Mini-Review

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Rheumatoid arthritis-associated bone erosions: evolving insights and promising therapeutic strategies

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SUMMARY The human immune system has evolved to recognize and eradicate pathogens, a process that is known as "host defense". If, however, the immune system does not work properly, it can mistakenly attack the body's own tissues and induce autoimmune diseases. Rheumatoid arthritis (RA) is such an autoimmune disease in which the synovial joints are predominately attacked by the immune system. Moreover, RA is associated with bone destruction and joint deformity. Although biologic agents have propelled RA treatment forward dramatically over the past 30 years, a considerable number of patients with RA still experience progressive bone damage and joint disability. That is to be expected since current RA therapies are all intended to halt inflammation but not to alleviate bone destruction. A better understanding of bone erosions is crucial to developing a novel strategy to treat RA-associated erosions. This review provides insights into RA-associated bone destruction and perspectives for future clinical interventions.

Keywords rheumatoid arthritis, bone erosions, RANKL, synovial fibroblasts

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with bone destruction that affects up to 1% of the general population all over the world (*1*). The autoimmunity triggers inflammatory responses that are evident in most of the clinical features of RA, such as joint redness, warmth, swelling, tenderness, and stiffness. Besides inflammation, RA also causes bone destruction and leads to progressive disability.

Bone damage is more likely within the first 2 years after the onset of disease, and it is more common in the synovial-lined peripheral joints of hands and feet, such as the metacarpophalangeal and metatarsophalangeal joints, as well as the knee joints. Intriguingly, synovial joints such as hip are rarely affected by RA (*2*). This specific anatomical distribution of joint involvement occurs even if immune system indices and genetic and environmental factors are the same, suggesting that a local predisposing factor within the joints is involved in the course of RA-associated bone destruction. Several studies using high-throughput sequencing have revealed joint-specific characteristics in terms of genomics, epigenomics, and even functions (*3-5*).

In arthritic joints, the synovium becomes hyperplastic. Synovium with an aggressive phenotype has the capacity to invade and destroy bone, which is mediated by bone-resorbing osteoclasts, the formation of which is significantly favored by the inflammatory milieu in arthritic joints (*6*). Recent studies have indicated that not only increased osteoclastic bone resorption but also suppressive osteoblastic bone formation is associated with bone damage due to RA (*7*). Synovial tissue is thought to be associated with the joint specificity of RA.

Over the past 30 years, therapies for RA have changed dramatically, as reflected in both their clinical goals and strategies. The development and current routine use of biologic agents can help to achieve disease remission in patients with RA, which is a feasible goal. Although there are differences between individuals, many patients with RA fail to respond and continue to suffer structural damage even if in remission (*8*). Therefore, a better understanding of bone destruction is urgently needed to optimize the avenues for future treatment of RA. Here, recent advances in the understanding of RA-associated bone destruction summarized and perspectives for bone-directed therapies are described.

2. Key features of RA

RA is a systemic autoimmune disease as evinced by the appearance of various autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein

antibodies (ACPAs). ACPAs in particular are highly specific to RA and thus are most widely used to diagnose RA at present (*1,9,10*). ACPAs positivity is strongly associated with structural damage in patients with RA (*11*), and immune complexes including ACPAs have been found to directly stimulate osteoclast formation (*12*). ACPAs are produced during autoimmune responses to citrullinated proteins. Thanks to the development of proteomic technology, over 100 citrullinated proteins have been identified in RA samples (*13,14*). The generation of citrullinated proteins requires citrullinating enzymes, mostly known as peptidylarginine deiminases (PADs). In arthritic joints, neutrophil extracellular traps (NETs) released from the activated neutrophils were thought to be one of the potential sources of PADs (*15*). Citrullinated proteins are immunogenic in RA, and the ensuing immune responses target these proteins, inducing inflammation and thus leading to tissue damage. However, protein citrullination indeed plays a critical role in many physiological processes such as skin moisturization (*16*) and hair follicle formation (*17*), suggesting that the autoimmune reactions to citrullinated proteins rather than their presence alone are relatively pathogenic in RA.

Autoimmune reactions in RA are thought to be closely associated with genetic risks and environmental factors, such as microbial activity at mucosal sites (18-20). These factors are likely to interact in a synergistic manner to drive autoimmune responses. However, numerous studies have found that autoantibodies appear years before the onset of clinically apparent arthritis (*21,22*), indicating that autoimmune responses are pathogenic in RA but that they alone may not cause joint disease. Further studies are needed to address what triggers the transition from pre-symptomatic autoimmunity to clinically erosive arthritis.

In addition to autoimmunity, a hallmark of RA is progressive bone destruction and joint deformities. As mentioned earlier, autoimmunity alone may not suffice to trigger bone destruction. Nevertheless, a point worth noting is that RA due to autoimmunity primarily affects the synovial joints and tissue, and arthritic synovium is capable of damaging bone.

The synovium is specialized connective tissue where synovial fluid is produced. This tissue primarily functions to lubricate and nourish the synovial joints and to support the joint structure by producing an extracellular matrix (*23*). A healthy synovium is typically acellular, while during the course of RA, the synovium becomes inflamed and hyperplastic due to both the influx of inflammatory cells and local proliferation of synovial fibroblasts (SFs). As a result, arthritic synovium is a common place for the formation of bone-resorbing osteoclasts, which directly cause bone destruction in RA.

3. RA-associated bone destruction

Owing to the advances in high-throughput technologies, researchers have become more aware of the process of bone destruction. RA-associated bone destruction is due to both excessive bone resorption by osteoclasts and defective bone formation by osteoblasts (Figure 1).

3.1. Excessive bone resorption by osteoclasts

Osteoclasts are multi-nucleated cells of hematopoietic origin that are derived from myeloid lineage precursor

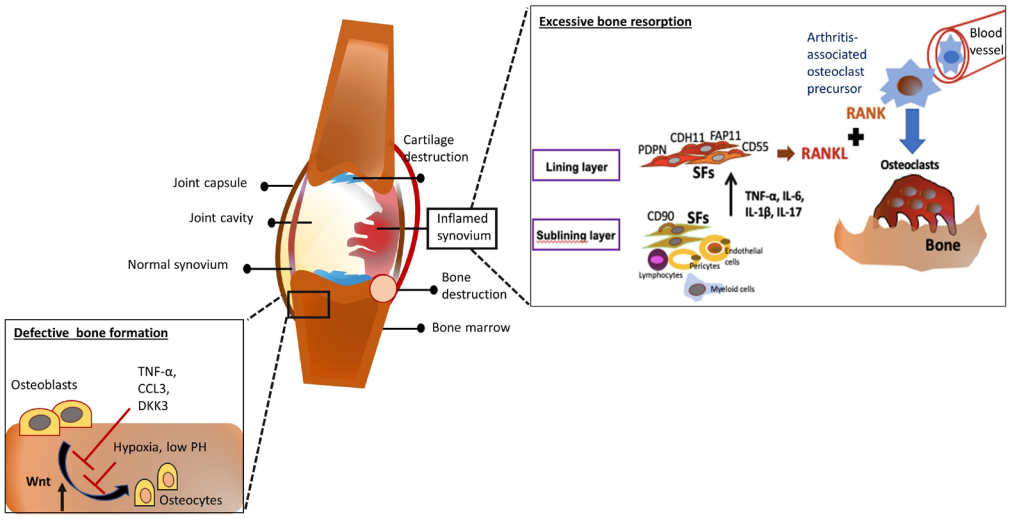

Figure 1. Potential mechanisms involved in RA-associated bone damage. Arthritic bone damage is caused by both excessive bone resorption by osteoclasts and by defective bone formation by osteoblasts. In the course of osteoclastic bone resorption, the osteoclast precursors in RA come from circulating blood and not synovial macrophages. Like RANKL-expressing SFs, osteoclast-supporting cells are thought to proliferate locally, and especially in the layer of cells lining bone. In RA, bone-forming osteoblasts are compromised by impaired Wnt signaling, which is negatively affected by intense inflammation in arthritic joints.

cells. The primary function of osteoclasts is to resorb bone. The essential roles of osteoclasts in RA-associated bone erosions have been identified in a series of human and genetically modified animal studies (*24,25*).

Osteoclasts are exclusively found attached to an area of bone resorption area in both patients with RA and murine models of arthritis. These findings lead to the question of whether or not osteoclasts cause arthritic erosions. A series of osteoclast-free models of arthritis have provided in vivo evidence. Transgenic mice that express human TNF (hTNFtg) failed to develop bone erosions when were crossed with c-fos-deficient mice, of which the functional osteoclasts were completely absent. A point worth noting is that the clinical signs of arthritis were equivalent between the hTNFtg and c-fos-knockout hTNFtg mice, indicating osteoclasts did function in bone erosions but not in inflammation (*25*).

Where do these osteoclasts come from? Osteoclast precursors can come from both circulating blood and resident cells in synovial tissue. Only recently did a study find that arthritic osteoclasts come from myeloid cells circulating in the blood and not the synovium (*26*). Remarkably, these arthritic osteoclast precursors are distinct in the transcriptome profile, compared to conventional osteoclast precursors that are responsible for physiological bone remodeling. This indicates that precisely targeting these arthritic osteoclasts could be a way to treat RA-associated bone erosions.

3.1.1. RANKL signaling governs osteoclast formation

Osteoclasts destroy bone in RA, so how osteoclasts are generated needs to be thoroughly investigated.

The receptor activator of the NF-κB ligand (RANKL), encoded by the Tnfsf11 gene, is essential for osteoclast formation and was identified in 1998 (*27*). The receptor of RANKL is RANK (encoded by the Tnfsf11a gene), which is highly expressed on osteoclast precursor cells. RANKL binds to RANK, inducing osteoclast formation. Mutations in the RANKL and RANK genes have been respectively identified in patients with osteopetrosis and familial expansile osteolysis (*28,29*). In addition, mice lacking either the RANKL or RANK gene display severe osteopetrosis due to a complete absence of osteoclasts. The same phenomenon occurs in arthritis. RANKL-deficient mice are protected from bone destruction even when attempts are made to induce arthritis, although they do have joint inflammation to a similar extent (*30*).

3.1.2. SFs are the major source of RANKL

In arthritic joints, which cells are responsible for RANKL production? Although RANKL was primarily reported to be expressed on activated T cells, in arthritic joints, SFs in synovial tissue are believed to be the major source of RANKL and thus primarily responsible for arthritic bone erosions (*31*). Because of their prominent role in RA-associated bone destruction, SFs have often been a topic of considerable interest in the past.

RA-SFs are mesenchymal lineage cells marked by the high expression of podoplanin (PDPN), cadherin 11 (CDH11), and fibroblast activation protein α (FAPα), all of which are barely expressed in a healthy individual (*32,33*). More recently, SFs within the rheumatoid synovium have been found to be heterogeneous, as evinced by different anatomical locations and protein markers as well as by specific functions (*32-37*). A single-cell RNA-seq analysis identified two functionally distinct SFs subsets. Lining layer SFs, which predominately express CD55 but lack CD90, cause bone destruction in arthritic mice via high levels of RANKL expression while sublining SFs that highly express CD90 are pro-inflammatory (*34*). That study demonstrated for the first time that functional distinct SFs subsets do exist in arthritic joints. The importance of SF heterogeneity may directly contribute to the distinctive features of RA. However, further studies are needed to clarify whether the two types of SFs are truly distinct cell subsets or just a single population. Are the distinct phenotypes only exhibited temporarily to cope with surrounding stimulatory signals and environmental insults? Inflammatory cytokines, such as tumor necrosis factor α (TNF-α), IL-6, IL-1β, and IL-17, are abundant in the inflammatory milieu of joints and are thought to be the most potent RANKL-inducing factors. In addition, biomechanical stimuli within joints, such as mechanical stress, have also been found to potentially induce RANKL expression (*38*).

3.2. Compromised bone formation by osteoblasts

Osteoblasts are derived from mesenchymal precursor cells in bone marrow and have the capacity to differentiate into osteocytes to form new bone. In RA, bone formation is compromised.

First, inflammation inhibits bone formation. TNF-α is considered to occupy the top position in the inflammatory cytokine cascade. As early as 1986, pioneering researchers reported that monocyte-derived TNF-α directly inhibited bone collagenase synthesis in osteoblast cultures (*39*). In addition, formation of mineralized bone at sites of inflammation decreased significantly compared to that at sites without inflammation in serum-transferred arthritic mice. Moreover, damaged bone could be repaired by osteoblasts if inflammation was eliminated (*40,41*). Enhanced bone formation in patients with RA was also observed after anti-TNF therapy (*42*). More recently, B cells located in the subchondral and endosteal bone marrow (BM) have been found to be involved in the mechanisms of RA-compromised osteoblasts since those B cells secrete TNF-α and CCL3 (*43*). This may partially explain clinical benefits in the form of

improved bone mineral density (BMD) and changes in bone turnover after treatment with rituximab (a CD20 blocker) in patients with RA.

Besides inflammation, localized hypoxia and a low PH environment in arthritic joints also affect osteoblast functions (*44*). Hypoxia suppresses the Wnt pathway, which is important for signaling bone formation in osteoblasts. A low PH directly prevents skeletal tissue mineralization, a process by which bone matrix is filled with calcium phosphate, thus improving bone strength. Noticeably, hypoxia and a low PH are commonly aggravated by the inflammatory milieu within arthritic joints. Accordingly, repaired bone is seen only when systemic inflammation is completely controlled.

4. Current treatment of RA-associated bone erosions and horizons for the future

4.1. Current treatment

Over the past few decades, the treatment of RA has changed dramatically due to the improved understanding of this disease (Figure 2).

Drug treatment options for RA have evolved from the era of nonsteroidal anti-inflammatory drugs (NSAIDs) in the 1930s, to glucocorticoid therapy in the 1950s, to disease-modifying anti-rheumatic drugs (DMARDs) in the 1980s, to biologics since the 2000s, and more recently to small-molecule DMARDs, which are mainly Janus kinase inhibitors (JAKis). The significant change in RA management has coincided with improved clinical outcomes.

NSAIDs only help with symptoms and pain relief, and DMARDs modify disease activity but do not affect structural alterations. Biologics, together with DMARDs, dramatically slow disease progression but still do not cure RA. JAKis target broad cytokine- and hormone-mediated signaling, so their long-term efficacy and safety remain unclear.

Biologics that inhibit key components of the immune system, such as inflammatory cytokines and activated immune cells, are the mainstay of current RA management and have resulted in significant structural improvements in patients with RA. In inflamed joints, inflammatory cytokines and activated immune cells fuel osteoclastic bone destruction and impair osteoblastic bone formation. One of the clearest examples of biologic agents that affect bone is TNF blockers. TNF directly regulates the osteoclast-intrinsic pathway and it stimulates RANKL expression on SFs to indirectly facilitate osteoclast formation. There are six different TNF blockers currently approved for treatment of RA, consisting of both monoclonal anti-TNF antibodies and soluble TNF receptors. TNF blockers have displayed the potential to arrest structural progression in RA, but nonetheless some patients are unresponsive or resistant to anti-TNF therapies (*45*).

JAKis, such as tofacitinib, baricitinib, and upadacitinib, regulate distinct cytokine- and hormone-mediated pathways and are currently approved for treatment of RA (*46*). Recent evidence has emerged to suggest that these JAKis play a role in bone biology. JAKis ameliorate bone loss by enhancing osteoblastic bone formation rather than by affecting osteoclastic bone erosions in models of both osteoporosis and arthritis (*47*). In patients with RA receiving 5 mg of tofacitinib twice daily for 2 years, bone formation is induced as revealed by high-resolution peripheral quantitative CT (*48*).

Denosumab (DMab), a fully human monoclonal antibody targeting RANKL, is the only anti-erosion agent that is currently available for treatment of RA. The clinical benefits of DMab therapy in patients with RA are the prevention of bone erosions as well as the alleviation osteoporosis (*49*). Thus, DMab has been approved for

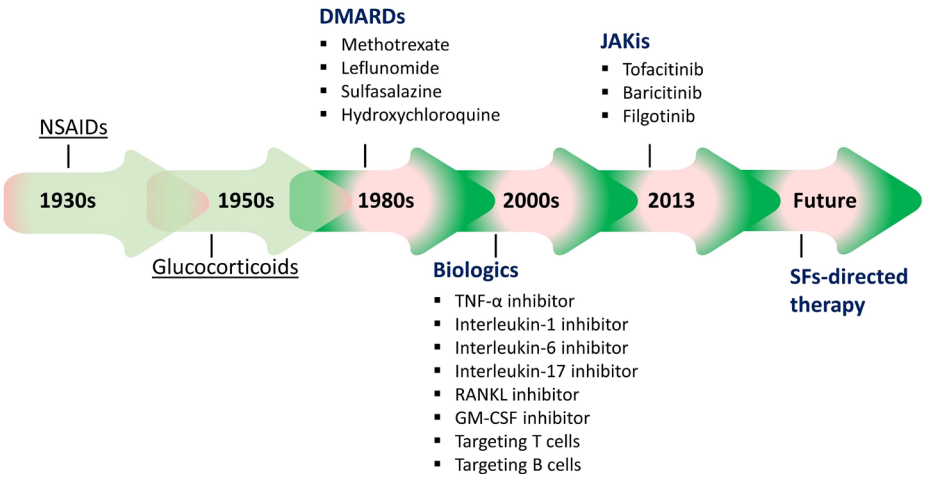

Figure 2. Key milestones during the evolution of treatments for RA. Drugs that are available for treatment of RA have dramatically evolved over the past few decades, though they cannot cure RA yet. Future SFs-directed therapies may potentially optimize the avenue for treatment of RA.

treatment of RA in Japan.

4.2. Horizons for the future

Researchers have increasingly recognized that RANKL-expressing SFs absolutely contribute to osteoclastic bone erosions. Perhaps lessons could be learned from experience with cancer-associated fibroblast-directed therapies. One such option is to target the surface proteins expressed on RA-SFs. Indeed, an early phase of a clinical trial of CDH11 therapy in patients with RA is now underway. In addition, RA-SFs in arthritic joints appear to be epigenetically imprinted, which potentially contributes to persistent aggressive phenotypes (*3*). Accordingly, histone-modifying inhibitors such as BET inhibitors may remodel RA-SFs to a normal landscape. However, one must keep in mind that there is still no unique cell marker with which to define erosive SFs, and the same challenge remains in relation to histone modifiers.

Targeting bone-destructive osteoclasts directly is also a potential strategy. For instance, a small molecule inhibitor of cathepsin K (CTSK) directly inhibits osteoclastic-bone resorption (*50*). Moreover, osteoclasts utilize oxidative phosphorylation to fulfill the energy demands for their resorptive functions (*51*), so targeting metabolic pathways may be another therapeutic option.

5. Conclusion

Despite vast improvement in the treatment of RA, achieving remission without medication is still impractical at present. In fact, most patients with RA do not respond optimally to these current therapies, particularly in terms of bone damage and joint deformities.

Bone destruction is a key feature of RA. Surprisingly, clinical therapeutic strategies to treat bone destruction are not being considered at present; most current therapies are based on a simplistic view and reductionist understanding. The complexity of RA-associated bone destruction has become increasingly clear: osteoclast-intrinsic mechanisms and the inflammatory milieu in joints both contribute to erosions. Most of the drugs available for RA are designed to modulate inflammation but not to treat bone directly. Structural damage may continue to progress even when inflammation diminishes since immune-suppressive drugs directly target neither osteoclasts nor RANKL-expressing SFs. Given the signature of this disease, a combined therapy that targets both the osteoclastic-intrinsic pathways and RA-related inflammation is expected to yield better clinical benefits.

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