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INVITED REVIEW

Clinical immunity in bone and joints

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Abstract
The immune system and bone metabolism influence each other. An imbalance in the immune system, resulting in inflammatory stimuli may induce an imbalance in bone turnover via induction of osteoclast differentiation and inhibition of osteoblast differentiation, leading to various pathological conditions including osteoporosis. T-cell subsets, helper T (Th)1 and Th17, which activate the immune system, induce osteoclasts, whereas regulatory T (Treg) cells, responsible for immunosuppression, inhibit osteoclastic differentiation. In addition, inflammatory cytokines, such as the tumor necrosis factor (TNF), also cause an imbalance in bone turnover, induction of osteoclasts and inhibition of osteoblasts. Treatments targeting the immune system may regulate abnormalities in bone metabolism, while also controlling immune abnormalities. In rheumatoid arthritis (RA), a representative autoimmune disease, immune abnormality and accompanying prolongation of synovial inflammation cause bone and cartilage destruction, periarticular osteoporosis, and systemic osteoporosis. Joint damage and osteoporosis in RA occur through totally different mechanisms. Stimulation by inflammatory cytokines induces the expression of the receptor activator for nuclear factor-κB ligand (RANKL) in T cells and synovial cells, thereby inducing bone destruction due to osteoblast-independent osteoclast maturation. However, biological products targeting TNF or interleukin-6 not only control disease activity, but also inhibit joint destruction. However, these biological products are not effective for osteoporosis. Conversely, anti-RANKL antibody inhibits osteoporosis and bone destruction, but exerts no influence on RA disease activity. Such differences in therapeutic efficacy may indicate the necessity for rethinking current theories on the mechanism of bone metabolism abnormality and joint destruction. Understanding the mechanisms underlying these pathologies via commonalities existing between the immune system and the metabolic system may lead to the development of new treatments.

Keywords Bone · Joint · Immunity · Rheumatoid arthritis · Osteoporosis

Introduction

The immune system is a biological defense mechanism against foreign antigens established during several million years of evolution, starting from microorganisms. Natural immunity is a primitive mechanism originating in microorganisms. This mechanism allows the macrophages, neutrophils, and NK cells, among others, to recognize bacteria and viruses that invade the host, and eliminate them via processes such as phagocytosis, enzymatic treatment, and production of active oxygen among others. On the other hand, vertebrates evolved the immune system, and acquired immunity mechanisms which can process a variety of antigen information and memorize such information in preparation for a second invasion in addition to self-tolerance. Thymus-derived naive T cells differentiate into memory T-cells that retain the memory of antigen information and homing information from dendritic cells in regional lymph nodes. Memory T-cells circulate into peripheral tissues, and quickly take charge of the immune response, using memorized antigen information. In contrast, T cells show immune tolerance to autoantigens. However, if such self-tolerance is broken by some factor, autologous reactive T cells will be activated to stimulate B cells to induce the production of autoantigens, causing autoimmunity.

The immune system is involved in the maintenance of normality, prevention of various pathological conditions via initiation of biological defense and formation and resolution of inflammation. The immune system and the metabolic system are both important biological regulatory mechanisms,

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and an abnormality in the immune system may influence the metabolic system. In autoimmune inflammatory conditions, caused by immune abnormalities such as rheumatoid arthritis (RA), bone metabolism abnormalities may be induced via immunocompetent cells and cytokines, resulting in consequent bone and joint destruction [1–5]. However, current understanding of the pathology of RA and advances in treatment indicate that bone and cartilage destruction and osteoporosis are caused by totally different mechanisms, requiring different therapeutic strategies. This paper presents an outline of the influence of the immune system on bone metabolism as well as the related therapeutic processes, while focusing on the pathology of RA.

Mechanism of bone metabolism

The skeleton is the structure that supports the body. It is also the organ in which bone and mineral metabolism take place. Bone and hard tissues impart structural rigidity and form to vertebrates, and enable bone and mineral metabolism which is vital for life. Bone tissue is composed of the bone matrix consisting of type I collagen with hydroxyapatite crystal deposits and cell groups such as osteoblasts and osteocytes. Osteoblasts, which differentiate from mesenchymal stem cells to produce the bone matrix, differentiate further into osteocytes which play a key role in maintaining bone structure. Osteoclasts are derived from hematopoietic stem cells. Precursor monocytes, which migrate into bone through blood flow, mature to become polynuclear osteoclasts, in response to stimulation by the receptor activator for nuclear factor-κB ligand (RANKL) expressed in osteoblasts and osteocytes, and when activated, induce bone resorption (Fig. 1).

Homeostasis of bone tissue is maintained bone remodeling cycle (bone turnover) of bone resorption by osteoclasts and bone formation by osteoblasts, via regulatory mechanisms that include the endocrine system [6–12] (Fig. 2). Various factors produced by osteocytes such as TGF-β and BMP also induce the differentiation of mesenchymal stem cells into osteoblasts and osteocytes, bone modeling. In addition, sclerostin and Dickkopf (DKK)-1 produced by osteocytes inhibit Wnt-mediated signals expressed in osteoblast precursors to control the differentiation and activation of osteoblasts. Osteocytes, which account for about 95% of all cell components in bone, possess many dendrites which support the three-dimensional structure of bone, thus playing a central role in both modeling and remodeling of bone. Abnormalities in modeling and remodeling may lead to abnormal bone metabolism, resulting in conditions such as osteoporosis.

Influence of rheumatoid arthritis on bone metabolism

Rheumatoid arthritis is a systemic autoimmune disease with synovitis in multiple joints as its principal pathological

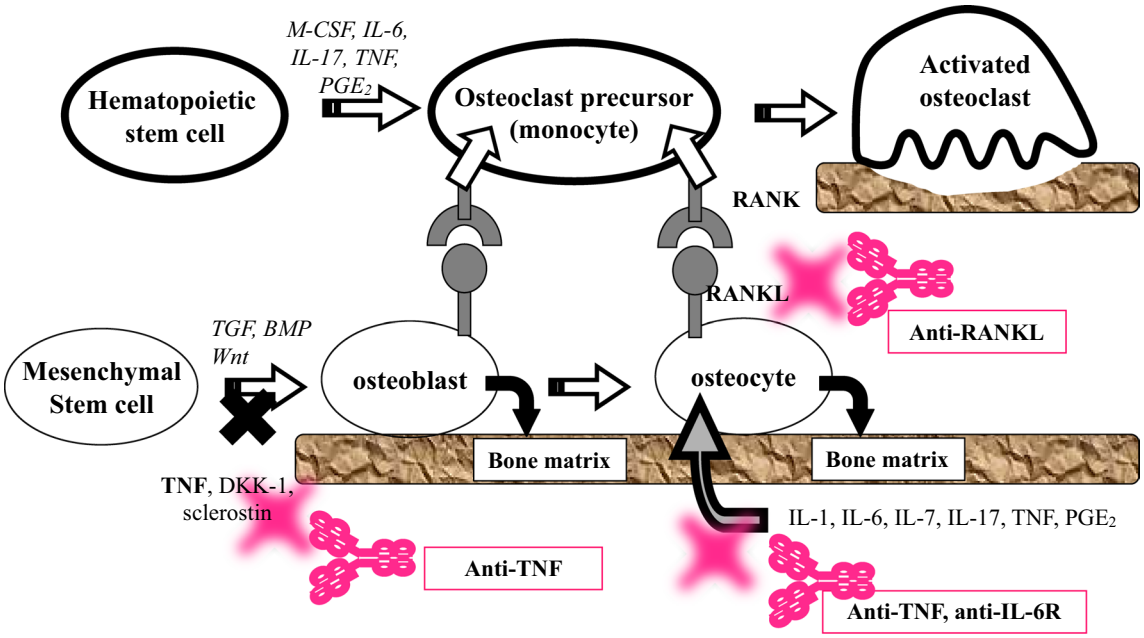

Fig. 1 Differentiation of osteocyte and osteoclast and its regulation. Osteoblasts and osteocytes differentiate from mesenchymal stem cells to produce the bone matrix and osteoclasts derived from hematopoietic stem cells are involved in bone resorption. Biological DMARDs targeting TNF and IL-6 inhibit bone destruction, but they do not exert any influence on systemic osteoporosis. The anti-RANKL antibody, denosumab, also inhibits the process of osteoclast maturation by RANKL expressed in synovial cells and T cells

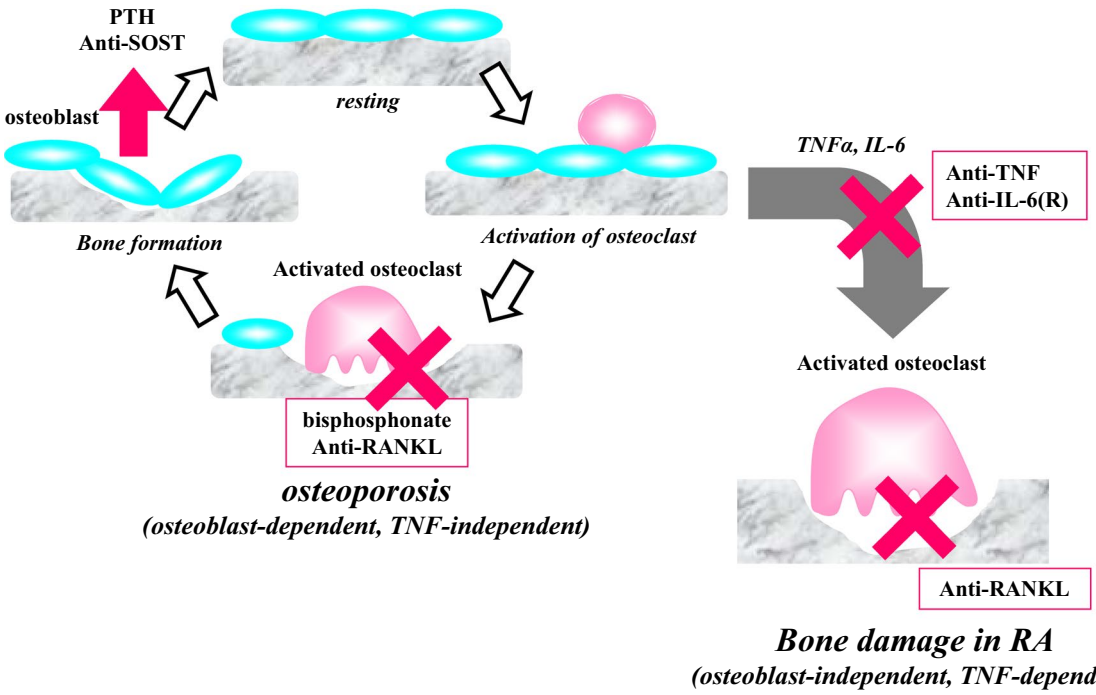

Fig. 2 Mechanisms and treatment strategies of osteoporosis and joint damage in RA. Homeostasis of bone is maintained bone remodeling cycle of bone resorption by osteoclasts and bone formation by osteoblasts via regulatory mechanisms. However, bone destruction associated with RA represents the maturation of osteoclasts enhanced in an osteoblast-independent manner, demonstrating deviation from bone turnover due to stimulation by TNF and IL-6

feature. This disease occurs frequently in women in their 30s and 50s, where the total number of patients is estimated to be about 7–800,000 in Japan. Clinical symptoms of RA such as pain, swelling, and stiffness of multiple joints and joint deformity markedly impair the daily-life activities of patients. Joint destruction begins to progress from early stages of RA-onset, and resulting joint deformities may cause irreversible physical impairment. Therefore, proper and prompt diagnosis and treatment are necessary. Immune abnormalities accompanied by prolongation of synovial inflammation in RA may cause pathological conditions due to organ damage, and induce bone and cartilage destruction due to synovitis, periarticular osteoporosis due to widespread synovitis, and systemic osteoporosis due to menopause, aging, immobility, and adrenocortical steroids.

Prolonged production of tumor necrosis factor (TNF) in inflammatory tissue due to RA synovitis induces DKK-1 and sclerostin in osteocytes, inhibits differentiation of osteoblasts and bone production, and induces apoptosis in osteocytes. Inflammatory cytokines such as TNF and interleukin (IL)-6 directly stimulate the migration, differentiation, and activation of osteoclasts. Furthermore, they induce the expression of RANKL in osteocytes, osteoblasts, synovial fibroblasts and T cells, thereby indirectly inducing maturation and activation of osteoclasts. Abnormality in T-cell subsets affects bone metabolism. Helper T (Th)1 and Th17 cells induce osteoclasts via the production of TNF and IL-17, and Th1 cells inhibit the expression of osteoprotegerin (OPG) via the production of interferon (IFN)-γ (Fig. 3). In contrast, regulatory T (Treg) cells inhibit the differentiation of osteoclasts by expressing cytotoxic T-lymphocyte antigen-4. In addition, transforming growth factor-β produced by Treg cells induces migration and differentiation of mesenchymal stem cells into osteoblasts. Therefore, immunological imbalance may induce osteogenic disorders by inhibiting differentiation of osteoblasts and induce bone resorption by the induction of osteoclast differentiation, thereby causing an imbalance in the bone metabolic system [13–22].

B cells express immunoglobulin (Ig) on the cell surface, and mature B cells differentiate into Ig-producing plasma cells that regulate humoral immunity. If gene mutation occurs in Burton tyrosine kinase (Btk), which is essential for differentiation of B cells into Ig-producing cells, B cell immunodeficiency may take place. Burton tyrosine kinase, which is activated by RANKL, is indispensable for the differentiation and fusion of osteoclasts, via induction of the transcription factor NFATc1. Thus, B cells and osteoclasts are much similar in the regulation of differentiation. In addition, B cells may act directly on bone metabolism, by producing OPG in response to T-cell stimulation and controlling bone resorption to regulate bone turnover [23].

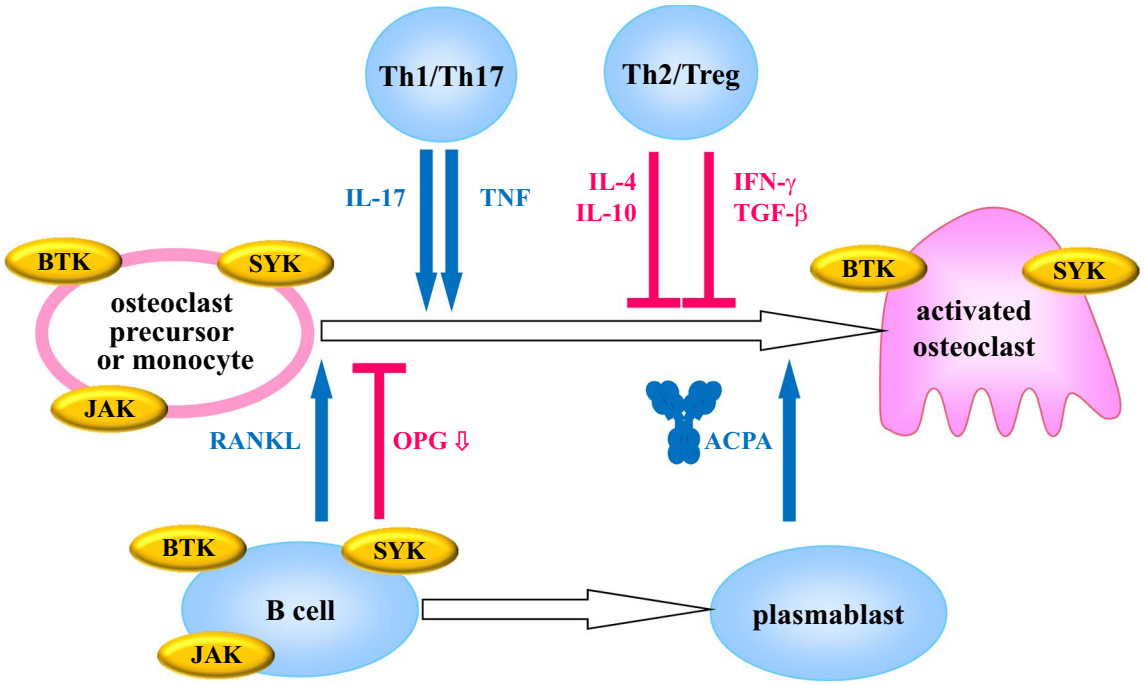

Fig. 3 Involvement of immunity during osteoclast differentiation. Th1 and Th17 cells induce osteoclasts via the production of TNF and IL-17, and Th1 cells inhibit the expression of OPG via the production of IFN-γ

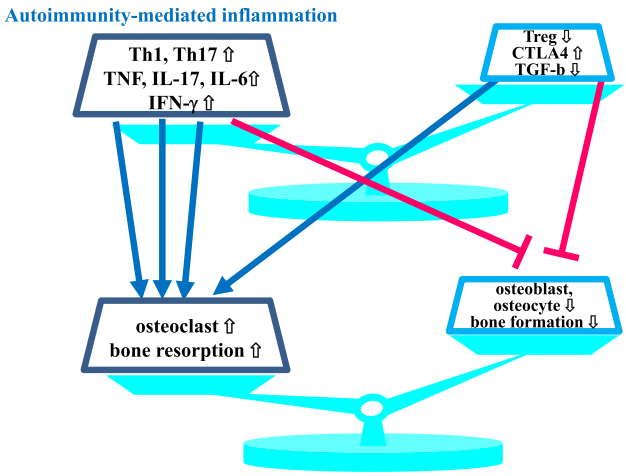

Fig. 4 Imbalance in immunity and bone metabolism. Immunological imbalance may induce osteogenic disorders by inhibiting differentiation of osteoblasts and induce bone resorption by the induction of osteoclast differentiation, thereby causing an imbalance in the bone metabolic system

Thus, immunological imbalance associated with RA may inhibit the differentiation of osteoblasts and facilitate the maturation of osteoclasts, causing an imbalance in bone metabolism as well (Fig. 4). The frequency of osteoporosis in RA patients is approximately twofold higher than that in age-matched counterparts. The risks of causing femoral and spinal fractures in patients not using glucocorticoids are reportedly 1.3 and 2.4-fold higher, respectively, suggesting that osteoporosis was induced by RA itself [24].

Joint destruction in rheumatoid arthritis

In RA patients, widespread synovitis and continuous production of inflammatory cytokines may cause bone and cartilage destruction and periarticular osteoporosis. However, the mechanism of bone and cartilage destruction is totally different from the mechanism of osteoporosis. In RA, continuous stimulation by inflammatory cytokines such as TNF causes the formation of inflammatory granulation synovial tissue, characterized by the accumulation of T cells, synovial proliferation, and angiogenesis. Matrix metalloproteinases (MMP)-1, 3, 9, and 13 are released from inflamed synovial tissue into the joint cavity and digest principal components of cartilage such as type II collagen, to diffusely resorb cartilage from the joint cavity [25]. MMP-3, which is the most abundantly produced MMP, is detectable in blood, and is used widely in clinical practice as an index of joint destruction. Cartilage as a whole thins gradually, and such thinning is visualized as joint-space narrowing on radiography as cartilage is radiolucent.

When inflammatory synovial tissue, with multilayers of proliferated synovial fibroblasts due to immune system involvement grows and comes into contact with bone, prominent bone resorption by activated osteoclasts is observed in the boundary area where the inflamed synovium directly

contacts bone. Although osteoclasts accumulate in this area, osteoblasts or osteocytes are not present in the surrounding areas. Cytokines such as TNF and IL-6 directly stimulate the maturation of osteoclasts and, at the same time, induce the expression of RANKL in synovial cells and T cells, thus facilitating osteoclast maturation even in the absence of osteoblasts [1–4]. Interestingly, in TNF transgenic mice, the following RA-like findings were obtained: synovial proliferation, increased osteoclasts at the point of contact between synovium and bone and bone erosion [26]. Accordingly, it is presumed that bone destruction associated with RA represents the maturation of osteoclasts enhanced in an osteoblast-independent manner, demonstrating deviation from bone turnover due to stimulation by TNF (Fig. 2). When joint space disappears, the opposing articular surfaces come in contact, and bone fusion occurs along with enhanced bone erosion. In addition, subluxation, dislocation, displacement, and deformation may occur when collapse of the articular structure, weakening of periarticular tissues including tendon, ligament and capsule, and the physical effects of mechanical stress are added.

Treatment of bone and joint destruction in rheumatoid arthritis

Osteoporotic changes and joint destruction in RA occur through different mechanisms, and therefore, medications for these conditions are different. Clinical symptoms such as pain, swelling, stiffness of multiple joints, and joint deformity associated with RA markedly interfere with daily living. Because joint destruction begins to progress in early stages of onset, and because joint deformity may cause irreversible physical impairment, proper and prompt diagnosis and treatment are necessary. In treating RA, immunosuppressants are used to control the disease by inhibiting immune abnormalities. These drugs are called disease-modifying anti-rheumatic drugs (DMARDs). DMARDs are broadly classified into two groups: synthetic DMARDs such as methotrexate (MTX); and biological DMARDs. The current goal of treatment is to achieve remission in all patients through the proper use of DMARDs. It has also been shown that maintenance of remission by DMARDs prevents structural damage to joints as well as the progression of physical impairment [27–29].

Evaluation using the modified total Sharp score, by which radiographic findings of joint-space narrowing and bone erosion are scored, indicates that proper use of DMARDs prevents bone and cartilage destruction. Biological DMARDs targeting TNF and IL-6 inhibit production of MMP by synovial cells and its release into synovial fluid as well as enzymatic degradation and resorption of the cartilage surface soaked in synovial fluid. These effects are visualized as decreased joint-space narrowing on radiography. In addition to directly inhibiting the maturation of osteoclasts, biological DMARDs cause decreased expression of RANKL in synovial cells and T cells, and increased expression of OPG, leading to inhibition of the differentiation and activation of osteoclasts [30]. Simultaneously, expression of sclerostin is inhibited, resulting in the differentiation of osteoblasts. Furthermore, correction of immunological imbalance appears to control bone destruction through induction of osteoblast differentiation and control of osteoclast differentiation. However, although TNF inhibitors and IL-6 inhibitors inhibit bone and cartilage destruction and periarticular osteoporosis, their influence on systemic osteoporosis is limited.

The anti-RANKL antibody, denosumab, inhibits the process of osteoclast maturation by RANKL expressed in synovial cells and T cells (Figs. 1, 2). Bisphosphonates, which inhibit bone resorption by inducing apoptosis in osteoclasts, are ineffective against joint destruction in RA. Although cortical bone is first to be eroded by synovium in the process of joint destruction, denosumab, which has a potent bone mass-increasing effect on cortical bone, effectively inhibits joint destruction in RA, and has therefore been suggested as an effective treatment for bone erosion [31].

In fact, in a phase II study performed in RA patients on MTX therapy in Japan, denosumab significantly reduced worsening of bone erosion scores at 1 year in comparison with a placebo [32]. In addition, although denosumab did not achieve disease control in patients with RA, it significantly improved the bone density in the lumbar vertebrae and the proximal femur. Similar effects were found in patients taking glucocorticoids. Similar results were also obtained in a phase III clinical study conducted in Japan; in 2017, denosumab was approved for treatment of progressive bone erosion in RA. Because denosumab does not control synovitis or the RA disease activity, it is not classified as a DMARD. Thus, it is clear that the mechanisms of bone and cartilage destruction and osteoporosis associated with RA are different in terms of therapeutic effects of drugs.

New developments of treatment for rheumatoid arthritis

While the use of biological products is limited to drip infusions or injections, molecular-targeted therapy with oral low-molecular-weight compounds which is equally effective has raised expectations. Low-molecular-weight compounds enter cells and inhibit activation sites of specific signaling molecules. In the pathogenic process of RA, intercellular signals from immunocompetent cells and synovial cells play a central role. When bound to receptors, cytokines and cell-surface molecules transmit intracellular signals which induce cellular functions. Janus kinase (JAK) is a representative tyrosine kinase that binds to receptors of cytokines. Following the binding of receptors, cytokines are phosphorylated

and transmit signals via the downstream transcription factor, STAT. Various combinations of 4 types of JAK and 7 types of STAT are involved in a variety of signaling pathways [33].

Tofacitinib was developed as a low-molecular-weight compound that competitively inhibits the ATP-binding site of JAK3. When tofacitinib was continuously introduced into severe combined immunodeficient mice implanted with synovium and cartilage from RA patients, proliferation of implanted synovium and invasion into cartilage was inhibited, resulting in a decrease in the production of IL-6 and MMP-3 [34]. In addition, when tofacitinib was added to CD4-positive cells extracted from synovial tissue in RA patients, cell proliferation and the production of IFN-γ and IL-17 was suppressed, indicating disease control via Th1 and Th17. Furthermore, tofacitinib inhibited the expression of co-stimulatory molecules and T cell stimulatory capacity through the regulation of type I IFN signals of dendritic cells, and also inhibited activation, antibody formation, and IL-6 production of B cells in the presence of IL-4 stimulation [35, 36]. In a global study including participants from Japan, combined use of tofacitinib and MTX in patients with RA refractory to MTX therapy achieved inhibition of joint destruction and a prompt and strong clinical effect comparable to TNF inhibitors [37]. Currently, the multitarget effects of tofacitinib are attracting much attention, and the drug is widely used following approval for use in RA as a JAK inhibitor.

Baricitinib binds to JAK1/2, and targets intracellular signaling induced by gp130 family molecules (e.g., IL-6 and IL-22), IL-12, IL-23, and IFN. Baricitinib in combination with MTX also demonstrated a potent clinical effect, which was superior to that of TNF inhibitors and a joint destruction-inhibitory effect comparable to TNF inhibitors in patients with RA refractory to MTX therapy [38]. Its use for RA has received approval in Japan and Europe. Following the success of these drugs, clinical studies of several JAK inhibitors and kinase-targeting drugs which target spleen tyrosine kinase (Syk) and Btk, are underway [39]. It is expected that an understanding of the role of such kinases in the pathogenesis of bone and joint destruction will be further clarified along with advances in treatment.

Conclusion

It is apparent that the mechanisms of joint destruction and osteoporosis associated with RA are totally different from each other. This difference in mechanisms has led to a difference in therapeutic strategies, leading to the development of more rational and efficient treatments. RANKL-stimulated activation of Btk in B cells and osteoclasts and activation of NFATc1 in T cells and osteoclasts indicate that the immune system and the bone metabolic system strongly influence each other, and therefore, an imbalance in the immune system may cause an imbalance in bone turnover, leading to osteoporotic changes. RANKL was earlier considered as an activator of dendritic cell expression in T cells, before being recognized as an osteoclast differentiation factor. Clarification of the similarity and universality of the immune system and the bone metabolic system, previously considered different systems, may lead to a more effective resolution of issues related to RA pathology and treatment.

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Compliance with ethical standards

Conflict of interest Y. Tanaka has received speaking fees and/or honoraria from Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, Abbvie, Pfizer, YL Biologics, Bristol-Myers, Glaxo-Smithkline, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, Asahi-kasei and has received research grants from Mitsubishi-Tanabe, Bristol-Myers, Eisai, Chugai, Takeda, Abbvie, Astellas, Daiichi-Sankyo, Ono, MSD, Taisho-Toyama.

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