Inflammation and repair mechanisms

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ABSTRACT

Although both rheumatoid arthritis (RA) and ankyosing spondylitis (AS) belong to the group of chronic inflammatory rheumatic diseases, they are quite different regarding mechanisms of inflammation and repair. While RA is an erosive destructive disease with the synovium as the primary site of inflammation, the immune response in AS takes place primarily at the cartilage/bone interface, and the pathological but also the clinical picture is determined by an until not yet well defined interaction between inflammation and new bone formation. Most recently, first insights into the molecular mechanisms between inflammation and bone destruction or new bone formation could be obtained. Key molecules involved in bone homeostasis seem to differ between RA and AS patients. While the molecules sclerostin and dickkopf 1, both inhibitors of osteoblasts, are elevated in RA they are found to be rather low in AS. It can be expected that the rapidly expanding new field of osteoimmunology will help to clarify the pathogenesis of the these two diseases with possible implications for new treatment targets.

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RA and AS share an important common clinical feature, which is the emergence of inflammatory infiltrates along bone. Despite disease processes in RA and AS usually manifest at different skeletal sites, with a dominance of RA in small peripheral joints and AS mainly affecting the axial skeleton, a tight interaction between inflammation and structural bone changes is a common feature in both diseases. Inflammation in RA and AS either affects synovial tissue localized outside the cortical bone lining ("synovitis") or the bone marrow within the cortical bone lining ("osteitis"). Usually, both synovitis and osteitis contribute to inflammation observed in RA and AS, although AS, in contrast to RA, can also affects sites with no direct contact to a synovial membrane such as the vertebral bodies.

Despite such common concept is shared by RA and AS, the disease are substantially different for several reasons: (i) Genetic background of patients with RA differs from individuals with AS, with associations to the shared epitope and PTPN22 in RA, but HLAB27 and IL23R in AS. (ii) Age and sex distribution is fundamentally different as well, with RA most frequently observed with increased age and in females, whereas AS is more frequently found in males. (iii) Localization and time course of RA and AS are different as well, with RA being a prototype of disease affecting peripheral diarthrodial joints and a chronic progressive disease course, whereas affection of the spine and variable disease activity over time is the hallmark of AS. (iv) Although both diseases are considered of autoimmune origin, only RA shows a strong autoantibody response in the majority of patients, whereas autoantibodies production is not a major component of AS. (v) Despite RA and AS share some extra-articular involvements such as increased risk for cardiovascular disease and osteoporosis due to their systemic inflammatory nature, most of the extra-articular organ involvements differ from each other, with RA associated with rheumatoid nodules, vasculitis and mononeuritis but AS associated with inflammatory bowel disease, psoriasis and anterior uveitis.

These differences are of pivotal importance to better understand diseases like RA and AS but also shape the specific gestalt of each of the 2 diseases, which we are familiar with. In addition, RA and AS differ in one more decisive feature, which significantly contributes the phenotype of the disease and allow further differentiation between RA and AS. RA is a bone erosive disease, leading to resorption of periarticular bone, cortical breaks and defects in the

bony architecture along inflamed joints. In RA bone is replaced by soft tissue, mostly inflammatory tissue (1). In AS, however, one can exactly find the opposite picture: Soft tissue along joints and intervertebral spaces is replaced by bone. AS is driven by an anabolic bone response with formation of bony spurs bridging intervertebral spaces (syndesmophytes), affecting peripheral joints (osteophytes) or the insertion sites of the tendons (enthesiophytes) (2).

Loss of periarticular bone in RA but apposition in AS can be explained by a profoundly different potential of repair. RA can be considered as hypo-regeneratory bone pathology, whereas AS is hyper-regeneratory. As bone is a dynamic tissue adapting to individual demands it can usually effectively respond to stress and even damage. The best example is fracture healing, which results in appropriate repair of damaged bone. In both RA and AS bone faces an inflammatory insult but repair mechanisms are inappropriate- whereas repair in RA is virtually lacking, it is inappropriate in AS due to bony overgrowth.

Absence of adequate response of bone in RA is evident from virtual lack of bone formation, even growth of bony spurs, which is surprising since bone has an enormous capacity to rebuild and to repair damage. This suggests that signals derived from inflammatory tissue actively block repair processes by inhibiting bone formation. Current concepts suggest that repair of bone is induced by osteocytes localized within tiny lacunae inside bone, which are connected by small canaliculi forming a communication network inside bone, which can sense damage (3). These osteocytes express sclerostin, a molecule specific to osteocytes, which acts as a Wnt-pathway antagonist and blocks bone formation. Low sclerostin expression leads to bone growth, whereas high expression inhibits bone formation. Recently, TNF has been identified as an inducer of sclerostin expression, which could explain low repair in disease like RA, where bone s exposed to high local levels of TNF (4). Interestingly, sclerostin expression is indeed high in periarticular bone of RA suggesting that bone formation is inhibited despite overt bone damage (5). Moreover, other repressors of bone formation may contribute to low degree of repair in RA as well. Dkk-1, for instance, is a Wnt-antagonist like sclerostin, which is induced by TNF and effectively blocks bone formation (6, 7). DKK-1 is expressed by synovial fibroblasts and its expression is induced through engagement of TNF receptor 1 and activation of mitogen-activated protein kinases. Induced expression of Dkk-1 in arthritic joints blocks essential pathways of bone formation and thus negatively affects repair of damage bone.

In AS, there is a profoundly increased capacity to form new bone. As new bone formation preferentially occurs at sites of inflammation, like vertebral bodies, sacroiliic joints and entheses, inflammation is conceived as crucial trigger for new bone formation, suggesting a response-to-injury concept (8). Data from longitudinal studies using MRI scanning have suggested that bone formation occurs preferentially at skeletal sites, which are affected by osteitis, although co-localization of osteitis and bony spurs is far from being complete (9-11). Incomplete correlation may be based on the fact that inflammatory lesions depicted by MRI are of limited duration and may regress after certain time either spontaneously or after therapy. In fact, regression of acute inflammatory lesions might be an important trigger for repair to start. It is thus likely that inflammation, particularly osteitis, is a trigger for new bone formation in AS and that bony spurs do not just emerge randomly with no relation to inflammation. Importantly, new bone formation is confined to very specific sites and does not occur throughout the entire skeleton in AS, which would result in osteosclerosis and thus not reflects the overall osteoporotic phenotype in AS patients.

It is unclear what kind of specific insult to bone is necessary to induce formation of bony spurs and whether it requires initial bone resorption or not. Newer data suggest that bony spur formation can occur in the absence of significant bone resorption and osteoclast activity, since these lesions can grow even if osteoclast activity is abolished right from the onset of arthritis (12, 13). These observations may point to a direct interaction between inflammation and bone formation, suggesting that either inflammatory signals themselves or signals involved in the resolution of inflammation trigger new bone formation in response to an inflammatory stimulus. Key drivers of the inflammatory response, such as TNF, for instance are not directly responsible for bony spur formation, as TNF- blockade has consistently failed to affect this repair process in both animal models of arthritis and AS patients (12, 14, 15). As TNF down regulates repair and inhibits bone formation by inducing inhibitors of bone formation, a direct role of TNF in new bone formation in AS is very unlikely (6). However, the link between TNF and new bone formation in AS could be an indirect one, since TNF fuels inflammation, which is considered a key trigger for repair. Early intervention of TNF- blocking agents, which neutralize inflammation before onset of bony repair could indeed be effective, reflecting the concept *less damage-less repair*.

Which are the molecular and cellular signals driving excessive repair in AS? Recent investigations suggests that expression of key molecules involved in bone homeostasis may differ among RA and AS patients (6). Sclerostin expression in osteocytes is low in AS, with most osteocytes negative for sclerostin, which is a key inhibitor of osteoblast activity (5). Moreover, expression of Dkk-1 another key antagonist of the Wnt-pathway is blunted in AS, which results in enhanced activation of beta-catenin and activation of genes which trigger osteoblast differentiation and new bone formation (6, 7). At the same time Wnt activation blocks osteoclast differentiation and thus further increases dysbalance of bone formation and bone resorption in favor of the former one, enabling bony overgrowth (6, 16). Aside Wnt, also activation of BMP signaling has been shown in bony spurs, particularly those localized along the entheses. That BMPs participate in formation of bone spurs is especially supported by expression and activation of Smad-3, a key molecule involved in

BMP signaling (17). How down-regulation of factors such as sclerostin and Dkk-1 is accomplished, however, and whether it is a primary event or rather influenced by factors involved in inflammation and/or resolution of inflammation remains unclear to date.

Since bony spur formation in AS is a reaction of resident tissue towards newly built inflammatory tissue, it can be considered as a repair strategy in response to an inflammatory insult. Bony spur formation requires a series of processes, which include proliferation of mesenchymal cells, homotypic cellular aggregation, differentiation of cells into hypertrophic chondrocytes and osteoblasts as well as remodeling of tissue into bone requiring vasculogenesis and influx of osteoclasts. At least part of bony spur formation is driven by endochondral ossification leading to differentiation of hypertrophic cartilage as an intermediate state before its remodeling into bone. It appears, however, that endochondral ossification is not the only pathway leading to bony spurs as also evidence for a role of membranous bone formation and chondroidal metaplasia has been obtained especially in case of new bone formation along enthesial sites (18).

In summary, RA and AS show profound differences in the interphase between inflammation and repair, with RA being chararacterized by absence of repair and AS by exaggerated repair even leading to ankylosis of joints. The underlying cause for these overt differences is not fully understood but may involve different mechanisms: (i) The anatomical sites affected by RA and AS are substantially different and a certain micro-environmental factors might be crucial for bony spur formation. Presence of fibrocartilage, for instance, has been considered to be important for bony spur formation and the amount of fibrocartilage present along joints significantly differs among various skeletal regions (19, 20). (ii) RA and AS are characterized by major differences in the disease course, with RA being a chronic progressive disease but AS a much more flare-like disease presumably allowing sufficient time for repair. (iii) RA is primarily driven by synovitis, whereas AS is a disease with prominent osteitis. Inflammation in the bone marrow could have substantially different effects on repair than synovitis given that osteitis in contrast to synovitis can effectively induce bone formation. (iv) Expression of molecular regulators of bone formation such as Dkk-1 and sclerostin, is substantially different expressed in RA than in AS, resulting in blocked bone formation in RA but activation of bone formation signals in AS. Importantly, these concepts are not necessarily exclusive as they could act in synergy contributing to the difference in repair observed in RA and AS.

References

1. MCINNES I, SCHETT G: Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Immunol* 2007; 7: 429-42.
2. SIEPER J, APPEL H, BRAUN J, RUDWALEIT M: Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. *Arthritis Rheum* 2008; 58: 649-56.
3. BONEWALD LF, JOHNSON ML: Osteocytes, mechanosensing and Wnt signaling. *Bone* 2008; 42: 606-15.
4. VINCENT C, FINDLAY DM, WELLDON KJ *et al*.: Proinflammatory cytokines TNF-related weak inducer of apcptosis (TWEAK) and TNFalpha induce the mitogen activated protein kinase (MAPK)-Dependent Expression of Sclerostin in Human Osteoblasts. *J Bone Miner Re*s 2009 Mar 17.
5. APPEL H, RUIZ-HEILAND G, LISTING J *et al*.: Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2009, in press.
6. DIARRA D, STOLINA M, POLZER K *et al*.: Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007; 13: 156-63.
7. UDERHARDT S, DIARRA D, KATZENBEISSER J *et al*.: Blockade of Dickkopf-1 induces fusion of sacroiliac joints. Ann *Rheum Dis* 2009 Mar 26.
8. SCHETT G, LANDEWÉ R, VAN DER HEIJDE D: Tumor necrosis factor blockers and structural remodeling in ankylosing spondylitis: what is reality and what is fiction? *Ann Rheum Dis* 2007; 66: 709-11.
9. MAKSYMOWYCH WP, CHIOWCHANWISAWAKIT P, CLARE T, PEDERSEN SJ, OSTERGAARD M, LAMBERT RG: Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: Evidence of a relationship between inflammation and new bone formation. *Arthritis Rheum* 2009; 60: 93-102.
10. SIEPER J, APPEL H, BRAUN J, RUDWALEIT M: Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. *Arthritis Rheum* 2008; 58: 649-56.
11. VAN DER HEIDE D, LANDEWÉ R, BARALIAKOS X *et al*.: MRI-inflammation of the vertebral unit only marginally contributes to new syndesmophyte formation in that unit: a muli-level analysis. *Ann Rheum Dis* 2008; 67, (Suppl. II): 130, OP-0259.
12. SCHETT G, STOLINA M, DWYER D *et al*.: TNF-α and RANKL blockade can not halt bony spur formation in experimental inflammatory arthritis. *Arthritis Rheum* 2009, in press.
13. LORIES RJ, DERESE I, LUYTEN FP: Inhibition of osteoclasts does not prevent joint ankylosis in a mouse model of spondyloarthritis *Rheumatology* (Oxford) 2008; 47: 605-8.
14. LORIES RJ, DERESE I, DE BARI C, LUYTEN FP: Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. *Arthritis Rheum* 2007; 56: 489-97.
15. VAN DER HEIJDE D, LANDEWÉ R, EINSTEIN S *et al*.: Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008; 58: 1324-31.
16. GLASS DA, BIALEK P, AHN JD *et al*.: Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. *Dev Cell* 2005; 8: 751-64.
17. LORIES RJ, DERESE I, LUYTEN FP: Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. *J Clin Invest* 2005; 115: 1571-9.
18. BENJAMIN M, TOUMI H, SUZUKI D, HAYASHI K, MCGONAGLE D: Evidence for a distinctive pattern of bone formation in enthesophytes. *Ann Rheum Dis* 2009; 68: 1003-10.
19. BENJAMIN M, MCGONAGLE D: The anatomical basis for disease localization in seronegative spondylarthropathy at entheses and related sites. *J Anat* 2001; 199: 503-26.
20. MCGONAGLE D, WAKEFIELD RJ, TAN AL *et al*.: Distinct topography of erosion and new bone formation in Achilles tendon enthesitis: Implications for understanding the link between inflammation and bone formation in spondyloarthritis. *Arthritis Rheum* 2008; 58: 2694-9.