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Review

Inflammatory signaling induced bone loss

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ABSTRACT

A broad spectrum of inflammatory disorders have the capacity to target the skeleton and to de-regulate the processes of physiological bone remodeling. This review will focus on the systemic inflammatory rheumatologic disorders, which target articular and peri-articular bone tissues. Many of these disorders also affect extra-articular tissues and organs, and in addition, have the capacity to produce systemic bone loss and increased risk of osteoporotic fractures. Attention will focus on rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and the seronegative spondyloarthropathies (SpAs), which include ankylosing spondylitis (AS), reactive arthritis (formerly designated as Reiter's syndrome), the arthritis of inflammatory bowel disease, juvenile onset spondyloarthropathy and psoriatic arthritis. The discussion will principally focus on RA, which is a prototypical model of an inflammatory disorder that de-regulates bone remodeling, but also will review the other forms of inflammatory joint disease to highlight the differential effects of inflammation on bone remodeling in these conditions.

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Contents

Introduction

A broad spectrum of inflammatory disorders have the capacity to target the skeleton and to de-regulate the processes of physiological bone remodeling. This review will focus on the systemic inflammatory rheumatologic disorders, which target articular and periarticular bone tissues. Many of these disorders also affect extra-articular tissues and organs, and in addition, have the capacity to produce systemic bone loss and increased risk of osteoporotic fractures. The articular inflammation and joint damage, as well as the generalized bone loss and additional systemic extra-articular manifestations, have a profound adverse effect on the quality of life and functional capacity of the affected individuals. Attention will focus on rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and the seronegative spondyloarthropathies (SpAs), which include ankylosing spondylitis (AS), reactive arthritis (formerly designated as Reiter's syndrome), and the arthritis of inflammatory bowel disease, juvenile onset-spondyloarthropathy and psoriatic arthritis. The discussion will principally focus on RA, which is a prototypical model of an inflammatory disorder that de-regulates bone remodeling, but also will review the other forms of inflammatory joint disease to highlight the differential effects of inflammation on bone remodeling in these conditions.

Structural organization of periarticular bone

To understand the articular and periarticular bone pathologies in the rheumatic diseases, it is important to appreciate the unique organizational features of the different joints. The joints can be divided into three categories based on their anatomic features [1]. They include the

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highly mobile diarthrodial joints, which are lined by a specialized synovial lining, *e.g.*, the knee, wrist and small joints of the hands and feet; the amphiarthroses in which the adjacent bones are separated by articular cartilage or a fibrocartilage disc and are associated with limited mobility, *e.g.*, the intervertebral discs; and synarthroses, in which fibrous tissue separates adjoining bones, *e.g.*, the sacroiliac joints. The periarticular bone of the diarthrodial joints is separated from the overlying articular cartilage by a zone of calcified cartilage, and the interface between the articular and calcified cartilage is demarcated by the "tide-mark", which can be identified by its enhanced metachromatic staining pattern. The bone beneath the calcified cartilage is organized into a plate-like structure of compact cortical bone and below the subchondral bone plate, the bone forms a network of cancellous trabecular bone that is surrounded by the bone marrow. The periosteal bone at the joint margins is in immediate contact with the joint capsule and synovial lining. The tendons and ligaments insert into the bone below the synovial reflection forming the unique structure of the enthesis [2]. As will be discussed below, in RA and SLE, the synovial lining is the site of an intense immune-mediated inflammatory process that results in synovial proliferation and production of potent inflammatory cytokines and soluble mediators that are responsible for the clinical signs of joint inflammation. Synovial inflammation also is present in the SpAs, but unlike the pattern of the joint inflammation in RA and SLE, the entheses are the initial sites of inflammation [3,4]. Subsequently, the inflammatory process extends to the synovial lining, although the distribution and pattern of joint involvement, as well as the response of the periarticular bone to the inflammation differ in RA and the SpAs [5,6].

Rheumatoid arthritis

RA is a systemic inflammatory disorder that is characterized by a symmetrical destructive polyarthritis. The etiology of RA is unknown, but both genetic and environmental factors are involved in its pathogenesis [7,8]. The hallmark of RA is the development of a chronic inflammatory polyarthritis that targets the synovial lining of diarthrodial joints. The earliest changes involve the proliferation of the synovial lining cells, consisting of a population of macrophage-like cells (A cells) and synovial fibroblasts (B cells). There also are extensive neovascularization and perivascular and interstitial infiltration of the synovium with lymphocytes, plasma cells, and activated macrophages. Multiple lines of evidence implicate a pathogenic role for autoantibodies and immune complexes in the development of the synovial lesion, which exhibits features consistent with activation of an adaptive immune response in which activated T and B cells play a key role as primary effectors of the inflammatory process [7–9].

Four distinct patterns of pathologic bone remodeling are observed in RA. These include periarticular osteopenia; focal bone erosions that initially are localized to the joint margins; subchondral bone erosions; and systemic osteoporosis. Juxta-articular bone loss at sites removed from the inflamed synovium is a common finding in RA and frequently precedes the development of marginal joint erosions. Histomorphometric analysis of periarticular bone from RA patients undergoing hand arthroplasty procedures for destructive arthritis shows evidence of both increased bone resorption and formation. Examination of the bone marrow in these regions reveals the presence of infiltrates with lymphocytes and macrophages, suggesting a potential role for local inflammation [10]. Immobilization and reduced mechanical loading are additional factors that have been implicated in the pathogenesis of periarticular bone loss. Importantly, the presence of periarticular bone loss has been shown to have high predictive value with respect to the subsequent development of marginal joint erosions in the hand [11–13].

The marginal joint erosions correspond to sites where the inflamed synovium comes into contact with the bone surface (Fig. 1). At these sites, the bone surface is lined by resorption lacunae containing mono- and multinucleated cells with phenotypic features of osteoclasts [14,15]. Similar sites of focal bone resorption can be identified on the endosteal surface of the subchondral bone. These regions of bone resorption may extend through the calcified cartilage into the overlying articular cartilage, which is then vulnerable to degradation by the invading inflammatory tissue. The initial observations implicating osteoclasts in the pathogenesis of marginal and subchondral bone erosions were based on cell morphology and expression of osteoclast associated genes, including tartrate resistant acid phosphatase (TRAP), cathepsin K and $\alpha V\beta 3$ integrin [14,15]. Studies in mice genetically engineered with an inability to form osteoclasts have more definitively established that osteoclasts are essential for the development of the marginal and subchondral bone erosions in murine models of RA as will be discussed below [16–18]. These conclusions are supported by studies in patients with RA in whom treatment with antiresorptive agents has been shown to reduce the development of joint erosions [19–21].

Studies have helped to establish that the chronic synovial inflammation in RA is dependent on a complex interaction between a network of cytokines and growth factors, as well as direct cell–cell interactions among the cells that populate the inflamed synovium. The development of therapeutic agents that target individual cytokines has revealed the somewhat surprising observation that despite the diversity of these cytokines, targeting of certain key cytokines can produce marked suppression of the synovial and systemic inflammation and retard or even prevent the development of joint destruction. The initial proof of concept studies came from the early clinical trials targeting TNF-α [22,23]. The success of these trials indicated that the cytokine networks and related inflammatory mediators and pathways intersected on an "activation node" involving TNF-α signaling [8]. Subsequently, the use of additional therapeutic agents targeting alternate cytokines, including IL-6 in RA, as well as IL-23 or IL-17 in the SpAs, represents additional "activation nodes" involving these cytokines [24–29]. Therapies targeting T cell co-stimulatory effector pathways also have been shown to be effective in controlling synovial inflammation and joint damage in RA [30]. More recently, therapies targeting B cells also have shown efficacy, providing evidence of the importance of both T and B cells in RA pathogenesis [31].

The capacity of the RA synovium to induce local articular bone resorption can be attributed to the production of a broad spectrum of products with the ability to recruit osteoclast precursors and induce their differentiation and activation into bone resorbing osteoclasts. These include a spectrum of proinflammatory cytokines, chemokines and pro-osteoclastogenic soluble mediators [32–34], including receptor activator of NF-$\kappa\beta$ ligand (RANKL), which is produced by synovial fibroblasts, T cells and B cells within the synovium [35–38]. Table 1 provides a list of the pro-osteoclastogenic cytokines and growth factors produced by the RA synovium. Among the T-cell subsets, both Th1 and Th17 (the major source of IL-17) cells have the capacity to produce RANKL, as well as TNF-α and multiple additional cytokines and mediators with osteoclastogenic activity [39,40]. In addition to the effects of RANKL and TNF-α, T cells also have the capacity to enhance osteoclastogenesis *via* a co-stimulatory pathway involving interaction of paired Ig-like receptor-A (PIR-A), which is expressed on the surface of T cells, and its signaling partner Fc receptor-γ (FcRγ) on osteoclast precursors [41].

The critical role of RANKL in the pathogenesis of joint erosions is provided by the observation that blocking RANKL in animal models of RA with osteoprotegerin (OPG), the RANKL antagonist, results in marked attenuation of joint erosions [42–44]. Additional evidence is provided by studies showing that genetic deletion of RANKL [17] or its receptor RANK [17] in animal models of RA protects animals from both articular and systemic bone loss. More recently, studies in human subjects with RA have shown that blockade of RANKL with Denosumab, a monoclonal antibody that blocks RANKL activity, significantly reduces bone erosions [19,20]. These results provide further evidence that RANKL and osteoclasts play a critical role in articular bone destruction in RA.

The RA synovium also is a source of inhibitors of osteoclastogenesis [32–34]. A list of several of these factors is included in Table 1. Many of