis and result in synovial hyperplasia. SPARC decrease is related to increased inflammation and secretion of cytokines such as TNF-α due to intense activation of the NF-kβ pathway [27][49][50][51].

In RA, SPARC was increased in joint synovial cells, and the mean levels of SPARC in synovial fluid from RA patients were significantly elevated, being down-regulated by inflammatory cytokines. SPARC has been shown to exist in numerous chondrocytes in the superficial and middle zones of the cartilages of RA patients, whereas it is not found in these zones of normal cartilages [36][52][53].

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