Differences in pathophysiology between rheumatoid arthritis and ankylosing spondylitis

R.J. Lories[1] and D.L.P. Baeten[2]

[1]*Laboratory for Skeletal Development and Joint Disorders, Division of Rheumatology, Department of Musculoskeletal Sciences, Katholieke Universiteit Leuven, Belgium;* [2]*Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, The Netherlands.*

Rik J. Lories, MD, PhD
Dominique L.P. Baeten, MD, PhD

Dr Lories is the recipient of a postdoctoral fellowship from the Flanders Research Foundation (FWO Vlaanderen). His work on spondyloarthritis is supported by Grants from FWO Vlaanderen and KU Leuven.
Dr Baeten is supported by a Vidi grant of The Netherlands Scientific Organisation and by the Dutch Arthritis Foundation.

Please address correspondence to:
Dr. Rik Lories,
Division of Rheumatology, UZ Leuven,
Herestraat 49,
B-3000 Leuven,
Belgium.
E-mail: Rik.Lories@uz.kuleuven.be

Dr. Dominique Baeten,
Department of Clinical Immunology and Rheumatology, F4-218,
Academic Medical Center,
Meibergdreef 9,
1105 AZ Amsterdam,
The Netherlands.
E-mail: D.L. Baeten@amc.uva.nl

Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55): S10-S14.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2009.

Key words: Ankylosing spondylitis, spondylarthritis, rheumatoid arthritis, synovitis, cartilage, bone, immune system diseases.

Competing interests: none declared.

ABSTRACT

Rheumatoid arthritis and ankylosing spondylitis are common and severe chronic inflammatory skeletal diseases. Recognizing the differences rather than emphasizing similarities is important for a better understanding of the disease processes, the identification of specific therapeutic targets and in the long-term better treatment options for the individual patients. We discuss a number of pathophysiological differences between rheumatoid arthritis and ankylosing spondylitis by looking at the anatomical characteristics, differences and similarities in the autoimmune and autoinflammatory reactions, association with other immune mediated inflammatory diseases, structural outcome, and their potential significance for further therapeutic developments. Further research into the differences between these diseases should focus on the specific nature of the immune/inflammatory components, the role of resident cells in the joint and joint-associated tissues, the types and mechanisms of tissue remodeling and the characteristics of the articular cartilage. Better insights into their individual characteristics may lead to better therapeutic strategies, specific targets and useful biomarkers.

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are common and severe chronic inflammatory skeletal diseases with a high burden on society, in particular since many patients are affected at a young age and no cure for the diseases is available. Although the cardinal signs of inflammation in the joint or spine are similar (*rubor, tumor, calor, dolor et functio laesa*), differences in clinical presentation, genetic associations and structural outcome clearly indicate that these chronic arthritides are distinct disorders with specific pathophysiological mechanisms. Recognizing the differences rather than emphasizing similarities is important for a better understanding of the disease processes, the identification of specific therapeutic targets and in the long-term better treatment options for the individual patients.

RA typically presents as a symmetric polyarthritis, affecting more women than men and is linked with the presence of autoantibodies in the serum such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF). HLA-DR genes are strongly associated with the disease. Axial involvement is very rare with the exception of the articulation between the dens and the atlas. Chronic inflammation in RA is leading to cartilage and bone destruction which is typically recognized as erosive disease on x-rays. In contrast, AS is characterized by axial disease involving the sacroiliac joints and the spine. Peripheral arthritis is less common and mainly non-symmetrical oligoarticular and typically found in the lower limbs. AS affects more men than women and is very strongly associated with HLA-B27. The long-term outcome is determined by ankylosis in the spine and sacroiliac joints but also by joint destruction (*e.g.* in the hips). AS is part of the spondyloarthritis (SpA) concept together with reactive arthritis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, juvenile and undifferentiated spondyloarthritis. All the diseases in the spondyloarthritis concept share clinical, genetic and pathophysiological characteristics.

This is clearly illustrated by the observation that the much more frequent appearance of peripheral arthritis in patients with psoriatic arthritis shows more genetic, epidemiological, histomorphological and molecular similarities with other spondyloarthritides than with RA (1-3).

Janssen Biotech, Inc.
Exhibit 2083
Accord v. Janssen
IPR2026-00259
Ex. 2083-001

In this review we discuss a number of pathophysiological differences between prototype diseases RA and AS by looking at the anatomical characteristics, differences and similarities in the autoimmune and autoinflammatory reactions, association with other immune mediated inflammatory diseases, structural outcome, and their potential significance for further therapeutic developments.

Anatomy

Synovitis is the central feature of RA and its involvement can explain most features of the disease including the extensive joint destruction that is commonly seen. Chronic inflammation in the synovium triggers a transformation of residing or infiltrating mesenchymal cells and macrophages into a so-called pannus tissue. This tumor-like tissue produces tissue destructive enzymes such as matrix metalloproteinases and stimulates osteoclast formation through the RANKL-RANK system. Of interest, synovial fibroblasts isolated from RA patients retain their aggressive phenotype in experimental systems (4, 5) and changes at the genetic level in these cells have been suggested (6, 7). Whereas these data indicate that RA is primary a synovial disease, a number of important questions remain to be solved, including the preferential involvement of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) over distal interphalangeal (DIP) joints and the absence of synovitis in sacroiliac joints. Moreover, recent evidence linking smoking to the development of ACPA antibodies has challenged the concept that the disease is initiated in the joint and emphasized the systemic nature of RA with potential involvement of lungs, lymph nodes and other tissues.

The primary target tissue in AS and related spondyloarthritis is more difficult to identify. AS is typically a disease of the axial skeleton but can also involve peripheral joints. Studies of the sacroiliac and zygoapophyseal joints in the axial skeleton and arthroscopy studies of peripheral joints provided solid evidence that the synovium is involved and that synovitis can be responsible for many symptoms of the disease. However, many manifestation of AS in the spine occur in the absence of synovial joints and suggest that the synovium is not the default centre of the pathophysiology. Two other tissues that are part of the skeletal system have been associated with AS and related spondyloarthritides: the enthesis and the bone.

The enthesis, an anatomical zone in which the fibers of tendons, ligaments and capsulae insert into the underlying bone was proposed as the primarily involved tissue in AS by Ball in his Heberden oratio (8). The relative lack of anatomy studies in patients with AS, mainly caused by the difficulties faced when trying to obtain material from the human spine, resulted in little progress to further define the role of the enthesis. The use of new imaging techniques such as nuclear magnetic resonance imaging (MRI) resulted in new studies and hypotheses on enthesitis (9, 10). Combining these MRI observations with anatomical studies linking the enthesis with biomechanical concepts, the work of McGonagle and Benjamin supported a model of the so-called enthesis organ as the primary target tissue in AS and related spondyloarthritides (11, 12). This enthesis concept explains many of the disease localizations that are not characterized by the presence of a synovial joint.

However, the use of enthesitis within the joint as a specific discriminating factor between AS and RA has been more controversial. Accordingly, MRI imaging has also demonstrated synovial and bone marrow involvement in the disease processes (13, 14). Additional histomorphological studies also support involvement of bone marrow and synovium in AS (15-19). Bone marrow involvement (osteitis) in particular can be considered as a third primary site of inflammation in AS.

Although the synovium, the enthesis, and the bone can be inflamed in SpA, the enthesis concept remains very useful to explain a number of specific features of the disease. The enthesis is subject to important biomechanical forces and prone to microdamage. We have recently proposed that microdamage could be the triggering factor to develop entheseal inflammation which, under specific circumstances, could give rise to a typical chronic arthritis (20). It explains spinal disease, fasciitis plantaris and other extra-articular manifestation such as achilles' tendon insertion involvement. Activation of progenitor cells in the enthesis may also be the trigger for the new cartilage and bone formation that is recognized in AS and related spondyloarthritides (20, 21). The relative resistance of the enthesis to vascular and cellular invasion however challenges the central role of the enthesis in chronic peripheral arthritis. A hypothesis to link the enthesis with chronic inflammation in the synovium and bone marrow was recently proposed (22). The close anatomic relationship between the latter sites and the enthesis and the immense potential for cell accrual in synovium and bone marrow may explain the development of chronic synovitis and bone marrow edema as a secondary phenomenon to entheseal involvement. However, as mentioned previously, this hypothesis is based on cross-sectional imaging studies and animal models and thus any statement about primary versus secondary lesions remains highly speculative. Alternatively, the same biomechanical stress factors that contribute to disease at the enthesis may also be crucial determinants of disease at other disease sites such as synovium and bone. Globally, the enthesitis hypothesis emphasizes the need for longitudinal studies in early AS and RA patients with combined MRI and histopathological assessment in order to better define the exact anatomical site of the original lesions and its relationship with biomechanical stress.

Synovitis and inflammation

Despite the differences in anatomical localization of the disease, synovial inflammation of large joints such as knees and ankles is a common feature shared by RA and AS/SpA. Moreover, the development of needle arthroscopy as minimally invasive methodology to samples synovial biopsies allows to study clinically relevant samples in early and active disease as well as to perform longitudinal studies during treatment (23). This approach has allowed a number of systematic comparisons of

Ex. 2083-002

the synovial inflammation in SpA and RA, leading to 3 important concepts.
Firstly, synovial features in RA support the concept that this disorder is driven by genuine T and/or B cell autoreactivity. Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies (ACPA) are produced locally in the joint (24), specific autoantigens are present and processed locally in the inflamed tissue (25-28), and synovial T cells display specific clonal alterations (29). Whereas these data indicate that the synovial membrane is an important target tissue of this autoimmune process, the debate remains open whether it also functions as secondary lymphoid organ (30). Indeed, synovial ectopic lymphoid neogenesis occurs as frequently in seropositve as seronegative disease and appears to be closely correlated with the degree of inflammation rather than with the production of autoantibodies or clonal T or B cell alterations (31, 32).
In contrast to RA, specific adaptive autoimmune features are not found in SpA synovitis, where the inflammation seems to be dominated by innate immune cells such as macrophages, polymorphonuclear cells, and mast cells (3, 19, 33, 34). The correlation of the presence of these innate immune cells with the degree of inflammation, the absence of known autoantibodies in SpA, and the fact that the disease can be triggered by microbial and biomechanical stress suggest an autoinflammatory rather than autoimmune origin.
Secondly, macrophages appear to be the main downstream effectors of synovial inflammation in both diseases. Accordingly, they are senstitive biomarkers of response to treatment (35, 36). However, further characterization of these synovial macrophage populations as well as of peripheral blood monocytes suggests the hypothesis that RA may be characterized by classically (IFN gamma driven) activated macrophages in comparison with the predominance of alternatively activated macrophages in SpA (37-39). Although this concept requires further validation, it seems to correlate with a clearly distinct inflammatory milieu in the inflamed joint with lower levels of soluble TNF and IL-1 in SpA than in RA (2).
Thirdly, beside the immune and inflammatory part of the synovial process, there are also clear differences in the structural, non-immune features of the synovitis. The most obvious ones are the strongly increased vascularity in SpA versus RA and the more pronounced synovial lining layer hyperplasia in RA (19, 33). However, both the origin of these features and the consequences for bone and cartilage destruction and remodeling remain uncertain. Indeed, a number of key mediators of tissue destruction (MMPs, RANK-RANKL-OPG system, cadherin-11) seems to be equally expressed in RA and SpA synovitis (40-42). The phenotype and functional behaviour of fibroblast-like synoviocytes, which contribute to cartilage destruction and promote osteoclast activation, has been extensively studied in RA but remains to be compared to SpA.
An important aspect of the interpretation of these data is whether the data obtained in knee and ankle joints can be extrapolated to other typical disease manifestations such as the small fingers joints and wrists in RA and the axial skeleton in SpA. In RA, one study systematically comparing the synovial immunopathology of large and small joints obtained similar findings in both disease sites (43). Moreover, both large and small joints appear to react similarly to treatment. In contrast, histopathological data on axial disease in SpA are scarce (15, 16, 18) and have not yet been systematically compared with peripheral arthritis. Moreover, axial and peripheral disease in SpA may react differently to specific drugs, as illustrated by sulphasalazine.
Another question which has not been resolved yet is why peripheral synovitis is usually persistent in RA. As discussed, this may relate to the exact nature of the trigger (ongoing autoimmune process in RA versus more transient microbial and/or mechanical triggers in SpA). Alternatively, the feed-back loops and amplification mechanisms governing the transition from acute to chronic inflammation may differ between the two conditions. Characterization of these mechanisms remains a major challenge for arthritis as well as other types of chronic inflammation.

Extra-articular manifestations

Besides the prototypical joint inflammation, both RA and SpA can affect other organs and tissues. The most striking extra-articular features in RA are rheumatoid nodules, vasculitis, pneumonitis, and scleritis. Interestingly, these manifestations appear to be correlated with the presence of HLA-DR4 and the presence of autoantibodies such as rheumatoid factor, pointing to the systemic autoimmune origin of these features. Accordingly, there is a prominent infiltration with $CD4^+$ T cells and B lymphocytes in RA pneumonitis (44).
SpA is frequently associated with inflammatory bowel disease (IBD), psoriasis, and acute anterior uveitis. Aortitis can also be observed. Although the presence of axial and peripheral arthritis, colitis, and skin and nail diseases in the HLA-B27 transgenic rat model (45) points towards a pathogenic relation between these features, it remains difficult the find the common denominator in human SpA. Genetically, uveitis is strongly related to HLA-B27, but IBD and psoriasis are not. Genome wide associations studies have recently revealed the presence of common genetic features such as SNPs in the IL-23R gene (46-48). Clinically, gut inflammation and peripheral arthritis seems to be associated both in time and in severity (49). This association is confirmed by histologic observations (37) as well as by the absence of both features in HLA-B27 transgenic rats kept in germfree conditions (50). In contrast, the link between skin psoriasis and joint inflammation in psoriatic arthritis is less obvious. The occurrence of arthritis is linked neither to the onset nor to the severity of skin psoriasis. More intriguingly, T cell directed therapies such as alefacept and efalizumab are very effective for skin disease but have no or moderate impact on arthritis (51, 52), suggesting that different cellular and molecular mechanisms are responsible for these lesions. In line with the postulated autoinflammatory origin of SpA, all extra-articular disease localization are highly exposed to microbial and/or mechanical triggers. Taken together, RA appears to be a systemic autoimmune disease whereas the different disease localization in SpA may rather reflect the sensitivity of specific organs and tissues

Ex. 2083-003

for autoinflammatory reactions to microbial and mechanical stress.

Bone and cartilage

Two important features appear to distinguish AS from RA when focusing on bone and cartilage. The first one is obvious. In RA joint damage is characterized by extensive destruction with little or now signs of tissue repair. In contrast, in AS joint and spine damage are mainly characterized by new cartilage and bone formation leading to ankylosis of the sacroiliac, zygoapophyseal joints and the spine. Also in patients with peripheral arthritis or extra-articular entheseal involvement, new cartilage and bone formation mainly presenting as enthesophytes are often found but complete joint ankylosis is much more rare. Another feature that has been less studied is the observation that cartilage damage in AS in patients with peripheral arthritis is much more limited than in patients with RA.

The remodeling phenotype of AS as compared to the destructive features of RA has only recently been studied at the molecular level. Data obtained in mouse models suggest that activation of bone morphogenetic protein and Wnt signaling pathways are critical in new cartilage and bone formation leading to ankylosis (20, 21, 53-55). The intruiging question from the pathophysiological point of view is how these developmental signaling pathways are activated (in AS) and eventually inhibited. The Leuven group has recently put forward the hypothesis that activation of bone morphogenetic signaling is due to entheseal stress or microdamage (20). Acute inflammation due to the microdamage can play a role in this initial activation but the process itself appears relatively independent from chronic inflammation suggesting that these are uncoupled processes (56,57). In contrast, high inflammation and in particular the presence of tumor necrosis factor appears to inhibit Wnt signaling by upregulating Wnt coreceptor antagonist Dickkopf1 (DKK1). Antibodies against DKK1 transform the destructive phenotype of arthritis in human TNF transgenic mice into a remodeling phenotype with osteophytes (54, 55).

The specific nature of new bone formation in AS remains an important issue. Current data suggest that direct bone formation by osteoblasts, endochondral bone formation by progenitor cells and cartilage metaplasia each have a role. Specific targeting of new tissue formation in AS and related spondyloarthritides may therefore need to taken all these phenomena into account.

Potential differences in cartilage remodeling between RA and SpA have been less well studied. Clinical and radiological observations suggest that joint space narrowing due to cartilage loss is less common in SpA than in RA. This may be related to the lower levels of soluble TNF and IL-1 beta in the inflamed SpA joint (3), as these two cytokines do not only drive cartilage destruction but also severely impair cartilage anabolism. Recent biomarker studies support this concept (58). An important question is whether the presumed resistance to damage of articular cartilage in SpA relates to the previously described mechanisms and genetic potential to form new cartilage and bone in AS.

Conclusions and perspectives

Current concepts of inflammation, tissue destruction and remodeling in RA and AS provide ample support for a clear distinction between these common forms of inflammatory joint and bone disease. RA is considered an autoimmune disease in which the synovial tissues transforms into a destructive pannus leading to erosion and loss of joint function. In AS and related spondyloarthritides, enthesitis, osteitis and synovitis reflect an autoinflammatory process that is less likely to cause classical tissue destruction but that is strongly associated with new cartilage and bone formation sometimes leading to ankylosis. Further research into the differences between these diseases should focus on the specific nature of the immune/inflammatory reaction, the role of resident cells in the joint and joint-associated tissues, the types and mechanisms of tissue remodeling and the characteristics of the articular cartilage. Better insights into the individual characteristics of AS and RA may lead to better therapeutic strategies, specific targets and useful biomarkers.

References

1. SAID-NAHAL R, MICELI-RICHARD C, D'AGOSTINO MA *et al*.: Phenotypic diversity is not determined by independent genetic factos in familial spondylarthropathy. *Arthritis Rheum* 2001; 45: 478-84.
2. KRUITHOF E, BAETEN D, DE RYCKE L *et al*.: Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. *Arthritis Res Ther* 2005; 7: 569-80.
3. VAN DOOREN B, NOORDENBOS T, AMBARUS C *et al*.: Absence of a classically activated macrophage cytokine signature in peripheral spondylarthritis, including psoriatic arthritis. *Arthritis Rheum* 2009; 60: 966-75.
4. MULLER-LADNER U, KRIEGSMANN J, FRANKLIN BN *et al*.: Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. *Am J Pathol* 1996; 149: 1607-15.
5. PAP T, MULLER-LADNER U, GAY RE, GAY S: Fibroblast biology. Role of synovial fibroblasts in the pathogenesis of rheumatoid arthritis. *Arthritis Res* 2000; 2: 361-7.
6. FIRESTEIN GS, ECHEVERRI F, YEO M, ZVAIFLER NJ, GREEN DR: Somatic mutations in the p53 tumor suppressor gene in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A* 1997; 94: 10895-900.
7. KAROUZAKIS E, GAY RE, GAY S, NEIDHART M: Epigenetic control in rheumatoid arthritis synovial fibroblasts. *Nat Rev Rheumatol* 2009; 5: 266-72.
8. BALL J: Enthesopathy of rheumatoid and ankylosing spondylitis. *Ann Rheum Dis* 1971; 30: 213-23.
9. MCGONAGLE D, GIBBON W, EMERY P: Classification of inflammatory arthritis by enthesitis. *Lancet* 1998; 352: 1137-40.
10. MCGONAGLE D, GIBBON W, O'CONNOR P, GREEN M, PEASE C, EMERY P: Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondylarthropathy. *Arthritis Rheum* 1998; 41: 694-700.
11. BENJAMIN M, MCGONAGLE D: The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 2001; 199: 503-26.
12. BENJAMIN M, MORIGGL B, BRENNER E, EMERY P, MCGONAGLE D, REDMAN S: The "enthesis organ" concept: why enthesopathies may not present as focal insertional disorders. *Arthritis Rheum* 2004; 50: 3306-13.
13. ZOCHLING J, BARALIAKOS X, HERMANN KG, BRAUN J: Magnetic resonance imaging in ankylosing spondylitis. *Curr Opin Rheumatol* 2007; 19: 346-52.
14. ESHED I, BOLLOW M, MCGONAGLE DG *et al*.: MRI of enthesitis of the appendicular skeleton in spondyloarthritis. *Ann Rheum Dis* 2007; 66: 1553-9.
15. FRANCOIS RJ, GARDNER DL, DEGRAVE EJ, BYWATERS EG: Histopathologic evidence that sacroiliitis in ankylosing spondylitis is not merely enthesitis. *Arthritis Rheum* 2000; 43: 2011-24.
16. APPEL H, KUHNE M, SPIEKERMANN S *et al*.: Immunohistologic analysis of zygapophyseal joints in patients with ankylosing spondylitis.

Ex. 2083-004

Arthritis Rheum 2006; 54: 2845-51.
17. APPEL H, LODDENKEMPER C, GROZDANOVIC Z *et al*.: Correlation of histopathological findings and magnetic resonance imaging in the spine of patients with ankylosing spondylitis. *Arthritis Res Ther* 2006; 8: R143.
18. APPEL H, KUHNE M, SPIEKERMANN S *et al*.: Immunohistochemical analysis of hip arthritis in ankylosing spondylitis: evaluation of the bone-cartilage interface and subchondral bone marrow. *Arthritis Rheum* 2006; 54: 1805-13.
19. BAETEN D, KRUITHOF E, DE RYCKE L *et al*.: Diagnostic classification of spondylarthropathy and rheumatoid arthritis by synovial histopathology: a prospective study in 154 consecutive patients. *Arthritis Rheum* 2004; 50: 2931-41.
20. LORIES RJ, LUYTEN FP, DE VLAM K: Mechanisms of new bone formation in spondyloarthritis. *Arthritis Res Ther* 2009; 1: 221.
21. LORIES RJU, 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.
22. MCGONAGLE D, LORIES RJ, TAN A, BENJAMIN M: The concept of a synovio-entheseal complex and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum* 2007; 56: 2482-91.
23. BAETEN D, VAN DEN BOSCH F, ELEWAUT D, STUER A, VEYS EM, DE KEYSER F: Needle arthroscopy of the knee with synovial biopsy sampling: technical experience in 150 patients. *Clin Rheumatol* 1999; 18: 434-41.
24. MASSON-BESSIÈRE C, SEBBAG M, DURIEUX JJ *et al*.: In the rheumatoid pannus, antifilaggrin autoantibodies are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum. *Clin Exp Immunol* 2000; 119: 544-52.
25. BAETEN D, PEENE I, UNION A *et al*.: Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium - Relevance to antifilaggrin autoantibodies. *Arthritis Rheum* 2001; 44: 2255-62.
26. DE RYCKE L, NICHOLAS AP, CANTAERT T *et al*.: Synovial intracellular citrullinated proteins colocalizing with peptidyl arginine deiminase type 2 as pathophysiologically relevant antigenic determinants of rheumatoid arthritis specific humoral autoimmunity. *Arthritis Rheum* 2005; 52: 2323-30.
27. STEENBAKKERS PGA, BAETEN D, ROVERS E *et al*.: Localization of MHC class II/ HC gp-39 complexes in synovia of rheumatoid arthritis patients using complex-specific monoclonal antibodies. *J Immunol* 2003; 170: 5719-27.
28. BAETEN D, STEENBAKKERS PGA, RIJNDERS AMW *et al*.: Specific presence of MHC/HC gp-39 complexes in rheumatoid arthritis synovitis as a new and independent histological marker. *Arthritis Rheum* 2004; 50: 444-51.
29. CANTAERT T, BROUARD S, THURLINGS RM *et al*.: Alterations of the synovial T cell repertoire in anti-citrullinated protein antibody positive rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 1944-56.
30. HUMBY F, BOMBARDIERI M, MANZO A *et al*.: Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium. *PLoS Med* 2009; 6: e1.
31. CANTAERT T, KOLLN J, TIMMER T *et al*.: Humoral autoimmunity in the rheumatoid joint is not driven by ectopic lymphoid neogenesis. *J Immunol* 2008; 181: 785-94.
32. CANETE JD, SANTIAGO B, CANTAERT T *et al*.: Ectopic lymphoid neogenesis in psoriatic arthritis. *Ann Rheum Dis* 2007; 66: 720-6.
33. BAETEN D, DEMETTER P, CUVELIER C *et al*.: Synovial histology is dependent on diagnosis and disease activity: a comparative study of rheumatoid arthritis, spondyloarthropathy and osteoarthritis. *Ann Rheum Dis* 2000; 59: 945-53.
34. BAETEN D, KRUITHOF E, DE RYCKE L *et al*.: Infiltration of the synovial membrane with macrophage subsets and polymorphonuclear cells reflects global disease activity in spondyloarthropathy. *Arthritis Res Ther* 2005; 7: 359-69.
35. HARINGMAN JJ, GERLAG DM, ZWINDERMAN AH *et al*.: Synovial tissue macrophages: highly sensitive biomarkers for response to treatment in rheumatoid arthritis patients. *Ann Rheum Dis* 2005; 64: 834-8.
36. KRUITHOF E, DE RYCKE L, VANDOOREN B *et al*.: Identification of synovial biomarkers of response to experimental treatment in early phase clinical trials in spondylarthropathy. *Arthritis Rheum* 2006; 54: 1795-804.
37. BAETEN D, DEMETTER P, CUVELIER CA *et al*.: Macrophages expressing the scavenger receptor 163: a link between immune alterations of the gut and synovial inflammation in spondyloarthropathy. *J Pathol* 2002; 196: 343-50.
38. BAETEN D, MOLLER HJ, DELANGHE J *et al*.: CD163+ macrophages and local production of soluble CD163 are associated with lower lymphocyte activation in spondyloarthropathy synovitis. *Arthritis Rheum* 2004; 50: 1611-23.
39. SMITH JA, BARNES MD, HONG D, DELAY ML, INMAN RD, COLBERT RA: Gene expression analysis of macrophages derived from ankylosing spondylitis patients reveals interferon-gamma dysregulation. *Arthritis Rheum* 2008; 58: 1640-9.
40. VANDOOREN B, KRUITHOF E, YU DT *et al*.: Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor alpha blockade in spondylarthropathy. *Arthritis Rheum* 2004; 50: 2942-53.
41. VANDOOREN B, CANTAERT T, NOORDENBOS T, TAK PP, BAETEN D: The abundant synovial expression of the RANK/RANKL/Osteoprotegerin system in peripheral spondylarthritis is partially disconnected from inflammation. *Arthritis Rheum* 2008; 58: 718-29.
42. VANDOOREN B, CANTAERT T, TER BORG M *et al*.: TNF alpha drives cadherin-11 expression in rheumatoid inflammation. *Arthritis Rheum* 2008; 58: 3051-62.
43. KRAAN MC, REECE RJ, SMEETS TJ, VEALE DJ, EMERY P, TAK PP: Comparison of synovial tissues from the knee joints and the small joints of rheumatoid arthritis patients: implications for the pathogenesis and evaluation of treatment. *Arthritis Rheum* 2002; 46: 2034-8.
44. ATKINS SR, TURESSON C, MYERS JL *et al*.: Morphologic and quantitative assessment of CD20+ B cell infiltrates in rheumatoid arthritis-associated nonspecific interstitial penumonia and usual interstitial pneumonia. *Arthritis Rheum* 2006; 54: 635-41.
45. HAMMER RE, MAIKA SD, RICHARDSON JA, TANG JP, TAUROG JD: Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. *Cell* 1990; 63: 1099-112.
46. DUERR RH, TAYLOR KD, BRANT SR *et al*.: A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; 314: 1461-3.
47. RAHMAN P, INMAN RD, GLADMAN DD, REEVE JP, PEDDLE L, MAKSYMOWYCH WP: Association of interleukin-23 receptor variants with ankylosing spondylitis. *Arthritis Rheum* 2008; 58: 1020-5.
48. SMITH RL, WARREN RB, EYRE S *et al*.: Polymorphisms in the IL-12beta and IL-23R genes are associated with psoriasis of early onset in a UK cohort. *J Invest Dermatol* 2008; 128: 1325-7.
49. RUDWALEIT M, BAETEN D: Ankylosing spondylitis and bowel disease. *Best Prac Res Clin Rheumatol* 2006; 20: 451-71.
50. TAUROG JD, RICHARDSON JA, CROFT JT *et al*.: The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; 180: 2359-64.
51. MEASE PJ, GLADMAN DD, KEYSTONE EC: Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006; 54 1638-45.
52. PAPP KA, CARO I, LEUNG HM, GAROVOY M, MEASE PJ: Efalizumab for the treatment of psoriatic arthritis. *J Cutan Med Surg* 2007; 11: 57-66.
53. LORIES RJ, DAANS M, MATTHYS P *et al*.: Noggin haploinsufficiency differentially affects tissue responses in destructive and remodeling arthritis. *Arthritis Rheum* 2006; 54: 1736-46.
54. DIARRA D, STOLINA M, POLZER K *et al*.: Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007; 13: 156-63.
55. UDERHARDT S, DIARRA D, KATZENBEISSER J *et al*.: Blockade of Dickkopf-1 induces fusion of sacroiliac joints. *Ann Rheum Dis* 2009 March 26 [Epub ahead of print].
56. LORIES RJ, DERESE I, DE BARI C, LUYTEN FP: Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondyloarthritis. *Arthritis Rheum* 2007; 56: 489-97.
57. LORIES RJ, DERESE I, LUYTEN FP: Inhibition of osteoclasts does not prevent joint ankylosis in a mouse model of spondyloarthritis. *Rheumatology* 2008; 47: 605-8.
58. VANDOOREN B, CANTAERT T, VAN LIEROP MJ *et al*.: Melanoma inhibitory activity, a biomarker of chondrocyte anabolism, is reversibly suppressed by proinflammatory cytokines in rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 1044-50.

Ex. 2083-005