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Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment

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Abstract

Bone erosion is a central feature of rheumatoid arthritis and is associated with disease severity and poor functional outcome. Erosion of periarticular cortical bone, the typical feature observed on plain radiographs in patients with rheumatoid arthritis, results from excessive local bone resorption and inadequate bone formation. The main triggers of articular bone erosion are synovitis, including the production of proinflammatory cytokines and receptor activator of nuclear factor κB ligand (RANKL), as well as antibodies directed against citrullinated proteins. Indeed, both cytokines and autoantibodies stimulate the differentiation of bone-resorbing osteoclasts, thereby stimulating local bone resorption. Although current antirheumatic therapy inhibits both bone erosion and inflammation, repair of existing bone lesions, albeit physiologically feasible, occurs rarely. Lack of repair is due, at least in part, to active suppression of bone formation by proinflammatory cytokines. This Review summarizes the substantial progress that has been made in understanding the pathophysiology of bone erosions and discusses the improvements in the diagnosis, monitoring and treatment of such lesions.

Introduction

The skeleton is composed of trabecular bone, the fine bony network hosting the bone marrow, and cortical bone, the dense bony shell that provides structural support in weight-bearing regions. Both types of bone are targeted for erosion in rheumatoid arthritis (RA). Moreover, RA is an independent risk factor for generalized osteopenia and osteoporosis, involving trabecular and cortical bone in the axial and appendicular skeleton. Articular bone erosion represents localized bone loss (osteolysis), initially involving cortical bone, and destruction of the natural barrier between the extraskeletal tissue and the intertrabecular

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spaces of the bone marrow cavity. Osteolysis results from an imbalance in which bone resorption by osteoclasts is favoured over bone formation by osteoblasts. Understanding the mechanisms that define the formation of bone erosions requires insight into the biology of bone homeostasis and the molecular regulation of the differentiation and function of osteoclasts and osteoblasts.[1–3]

Although several pathological processes can lead to bone erosion, including malignancy, metabolic processes such as hyperparathyroidism, and chronic inflammatory diseases such as histiocytosis and sarcoidosis, the most common cause is RA. Initially described more than 100 years ago,[4,5] articular bone erosions have now become a central element in the diagnosis, treatment and monitoring of RA. Moreover, these lesions are an expected consequence of seropositive RA if the disease is not treated in a timely and effective fashion. Erosions reflect the clinical consequence of the tight interaction between immune activation and skeletal modelling and remodelling. Indeed, research into the interface between the immune system and bone has now led to a new field, termed osteoimmunology.[6–9]

Definition of bone erosion

Bone erosion is a radiological term and reflects the fact that imaging is used for detection.[10] Erosions are visible on plain radiographs as breaks in the cortical bone surface, and are often accompanied by loss of the adjacent trabecular bone. By contrast, bone cysts are areas of osteolysis inside the trabecular bone compartment, without any signs of cortical bone destruction. Although erosions can also be observed in forms of arthritis other than RA, such as gout, psoriatic arthritis, spondyloarthritis and even osteoarthritis, they are included in the diagnostic criteria for RA.[11] Owing to the severity and typical distribution pattern along multiple peripheral skeletal sites, as well as absence of concomitant new bone formation, the appearance of bone erosions is unique in RA and is substantially different from other types of arthritis.

Bone erosions constitute a key outcome measure in RA and are predictive of a more severe course of disease with a higher degree of disability and increased mortality. [12–14] Clinical trials with all major antirheumatic agents approved for disease-modification of RA have been validated for their ability to retard, or even arrest, structural damage, which is a composite of bone erosion and cartilage degradation. Furthermore, radiography is widely used to assess structural damage in clinical practice and to monitor the efficacy of therapy in retarding structural damage. Thus, at present, detection and quantification of bone erosion constitutes a major instrument for disease diagnosis, as well as for monitoring and measurement of efficacy of drug therapy in patients with RA. This Review focuses on bone erosion in RA, and does not discuss cartilage damage. Nonetheless, cartilage damage is an equally important feature of structural damage in RA that occurs through fundamentally different mechanisms to bone erosions.[15]

Anatomic factors and microstructure

Bone erosions do not emerge at random locations, but show a predilection for certain anatomical sites. Detailed analysis of the distribution of bone erosions has been conducted

by high-resolution CT, high-resolution ultrasonography and MRI. The radial aspects of the finger joints were revealed to be 'hot spots' for bone erosions, whereas the ulnar aspects were less frequently affected, and the palmar and volar surfaces of the joints were virtually spared from such lesions.[16–18] This distinct localization pattern of bone erosion in RA is intriguing and could be linked with certain anatomical features, as described later. Moreover, bone erosions typically emerge at the site at which the synovium comes into direct contact with bone (known as bare areas), suggesting that anatomical factors render these areas of juxta-articular bone susceptible to erosion.[19,20] This concept is also supported by studies in healthy individuals using high-resolution CT, which have shown that bone erosions of less than 2 mm in diameter can be found in healthy individuals, with a distribution pattern that exactly reflects that of the erosive lesions seen in patients with RA.[15,21] Anatomical factors that predispose skeletal sites for erosions include: the presence of mineralized cartilage, a tissue particularly prone to destruction by bone-resorbing cells; the insertion sites of ligaments to the bone surface, which transduce mechanical forces to the bone and could induce microdamage;[22] and inflamed tendon sheaths (termed tenosynovitis), which pass by the bone surface, and enable the spread of inflammation from the tendon to the articular synovium.[23]

The small bone channels that penetrate cortical bone carry microvessels and bridge the outer synovial membrane and the inner bone marrow space; these channels are also prone to erosive change early in the course of RA. The microvessels located within these channels facilitate homing of osteoclast precursor cells to the bone, which, upon contact with bone and receipt of the appropriate molecular signals, differentiate into osteoclasts. Widening of cortical bone channels, as a result of osteoclast-mediated bone resorption, is a typical early change in animal models of arthritis.[24,25] Moreover, cortical fenestrations have been described in high-resolution CT scans of joints from patients with RA, which probably reflect such widening of cortical bone channels.[15] These changes are in accordance with the known reduction in cortical bone mass in RA, which has been documented in several studies in patients with RA and seems to be closely related to disease activity and the development of bone erosions.[26–30]

Evolution of bone erosions

Longitudinal radiographic studies have shown that bone erosions emerge early in the pathogenesis of RA, affecting approximately half of untreated patients by 6 months after disease onset.[31] Radiographic studies in patients with RA of less than 3 months' duration suggest that bone erosions can be detected as early as a few weeks after disease onset in some patients.[32] Moreover, several studies in patients with RA have shown that relationships exist between bone erosions and the development of osteopenia and osteoporosis.[33–35]

Detection of bone erosions has improved owing to marked technological advances in musculoskeletal imaging. CT, high-resolution ultrasonography and MRI can reliably detect even small bone erosions in patients with RA.[36,37] Imaging has also highlighted and substantiated the role of inflammation in triggering bone erosions, showing that not only synovitis, but also inflammation of the adjacent intertrabecular space (osteitis), correlates

with the development of radiographic bone erosions.[38,39] Whether bone erosions lead to osteitis, or osteitis is a result of bone erosion, remains unclear.[40] Bone erosions are usually considered as irreversible damage, although detailed longitudinal assessment of these lesions with respect to repair is still scarce. Spontaneous repair, however, is rare, which contrasts with the substantial periosteal bone-formation response noted in conjunction with bone erosions in patients with psoriatic arthritis or osteoarthritis.[41]

Osteoclasts mediate bone erosion

Osteoclasts, giant multinucleated cells derived from the monocyte lineage, are the only cells capable of resorbing bone in the body.[2,3] Osteoclasts are designed to resorb bone by adhering tightly to the bone surface through interactions with both integrins and extracellular matrix proteins, as well as by assembling junctions, which seal the bone surface and the osteoclast and thereby separate bone from the surrounding extracellular space. Proton pumps along the osteoclasts' ruffled border then create an acidic milieu, enabling solubilization of calcium from bone. Matrix enzymes synthesized by the osteoclast, including cathepsin K, matrix metalloproteinase 9 and tartrate-resistant acid phosphatase type 5 (TRAP), degrade the bone matrix.[2]

Osteoclasts populate the interface between inflammatory synovial tissue and the periarticular bone surface. The first indirect description of bone-resorbing cells in RA dates back to the 19th century,[5] and was revisited by Bromley and Woolley[42] and by Leisen *et al.*[43] in the 1980s. Osteoclasts in RA were definitively identified and characterized in detail by use of modern immunohistochemical and molecular techniques by Gravallese *et al.*[44] in 1998. The multinucleated cells at the pannus–bone interface demonstrate all of the phenotypic features of bona fide osteoclasts, including formation of a ruffled border and expression of specific markers including TRAP, cathepsin K and the calcitonin receptor. Osteoclast precursor cells accumulate inside the so-called synovial pannus —the dense inflammatory synovially derived tissue located both at the interface with bone and inside the bone erosions themselves. Similar changes are also found in all relevant animal models of inflammatory arthritis, and studies involving these animal models demonstrated the crucial role of osteoclasts in the pathogenesis of articular bone erosion in arthritis induced by adjuvant,[45] collagen,[46,47] serum transfer[48] and TNF.[49,50] By inducing arthritis in osteoclast-free mice, it was shown that these mice are completely protected from bone erosions.[48,49] Osteoclasts have, therefore, emerged as an essential cell type in the erosive process.

Pathways for osteoclast differentiation

Development of osteoclasts occurs locally in the synovial tissue as a result of expression of the two essential osteoclastogenic mediators, macrophage colony-stimulating factor 1 (M-CSF)[51,52] and receptor activator of nuclear factor κB ligand (RANKL; also known as TNF ligand superfamily member 11).[53–58] This process involves the migration of monocyte-lineage cells from the bone marrow into the secondary lymphatic organs and finally into the joints. The differentiation step at which monocytes enter the joint is unclear. Indeed, monocytes could be already committed to a certain monocyte lineage, such as M1 or M2 macrophages, dendritic cells or osteoclast precursor cells when they enter the joint. Some

data suggest that TNF, a key proinflammatory cytokine expressed in RA synovial tissue, stimulates the migration of osteoclast precursor cells from the bone marrow into the periphery.[59,60] In addition, TNF stimulates expression of surface receptors such as osteoclast-associated immunoglobulin-like receptor before the precursor cells enter the joint, and these receptors facilitate differentiation. [61] Once within the microenvironment of the joint, these cells are exposed to M-CSF and RANKL, and differentiate toward osteoclasts. Final differentiation into bone-resorbing osteoclasts is then achieved following contact with the bone surface.

Blockade of osteoclast differentiation by inhibiting RANKL, or M-CSF plus RANKL, has been shown to arrest bone erosion in virtually all animal models of inflammatory arthritis.[45–50,62] One clinical trial in patients with RA has also shown that blockade of RANKL using a neutralizing antibody (denosumab) slows the progression of bone erosion, whereas it does not retard inflammation.[63] Thus, direct targeting of osteoclasts in RA protects bone from the consequences of inflammation even in the absence of inhibition of inflammation itself. This observation also largely excludes the possibility that bone resorption exerts positive feedback loops on synovial inflammation.

Triggers of bone erosion

Preclinical autoimmunity

Autoimmunity is among the strongest prognostic indicators of structural damage in RA. Compelling evidence for the link between autoimmunity and articular erosion was revealed by the presence of anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies in the serum of patients with RA, which can emerge long before the onset of synovitis and independently predict bone erosion in these patients.[64–67] This observation is consistent among several cohorts of patients with RA and is independent of measures of disease activity, such as 28-joint disease activity score, or inflammation, as measured by levels of C-reactive protein.[64–67] A study in 2012 revealed that ACPA recognize citrullinated vimentin expressed on the surface of osteoclast precursor cells.[68] Binding of ACPA to the cell surface increases cellular differentiation to bone-resorbing osteoclasts via autocrine stimulation of TNF production. Osteoclasts express high levels of the enzyme peptidyl-arginine deiminase type 2 (PADI2), which is induced by calcium flux and is responsible for protein citrullination (Figure 1). In osteoclast-lineage cells, PADI2 activation leads to preferential citrullination of vimentin, inducing a change in its subcellular localization and rendering it accessible for ACPA binding. Induction of osteoclastogenesis by ACPA binding is also highlighted by high levels of markers of bone resorption in the serum of patients with RA,[9] reflecting osteoclast-mediated bone resorption. It will be of interest to determine if this effect is specific to citrullinated vimentin or if antibodies specific to other citrullinated proteins have similar effects. These findings shed new light on the interplay between inflammation and bone damage in RA, and support the concept that structural changes to bone occur at disease onset, or even before disease onset, in patients with RA (Figure 2).

Innate immunity

Amassing evidence is indicating a role for the innate immune system in bone erosion in RA. Osteoclasts are viewed as key innate immune cells in bone, as they express innate immune receptors, analogous to macrophages and dendritic cells, which regulate their ability to respond to inflammation in the joint, and thus direct their fate and function. These receptors include immunoreceptor tyrosine-based activation motif (ITAM)-bearing receptors, which have an important co-stimulatory role with RANKL and M-CSF in osteoclastogenesis. [69] A role for Toll-like receptors (TLRs) in the pathogenesis of inflammation and bone erosion in RA has also been proposed, as TLR stimulation of synoviocytes induces expression of RANKL, thereby favouring osteoclastogenesis. TLR ligands can also activate pathways that suppress osteoclastogenesis, by inhibiting expression of receptor activator of NFκB (RANK; also known as TNF receptor superfamily member 11A), thus limiting pathologic bone loss associated with inflammation.[70] The role of the innate immune system in bone erosion in RA thus remains a fertile area for further research.

Transition from autoimmunity to inflammation

Changes in immune balance could be capable of retarding or even preventing the transition from ACPA-positive healthy individuals to patients with inflammatory arthritis. Regulatory mechanisms involving a balance of T-cell subsets might be crucial in blocking the clinical manifestations of RA. Although T cells, and in particular type 17 T-helper (T_H17) cells, have always been considered to be the cell types that trigger osteoclastogenesis,[62,71] T cells may also facilitate maintenance of bone homeostasis. For example, expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) on T cells, in particular regulatory T (T_{REG}) cells, is a potent signal for blockade of osteoclast differentiation. [72–75] CTLA4 disrupts the co-stimulation of T cells and thereby acts as an immunomodulatory signal. Binding of CTLA4 to the cell surface receptors CD80 and CD86 on osteoclast precursors arrests further differentiation of these cells into osteoclasts, even in the presence of the stimulatory factors M-CSF and RANKL.[75] This concept has been translated into therapeutic use in patients with the introduction of CTLA4–Ig (abatacept), which blocks T-cell co-stimulation and thus blocks inflammation and bone erosion in patients with RA. Moreover, the fact that an immunoregulatory molecule protects bone extends the spectrum of currently described immune–bone interactions and demonstrates dual roles for cell types and factors in both the immune system and the skeleton. Thus, immune activation facilitates bone resorption, whereas immune modulation has protective effects on the skeleton.

Synovitis

Once synovial inflammation develops from autoimmunity in RA, additional triggers augment the process of bone erosion. It follows, then, that tight control of synovial inflammation would protect from bone erosion progression; this prediction has held true in patients with RA receiving tightly controlled anti-inflammatory treatment with DMARDs and glucocorticoids.[76,77] Synovitis is a rich source of proinflammatory cytokines, which drive the process of osteoclast differentiation.[15] TNF, IL-1 and IL-6 enhance osteoclastogenesis through permissive action on RANKL expression in mesenchymal cells, as well as through direct effects on osteoclast precursor cells, and in so doing generate an

appropriate microenvironment for osteoclastogenesis. Moreover, the expression of receptors for osteoclast differentiation, such as RANK, is stimulated by synovially derived cytokines (Table 1).[78–83] It should be noted that the greater the severity of synovitis, the more extensive the erosive process. In accordance, both ultrasonography and MRI studies have shown that the extent of synovitis and osteitis is related to the likelihood of later bone damage.[38,39] Furthermore, it seems that levels of acute phase reactants, such as C-reactive protein, are also positively correlated with the likelihood of the development of bone erosions in RA.[84] As synovitis develops shortly before clinical disease onset in patients with RA, it is not surprising that the risk of bone erosions increases after the clinical onset of disease.[85,86]

Early intervention with antirheumatic therapy is the most efficacious strategy for the prevention of bone erosions. Standard small-molecule antirheumatic drugs for RA, such as glucocorticoids, methotrexate and leflunomide, seem to have bone-sparing effects simply based on their ability to effectively reduce synovitis.[87,88] It is noteworthy that even glucocorticoids, which definitely show negative effects on bone balance, can enable protection from bone erosions by effectively reducing the burden of synovitis. By contrast, incomplete control of synovitis enables osteoclast-mediated bone erosions to advance, resulting in progression of structural damage.[89–91] Thus, patients with a low level of disease activity and even those in clinical remission can demonstrate progression of bone erosion, particularly if treated with conventional antirheumatic drugs.[89–91] It is likely that progression of bone erosion in these patients is a result of residual, subclinical synovitis and osteitis, which is sufficient to trigger continued osteoclast differentiation and bone erosions. However, one can not exclude the possibility that, in some patients with RA, the processes of inflammation and bone erosion become dissociated and bone erosion may continue after inflammation has ceased. Thus, for instance, altered mechanical load and other mechanical factors might precipitate further bone damage in RA.

Proinflammatory cytokines in bone erosion

Cytokine inhibition, including with TNF blockers (infliximab, etanercept, adalimumab, certolizumabpegol and golimumab) and IL-6 receptor (IL-6R) blockade (tocilizumab), is one of the most effective approaches to slow or arrest the bone erosive process in RA (Figure 3) and may prevent the progression of systemic bone loss.[88] The explanation for this effect is twofold. First, cytokine blockade is typically more effective than traditional antirheumatic drugs in reducing synovitis, including subclinical synovitis. However, at this time, no evidence has shown that the burden of synovitis is different amongst patients with RA in remission, treated with either conventional drugs or by cytokine blockers. Second, blockade of TNF and IL-6R exerts direct effects to limit the process of osteoclastogenesis. This concept is supported by observations from clinical trials[92] as well as by pathophysiological studies showing that TNF and IL-6–IL-6R complexes directly induce differentiation of osteoclast precursor cells to become bone-resorbing osteoclasts.[78,82]

The direct effect on osteoclastogenesis may not be limited to cytokine-blocking agents, but may also apply to inhibitors of intercellular protein kinases.[93] Novel compounds in clinical testing for their disease-modifying effect are tofacitinib, an inhibitor of Janus-associated

kinase (JAK),[94,95] and fostamatinib, a tyrosine-protein kinase inhibitor that targets spleen tyrosine kinase (SYK).[96] These tyrosine kinases are expressed by immune cells, including osteoclasts, and function to integrate cytokine signalling and cellular responses during inflammation.[96] As a consequence, their inhibition may simultaneously result in anti-inflammatory as well as anti-erosive effects in patients with RA. Direct inhibition of osteoclasts and bone erosion is particularly probable when kinases, such as SYK[97] and Bruton tyrosine kinase (BTK), are targeted by small-molecule drugs as these kinases are preferentially expressed by antigen-presenting cells such as B cells and monocytes.[98] As previously discussed, IL-1 might participate in triggering bone erosions in patients with RA.[99] This cytokine has been shown to be a pivotal trigger for cartilage and bone loss in animal models of inflammatory arthritis.[79,80] In RA, however, the role of IL-1 blockade in improving clinical signs of disease is limited. Nevertheless, IL-1 blockade yields protection from bone erosion in RA.[99] Even when taking into account its modest anti-inflammatory effect in RA, the role of IL-1 blockade in protecting patients from bone erosion in diseases that are triggered by IL-1, such as gout, may be substantial.

Candidate cytokines that combine proinflammatory and pro-osteoclastogenic properties include IL-17 and IL-15. IL-17 is a proinflammatory cytokine that induces production of prostaglandins, nitric oxide, cytokines and chemokines. IL-17 induces the production of IL-1 and TNF in macrophages and fibroblasts and is synergistic with IL-1 in the upregulation of inflammatory mediators released by synovial fibroblasts.[100–102] Thus, a role for IL-17 in RA pathogenesis has been highlighted.[103] IL-17 is produced by several cell lineages including T_H17 cells and mast cells, and is a potent inducer of RANKL expression on the surface of osteoblasts and synovial fibroblasts.[104,105] At the same time, IL-17 blocks the function of compensatory anti-osteoclastogenic factors such as T_{REG} cells and IL-4, and thereby inhibits local bone erosion as well as systemic bone loss in a mouse model of TNF-mediated arthritis.[106] IL-15 is another proinflammatory cytokine that regulates innate and adaptive immune responses, as well as mediating osteoclastogenesis and bone erosion.[107] Single-nucleotide polymorphisms in the gene encoding IL-15 were shown to be correlated with joint destruction in RA in a multicohort study, supporting a direct role for this cytokine in articular bone erosion.[108]

Not all proinflammatory cytokines trigger bone loss. For instance, the alarmin IL-33 and the dendritic cell-derived cytokines IL-23 and IL-12, as well as the type I and type II interferons, are all potent suppressors of osteoclastogenesis.[6,109,110] Although these factors are also expressed in synovial tissue, their actions cannot outweigh the bone-resorptive effects of the aforementioned proinflammatory signals within RA synovium, which result in net bone loss.

New advances to promote erosion repair

Once established, bone erosions rarely repair.[111,112] Indeed, spontaneous repair of erosions is virtually absent and, even with the use of potent anti-inflammatory therapeutic strategies such as blockade of TNF or IL-6R, only limited signs of repair of bone erosions are noted.[113,114] If present, repair manifests as new bone apposition (that is, sclerosis) at the base of the erosion and seems to involve the juxta-articular bone marrow.[113] Indeed,

histopathology of synovial tissue of patients with RA has revealed an abundance of osteoclasts in bone erosions, but a paucity or even absence of mature osteoblasts, [115] suggesting that certain molecules in the synovium effectively block differentiation of bone-forming osteoblasts. Histomorphometric studies in a mouse model of RA demonstrated that bone formation at sites of erosion is markedly limited, with bone formation rates similar to those in healthy controls.[115,116] Synovitis in RA thereby seems to foster focal articular bone loss by blocking local bone formation, which leads to a fundamental imbalance in bone homeostasis (Figure 4). By contrast, data in an animal model has shown that, once synovitis resolves, osteoblasts do populate the surfaces of eroded bone and form new bone to repair erosions.[117] The implication of this finding is that in patients in whom repair is not seen, inflammation might not be fully controlled. Indeed, when sensitive radiographic techniques are used to study the joints of patients thought to be in clinical remission, residual inflammation is often seen.[91] The relevance of erosion repair to functional status will be important to determine, as will understanding the possible detrimental effects of residual inflammation on the cardiovascular system and on bone in the axial and appendicular skeleton.

Limited repair of bone erosions in RA seems to involve the induction of signals that block new bone formation. Administration of parathyroid hormone has been shown to achieve repair of bone erosions in a mouse model of arthritis, when combined with TNF inhibitors.[118] Other candidate molecules that could limit bone formation and repair include antagonists of the Wnt signalling pathway, one of the strongest bone anabolic pathways. Production of Dickkopf-related protein 1 (Dkk-1), for instance, is induced by TNF in synovial fibroblasts and is expressed in the synovium of patients with RA.[116] Dkk-1 potently interferes with Wnt signalling and blocked new bone formation in a mouse model of RA.[116] Moreover, expression of other Wnt antagonists such as secreted Frizzled-related protein-1 and sclerostin can be induced during inflammation and may also inhibit repair of bone erosion by suppressing bone formation.[117,119,120] Whether blockade of Dkk-1 or other Wnt antagonists such as sclerostin will trigger repair or even healing of bone erosion is, however, unclear at present, and despite some evidence from animal models of arthritis, appropriate clinical studies have to be undertaken to address this question.

Conclusions

In summary, articular bone erosion is a hallmark of RA and is relevant for diagnosis, treatment and monitoring of the disease. Knowledge of the mechanisms that induce bone erosion has increased substantially owing to refinements in imaging technologies as well as new insights into pathophysiology. Data obtained over the past few years have further revised the concepts of pathogenesis, shifting us from a perception of erosions as irreversible, end-stage lesions to a dynamic view of erosion as an active process. Most importantly, bone erosion begins early in the course of RA and is integrally entwined with innate immune mechanisms, autoimmunity and synovitis. Further insights into the molecular pathways of bone loss and bone formation during inflammation should facilitate the development of new therapeutic strategies for repair of bone erosions.

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Key points

- Articular bone erosions are a central clinical feature of rheumatoid arthritis
- Imaging techniques enable early detection of bone erosions and provide insights into disease pathogenesis
- Bone erosion is a result of enhanced osteoclast differentiation and inhibition of osteoblast-mediated bone repair
- Autoantibodies and cytokines, including proinflammatory cytokines and receptor activator of nuclear factor κB ligand, are the major precipitating factors in bone erosion in rheumatoid arthritis
- Antirheumatic therapies block progression of bone erosion by mitigating synovial inflammation and restoring bone balance

Review criteria

A search for original articles published between 1970 and 2012 was performed using the PubMed database with the search terms “rheumatoid arthritis”, “bone” and “erosion”, both alone and in combination. Only full-text papers published in the English language were considered. The reference lists of identified papers were also used to identify further relevant articles.

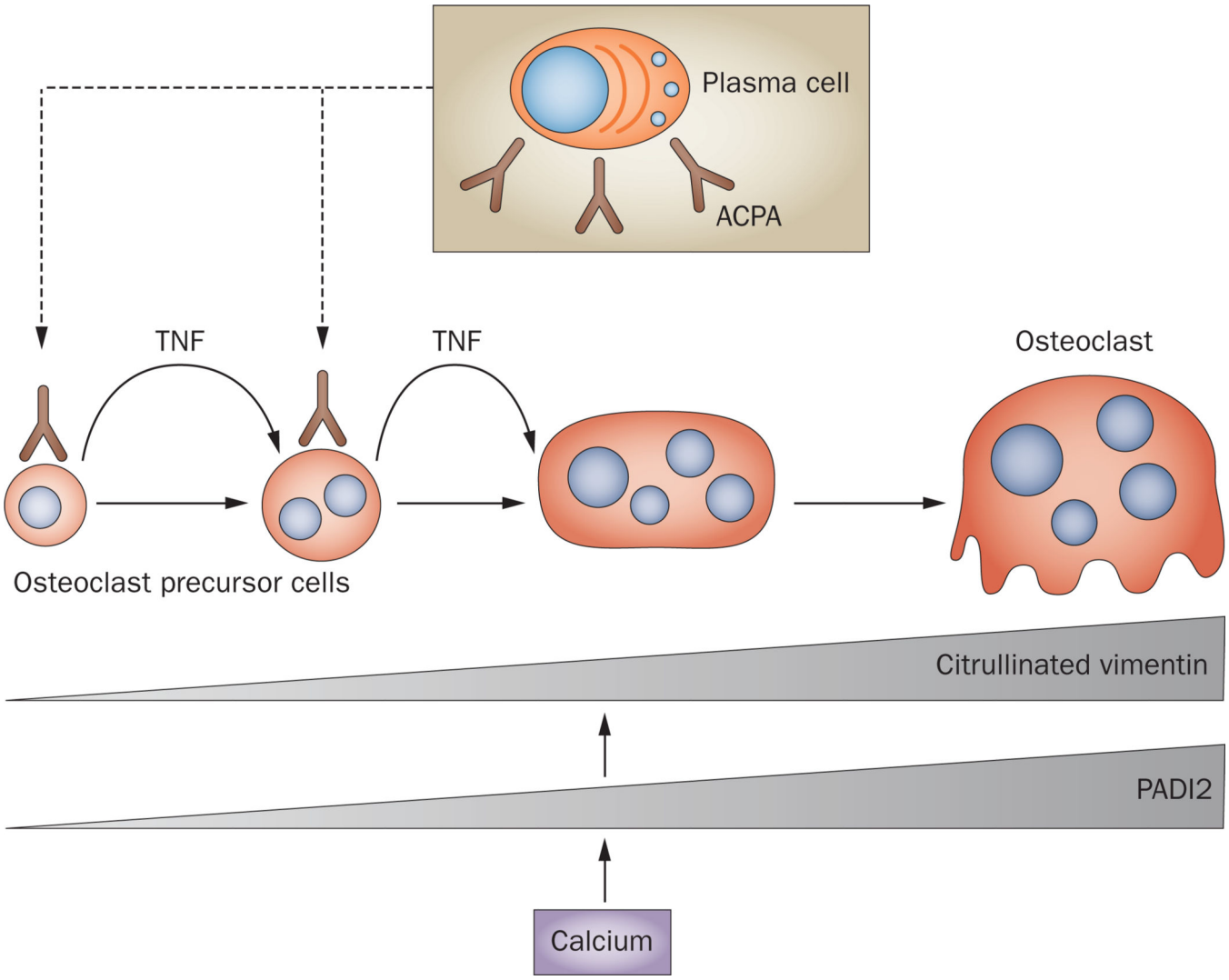

Figure 1.

Autoantibodies against citrullinated proteins and osteoclastogenesis. Plasma cells produce ACPA with specificity for citrullinated vimentin, which bind to osteoclast precursor cells and stimulate the release of TNF, which in turn enhances the differentiation of these cells into mature osteoclasts. During the osteoclast differentiation process, production of the PADI2 enzyme is induced by calcium. The activity of PADI2 leads to citrullination of vimentin, which is abundantly expressed on the surface of osteoclast-lineage cells. Abbreviations: ACPA, anti-citrullinated protein antibodies; PADI2, peptidyl-arginine deiminase type 2.

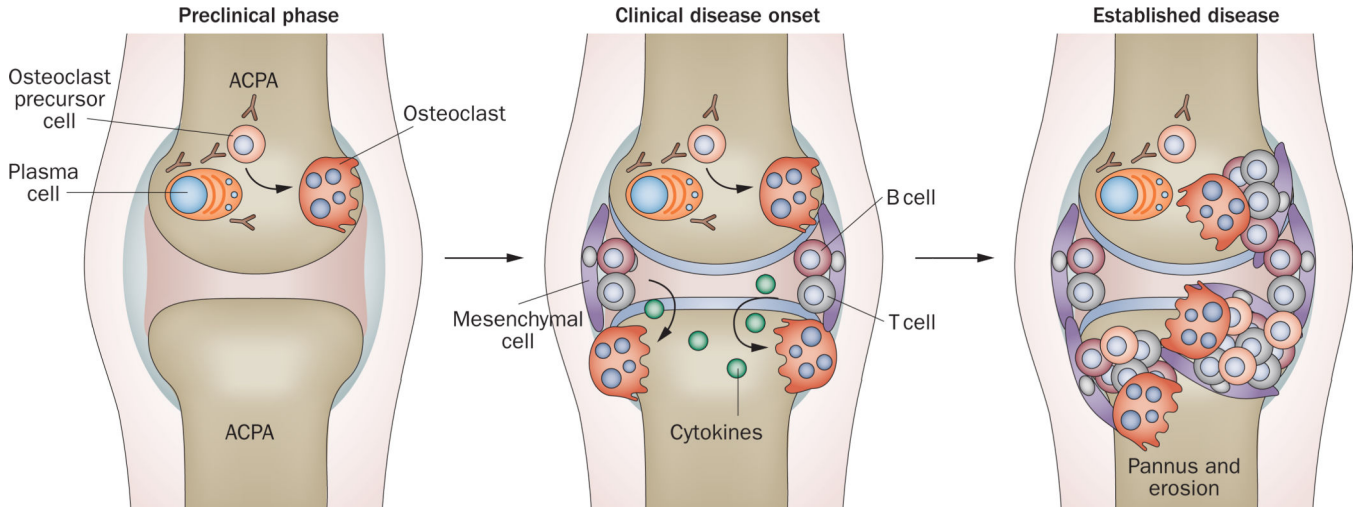

Figure 2.

Evolution of bone erosion in the course of RA. During the preclinical phase of RA, ACPA are produced early on by plasma cells. ACPA can stimulate osteoclast differentiation and lead to initial bone loss. These early changes may initiate in the bone marrow adjacent to the joint. Synovitis at the onset of clinical disease leads to production of cytokines, which stimulate osteoclastogenesis by inducing expression of RANKL, and synergize with RANKL to enhance bone erosion. Established RA is characterized by the presence of large bone erosions filled with inflamed, synovially derived pannus tissue. Abbreviations: ACPA, anti-citrullinated protein antibodies; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor κB ligand.

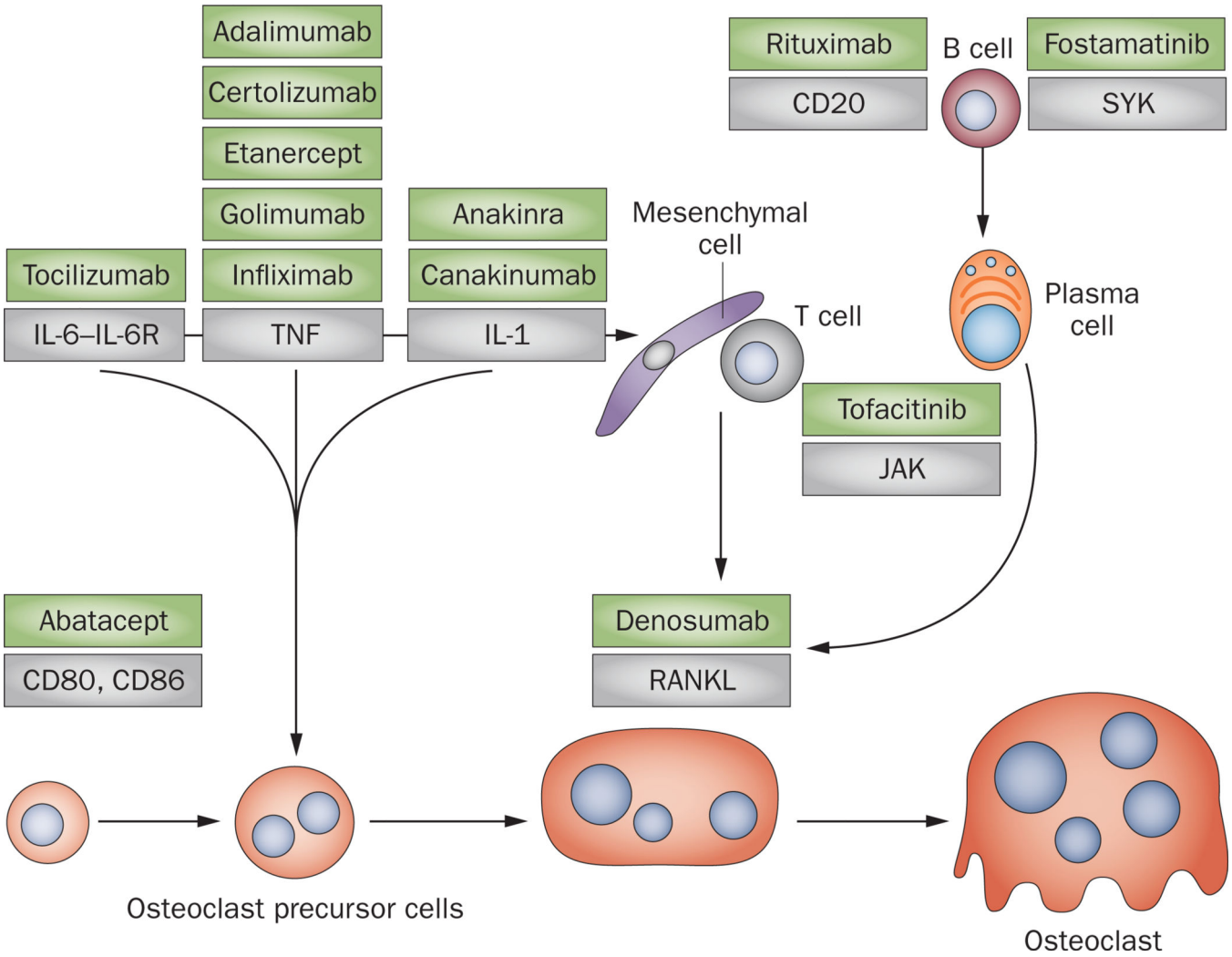

Figure 3.

Site of action of antirheumatic drugs on osteoclast differentiation and bone erosion. Inhibitors (green boxes) of TNF, IL-1 and IL-6R block the expression of RANKL by mesenchymal cells and T cells; they also directly interfere with osteoclastogenesis. Abatacept inhibits osteoclast differentiation by directly engaging CD80 and CD86 on the surface of osteoclast precursor cells. T-cell activation is targeted by small-molecule tyrosine kinase inhibitors such as tofacitinib, an inhibitor of JAK. B cells differentiate into plasma cells, which are a source of RANKL. B cells are depleted by an antibody against CD20 (rituximab) and are inhibited by small-molecule tyrosine kinase inhibitors such as fostamatinib, an inhibitor of SYK. Abbreviations: IL-6R, IL-6 receptor; JAK, Janus kinase; RANKL, receptor activator of nuclear factor κB ligand; SYK, spleen tyrosine kinase.

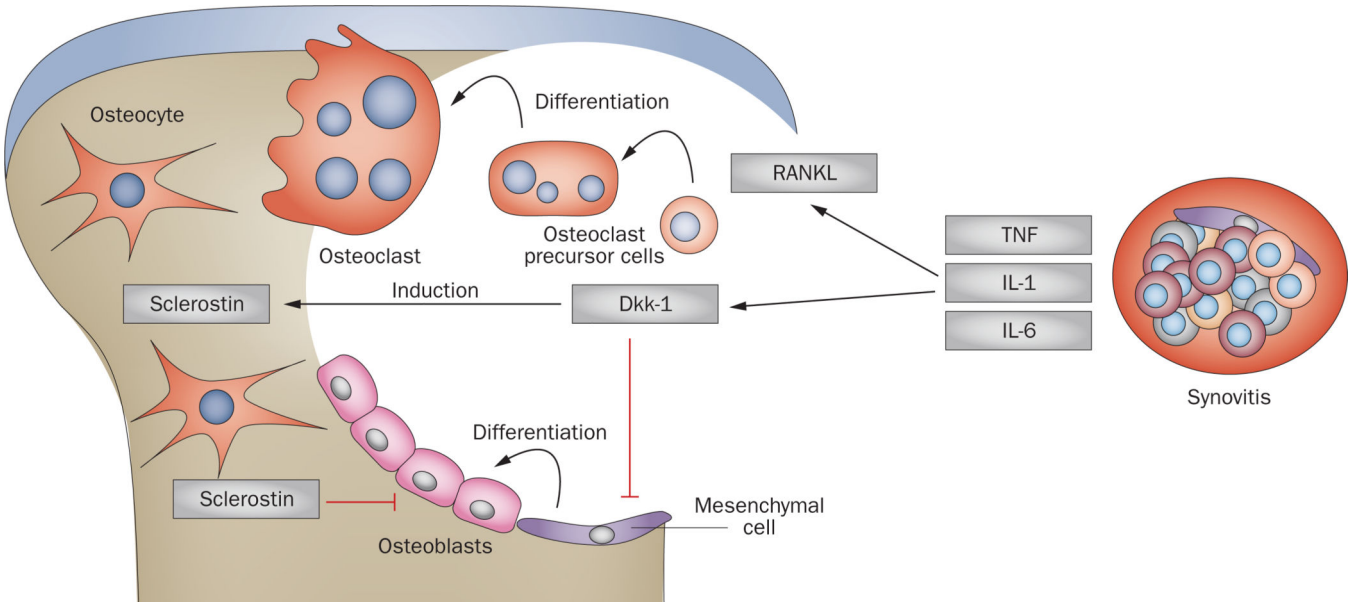

Figure 4.

Disruption of bone homeostasis by synovitis. Inflammation within synovial tissue induces osteoclastogenesis through increased expression of RANKL, and by the production of proinflammatory cytokines that drive osteoclastogenesis and synergize with RANKL. In addition, expression of Dkk-1 by synovial fibroblasts leads to inhibition of osteoblast differentiation and consequently of bone formation. Dkk-1 itself induces expression of another anti-anabolic molecule, sclerostin, by osteocytes. Abbreviations: Dkk-1; Dickkopf-related protein 1; RANKL, receptor activator of nuclear factor κB ligand.

Table 1

The clinical effects of cytokines during RA

Cytokine	Proinflammatory effect	Skeletal effect
TNF	Key inhibitor of bone formation in RA	Pro-osteoclastogenic by inducing RANKL and by direct stimulation of osteoclast precursors through TNF receptor 1; also inhibits bone formation
IL-6	Major proinflammatory cytokine in RA	Pro-osteoclastogenic by inducing RANKL and by direct stimulation of osteoclast precursors through induction of gp130 signalling
M-CSF	Growth factor with potential proinflammatory effects	Essential factor for osteoclast differentiation
RANKL	No effect on inflammation	Essential factor for osteoclast differentiation
IL-1	Moderate proinflammatory effects in RA	Pro-osteoclastogenic by inducing RANKL and RANK expression
IL-17	Potential proinflammatory effects in RA	Pro-osteoclastogenic by inducing RANKL and by blocking anti-osteoclastogenic factors, such as IL-4, IFN-γ and IL-12
IL-15	Cytokine involved in innate and adaptive immune responses with potential proinflammatory effects in RA	Pro-osteoclastogenic by inducing RANKL
IL-33	Proinflammatory and antiinflammatory effects; no definite role in inflammation in RA	Potent inhibitor of osteoclastogenesis and bone resorption
Dkk-1	Wnt inhibitor with no effect on inflammation in RA	Key inhibitor of bone formation in RA

Abbreviations: Dkk-1, Dickkopf-related protein 1; IFN-γ, interferon-γ; M-CSF, macrophage colony-stimulating factor; RA, rheumatoid arthritis; RANK, receptor activated of nuclear factor κB; RANKL, receptor activated of nuclear factor κB ligand.