Abstract
Joint destruction and tissue responses determine the outcome of chronic arthritis. Joint inflammation and damage are often the dominant clinical presentation. However, in some arthritic diseases, in particular the spondyloarthritides, joint remodeling is a prominent feature, with new cartilage and bone formation leading to ankylosis and contributing to loss of function. A role for bone morphogenetic proteins in joint remodeling has been demonstrated in the formation of both enthesophytes and osteophytes. Data from genetic models support a role for bone morphogenetic protein signaling in cartilage homeostasis. Finally, this signaling pathway is likely to play a steering role in the synovium.

Introduction
The classic signs and symptoms of arthritis - rubor, tumor, calor, dolor et functio laesa - cover a vast world of dynamic systemic and local processes with complex interactions between networks at the cellular and molecular levels. Major advances in our understanding of the pathology of chronic arthritis and new imaging techniques have highlighted distinct mechanisms of disease. In the joint, these include the development and persistence of an inflammatory and immune reaction, the activation of tissue destructive enzymes and cells, and the suppression or stimulation of molecular pathways regulating homeostasis, repair and remodeling (Figure 1).

Mechanisms of inflammation and auto-immunity have been studied most extensively, leading to the identification of key cell populations, such as T cells, B cells and macrophages, and of important messenger molecules, including cytokines such as tumor necrosis factor-α (TNFα). As a result, innovative targeted therapeutic strategies have an unprecedented effect on both rheumatoid arthritis (RA) and the spondyloarthritides (SpA). In addition, new immunological targets are identified at an amazing pace [1].

Two discoveries have recently opened up new paths of investigation for cartilage and bone destruction: the molecular characterization of osteoclast differentiation and activation [2] and the transformation of the synovium into tissue-destructive pannus tissue [3]. In addition, the success of the current treatment strategies has prompted new attention to be focused on repair and remodeling responses of joint tissues [4].

Tissue responses to inflammation or destruction in the joint can be physiological or pathological. Normal tissue responses include the regeneration or repair of soft and hard tissues, including cartilage and bone. Tissue regeneration involves a complete restoration of the original tissue with maintenance of function and homeostasis. This is perceived as a rare event. In tissue repair, the damaged tissue is replaced by a surrogate tissue with, at best, a partial restoration of its function. This is likely less durable and may evolve over time into functional failure. The articular cartilage has a very limited tissue restoration and repair capacity [5]. In bone, a tissue with a remarkable repair potential, such responses appear suppressed, probably by persistent inflammation [6]. In addition, abnormal tissue responses leading to joint remodeling, such as new cartilage and bone formation, may result in joint ankylosis and further loss of function [7].

We have used these tissue responses as a basis for an alternative mechanistic classification of chronic arthritis [8]. The disease can be defined as a ‘destructive’ arthritis, a ‘steady-state’ arthritis, and a ‘remodeling’ arthritis. In the first form, very little, if any, restoration or repair is observed, even with control of the inflammatory process. In the second form, local restoration or repair responses may be sufficient for many years, although ultimately joint homeostasis can be lost, resulting in joint failure. Finally, remodeling with neocartilage
and bone formation can be present. This may result in excessive responses, causing joint ankylosis, thereby directly contributing to loss of joint function and disability. In this concept, existing clinical boundaries are of less importance for the understanding of the molecular processes involved. More importantly, translation of this concept into animal models of disease could further strengthen our mechanistic approach to chronic arthritis.

Bone morphogenetic proteins

Reactivation of molecular signaling pathways that are critical for tissue formation during development and growth is increasingly recognized in the homeostasis, repair and remodeling of postnatal tissues. We have hypothesized that such signaling pathways including bone morphogenetic proteins (BMPs) may also be of importance in arthritis [4,8,9]. BMPs and closely related growth and differentiation factors comprise a large group of structurally related polypeptides that belong to the transforming growth factor-β (TGFβ) superfamily [10]. The original discovery of BMPs as protein factors that ectopically induce a cascade of endochondral bone formation in vivo [11] has strongly stimulated the study of their function in skeletal development (for a review, see [12]) and joint morphogenesis (for a review, see [13]). However, BMPs are involved in a wide array of biological processes, both during development and in postnatal life [14]. These include the specification of the dorso-ventral body axis and the development, growth and homeostasis of many organs. BMPs can act as morphogens, growth factors or cytokines depending on their spatio-temporal expression and target cells. Their downstream effects include cell lineage determination, differentiation, motility, adhesion and death [14].

BMPs induce ligand-dependent type I and type II receptor heterodimerization. These receptors are transmembrane serine-threonine kinases and phosphorylate intracellular receptor-smad signaling molecules (R-smad1/5) that bind common smad4 (co-smad4) and then translocate to the nucleus [10]. The diversity of cell responses to BMPs can at least partially be explained by differences in the affinities of different ligands for specific type I and II receptor combinations. BMP signaling is further regulated by extracellular antagonists such as noggin, chordin, gremlin, the DAN/Cerberus family, follistatin, follistatin-related protein and sclerostin (for a review, see [15]), by accessory receptors and by intracellular inhibitors. Transcriptional responses to BMP signaling are tightly controlled by different co-activators and co-repressors [10]. BMPs can also activate mitogen activated kinases such as p38 [16].

Bone morphogenetic proteins in ‘remodeling arthritis’

Our group has been investigating the role of BMPs in an animal model of remodeling arthritis [17,18]. Spontaneous arthritis in aging male DBA/1 mice is characterized by new cartilage and bone formation at the entheses, progressively leading to joint ankylosis [19]. The proximal interphalangeal joints or ankles of the hindpaws are mainly involved. Other features of the model include dactylitis and nail lesions. We therefore consider this murine arthritis a model for tissue remodeling in SpA and, in particular, in psoriatic arthritis [19].

The exact trigger for enthesal new tissue formation is not clear. Injury, mechanical stress, hormones and activation of the immune system may all play a role [19-21]. Joint remodeling in this model is characterized by accumulation of spindle-shaped fibroblast-like cells, chondrogenic differentia-
tion, chondrocyte hypertrophy and replacement of the cartilage by bone. This is a typical cascade of endochondral bone formation. However, in continuity with the endochondral bone front, a small zone of direct bone formation is also recognized.

We studied the presence of different BMPs in this process [17]. BMP2 was associated with early events whereas BMP7 and BMP6 were mainly found in pre-hypertrophic and hypertrophic chondrocytes, respectively. Overexpression of noggin, a non-specific endogenous BMP antagonist, inhibited both clinical onset and severity of disease in a preventive and therapeutic strategy [17]. Detailed histomorphological analysis revealed that BMP signaling is critically important in the early stages of the disease processes, in particular in the commitment of progenitor cells to the chondrogenic lineage. Phosphorylation of smad1/5 molecules was used as a marker for activation of the BMP signaling pathway. Active BMP signaling was found in cells entering chondrogenic differentiation. These data were further corroborated by immunohistochemistry for phosphorylated smad molecules on human biopsies from entheseal lesions at the achilles tendon insertion of SpA patients [17].

However, the role of BMP signaling in the cascade of endochondral bone formation as seen in this model is more complex. Endogenous expression of noggin is important to counteract the BMP signal once the cells start chondrogenesis to allow progression towards chondrocyte hypertrophy and new bone formation [18]. Therefore, in noggin haploinsufficient mice, where endogenous noggin levels are reduced by about 50%, incidence of disease is not different from the wild type but progression of disease is delayed [18].

As for all animal models of disease, this model has both strengths and weaknesses. It allows the molecular analysis of ankylosis originating from the entheseal sites. However, the role of inflammation, innate and adaptive immunity in the murine disease is not yet clear and the specific relevance thereof for human SpA remains to be defined.

BMP and related TGFβ signaling have also been studied in osteophyte formation in mouse models of osteoarthritis (OA). Injection of recombinant BMP2 into healthy murine knees enhanced proteoglycan synthesis in the articular cartilage but also stimulated osteophyte formation. Interestingly, osteophytes induced by BMP2 injection were found predominantly in the regions where the growth plate met the joint space, whereas TGFβ-induced osteophytes originated from zones of the periosteum that were more remote from the growth plate [22,23]. Synovial macrophages appear to be critical in this process as osteophyte formation induced by TGFβ was reduced after depletion of macrophages by intra-articular liposomes. The number of BMP2 and BMP4 positive cells in these experiments declined upon depletion of the macrophages [24]. Similarly, depletion of macrophages also inhibited osteophyte formation in collagenase-induced arthritis, a mouse model of joint instability leading to osteoarthritis [25]. Papain-induced arthritis is a mouse model in which direct injection of papain depletes articular cartilage proteoglycans, leading to accelerated osteoarthritis-like lesions. Osteophyte formation in this model can be inhibited by adenoviral overexpression of both BMP and TGFβ antagonists. Again, expression of BMP2 and BMP4 in this model was markedly increased in the synovium [26]. Further analysis in this model and in a spontaneous model of osteoarthritis suggested that BMP2 expression occurs at later stages than TGFβ3 [27].

Two groups have studied expression of BMPs in human osteophytes [28,29]. Zoricic and colleagues [28] observed three different types of bone formation in the growing osteophyte: endochondral, and membranous from the periost and from the endosteum. Immunohistochemistry demonstrated BMP2 in both fibrous matrix and osteoblasts. BMP3 was found in osteoblasts and osteoclasts, BMP6 in osteocytes and osteoclasts, and BMP7 in hypertrophic chondrocytes, osteoblasts and osteocytes. Nakase and colleagues [29] demonstrated BMP2 in fibroblastic mesenchymal cells, fibrochondrocytes, chondrocytes and osteoblasts at both the mRNA and protein levels.

A key question is whether remodeling in SpA and OA are different (Figure 2). The enthesis has been suggested as the primary site of disease in SpA [30]. New tissue formation at the enthesis is a factor that contributes to pathology in SpA. The exact nature of the process is controversial. A classic point of view suggests that the formation of enthesisphyes is a repair phenomenon [31]. However, the tissue response is excessive, suggesting that the process contributes more to pathology than to restoration of tissue function.

Osteophyte formation as typically seen in osteoarthritis may be of a different nature. It does not arise from the insertion sites but at the junctional zone where the synovium overlies the bone [32] (Figure 2). There is no evidence that the osteophyte contributes to the signs and symptoms in peripheral joints. Rather, it is hypothesized that osteophytes represent an attempt at repair and a stabilizing effort in a damaged joint [33]. Ankylosis is rarely, if ever, seen. Therefore, the nature of osteophytes in OA and enthesophytes in SpA is very different. Enthesophyte formation in SpA is a potential therapeutic target, in particular since new tissue formation and inflammation appear to be at least partially uncoupled events [34].

**Bone morphogenetic proteins in ‘steady-state’ arthritis**

The articular cartilage is a highly specialized tissue with unique properties. Its function is critically dependent on the interaction between the cells (chondrocytes) and their extracellular matrix and it is resistant to vascular invasion and mineralization. The complex regulation of extracellular matrix synthesis suggests that the articular chondrocytes can retain...
Intra-articular injections of BMP2 in the mouse knee have been used to assess the effect of this BMP on articular cartilage in vivo. BMP2 stimulates proteoglycan synthesis in normal knees but cannot do this in a model of destructive arthritis [36].

### Bone morphogenetic proteins in joint destruction

The role of BMPs in the normal and inflamed synovium, in particular in a destructive arthritis such as RA, is less clear. The increasing interest in mesenchymal populations in the synovium and the role of stem cells in arthritis [37-39] has stimulated research into embryonic signaling pathways that typically guide mesenchymal stem cell behavior [4,40] (Table 2). We have demonstrated that BMP2 and BMP6 are expressed in synovial biopsies obtained from patients with chronic arthritis [9]. Protein levels of BMP2 and BMP6 were significantly higher in patients with RA and SpA compared to non-inflammatory controls. BMP2 and BMP6 protein was found in both macrophages and fibroblast-like synoviocytes as demonstrated by immunohistochemistry [9]. BMP2 and BMP6 expression in fibroblast-like synoviocytes in vitro was

### Table 1

| In vivo evidence supporting a role for BMPs in cartilage homeostasis |
|---------------------------------------------------------------|
| Pro-homeostatic effects                                      |
| Normal BMP receptor type la [35]                             |
| Noggin haploinsufficiency [18]                               |
| Injection of BMP2 [22]                                       |
| Anti-homeostatic effects                                     |
| Noggin overexpression [18]                                   |

BMP, bone morphogenetic protein.

Our group studied the effect of noggin (Nog) haploinsufficiency on joint destruction in two different models of arthritis, collagen-induced arthritis and methylated bovine serum albumin (mBSA) induced arthritis [18]. Noggin is expressed in articular cartilage. Reduction of noggin levels by about 50% (haploinsufficient Nog^floxP/floxP mice) did not affect severity of inflammation in both models. However, reduced noggin levels in Nog^floxP/floxP mice protected the articular cartilage in mBSA arthritis (Table 1). This was associated with enhanced BMP signaling in the articular cartilage as demonstrated by immunohistochemistry for phosphorylated smad1/5. Overexpression of noggin in wild-type mice in both models increased cartilage damage, probably by reducing BMP activity [18].

Cartilage homeostasis to a certain degree or for a limited period in case of chronic or progressive strain such as seen in OA. This homeostasis is critically dependent on the balance between, and the magnitude of, anabolic and catabolic molecular pathways. However, the restoration and repair capacity of the articular chondrocytes is limited [5]. Chondral lesions without injury to the subchondral bone do not heal spontaneously and gradually worsen. Osteochondral defects penetrate into the bone and show some attempts at repair, with invasion of mesenchymal progenitor cells from the subchondral bone marrow cavities. However, fibrocartilaginous rather than articular cartilage tissue is formed.

The role of BMPs in articular cartilage homeostasis and repair has been extensively studied in vitro and ex vivo (for a review, see [8]). More recently, the positive or anabolic effects of BMPs in this context have been further corroborated by in vivo data [18,35] (Table 1). Rountree and colleagues [35] developed a conditional gene deletion system that takes advantage of the expression of Gdf5, the murine homolog of cartilage derived morphogenetic protein-1 in the joint interzone during morphogenesis. Heterozygous BMP-receptor (Bmpr)-Ia^+/− mice, engineered to express a Cre recombinase in the Gdf5 locus (Gdf5^Cre/+;BmprIa^+/−) were crossed with mice that carry a floxed Bmprla allele (Gdf5^+/+;Bmprla^floP/PrfP). The Gdf5^Cre/+;Bmprla^floP conditional knockout progeny were viable and showed some mild developmental defects (short ears, soft tissue syndactyly between digit 1 and 2 and tarsal joint ankylosis). Importantly, Gdf5^Cre/+;Bmprla^floP mice failed postnatally to maintain articular cartilage in many joints compared to litter mate ‘control’ (Gdf5^+/+;Bmprla^+PrfP) mice. At birth the digit joints appeared normal, with high expression of both aggrecan and collagen type II mRNA in the two groups. As soon as one week after birth and more clearly by two weeks, changes in the articular cartilage had occurred. Expression of proteoglycans and collagen type II mRNA was greatly reduced. In other joints of forefeet and hindfeet similar changes were observed at seven weeks. By nine months of age, many regions of the cartilage were severely damaged. Progressive degenerative changes were also observed in the knee joints and triggered a loss of function.

Figure 2

Enthesophytes and osteophytes are different. (a) The enthesophyte originates from the insertion of capsule and tendons (arrows). The chondro-osseous border of the articular cartilage is not involved (asterisks). (b) Osteophyte originating from the border of the articular cartilage (asterisks). In contrast, the enthesis is normal (arrows).
upregulated by pro-inflammatory cytokines such as IL1 and TNFα. We also demonstrated that BMP2 is associated with fibroblast-like synoviocyte apoptosis in vitro and in vivo [9]. In contrast, BMP4 and BMP5 were downregulated at the mRNA level in RA and OA samples versus normal controls as demonstrated by Bramlage and colleagues [41]. In normal synovium, BMP4 and BMP5 positive cells were found mainly in the lining layer, whereas in RA these cells were more scattered.

It is noteworthy that the presence of BMPs in the synovium is not associated with local cartilage or bone formation at these sites. This again highlights the complex biology of BMPs that should be considered as pleiotropic cytokines and growth factors with distinct effects on different cell types. Identification of target cells for BMP signaling in synovium and their biological relevance is, therefore, an important challenge. Our preliminary observations suggest that both blood vessel associated cells and mesenchymal cells in the synovium can be activated by BMPs (unpublished observations). Expression of different BMP receptors is present in fibroblast-like synoviocyte cultures [42]. Again, the local balance with antagonists and the processing of pro-peptides into mature forms will ultimately determine the impact of BMP signaling at the single cell and tissue level.

Further evidence may again come from animal models. BMP-Rla positive cells have been identified as potential mesenchymal stem cells in both RA [38] and joints from mice with collagen-induced arthritis, a model of RA [39]. Surprisingly, infiltration of cells into the synovium from the bone marrow apparently precedes the onset of symptoms in the induced model and a specific role for this cell population in disease pathogenesis has been hypothesized [39].

Of particular interest are recent data on the epithelioid character of the lining layer and its transformation towards a more typical mesenchymal cell type in arthritis [43]. RA synovial fluid stimulated this so-called epithelial-mesenchymal transition of normal fibroblast-like synoviocytes, an effect that could be inhibited in vitro by BMP7.

All these data provide further evidence that BMPs may act as regulatory molecules within the healthy and inflamed synovium (Table 2).

### Perspectives

There is accumulating evidence that the tissue-resident cells of the normal synovium are critically involved in chronic arthritis [44]. These cells include both the mesenchymal fibroblast-like cells, macrophages and endothelial cells. Little is known about the role of these cell populations in joint remodeling - some of them may be targets for BMP signaling. Different hypotheses have been formulated to explain the role of such populations in arthritis.

The ‘transformation hypothesis’ proposes that fibroblast-like synoviocyte are stably transformed by the chronic inflammatory processes in the synovium. This results in a more aggressive cell type, pannocytes, with distinct morphological characteristics and the ability to attach to and invade the articular cartilage, as elegantly demonstrated in in vivo models of cartilage and synoviocyte co-implantation in SCID mice [45]. Mutations in tumor suppressor genes such as that encoding p53 have been documented and could explain some aspect of this altered cell behavior [46]. An alternative view suggests that low activity fibroblast-like synoviocyte/mesenchymal stem cells from the sublining zone acquire phenotypical characteristics of lining layer cells but lack positional information with overgrowth and invasion of cartilage and bone [47].

The transformation hypothesis was incorporated in the ‘effector cell hypothesis’. The late destructive phase of RA, typically characterized by pannus, osteoclast activation and secretion of tissue-destructive enzymes, is considered mainly T-cell independent as it seems to be driven by an ‘autonomous’ fibroblast-like synoviocyte population, as suggested by the transformation hypothesis. Expansion and influx of mesenchymal cell populations are considered as a contributing factor in these processes [48].

These two hypotheses clearly focus on the tissue-destructive aspect of arthritis. There is also increasing evidence that the tissue-resident cell populations (mesenchymal cells, macrophages and endothelial cells) and embryonic signaling pathways play a part in the initiation and progression of arthritis. The ‘stromal code’ hypothesis [49] states that the stromal cell population of an organ provides differentiation, retention and exit signals for immune cells. The endothelium defines a stromal address code regulating cell entry by a number of selectins, integrins and chemokines. The code within the tissue further steers behavior of cells that have invaded the synovium.

Based on these theories and new experimental evidence from both developmental biology and arthritis research, we have proposed the ‘signaling center hypothesis’ [37]. Inflammation
and tissue destruction trigger a reaction aimed at repairing and conserving tissue function. However, in some cases this process is ill-coordinated within an inflammatory environment and leads to changes in the tissue-resident cell populations. Mesenchymal cells accumulate either by local proliferation, transdifferentiation or influx from other compartments such as blood or bone marrow. These cell populations can typically form signaling centers that regulate the behavior of surrounding cells. This concept from developmental biology places the stromal code hypothesis in a broader biological context. It enables understanding of not only the destructive but also the remodeling processes as the molecular signaling centers can guide both, dependent on the balance between tissue-destructive and homeostatic/repairative molecular signaling. As summarized above, there is increasing evidence that BMPs are involved in these processes. Moreover, interactions between mesenchymal cells and immune cells are likely to be critical in this process and may contribute to the differences between destructive and remodeling arthritis. In this context it is noteworthy that we and others identified macrophages as a source of BMPs in the joint [9,24].

Conclusion

BMPs are pleiotropic cytokines, growth factors and morphogens. Increasing evidence supports a critical role for BMP signaling in joint remodeling, particularly in entheseophyte formation in SpA. In addition, BMPs support cartilage homeostasis and repair. The role of BMP signaling in synovitis is still unclear, but a role as regulatory molecules is hypothesized.

Competing interests

The authors have filed a patent on the use of BMP inhibitors for the treatment of spondyloarthritis.

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References

1. Mclnnes IB, Liew FY: Cytokine networks - towards new therapies for rheumatoid arthritis. Nat Clin Pract Rheumatol 2005, 1: 31-39.
2. Sato K, Takeyanaig H: Osteoclasts, rheumatoid arthritis, and osteoimunology. Curr Opin Rheumatol 2006, 18:419-426.
3. Karouzas E, Neidhart M, Gay RE, Gay S: Molecular and cellular basis of rheumatoid joint destruction. Immunol Lett 2006, 106: 8-13.
4. Luyten FP, Lories RJ, Verschueren P, De Vlam K, Westhovens R: Contemporary concepts of inflammation, damage and repair in rheumatic diseases. Best Pract Res Clin Rheumatol 2006, 20:829-848.
5. Buckwalter JA: Articular cartilage injuries. Clin Orthop 2002, 402:21-37.
6. Rau R: Is remission in rheumatoid arthritis associated with radiographic healing? Clin Exp Rheumatol 2006, 24:S041-S044.
7. De Vlam K, Lories RJ, Luyten FP: Mechanisms of pathologic new bone formation. Curr Rheumatol Rep 2006, 8:332-337.
8. Lories RJ, Luyten FP: Bone morphogenetic protein signaling in joint homeostasis and disease. Cytokine Growth Factor Rev 2005, 16:267-298.
9. Lories RJU, Derese I, Ceuppens JL, Luyten FP: Bone morphogenetic proteins 2 and 6, expressed in arthritic synovium, are regulated by proinflammatory cytokines and differentially modulate fibroblast-like synoviocyte apoptosis. Arthritis Rheum 2003, 48:2807-2818.
10. Miyanaga K, Maeda S, Inamura T: BMP receptor signaling: transcriptional targets, regulation of signals, and signaling cross-talk. Cytokine Growth Factor Rev 2005, 16:251-263.
11. Urist MR: Bone: formation by autoinduction. Science 1965, 150:893-899.
12. Brennenberg HM: Developmental regulation of the growth plate. Nature 2003, 423:332-336.
13. Luyten FP, Lories RJ, De Bari C, De Valck D, Dell’Accio F: Bone morphogenetic proteins and the synovial joint. In Bone Morphogenetic Proteins: Regeneration of Bone and Beyond. Edited by Vukicevic S, Sampath KT. Basel: Birkhüser AG; 2004:187-212.
14. Martinovic S, Borovecki F, Sampath KT, Vukicevic S: Biology of bone morphogenetic proteins. In Bone Morphogenetic Proteins: Regeneration of Bone and Beyond. Edited by Vukicevic S, Sampath KT. Basel: Birkhüser AG; 2004:45-72.
15. Balemans W, Van Hul W: Extracellular regulation of BMP signaling in vertebrates: a cocktail of modulators. Dev Biol 2002, 250:231-250.
16. Hoffmann A, Preobrazhenska O, Wodarzycz K, Medler Y, Winkel A, Shahab S, Huylenbroeck D, Gross G, Verschueren K: Transforming growth factor-beta-activated kinase-1 (TAK1), a MAP3K, interacts with Smad proteins and interferes with osteogenesis in murine mesenchymal progenitors. J Biol Chem 2005, 280:27271-27283.
17. Lories RJU, Derese I, Luyten FP: Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing spondylitis. J Clin Invest 2005, 115:1571-1579.
18. Lories RJ, Daan S, Matthys P, Kaaran A, Tyzianowski P, Ceuppens JL, Luyten FP: Noggin haploinsufficiency differentially affects tissue responses in destructive and remodeling arthritis. Arthritis Rheum 2006, 54:1736-1746.
19. Lories RJ, Matthys P, Derese I, De Vlam K, Luyten FP: Ankylosing spondylitis, dactylitis and onychoperiostitis in a mouse model of psoriatic arthritis. Ann Rheum Dis 2004, 63:595-598.
20. Holmdahl R, Jansson L, Andersson M, Jonsson R: Genetic, hormonal and behavioural influence on spontaneously developing arthritis in normal mice. Clin Exp Immunol 1992, 88: 467-472.
21. Matthys P, Lories RJ, De Klerck B, Heremans H, Luyten FP, Billaud M: Dependence on interferon-gamma for the spontaneous occurrence of arthritis in DBA/1 mice. Arthritis Rheum 2003, 48:2983-2988.
22. Glansbeek HL, van Beuningen HM, Vitters EL, Morris EA, van der Kraan PM, van den Berg WB: Bone morphogenetic protein 2 stimulates articular cartilage proteoglycan synthesis in vivo but does not counteract interleukin-1alpha effects on proteoglycan synthesis and content. Arthritis Rheum 1997, 40:1020-1028.
23. van Beuningen HM, Glansbeek HL, van der Kraan PM, van den Berg WB: Differential effects of local application of BMP-2 or TGFI-beta 1 on both articular cartilage composition and osteophyte formation. Osteoarthritis Cartilage 1998, 6:306-317.
24. van Lent PL, Blom AB, van der KP, Holthuysen AE, Vitters E, van Rooyen N, Smeets RL, Nabbe KC, van den Berg WB: Crucial role of synovial lining macrophages in the promotion of transforming growth factor beta-mediated osteophyte formation. Arthritis Rheum 2004, 50:103-111.
25. Blom AB, van Lent PL, Holthuysen AE, van der Kraan PM, Roth J, van Rooyen N, van den Berg WB: Synovial lining macrophages mediate osteophyte formation during experimental osteoarthritis. Osteoarthritis Cartilage 2004, 12:627-635.
26. Scharstuhl A, Vitters EL, van der Kraan PM, van den Berg WB: Reduction of osteophyte formation and synovial thickening by adenoviral overexpression of transforming growth factor beta/bone morphogenetic protein inhibitors during experimental osteoarthritis. Arthritis Rheum 2003, 48:3442-3451.
27. Blaney Davidson EN, Vitters EL, van der Kraan PM, van den Berg WB: Expression of transforming growth factor-beta
44. Filer A, Pitzalis C, Buckley CD, et al.: Expression of bone morphogenetic proteins and cartilage-derived morphogenetic proteins during osteocyte formation in humans. J Anat 2003, 202:269-277.

45. Nakase T, Miyaji T, Tomita T, Kaneko M, Kuriyama K, Myoui A, Sugamoto K, Ochi T, Yoshikawa H: Localization of bone morphogenetic protein-2 in human osteoarthritic cartilage and osteocyte. Osteoarthritis Cartilage 2003, 11:278-284.

46. McGonagle D, Gibbon W, Emery P: Classification of inflammatory arthritis by enthesis. Lancet 1998, 352:1137-1140.

47. Francois RJ, Braun J, Khan MA: Entheses and enthesis: a histopathologic review and relevance to spondyloarthritides. Curr Opin Rheumatol 2001, 13:255-264.

48. Moskowitz RW: Bone remodeling in osteoarthritis: subchondral and osteophytic responses. Osteoarthritis Cartilage 1999, 7:323-324.

49. Menkes CJ, Lane NE: Are osteophytes good or bad? Osteoarthritis Cartilage 2004, 12(Suppl A):S53-S54.

50. Moreau E, Derese I, Lories RJ: Mesenchymal stem cells in arthritis. In Rheumatoid Arthritis: Frontiers in Pathophysiology and Treatment. Edited by Panayi GS, Firestein GS, Wollheim FA. Oxford: Oxford University Press; 2005:551-559.

51. Marinova-Mutafchieva L, Taylor P, Funa K, Maini RN, Zvaifler NJ: Mesenchymal cells expressing bone morphogenetic protein receptors are present in the rheumatoid arthritis joint. Arthritis Rheum 2000, 43:2046-2055.

52. De Bari C, Dell’Accio F, Tylzanowski P, Luyten FP: Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 2001, 44:1928-1942.

53. Steenvoorde MM, Tolboom TC, van der PG, Lowik C, Visser CP, Degroote J, Gittenberger-Degroote AC, Deruiter MC, Wisse BJ, Huizinga TW, et al.: Transition of healthy to diseased synovial tissue in rheumatoid arthritis is associated with gain of mesenchymal/fibrotic characteristics. Arthritis Res Ther 2006, 8:R165.

54. Filer A, Pitzalis C, Buckley CD: Targeting the stromal microenvironment in chronic inflammation. Curr Opin Pharmacol 2006, 6:393-400.

55. Muller-Ladner U, Kriegsmann J, Franklin BN, Matsumoto S, Geiler T, Gay RE, Gay S: Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. Am J Pathol 1996, 149:1607-1615.

56. Yamanishi Y, Boyle DL, Pinkoski MJ, Mahboubi A, Lin T, Han Z, Zvaifler NJ, Green DR, Firestein GS: Regulation of joint destruction and inflammation by p53 in collagen-induced arthritis. Am J Pathol 2002, 160:123-130.

57. Edwards JC: Fibroblast biology. Development and differentiation of synovial fibroblasts in arthritis. Arthritis Res 2000, 2:344-347.