Contemporary concepts of inflammation, damage and repair in rheumatic diseases

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Chronic arthritis has been regarded as a disease resulting from a disequilibrium in pro- and anti-inflammatory cytokines. Restoration of this imbalance by using blocking antibodies or soluble receptors against a variety of inflammatory components has been the focus of most therapeutic interventions so far. More recently, other destructive mechanisms partially independent of inflammation have been elucidated, including osteoclast mediated bone resorption driven by the RANKL/RANK system. Despite efficient control of inflammation and destruction, little joint tissue repair has been observed. In addition, abnormal tissue responses such as cartilage calcification and ankylosis may contribute to disease progression and loss of joint function. We propose that ‘true’ disease remission may only be achieved with appropriate activation of local joint tissue responses leading to restoration of joint homeostasis and recovery of joint function. Understanding the molecular networks of joint homeostasis, repair and remodelling will be required to achieve this goal. Defining and validating clinical outcomes evaluating remission remain a challenge.

Key words: joint homeostasis; destructive mechanisms; tissue repair; remodelling; disease remission.

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CHRONIC ARTHRITIS: FROM A DISEQUILIBRIUM OF PRO- AND ANTI-INFLAMMATORY CYTOKINES TOWARDS A BALANCE BETWEEN TISSUE DESTRUCTION AND REPAIR

Chronic arthritides, in particular rheumatoid arthritis (RA), the spondyloarthritides (SpA) and osteoarthritic diseases (OA), are a major cause of disability. Studies on the pathogenetic mechanisms have focused on the immune system and its components, including autoantibodies, immune complexes, macrophages, T and B-lymphocytes and dendritic cells and its interactions with fibroblast-like synoviocytes, osteoclasts and chondrocytes. For RA, a multistage model has been proposed, with activation of innate immunity in early disease, followed by the appearance of adaptive immune responses ultimately leading to a destructive phase. Studies of cytokine expression and their biology indicated a disequilibrium between pro-inflammatory and anti-inflammatory cytokines, with tumor necrosis factor (TNF)-α at the apex of a pro-inflammatory cascade. Our understanding of the critical cytokines involved in the chronic inflammatory processes in RA has evolved into successful targeted therapies such as TNFα blockade (for a review, see Feldmann). Although this paradigm is less clear in SpA, a similar approach was taken and the efficacy of TNF blockade in this patient population (for a review, see Braun & Sieper) further supported the principle of cytokine disequilibrium. More recently, the cellular and molecular mechanisms underlying joint destruction have been partially identified. Molecular insights into osteoclast biology, in particular, have revealed that inflammation and destruction are linked but largely independent processes (for a review, see Lories & Luyten). However, it is unclear at this point whether control of inflammation and other destructive pathways will be sufficient to restore joint homeostasis, structure and function. In fact, it is striking that despite more efficient control of inflammation by TNF blockade, little if any genuine joint tissue repair is observed. These observations led us to develop a ‘systems biology’ approach.

Indeed, chronic arthritis can be characterised by an imbalance between tissue destruction caused by several underlying mechanisms including inflammation, but also biomechanical factors such as joint instability, as well as the tissue response to this injury in an attempt to maintain integrity and repair the damage (Figure 1). In this model, we propose that disease remission may only be achieved by adequate blocking of inflammation and other destructive mechanisms, together with appropriate activation of local tissue repair processes, ultimately leading to restoration of joint homeostasis and proper function. From this more systems biology-driven point of view, RA is a chronic disease with limited tissue response or repair despite adequate suppression of the inflammatory process. In OA, a disease with more limited inflammation, attempts to maintain tissue function and local repair responses apparently suffice for many years, but ultimately joint homeostasis is lost and this results in joint failure. In SpA, inflammation and excessive or untimely reparative responses may lead to inappropriate cartilage and bone formation causing joint ankylosis and loss of joint function. There is increasing evidence that molecular pathways, which are responsible for cell and tissue differentiation during development, play an essential role in the regulation of homeostasis and maintenance of adult tissues. In addition, since many aspects of tissue repair mimic embryonic tissue formation, we anticipate that signalling pathways critically involved in the formation of joint and joint-associated tissues, such as cartilage and bone, may provide a molecular basis for tissue response and thus complementary or alternative therapeutic targets for repair in patients with chronic arthritis. Recent findings
confirm and corroborate our hypothesis that some of these signalling pathways, in particular bone morphogenetic protein (BMP) and Wnt signalling are of relevance to postnatal joint homeostasis and disease and are discussed in more detail below.

**JOINT HOMEOSTASIS**

The balanced cooperation of the different tissues within the synovial joint allows an individual to move. The joint is a complex organ composed of the articular cartilage, the underlying subchondral bone, the synovial membrane, the joint capsule, tendons and ligaments and eventually menisci. Precise and efficient movement requires extreme low-friction contact between the bony bearings, continuous lubrication of the contact surfaces and multiplanar stabilising forces that prevent dislocation. The continuous strain carried by the synovial joints during movement and rest, requires an enduring homeostatic process in which the balance between anabolic and catabolic processes is tightly regulated.

Homeostatic processes within the joint occur at the cellular, tissue and organ level. Understanding the molecular events required for homeostasis involves knowledge of the active signalling pathways, their interactions with each other and with structural components such as the extracellular matrix and collagen fibers. Finally, integration of molecular signalling networks between the different tissues that constitute the joint is critical.

The *synovial membrane* connects the bones and lines the inner cavity of the joint. This membrane has a thin *lining layer* of 1–3 cell layers. Two different cell types are present within the lining layer: type A synoviocytes or macrophages and type B synoviocytes or fibroblast-like cells (FLS). This latter cell population is, at least partially, derived from the joint interzone cells that define the prospective joint cavity during development. These cells show some remarkable properties but many aspects of the biology of the pseudo-epithelial FLS remain unclear. They are capable of
anchorage-independent growth in vitro and contain a population of multipotent mesenchymal stem cells. The sublining zone is a loose and vascular connective tissue with few cells. Adherent cell cultures after synovial digestion show a remarkable phenotypic convergence between lining and sublining FLS. It is not clear whether this phenomenon is also present at the molecular rather than the morphological level.

Recently, cadherin-11 has been associated with the pseudo-epitheloid organisation of the lining layer. Cadherins are tissue-restricted transmembrane glycoproteins that form adherence junctions between cells by homophilic interactions. The precise involvement of cadherins in homeostatic and pathological processes remains to be defined. Cadherin-11 in FLS is also present in hyperplastic inflammatory lining layers. Regulatory mechanisms of cadherin-11 expression are also not known. Remarkably, cadherin-11 null mice seem to be protected against serum-transfer induced arthritis in the KRN anti-GPI antibody-induced mouse model (mice transgenic for T-cell receptor recognizing an epitope of borne RNASE bred into non-obese diabetic (NOD) background) (K/BxN) model. As a normal lining layer is likely to be important for normal joint function, it remains to be studied whether cadherin-11 mice develop accelerated OA. Some evidence from other systems indicates that cadherin-11 expression is influenced by BMPs and Wnts in osteogenic differentiation of mesenchymal cells and Xenopus model systems, respectively. We hypothesise that such signalling pathways play a role in the maintenance of the normal lining layer by regulating cadherins and other adhesion molecules such as vascular cell adhesion molecule (VCAM)-1 and integrin α4β1. It remains to be studied whether synovial hyperplasia is directly caused by pro-inflammatory signals or is the consequence of an inflammation-induced disequilibrium in signals that orchestrate normal tissue structure, such as the BMPs. Indeed, overexpression of BMPs and transforming growth factors (TGFs) in the synovial lining layer is associated with joint remodelling but also with some lining hyperplasia.

The normal synovium is collapsed upon itself and onto the articular cartilage. The joint cavity contains the minimum amount of synovial fluid necessary for boundary-layer lubrication. Lubricin is a small glycoprotein that binds to articular cartilage and can retain a protective layer of water molecules. This molecule is essential for the extreme low-friction state between both cartilages. Lubricin expression is only found after joint cavitation. Mice deficient in the PRG4 gene, which codes for lubricin, show progressive postnatal cartilage loss and synovial hyperplasia. The factors regulating lubricin production by FLS remain to be identified. Hyaluronic acid cushions the synovium—cartilage contact and prevents pinching of the synovial membrane. The thin layer of synovial fluid is resistant to distractive forces and thereby contributes to joint stability.

The articular cartilage is essential for the soft movement of the joint. Under normal circumstances, it is a unique cartilage tissue resistant to chondrocyte hypertrophy, mineralisation and vascular invasion. Identification of the molecular signals that maintain the stable articular chondrocyte, both in vivo and in vitro, remains a challenge. We and others have provided increasing evidence that embryonic molecular signalling pathways, such as BMPs, TGFβs and Wnts, are likely to be critical in this process. The induction of OA characterised by terminal differentiation of chondrocytes in adult mice with tissue-specific overexpression of a dominant negative TGFβ type II receptor would support this concept. More importantly, it was recently demonstrated that the loss of BMP type Ia receptor in the articular cartilage using mouse genetic approaches resulted in a complete loss of the articular
cartilage in postnatal joints, a pathological process reminiscent of osteoarthritis in man.\textsuperscript{22} Cartilage derived morphogenetic protein-1 (CDMP-1), also called growth and differentiation factor (Gdf)-5, is associated with the initiation of the joint interzone (for reviews, see Luyten et al)\textsuperscript{23,24} and is also present in normal human adult articular cartilage.\textsuperscript{25} Its expression is mostly restricted to the superficial cartilage in normal joints, while in osteoarthritic cartilage its expression domain is extended to damaged areas.\textsuperscript{25} These data suggest a possible role for CDMP-1/GDF-5 in the homeostasis of normal cartilage, as well as in repair processes. Accordingly, recombinant CDMP-1 increases proteoglycan biosynthetic activity in adult articular cartilage that has been partially matrix-depleted by mild trypsin treatment.\textsuperscript{25} The presence of BMP-7/osteogenic protein (OP)-1 and BMP-2 as well as different BMP antagonists\textsuperscript{26} was demonstrated in normal adult human articular cartilage, as determined by in situ hybridisation, Western blotting and immunohistochemistry.\textsuperscript{27,28} This further corroborates a possible autocrine/paracrine function for BMPs in the maintenance of the articular surface.

The complex regulation of these pathways may be a tough hurdle to tackle experimentally but the ability to fine-regulate such pathways with different ligand—receptor interactions, intra- and extracellular antagonists, extracellular matrix binding and interactions with other signalling pathways seems essential. For instance, activation of the BMP signalling pathway leading to phosphorylation of intracellular smads (received their name as a contraction of the names of the \textit{C. elegans} Smα and Drosophila Mad, the first identified members of this class of signaling effectors) and p38 phosphorylation results in cartilaginous differentiation of synovial fibroblast-like synoviocyte derived cells. However, overstimulation of the p38 pathways leads to chondrocyte hypertrophy and terminal differentiation.\textsuperscript{29}

It is clear that synovium and cartilage allow movement in the individual joints. However, this movement will create stress and forces within the joint that may disturb the equilibrium reached. Movements are triggered by muscle contractions. Movements are counter-balanced by antagonistic muscles but more directly by ligaments and capsules that constrain the range of motion. Both muscles and ligaments insert into the bones they move or restrict in an enthesis.\textsuperscript{30} This anatomical zone is mostly fibrocartilaginous and shows different regions and fibres inserting into the underlying bone. As well as its insertional function, this structure importantly allows stress dissipation, which retains tissue attachment and integrity. Although little is known about the enthesis, the synthesis of extracellular matrix and fibres seems tightly coordinated at the molecular level. Recent data identify a key role for BMPs in its homeostasis and the process of ankylosing enthesis.\textsuperscript{31}

\section*{FROM TRANSIENT TO CHRONIC ARTHRITIS}

In arthritis, several key features have been recognised including infiltration of immune cells, hyperplasia of the lining layer, hypervascularity and organisation of lymphoid follicles. However, understanding the evolution of arthritic disease towards chronicity remains a major challenge. Different hypotheses have been formulated, several among them focusing on the potential role of FLS populations in arthritis.

The \textit{transformation hypothesis} put forward the idea that FLS were stably transformed by the chronic inflammatory processes in the synovium. This resulted in a more ‘aggressive’ cell population called pannocytes, with distinct morphological characteristics\textsuperscript{32} and the ability to attach to and invade the articular cartilage as demonstrated in
in vivo models in severe combined immune-deficient (SCID) mice.\textsuperscript{33,34} Mutations in tumour suppressor genes, such as p53, were documented and could explain some aspects of this altered cell behaviour.\textsuperscript{35–37} An alternative view suggested that low activity FLS from the sublining zone acquired the phenotypical characteristics of cells of the lining layer but lacked positional information resulting in overgrowth and invasion of cartilage and bone.\textsuperscript{11}

The transformation hypothesis was incorporated into the \textit{effector cell hypothesis}. Increasing evidence supported the notion that the complex process of synovitis consisted of both T-cell dependent auto-immune and T-cell independent mechanisms, including macrophages and FLS.\textsuperscript{38,39} The late destructive phase of RA, typically characterised by pannus formation, osteoclast activation and secretion of tissue-destructive enzymes, was considered to be predominantly T-cell independent as it appeared to be driven by an ‘autonomous’ FLS population, as suggested by the transformation hypothesis. Expansion and influx of FLS with mesenchymal stem cell (MSC) characteristics was considered a factor contributing to these processes.\textsuperscript{40}

These two hypotheses clearly focused on the tissue-destructive aspect of arthritis. There is also increasing evidence that FLS/MSC populations play a part in the initiation and progression of arthritis. The recent \textit{stromal code hypothesis}\textsuperscript{41,42} proposed that the stromal cell population of an organ (e.g. FLS/MSC in the synovium), 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 mesenchymal code within the tissue further steers the behaviour of cells that have invaded the synovium. However, it is not clear what is the primary origin of the stromal code and of the FLS/MSC involved and what triggers the switch from normal to pathological code.

Based on these theories and new experimental evidence from both developmental biology and arthritis research, we have defined the \textit{signalling centre hypothesis}.\textsuperscript{43} Inflammation and tissue destruction trigger a physiological reaction aimed at repairing and conserving tissue homeostasis and function. However, in some cases, this process is ill-coordinated in an inflammatory environment and leads to phenotypic changes in the stromal cell population. FLS with MSC characteristics accumulate either by local proliferation, de- or transdifferentiation of residing cell populations and/or there is influx of stem cells from other compartments such as blood or bone marrow. These distinct cell populations can typically form ‘signalling centres’ that regulate the behaviour of surrounding cells. This concept from developmental biology places the stromal code hypothesis in a broader biological context. It allows not only the understanding of destructive but also remodelling processes, as these signalling centres can guide and coordinate both tissue-destructive and homeostatic/reparative processes.

\section*{JOINT TISSUE DESTRUCTION}

Inflammation is the common driving force leading to cartilage, bone and soft tissue destruction in chronic arthritis. Many factors involved in the regulation of normal tissue turnover, in particular of cartilage and bone, are deregulated in arthritic disease.\textsuperscript{44,45} Animal models of arthritis have demonstrated the important role of a number of cytokines, cells and effector enzymes in joint destruction. Proinflammatory cytokines such as TNF-\textit{\alpha} and interleukin (IL)-1 are abundant in the synovium of patients with different types of chronic arthritis and are disrupting normal tissue homeostasis in cartilage and bone. Apart from effectively controlling inflammatory disease activity,
biological therapies targeting IL-1 and, in particular TNF-α, have proven to have a substantial effect on the process of cartilage and bone destruction in RA patients, hereby confirming the key role of these cytokines in the destructive processes of this disease. Recent reports have suggested a central role for IL-17R signalling in the pathophysiology of destructive arthritis, possibly upstream of IL-1 and TNF-α (for a review, see Miossec)\textsuperscript{47} Additive and synergistic effects with IL-1 and TNF-α in joint damage have been shown in vitro and in vivo. Moreover, IL-17 has the capacity to induce joint destruction in an IL-1 independent manner and bypass TNF driven arthritis (for a review, see Lubberts et al.).\textsuperscript{48}

**Osteoclasts** are essential for bone destruction. The balance between receptor activator of nuclear factor kappa β ligand (RANKL), receptor RANK and decoy receptor osteoprotegerin (OPG) determine osteoclast differentiation and activation and, thus bone destruction. The inflamed synovium is a major source of RANKL.\textsuperscript{49–51} Synovial expression of RANKL is particularly increased in patients with active RA and some patients with active SpA in comparison to OA patients and patients without active joint disease.\textsuperscript{52} Synovial OPG expression, on the contrary, seems deficient in RA patients with active synovitis in contrast to that seen in SpA patients with active disease, RA and SpA patients without active disease, patients with OA and normal controls.\textsuperscript{51} Different cytokines including TNF, IL-1, IL-17, IL-6 and inflammatory mediators such as prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) influence osteoclast precursors, differentiation, maturation and function (for a review, see Walsh et al.).\textsuperscript{45} In RA, bone destruction has a major impact on joint function and is certainly osteoclast-mediated. There is an increased influx of mononuclear cells that can serve as candidate osteoclast precursor cells in the synovium. There is solid evidence that multinucleated cells carrying phenotypic characteristics of osteoclasts are present in regions where pannus tissue invades bone.\textsuperscript{53} Evidence for the key role of osteoclasts and RANKL in focal bone loss in arthritis comes mainly from animal models in which osteoclast differentiation and activity have been impaired either by selective deletion of genes involved in osteoclast formation or by targeting RANKL with OPG.\textsuperscript{54–57} In RA the synovial inflammatory tissue in which osteoclasts are embedded can break through the cortical bone barrier and reach the underlying bone marrow. This results in formation of B-cell rich aggregates at the interface between the invading synovial tissue and the bone marrow as well as increased formation of new bone.\textsuperscript{58} It seems that the synovial side of the cortical bone is affected by resorption, whereas bone formation, as an attempt to repair bone comes from the inner endosteal area, which supports the hypothesis that in RA bone erosion starts from the outside rather than from the bone marrow. These observations have been confirmed and analysed more deeply in hTNF-transgenic mice. Endosteal bone formation in this model of arthritis is associated with BMP-6 and BMP-7 expression by B-lymphocytes in these aggregates.\textsuperscript{59}

During inflammatory arthritis, cartilage degradation is enhanced and matrix synthesis and repair is suppressed indirectly by the effect of several pannus-derived cytokines on articular chondrocytes. Several studies have shown that IL-1 stimulates articular chondrocytes to increase the production of matrix metalloproteinases (MMPs) and other matrix degrading products (for reviews, see van Den Berg & Bresnihan\textsuperscript{61}; Mengshol
et al; Burrage et al. TNFα has similar effects on cartilage degradation and acts synergistically with IL-1. Both these cytokines have also been shown to decrease the synthesis of cartilage specific collagens and glycosaminoglycans by chondrocytes. The inflamed synovium itself is also a source of enzymes that can directly degrade the articular cartilage matrix. Fibroblast-like synoviocytes, for instance, contribute significantly to cartilage matrix degradation in RA through the expression of matrix degrading enzymes such as MMPs and cathepsins, but the balance between these and their natural inhibitors, such as tissue inhibitors of metalloproteinases (TIMPs), is shifted towards a pro-destructive level. Despite the accumulating circumstantial evidence on the role of MMPs, individual effects are much harder to document and precise therapeutic targets are hard to define.

ABNORMAL TISSUE RESPONSE

When tissue homeostasis is lost, some form of injury results. Postnatal tissue response to injury, regardless of its nature, can be physiological or abnormal (Figure 2). Normal tissue responses include tissue regeneration or repair. In the latter, the damaged tissue is replaced by a surrogate tissue but with (partial) restoration of function. In contrast to tissue regeneration, tissue repair often evolves in functional decompensation with loss of function and subjective complaints at short or mid-term. If physiological repair mechanisms fail, abnormal tissue response can result in further loss of function rather than partial restoration. Tissue repair and abnormal tissue responses can be considered as remodelling. Some tissues seem more prone to abnormal tissue response than others. Different types of tissue response are listed in Table 1.

Joint inflammation invariably elicits a response involving anti-inflammatory cytokines such as IL-10 and TGFβ but also lipoxins, different mediators of innate immunity as well as regulatory cells and mechanisms of adaptive immunity including naturally occurring T regulatory cells (TREGs) and cytotoxic T-lymphocyte antigen. In the different forms of chronic arthritis, as mentioned above, these mechanisms fail to restore the balance. Infiltrating and proliferating cells do not receive proper exit signals and the synovium or synovio—enthesial complex remains hypercellular.

The hypothesised mechanism in tissue regeneration and repair involves activation of resident or recruitment of progenitor cells and differentiation towards phenotypically and functionally normal cells with restoration of tissue architecture. Increased cell metabolism, proliferation and reactivation of embryonic signalling pathways guiding cell

Restoration of structure and function
Repair with preserved function
Repair with partially preserved function
Repair with rapid loss of function
Remodelling with partially preserved function
Remodelling with loss of function
No repair no remodelling

Figure 2. Different types of tissue responses to injury. Responses can be physiological and/or pathological.
growth and differentiation are probably involved. It is unclear to what extent similar mechanisms are involved in abnormal tissue response and what causes the process to go wrong. In tissue repair, either the cell potential or the steering molecular cascades are insufficient at restoration and the process leads to scar formation. In abnormal remodelling, repair is ill-timed, ill-localised or exaggerated leading to further tissue damage.

Neo- or hypervascularisation is an important feature of tissue responses and downregulation of this process may be essential for restoration but also support pathological remodelling. The articular cartilage, in particular, is normally resistant to vascular invasion. Hyaline cartilage, tendon and ligaments exhibit powerful anti-angiogenic resistance by the presence of tissue-type specific inhibitors of angiogenesis such as chondromodulin-I and tenomodulin. Chondromodulin-I is decreased in the cartilage of experimental OA but has not yet been studied in RA or SpA.

Articular cartilage repair efforts lead to formation of fibrocartilage, metaplasia, hypertrophy and calcification. These attempts are clearly insufficient to restore tissue homeostasis and will contribute to further loss of the integrity of articular cartilage and joint function. The process of cartilaginous metaplasia is not well understood. Cartilaginous metaplasia is found at the sacroiliac joints of ankylosing spondylitis (AS) patients but is not described in RA. In AS, cartilaginous metaplasia is considered to be a preliminary stage in ankylosis of the joint. Calcification of cartilage is uncommon in hyaline cartilage. The ANK gene is critical in maintaining the balance between extracellular and intracellular in organic pyrophosphate in cartilage and in the prevention of calcium deposition in cartilage. Mutations in ANK are associated with cartilage ageing and with idiopathic, metabolic and certain familial forms of chondrocalcinosis, as well as in many subjects with OA.

Synovial tissue has a strong capacity to regenerate and not surprisingly MSCs have been isolated from synovium. Usually synovial tissue regenerates without apparent scar formation, e.g. after a biopsy. In large injuries, such as chemical or surgical synovectomy, the synovial tissue may be replaced by scar tissue. In inflammatory arthritis the synovial tissue tends to proliferate in response to the presence of various cytokines and growth factors.
Hypertrophic villi develop through local proliferation of synovial fibroblasts, illustrated by the presence of Ki67 antigen and, potentially, also by proliferation and influx of MSCs. The proliferation of synovial fibroblasts is dependent on the presence of locally accumulated cytokines and growth factors via autocrine and paracrine loops. It is known that synovial fibroblasts of RA and psoriatic arthritis (PsA) have greater proliferative response to several growth factors and cytokines than those from synoviocytes of osteoarthritic joints. Hypertrophic villi are abundant in both RA and spondyloarthropathies but differ mainly in their vascularisation pattern. In osteoarthritis, villi are less vascularised and less prominent. The persistence of synovial inflammation and its structural reorganisation as proposed by different groups, can be considered as a remodelling process in which the resident cell populations are phenotypically altered and sustain the chronic inflammatory process.

Bone tissue remodelling in arthritis can occur in existing bone (orthotopic bone formation) or in surrounding or adjacent tissues (heterotopic bone formation). Osteosclerosis and subchondral sclerosis are orthotopic. Heterotopic bone appears as appositional bone (i.e. in continuity with existing bone) or as ectopic bone (i.e. in fibrocartilage, fibrotic tissues, muscles, ligaments, capsules and fascia in discontinuity with existing bone). Osteosclerosis is seen in SpA, especially in psoriatic arthritis and synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome. Subchondral sclerosis is seen in OA (primary and secondary) and SpA. In general new bone formation is uncommon in RA.

Appositional bone formation is typically found in osteophytes and enthesophytes, manifestations of OA and SpA. Bone responses clearly distinguish RA and SpA. It is not clear if this difference is related to the pathogenesis or the underlying different genetic background or a combination of both. Extensive histology, gene expression and cellular analysis have not revealed convincing differences in the inflammatory process between RA and SpA. However, periarticular osteoporosis in peripheral joints is absent in PsA/SpA in contrast to RA and often during the disease course periarticular or bone sclerosis is seen in PsA. Even within the SpAs markers for bone formation are divergent: bone-specific alkaline phosphatase is increased in PsA, but not in AS. Osteocalcin levels were only elevated in AS. This is reflected in normal dual energy X-ray absorptiometry measurements of the spine and the hip in PsA, while they are decreased in AS. Osteosclerosis in AS is seen at the corners of the vertebral bodies (shiny corners) and the peripheral entheses. Hyperostosis or sclerosis of the sternoclavicular joints and the long bones is characteristic for SAPHO syndrome. Osteophytes have a horizontal course and are seen in the spine or at the peripheral joints in OA. Syndesmophytes are vertically orientated and are seen in the spine of SpA and tend to ankylose in some patients. Enthesophytes and parasyndesmophytes are seen in diffuse idiopathic skeletal hyperostosis and PsA and have an intermediate morphology between osteophytes and syndesmophytes. Appositional bone growth starts from the periosteum or enthesis and is characterised by endochondral bone formation. Membranous bone formation is likely to contribute to the process but does not seem primary. In PsA, cortical bone formation also occurs without the development of enthesophytes, especially at the diaphysis of the long bones. The underlying mechanisms of cortical thickening are not fully understood. The signalling pathways involved in both types of bone formation need to be investigated. In OA, IL-1 messenger RNA is found in sites of intramembranous bone formation but is absent at the site of endochondral bone formation. TGF-β1 is present in OA near the calcified cartilage and bone, while in AS, TGF-β is detected in the sacroiliac joint near the site of ossification. We have demonstrated that the process of ankylosing
enthesitis in a mouse model of PsA and SpA is characterised by active BMP signalling. Inhibition of BMP signalling by gene transfer of the natural antagonist, noggin, inhibits both the incidence and severity of arthritis and joint remodelling. Importantly gene transfer interferes with the early stages of cartilage and bone formation as BMP signalling is active in proliferating and differentiating progenitor cells.31 Active BMP signalling is also present in human enthesitis.31 Osteophyte formation in experimental OA has also been linked to active BMP and TGF-β signalling.51

Ossification of the posterior longitudinal ligament of the spine (OPLL) is characterised by ectopic bone formation in the spinal ligaments. Mechanical stress, which acts on the posterior ligaments, is thought to be an important factor in the progression of OPLL. Messenger RNA transcripts of alkaline phosphatase (ALP), osteopontin, BMP-2, BMP-4 and BMP receptors, as well as the secretion of BMP ligands and the expression of Cbfa1 are increased in OPLL cells by cyclic stretch.88 This, in combination with an increased tendency for accelerated bone formation due to a dysfunction in the NPPS gene may constitute the underlying molecular basis of OPLL.89

HOW DO WE TRANSLATE THIS INTO CLINICAL PRACTICE?

In the last decade the enormous progress in our understanding of the inflammatory and destructive mechanisms in chronic arthritis has led to novel therapeutic strategies and new drugs such as TNFα-blockers, which control disease activity much better and also decrease the progression of disease.

Measuring disease activity and destruction has been standardised by the efforts of outcome measures in rheumatology (clinical trials)90 and standardised evaluation methods have found their way into daily practice.90,91 Functional capacities and quality of life are evaluated mainly in groups of patients but with the patient’s perspective coming more into the picture, evaluation of individual disease impact will gain importance.

So far, it has been proposed that the achievement of remission requires the eradication of the inflammatory process to such an extent that no further destruction occurs. It would be even better to intervene in early disease (less than 4 months) so that destruction can be avoided. It is, however, clear that there are major problems in defining remission and that the term ‘remission’ has been misused extensively. Indeed, DAS 28 remission for instance, which is defined as a score of below 2.6, still allows for the presence of clinically active synovitis. In a recent editorial, it was suggested that a cumulative low disease activity state is perhaps a better goal than difficult-to-define remission. This brings the time frame into the discussion and is certainly also in the interest of the patient.90,92

It is also clear from biopsy data that clinically inactive joints show abnormalities93, that there is persistence of activation of destructive signalling pathways (R.J.U. Lories et al, unpublished results) and that inflammation and destruction are linked but autonomous processes.94 Disease modification is a treatment goal but this may cover different outcomes according to the specific disease. In contrast to RA, remodelling in AS may lead to enhanced ankylosis and loss of joint function. Therefore, the ultimate goal of treatment in chronic arthritis must be the induction and sustainability of durable remission with full restoration of joint homeostasis and function.

Defining restoration, repair and remodelling and their measurement, is perhaps an even more complex task and appears tricky from a clinical point of view. Using standard X-rays as an evaluation method, healing of erosions has been reported in individual case reports95 and supportive studies96 in RA patients, particularly when using
biological agents. There is no agreement on all of the features of the restoration-repair-remodelling triad: is it filling of erosions, sclerosis, restoration of bone cortices. Strikingly, most experts are not able to judge repair when reading X-rays in random order. It is also not well known if progression of destruction in one joint can occur while in another joint from the same patient repair is seen. Recently, van der Heijde et al reported on the use of probability plots to demonstrate factual repair at a group level in both RA and AS.97

Part of the problem of repair from the clinical point of view is, therefore, defining the goal for our approaches.

1. Maintenance of homeostasis involves a process that is opposite to inflammation and destruction and which occurs gradually and in parallel. This would only be measurable at a tissue or disease process level. Targeting this maintenance would thus involve the stimulation and control of molecular signalling that continuously counteracts inflammatory or other destructive mechanisms.

2. Restoration would mean restoring joint integrity with complete healing of erosions. Simply aiming for inactivation of inflammation and destruction would be sufficient in some patients at a very early disease stage. However, in most patients, additional therapies targeting tissue restoration involving cell proliferation and differentiation might be needed to achieve the ultimate goal of complete recovery of structural integrity.

3. Restoration may involve the ‘moulding’ of new joints (formation of neo articulars) in such a way that function is largely restored. This repair phenomenon can be observed in individual patients, in particular in juveniles, as shown in Figure 3.

4. In some disease processes, restoration may imply the control of pathological remodelling, which is also contributing to joint damage. This is exemplified in SpA and its animal model. The capacity of a joint to regenerate or repair will be dependent on a number of variables, including the degree and duration of inflammation, patient characteristics (younger patients with higher regenerative capacities), the joints involved (small hand joints and shoulders that are continuously in movement more than weight bearing joints of lower limbs) and disease characteristics (RA versus SpA versus OA). It is likely that most joints would need additional specifically targeted therapeutic approaches to achieve substantial repair.

In measuring the restoration-repair-remodelling triad as defined above, the main outcome should be function, hence more sophisticated measurements of function need to be developed and validated.

Finally, even with this focus on function critical issues and potential pitfalls remain, such as disease perception. Indeed, after a period of severe inflammation, even when ‘true’ remission is achieved with restoration of joint homeostasis and full functional recovery, psychosocial consequences such as work loss and chronic illness behaviour could be difficult to overcome.

RESTORING THE JOINT IN ARTHRITIS: FUTURE APPROACHES

Targeting restoration and functional repair

Several therapeutic opportunities can be identified for restoring tissue homeostasis and enhancing tissue restoration and functional repair. They include targeting specific
embryonic signalling pathways, such as BMP and Wnt signalling (see above). The stem cell pool, as a cell phenotype with developmental characteristics, most probably responds to embryonic signalling. Therefore, it is expected that modulating these signalling pathways will selectively affect the stem cell pool. A striking example is seen in models of kidney injury. There is overwhelming evidence that modulating BMP signalling by the administration of exogenous BMP-7/osteogenic protein-1, enhances the recovery of kidney function in animal models of both acute and chronic renal injury.\textsuperscript{98,99} Mechanistically, the experimental findings suggest that renal ‘fibroblasts’ with MSC characteristics retain parts of their original epithelial imprint and plasticity, which can be re-activated by modulating BMP signalling, resulting in epithelial cell formation mediating repair of tubular injury in an inflamed and fibrotic kidney. There have been more recent reports indicating that targeting adult stem cell populations may be valuable. The mobilisation of endothelial precursor cells by granulocyte-macrophage colony stimulating factor accelerates re-endothelialisation and reduces vascular inflammation in a model of intravascular radiation in rabbits.\textsuperscript{100} At this point, a further understanding of the processes involved and their relationship to inflammation is essential to assess the risks/benefits of these interventions.\textsuperscript{101}

Although similar processes may take place in the inflamed synovium, very little is known about the stem cell niches in arthritic diseases. Recent data have indicated the recruitment of Bone Morphogenetic Protein Receptors expressing stem cells in the early phase of inflammatory destructive joint disease such as RA.\textsuperscript{102,103} Further in vivo experimental approaches are needed to identify the role of these MSC populations in arthritic disease (for a review, see Luyten).\textsuperscript{43}

Figure 3. Evolution of metacarpophalangeal joint III right hand in a patient with juvenile idiopathic arthritis (polyarticular onset, rheumatoid factor, ANA and CCP negative) since the age of 14. A, after 6 years of disease; B, after 11 years of disease; C, after 14 years of disease (treated with tumour necrosis factor \( \alpha \) (TNF) blockade for 4 years).
Joint tissue engineering

For joint tissue restoration and guided repair, treatments with cell-based products are reaching the clinical arena, and with some success. A number of these applications have been described in more detail in recent reviews. In the field of joint surface repair, autologous chondrocyte implantation (ACI) may be a promising treatment for deep symptomatic cartilage defects on the basis of mostly retrospective studies. Very recent prospective studies have confirmed the good clinical outcome of ACI. Prospective long-term follow up studies are required to position this approach versus other procedures used. It is important to indicate that ACI is performed for cartilage defects in an otherwise healthy joint. Therefore, it is unclear, at this point, what the potential role and success of cell-based repair would be in an arthritic joint. Loss of joint homeostasis and arthritic disease create a very different microenvironment and thus will influence cell engraftment and tissue differentiation.

Remarkable results with MSCs were recently reported in a large animal model of OA. OA-like disease was induced by medial meniscectomy and resection of the anterior cruciate ligament in the knee joints of goats. Local delivery of labelled adult MSCs, isolated from bone marrow, to injured joints resulted in engraftment in the meniscus, fat pad and synovium, as well as some, although limited, in the articular surface. Formation of a neo-meniscal-like tissue and retardation of joint destruction, particularly of the articular surface, were the most striking findings. These data indicate that there are opportunities for these local MSC-based treatments in arthritic disease.

SUMMARY

Our understanding of the processes underlying inflammation with disequilibrium between pro-inflammatory and anti-inflammatory cytokines has had a major impact on the development of new therapeutic approaches in chronic arthritis. The clinical success of TNFα blockade, at the apex of the inflammatory cascade, further corroborated the importance of this cytokine imbalance. However, despite clinically relevant control of inflammation and tissue destruction, the existence of non-responders and the lack of tissue restoration revealed new challenges. Indeed, patients and physicians have heightened their expectations and are seeking disease remission, with restoration of joint homeostasis and full recovery of joint function. This has led to a keen interest into the processes underlying joint homeostasis and the molecular pathways driving tissue response. Increasing evidence supports the concept that molecular signalling cascades essential in embryonic tissue formation play a critical role in postnatal growth and tissue homeostasis. These developmental pathways include TGFβ/BMP and Wnt signalling. They are likely to act in concert with anti-inflammatory and anti-destructive feed-back mechanisms such as cytokine antagonists, inhibitors of tissue destructive enzymes and other immunoregulatory mechanisms. Besides physiological repair mechanisms, an abnormal tissue response may contribute to disease progression and loss of joint function. Cartilage metaplasia, cartilage calcification, synovial hypertrophy and fibrosis, ectopic and heterotopic bone formation with ankylosis are all consequences of disturbed tissue responses and an understanding of their cellular and molecular basis is required to control these inappropriate events. In view of this, several new therapeutic targets and therapeutic approaches to restore joint homeostasis and tissue integrity have been identified. However, proper evaluation of these novel
approaches will require the development of new tools and methodologies to assess tissue repair and disease remission.

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Practice points

- Aim for early diagnosis and intervention.
- Incorporation of measurements of disease activity, joint damage and function into daily practice.
- Tight disease control with the goal of restoring and maintaining joint homeostasis.
- Develop and apply therapeutic interventions seeking induction of disease remission.

Research agenda

- Studies of molecular networks and their hierarchy in joint formation and tissue specification.
- Investigate the cellular and molecular basis of joint homeostasis.
- Identify the molecular events leading to abnormal tissue responses such as joint ankylosis.
- Develop and validate tools to assess tissue repair.
- Investigate the relationship between damage, restoration, remodelling and function.
- Develop and validate methods to define disease remission and joint function.
- Develop therapeutic approaches leading to tissue repair.

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