CHAPTER 8

Bone Formation Versus Bone Resorption in Ankylosing Spondylitis

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Abstract

Ankylosing spondylitis (AS) and other forms of seronegative spondylarthritis (SpA) are characterized by two major processes in joints—the first is chronic inflammation and the second is progressive ankylosis. Both features go hand-in-hand and determine the clinical picture of disease, which is joint pain, progressive stiffness and, in case of peripheral joint involvement also joint swelling. The interplay between inflammation and ankylosis is best illustrated in AS, where chronic inflammation of the spine leads to progressive stiffness, reduced spinal mobility and kyphosis. AS may thus be considered as a synthesis of inflammatory disease and bone disease.

Introduction

It is commonly accepted that inflammation is the driving force for structural damage in inflammatory arthropathies. Inflammation in AS is particularly found in the sacroiliac and small facet joints, at the insertion sites of the tendons (enthesis) and along the spinal ligaments. Thus, the localization of inflammatory lesions differs profoundly between AS and rheumatoid arthritis (RA). Whereas RA is considered as a disease primarily affecting the synovial membrane, inflammation in AS is much more pronounced at periarticular sites and has a close relation to insertion sites of ligaments and tendons. Inflammation clearly dominates the clinical picture of AS and precipitates pain, stiffness and loss of function, all of which are reduced by effective therapy. Current knowledge suggest that tumor necrosis factor (TNF) is a pivotal cytokine fueling inflammation in AS, which is backed by the success of treatment of AS by all 3 TNF-neutralizing agents currently on the market.[1-3] The role of other cytokines in AS is much less established at the moment. Moreover there is a central contribution of cyclooxygenase in the clinical features of AS suggesting that the production of small inflammatory lipid mediators like prostaglandin E2 significantly contributes to inflammation in this disease.

The consequences of chronic joint inflammation on articular architecture are entirely different in RA and AS, with the latter showing a much more complex reaction.[4] However, despite these overt differences it is evident that the architectural changes of joints are a consequence of the initial inflammatory attack in both disease entities, since there is clear colocalization between inflammation and structural remodeling.

Lessons from Rheumatoid Arthritis

RA is a prototype of an inflammatory joint disease, which links chronic inflammation with bone damage.[5] The skeletal lesions in RA are basically holes screwed into the juxta-articular bone and show parallels to bone metastases. These lesions form in consequence of chronic inflammatory synovitis,

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which invades and degrades mineralized tissue. Bone destruction in RA is exerted by osteoclasts, which are raised from monocytes/macrophages infiltrating the synovial tissue and differentiate into mature osteoclasts upon cytokine challenge.[6] In RA, bone damage continuously progresses leading to the destruction of the joints by bone erosion, leading to instability and loss of joint function.[7,8] It is an important feature of RA, that there are no major signs of bone and cartilage response towards the inflammatory attack, which allows bone destruction to progress over time. In case of inactive disease these lesions tend to show "sclerosis" on radiographs suggesting that there is at least some reactivity of skeletal tissue. Still bony responses are not an essential part of the clinical picture of RA and instability rather than ankylosis and stiffening is the faith of a joint affected by RA.

Structural Damage in Ankylosing Spondylitis

The hallmark of structural damage in AS is bony ankylosis. Ankylosis is the end stage of an excessive bone formation starting from periosteal sites close to the joint and the intervertebral spaces. Focal bone growth, which starts from the periosteal lining, is termed an "osteophyte", which is a bony spur. Whereas such lesions are virtually absent in RA, they constitute a frequently found pathology in AS, psoriatic arthritis and osteoarthritis. Osteophytes are built up at specific sites, which are usually the edges of bones next to the intra-articular space or to the intervertebral spaces (then termed spondylophytes and syndesmophytes). Syndesmophytes, vertical bony spurs, ultimately leading to a bridge between vertebrae, are a hallmark of AS. Similar lesions, now more horizontally oriented, are also found in degenerative joint diseases such as OA, psoriatic arthritis or hemochromatosis arthropathy. Osteophytes also emerge at insertion sites of the tendons, especially the Achilles tendon and cause pain upon movement. AS teaches us that bone spurs can bridge the entire distance between neighboring skeletal structures, fusing the joint and creating bony ankylosis.

How does this process work? There is yet no full molecular explanation of ankylosis but novel insight in the developmental process of joint formation may help to better understand its basic principles.

Mechanism of Joint Formation—Molecular Lessons for Joint Fusion

Joints and intervertebral spaces form gaps between bones, which allow motion and flexibility. These gaps are actively formed during early development, when chondrogenic formation of the vertebral column and limbs start to branch and build segments. Formation of these gaps depends on the expression of proteins involved in mesenchymal cell differentiation, like cartilage-derived morphogenic proteins- 1 (CDMP-1, also called GDF5) as well as bone morphogenic protein-5 (BMP-5)[9,10] Without these proteins no joints are formed since the appropriate differentiation of cells, which form the synovial membrane, are lacking. Wingless (Wnt) proteins, such as Wnt-14 (also known as Wnt-9a) are also crucial for the initiation of joint formation in the limbs.[10] Joint formation can thus be considered as an active differentiation process, which replaces chondrogenic matrix by specified fibroblast like cells that form the synovial membrane, the periosteum and the joint capsule.

Bony Protrusion as a Stress Response of the Joint

Joints allow maintaining motion, which, however, requires a structurally intact joint space for smooth gliding of articular surfaces. Inflammation leads to joint damage, which causes pain, swelling, stiffness and functional impairment in patients with chronic inflammatory and degenerative joint disease. Under these conditions motion is an exacerbating factor, which enhances symptoms and worsens inflammation. This stress factor can be circumvented by turning on the programs, which regulate bone growth to attempt a bridging of the inflamed and instable joint. Induction of these programs requires the differentiation of cells, which induce bone formation- the osteoblasts. Osteoblasts originate from resident mesenchymal cells, which undergo a series of differentiation steps before becoming major osteoblasts. Upon final differentiation these cells produce bone matrix and facilitate the deposition of hydroxyapatite crystals. Osteoblasts are the natural counterparts of

osteoclasts, the primary bone resorbing cells. Osteoblasts and osteoclasts are functionally coupled and mutually regulate their function. During physiological conditions bone resorption and bone formation are coupled. Osteophyte formation indicates a state, where bone formation by osteoblasts by far outweighs bone resorption by osteoclasts. The attempt of closing the joint and providing stability is thus dependent on a sufficient number of cells, which enter the osteoblast lineage and built up new bony structures.

Osteoblast—The Bone Forming Cells

Differentiation of osteoblasts from mesenchymal cells requires a series of key signals such prostaglandin E2 (PGE2), IGF-1, parathyroid hormone (PTH), bone morphogenic proteins (BMPs) as well as wingless proteins (wnt). All these signals help to drive mesenchymal cells into pre osteoblast and finally into mature osteoblasts, which are cuboid- shaped cells producing the bone matrix. Osteoblastogenesis is regulated by specific transcription factors such as Cbfa-1 (Runx-2) and Osterix, which are required to built up bone. Under physiological conditions very few osteoblasts are found in a joint, which is usually a region of slow bone remodeling, particularly if peripheral joints with a high proportion of cortical bone are examined. Osteoblasts also provide signals to the osteoclast allowing their differentiation form hematopoietic precursors and providing a cellular and molecular link between the bone forming and bone resorbing cells.

From the Osteoblast to the Osteophyte

Osteophyte formation requires bone deposition, which is linked to the osteoblasts. There are two pathways of bone formation, one is the direct differentiation of mesenchymal cells into bone forming osteoblasts and the other more frequent form is endochondral bone formation, which first leads to differentiation of hypertrophic chondrocytes and proteoglycan rich matrix deposition before bone is built up. Formation of osteophytes is usually linked to endochondral bone formation and osteophytes start to grow from periosteal sites close to the articular cartilage (Fig. 1). Insertion sites of tendons are predilection sites for osteophyte formation and point to a mechanical factor, which supports enhanced mesenchymal cell differentiation.[11-13] Alternatively some of the bony spurs observed in AS, especially calcification of the longitudinal ligaments may not be based on endochondral bone formation but rather involve the differentiation of mesenchymal cells into bone forming cells allowing the remodeling of the ligament into a bony bridge. It is not yet clear, which mechanisms dominates bone formation in AS. Morphological studies of the small facet joint of the vertebral column suggest that endochondral ossification participates in joint fusion, building a bridge of hypertrophic chondrocytes filling the joint gap.[14] These cells are then likely replaced by bone when the remodeling of cartilage starts.

Molecular Regulation of Osteophytes

BMPs and Wnt proteins a currently considered as key components, which induce osteophyte formation. Immunohistochemical analysis of osteophytes of the Achilles tendon has demonstrated the expression of phosphorylated and thus activated Smad 3, which is a key component of BMP signaling.[13] This suggests that BMPs induce the differentiation of mesenchymal cells into osteoblasts and drive bone formation, which builds up bony protrusions.[15] Indeed experimental animal models of arthritis, which are characterized by a prominent bone proliferative response such as male DBA mice, exhibit an activation of BMP signaling.[16,17] Moreover, noggin an inhibitor of the BMP pathway can block this proliferative response.[13] Recently, the role of Wnt proteins in osteophyte formation has been investigated. Wnt proteins act synergistic with BMPs in bone formation and are expressed in human joints.[18,19] Activation of the Wnt pathway appears to significantly contribute to bone formation. This is reflected by the effects of blockade of Dickkopf (DKK)-1, an antagonist of Wnt, by neutralizing antibodies.[20] DKK-1 blockade increased Wnt signaling by enhancing the activation of the intracellular signaling molecule beta-catenin and leads to osteophyte growth even in models, where osteophyte formation is normally absent. Increased activation of DKK-1 is observed in RA and may explain the failure of skeletal response towards

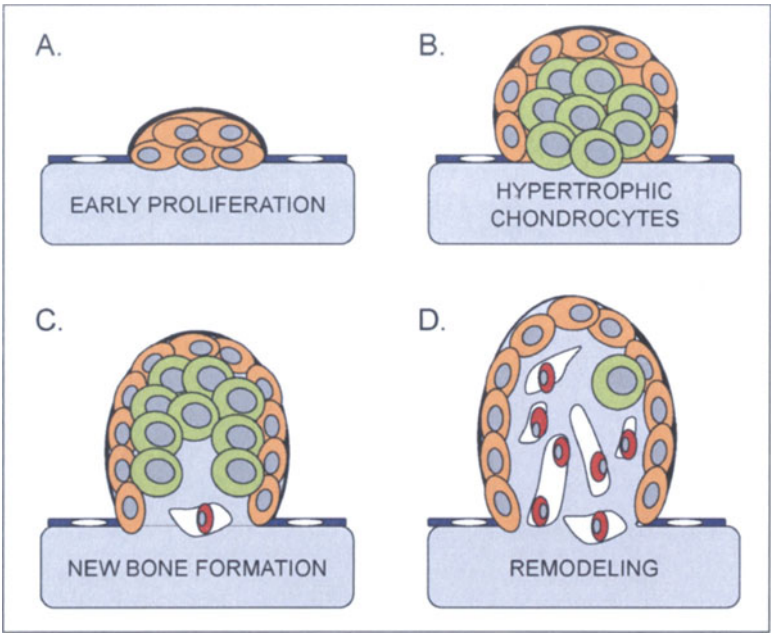

Figure 1. Sequence of osteophyte growth. A) Mesenchymal cell proliferation (orange) at the periosteum; B) Differentiation to hypertrophic chondrocytes (green) in the center and growth by mesenchymal cell proliferation at the top. C) Bone growth (grey) starting when remodeling of primary matrix is initiated; D) Remodeling of the osteophyte by replacing the primary chondrocytic matrix by bone. Vascularization and osteoclast-based bone remodeling (red).

the attack of synovial inflammatory tissue.[20] In AS the levels of DKK-1 are very low, even below normal individuals supporting that Wnt signaling is active in AS. DKK-1, as a major Wnt inhibitor, is regulated by TNF and the failure of TNF to up regulate DKK-1 in AS in contrast to RA remains elusive. These data suggest that BMPs and Wnts are the main driver for the formation of bony spurs. These protein families are involved in mesenchymal cell differentiation and support osteogenic commitment of cells. Other Wnt inhibitors such as FrzB might act similar and affect osteophyte formation by down regulating Wnt signaling.[21]

Concepts of Osteophyte Formation

Osteophyte origin from the periosteum, which is the outer lining layer of bone (Fig. 2). The periosteum covers bone and consists of dense collagen fibers, which are in close contact to mesenchymal cells and microvessels. These cells obviously contain a great potential to proliferate and to differentiate into the various mesenchymal lineages particularly into chondroblasts and osteoblasts. This proliferative burst of mesenchymal cells and their differentiation into chondroblasts and osteoblasts results in a cell cluster close to the bone surface, which then remodels into cartilage and bone based on the matrix deposition by chondroblasts and osteoblasts. Chondroblasts in osteophytic lesions are usually metabolically active hypertrophic chondrocytes similar as they are found in the growth plate. Proteoglycan deposition can occur within osteophytes although proteoglycan content does not meet the one found in articular cartilage. Deposition of bone matrix by osteoblasts is the prerequisite for giving stability to the osteophyte, which then appears as solid bony "swelling" typically seen when peripheral joints are affected. Newly formed bone within the osteophyte contains cartilage and has strong similarities with the primary spongiosa underneath the growth plate. Upon invasion of osteoclasts into osteophytes, which require the

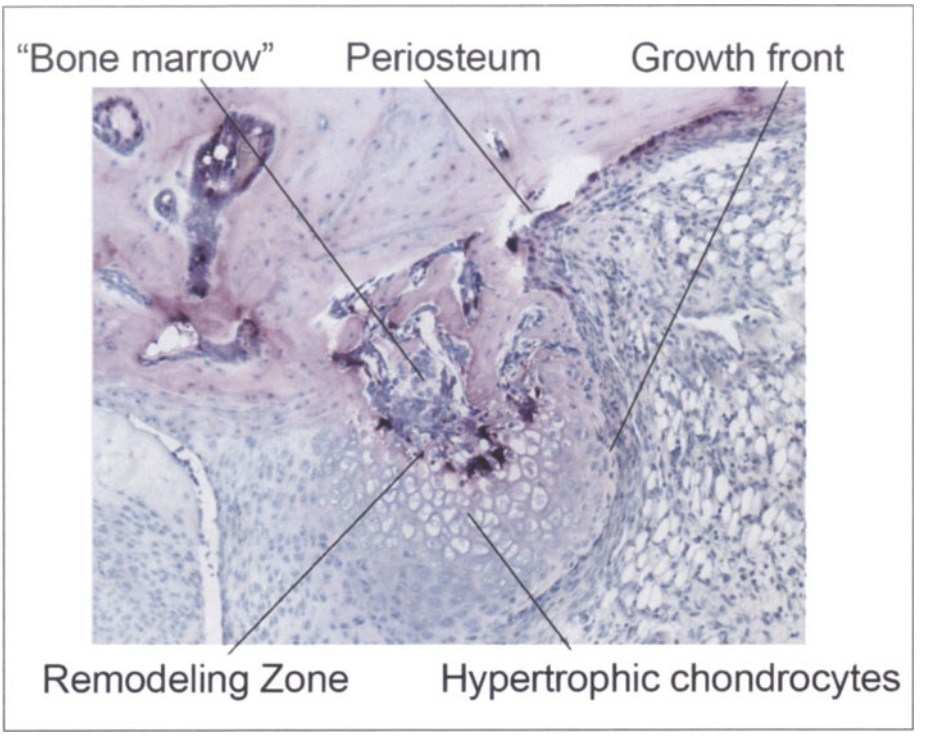

Figure 2. Photomicrograph of an osteophyte. Tartrate-resistant acid phosphatase staining of a section through an osteophyte in a murine model of arthritis. Osteoclasts appears purple and are linked to a newly formed "bone marrow cavity". They are localized at the remodeling front bordering hypertrophic chondrocytes. The periosteum forms the basis of the bony spur; the apex is composed of proliferating mesenchymal cells (growth front).

vascularization of these structures, this primary bone is then rebuilt into secondary spongiosa, which is the mature bone and does not contain cartilage remnants any more. Large osteophytes can even contain bone marrow, which is a consequence of cavity formation within the osteophyte due to osteoclast influx.

Why Do Osteophytes Grow in as and not in RA?

Although RA and AS are both considered as chronic inflammatory joint diseases and share common mediators of inflammation, such as TNF, they exhibit an entirely different clinical picture.[22] AS is a primary osteoproliferative disease, whereas RA is primarily osteodestructive. It is noteworthy that systemic bone is degraded in both RA and AS resulting in osteoporosis and increased fracture risk.[23,24] Systemic bone loss in RA and AS is most likely a consequence of inflammation, which is an independent risk factor for osteoporosis.[25] The reason for the profoundly different pattern of bone remodeling between AS and RA is unclear although there are several hypotheses (Fig. 3).

Differential Distribution

Whereas RA is a disease, which predominantly involves the small joints and spares the vertebral column, except the upper cervical spine, AS is mostly affecting the lower spine and the sacroiliac joints. It may well be, that these different compartments react differently among stress and show a differential susceptibility to osteophyte formation. It is also conceivable that joints like that sacroiliac joint and the intervertebral spaces show a different reaction pattern towards stress as compared

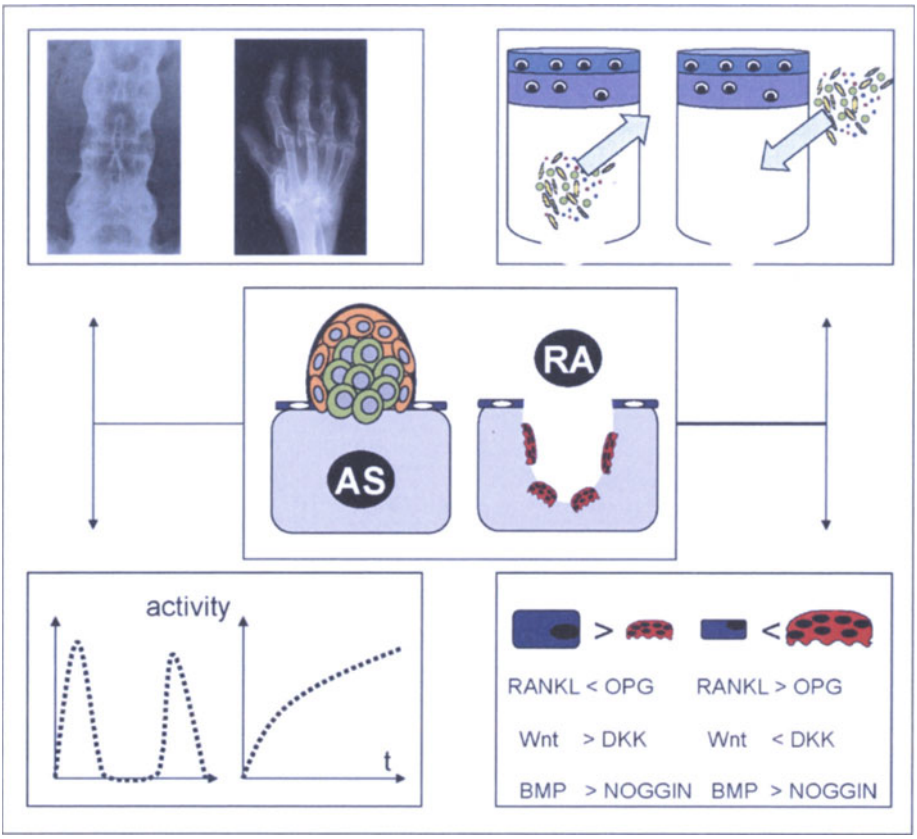

Figure 3. Hypotheses for differential joint remodeling in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Center: Ankylosing spondylitis (AS) is an osteoproliferative condition, whereas rheumatoid arthritis (RA) is an osteodestructive process. Upper left: Different distribution of disease with AS in the spine and RA in the hand. Upper right: Different compartments involved in joints: Prominent bone marrow involvement in AS with the potential for an "inside-to-the-outside" process and synovitis with bone erosions in RA as a potential "outside-to-the-inside" process. Lower left: Intermittent disease course with flares of high activity in AS and chronic progressive course in RA. Lower right: Differences in bone remodeling with high osteoblast activity and increased expression of OPG-, Wnt- and BMP proteins in AS.

to peripheral joints. However, in case of involvement of peripheral joints in AS, the aspect of joint swelling differs from synovitis in RA, involving periarticular structures and the insertion site for ligaments and tendons. This could mean that the articular compartments primarily affected by AS and RA differ from each other even in the same joints.

Bone Marrow Inflammation

As discussed, the compartments of the joint affected by AS and RA differ from each other. Most prominently, this is seen in case of bone marrow involvement. Bone marrow changes are prominent and widespread in AS. The sacral and iliac bones as well as the vertebral bodies show extensive bone marrow inflammation (osteitis), which are a hallmark of AS and detected in MRI scans.[26] In RA, areas of bone marrow changes are usually smaller and more localized. In most cases they are linked to an erosion of the cortical bone layer, which results in bone marrow changes.[27]

Bone marrow inflammation is an important trigger for osteosclerosis. Mixed aggregates of B-cells and T-cells for instance are present in such bone marrow infiltrates and their production of BMPs drives osteoblastogenesis in the bone marrow.[28] Bone marrow inflammation might be a primary event in AS affecting bone formation at periosteal sites. In contrast, RA is dominated by synovitis, which starts outside the cortical bone barrier and invades bone from the outside.

Different Time Courses

In contrast to RA, which is mostly a chronic progressive condition, AS is of a much more episodic character with flares followed by periods of low disease activity. This intermittent course with phases of high and low disease activity in AS might allow joints to respond to the inflammatory attack by new bone formation during periods of low disease activity. This means that disease course in AS has its breaks, which are used for rebuilding of bone as a kind of a stress response. This is an interesting concept since chronic inflammation as it is evident in RA induces the continuous differentiation of osteoclasts, which resorb bone and do not allow an adequate regenerative response.

Molecular Differences

The obvious imbalance between bone formation and bone resorption in AS and RA, with the former dominating in bone formation and the latter being a primarily resorptive disease, is based on differential activation of signaling pathway regulating bone homeostasis. The balances between RANKL and osteoprotegerin (OPG), BMPs and noggin as well as Wnts and DKKs may essentially influence bone remodeling in AS and RA. For instance, Wnt activity is high in AS but not RA and the natural regulators of Wnt, the DKK proteins are blunted in AS but not in RA. Moreover, there is a tight cross talk between these protein families. For instance Wnt proteins induce the activation of OPG, which blocks RANKL activity and thus bone resorption by osteoclasts (20,29).

Conclusions

Although bony proliferations in form of osteophytes, spondylophytes and syndesmophytes can be considered as a response-to-stress strategy of the joint, these lesions affect the function of joints and thus the quality of life. Bone ankylosis is the final consequence of osteoproliferation, which fuses and immobilizes the joint. Thus prevention of ankylosis is a therapeutic aim in AS, which may either achieved by early intervention before bone proliferation has been established or by directly inhibiting the proliferative response by novel drugs, which specifically interfere with bone formation. Both strategies have not been established in AS, although the fact that continuous blockade of cyclooxygenase has proven to be superior to an on-demand use with respect to structural progression in AS.[30] This is particularly interesting since cyclooxygenase is involved in bone formation through generation of PGE2, which is a potent stimulator for bone formation. Thus nonsteroidal anti-inflammatory drugs could indeed have their role in controlling structural damage in AS. Further understanding in the regulation of osteoproliferation in AS is thus warranted and will help to tailor the therapeutic interventions, which prevent structural remodeling in AS.

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