The Relationship Between Inflammation, Destruction, and Remodeling in Chronic Joint Diseases

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1 Introduction: Chronic Joint Diseases, a Major Health Problem

Chronic joint diseases are a major health problem as they are linked to pain, loss of function, and increasing disability. Osteoarthritis (OA) is the most prevalent disorder and is generally considered a degenerative disease associated with aging, tear-and-wear, trauma, and acquired factors such as obesity [1]. In contrast, rheumatoid arthritis (RA) and the different forms of spondyloarthritis (SpA) are chronic inflammatory diseases, affecting younger people, steered on by persistent activation of the immune system [2, 3]. These inflammatory joint diseases can be further defined as a group of chronic musculoskeletal disorders with common inflammatory pathways, characterized by joint organ and tissue damage, increased morbidity and mortality, and reduced quality of life. From a pathological perspective, not only changes in the adaptive and innate immune system but also molecular and cellular pathways that determine joint tissue homeostasis, repair and remodeling will determine the outcome of these diseases [4].

RA is the best-known form of chronic arthritis and typically affects the peripheral joints in a symmetric fashion. The small joints of hand and feet are most commonly involved. RA affects more females than males and is associated with specific HLA

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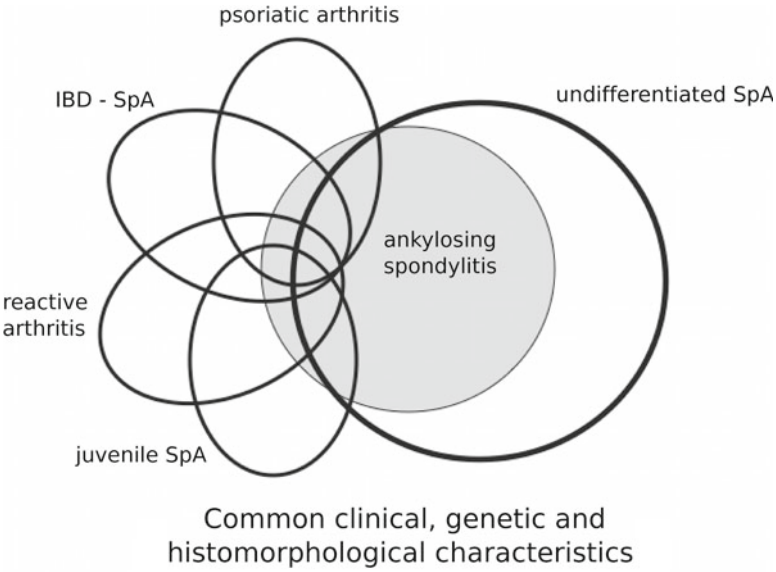

Fig. 1 The spondyloarthritis concept. Ankylosing spondylitis represents that paradigm disorder for this group of related diseases. Other diagnostic entities include psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease (IBD), a juvenile and an undifferentiated form. As clinical symptoms overlap, the first diagnosis may be made by the initial presentation but the disease phenotype may change over time resulting in either reclassification or fit in different entities

genes (HLA-DRB1) as well as with other polymorphisms in genes with a role in the immune system [5]. Autoantibodies against specific antigens play a role in pathogenesis, course and diagnosis of the disease. Among these, antibodies directed against citrullinated proteins and rheumatoid factor appear most important. RA affects between 0.3 and 1% of the population and typically starts between the ages of 30 and 60 years.

The SpA concept groups distinct diagnostic entities that share common clinical, genetic, and morphological characteristics [6]. Ankylosing spondylitis (AS) formerly known as Bechterew's disease, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease, a juvenile and an undifferentiated form are all part of the SpA concept (Fig. 1). The axial skeleton, in particular the sacroiliac joints and the lower spine, are commonly involved. Peripheral arthritis, if present, mainly manifests as a nonsymmetrical oligoarticular disease. SpAs and in particular AS affect more males than females and are genetically strongly associated with the HLA-B27 antigen. Other genetic factors have recently been identified and include a number of genes linked to immunity or inflammation [7]. In contrast with RA, these diseases are not associated with autoantibody formation. Like RA, the disorders that make up the SpA concept affect between 0.3 and 1% of the population in the Western world.

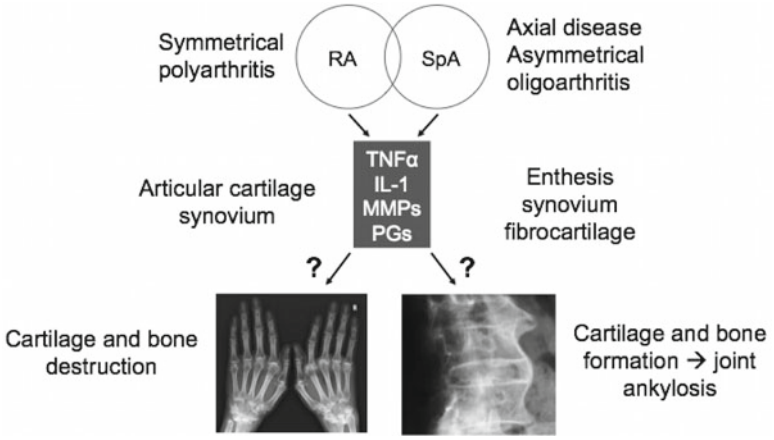

Fig. 2 Differences and similarities between different rheumatoid arthritis and spondyloarthritis. Despite the presence of similar symptoms at the individual joint level and the existence of comparable immune mechanisms, anatomic sites where the disease processes start as well as the long-term outcome may be very different. Rheumatoid arthritis is associated with the synovium and the articular cartilage, whereas increasing evidence supports a central role for the enthesis in spondyloarthritis. In rheumatoid arthritis structural damage is characterized by joint destruction, in spondyloarthritis by ankylosis

2 Similar Symptoms But a Strikingly Different Outcome of the Diseases

Clinical manifestations of RA and the different SpAs are much alike (Fig. 2). Affected joints show swelling, redness, pain, warmth, and loss of function. As mentioned above, the pattern of joints involved may be very different, in particular with the dominance of axial disease in SpA. Nevertheless at the tissue level, common effector mechanisms and inflammation-driving processes are easily recognized [8]. Proinflammatory cytokines such as interleukin-1 (IL1) and tumor necrosis factor-alpha (TNFa) are present, different types of immune cells invade the joint tissues, prostaglandins are activated and a number of tissue destructive enzymes are activated including matrix metalloproteinases (MMPs). However, the specific tissues within the joint that are the primary target of the disease process may be different between RA and SpA (Fig. 2) [8]. In RA, the synovium and the articular cartilage appear primarily involved. In SpA, strong evidence links the onset of disease to the enthesis, an anatomical zone in which tendons and ligaments insert into the underlying bone and thus a site in which biomechanical stresses are transferred from the soft tissues to the skeleton.

The most surprising feature when considering both groups of chronic arthritis is found in the outcome of the diseases (Fig. 2). RA is typically characterized by extensive cartilage and bone destruction, whereas in AS and related SpAs often new

cartilage and bone formation can be seen which is leading to the formation of syndesmophytes, osteophytes, or enthesophytes and which may result in progressive ankylosis of the sacroiliac joints and the spine.

3 Arthritis: Research Progress Translating Symptoms into Molecular Pathology

Over the last decades considerable progress has been made in our understanding of the basic mechanisms that underlie the signs, symptoms, and outcome in the different forms of chronic arthritis. Most progress has been made in understanding the inflammatory cascades [2]. This has, among others, resulted in the identification of key cytokines (TNFa and IL6), key cell populations (T cells, macrophages, B cells) in these diseases and some of these findings have been translated into new advanced therapeutic strategies that have an unprecedented impact on the management and wellbeing of patients. Current biological therapies thus include antibodies and soluble receptors directed against TNFa, antibodies against the IL6 receptors, T cell modulators such as CTLA4-Ig and antibodies depleting B cell precursors [9].

The rapidly emerging field of osteoimmunology research has also unveiled many of the molecular mechanisms that underlie progressive joint destruction. Osteoclasts have been identified as key cells in the destruction of bone and the formation of bone erosions and the molecular system supporting their differentiation, maturation, and activation has been discovered [10]. Recently antibodies against receptor of NFkB ligand (RANKL), one of the key factors, have also been introduced in clinical practice. These are currently used in the treatment of osteoporosis but are also studied in different joint diseases [11, 12]. Similarly, the research community has better understood mechanisms leading to activation and transformation of synovial fibroblasts, mainly in rheumatoid arthritis [13]. By producing tissue destructive enzymes such as MMPs and by expressing RANKL these cells play an essential role in the progression of joint destruction.

The molecular cascades underlying new cartilage and bone formation that is leading to ankylosis, have been less studied. However, in the last couple of years, we and other groups have started to understand some of the basic mechanisms that steer ankylosis and how these are linked to the inflammation characteristic of chronic arthritis [14]. These studies have been hindered by the limited availability of tissue samples from human patients as biopsies from spinal lesions can only rarely be obtained. Advanced imaging techniques in patients including the widespread availability of nuclear magnetic resonance have clearly demonstrated the inflammatory lesions in AS and related SpAs but new bone formation, which is a slower process, remains difficult to dynamically visualize and even consistently measure on convential X-ray images [15].

4 Successful Treatment of Signs and Symptoms in Arthritis May Not Always Be Sufficient to Obtain Full Control of the Diseases

The introduction of anti-TNF treatments in RA has not only transformed the management of the patients as signs and symptoms could be more effectively controlled but also changed the outcome of the disease. Anti-TNF therapy, in particular when combined with conventional immunomodulating drugs such as methotrexate, also appears to successfully stop the radiographic progression of disease [16]. Joint erosions and damage predict loss of function and disability and control of these processes therefore adds an additional level of benefits for patients and society. However, such a structural effect has only been recognized for joint destructive processes as seen in RA and some forms of psoriatic arthritis [17] but has not been demonstrated for joint remodeling leading to ankylosis in AS and other SpAs. Three different studies comparing treatment with anti-TNF to a historical cohort over a 2-year period could not demonstrate a benefit in terms of radiographic disease progression [18–20]. Nevertheless, it would be a mistake to downplay the effect that anti-TNF drugs have on both the short- and long-term outcome of patients with AS [21]. A recent study demonstrates that this outcome is determined by both inflammation and structural damage [22]. However, these observations also show that other mechanisms may play a role in the remodeling processes and that there is additional room for other or better interventions. Moreover, the differences between RA and SpA may also point towards specific mechanisms of disease and change the prevalent concepts of chronic arthritis.

Different hypotheses have been put forward to explain these differences between RA and SpA or between effects of anti-TNF on joint destruction and remodeling. Sieper et al. propose the existence of fundamental differences in the pattern and duration of inflammation between RA and AS [23]. In RA, inflammation is hypothesized to be a continuous and persisting process leading to progressive erosive disease. In AS and related SpAs, inflammation may be more fluctuating, leading to minor erosive damage and when it subsides, would leave a window of opportunity for repair processes to occur. This repair phenomenon, called osteoproliferation, however does not respect the original confinement of the damaged tissues and is exaggerated leading to syndesmophyte formation and ankylosis.

Although differences in inflammation between RA and AS are clear, some aspects of this hypothesis may be challenged. We and others demonstrated that inhibition of osteoclasts does not have an effect on joint remodeling and ankylosis in different mouse and rat models of arthritis thereby suggesting that erosion of bone is not necessary to trigger new bone formation [24, 25]. Also, in OA, osteophyte formation is often considered a stabilizing effort in a damaged joint. Moreover, the striking paradox in AS that new bone formation from the edges of the vertebra and trabecular bone loss are occurring at the same time at sites that are in close proximity suggests that the mechanisms underlying new bone formation are at least

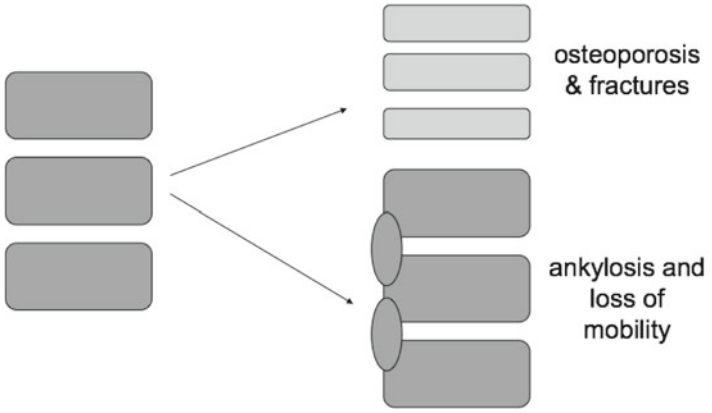

Fig. 3 The bone paradox in ankylosing spondylitis. Inflammation causes loss of trabecular bone leading to osteoporosis and enhanced fracture risk. In the same vertebrae, new bone formation may take place at the edges leading to ankylosis

partly independent from inflammation (Fig. 3). This view is further corroborated by ultrasound studies in AS patients, which show that sites of inflammation and bone erosion are distinct from the sites in which new bone formation occurs [26].

5 Molecular Aspects of Ankylosis

As mentioned above, molecular studies on human bone samples are not easily performed and therefore most experimental evidence has been obtained in animal models. This first lead to the observation that ankylosis in different models mainly occurs through a process of endochondral bone formation [27] that is well known from bone development [28]. Here, progenitor cells at the enthesis or periosteum appear to proliferate, condensate and start differentiating into chondrocyte-like cells. Subsequently the core of these cells further differentiates into hypertrophic chondrocytes. These cells produce not only collagen type X but also MMPs and Vascular Endothelial Growth Factor which leads to invasion by vessels, osteoclastic breakdown of the matrix and growth of osteoblasts and bone. Much alike the developmental cascades an outer core of direct bone formation appears present and the whole process is driven by a number of feedback mechanisms stimulating growth of the osteo- or enthesophyte.

Based on this striking resemblance between pathological bone formation leading to ankylosis and developmental cascades, different signaling pathways could play a role in ankylosis. We have extensively studied the role of bone morphogenetic proteins (BMPs) [29, 30]. BMPs were originally identified for their in vivo bone inductive properties but, as members of the transforming growth factor superfamily, have distinct effects on a variety of cell types. Some BMPs, including BMP2, play an important role in early chondrogenesis. We therefore targeted BMP signaling in a

specific mouse model. DBA/1 mice, an inbred strain that is considered immunologically normal, spontaneously develop arthritis in the hind paws upon grouped caging of aging males from different litters [27]. This unusual arthritis is characterized by entheseal cell proliferation, local endochondral bone formation, and progressive joint ankylosis. Different BMPs are expressed in these processes and overexpression of a broad BMP extracellular antagonist noggin inhibits both onset and progression of disease. BMP target cells were identified in the early processes in which progenitor cells are progressing towards chondrogenic differentiation [29].

The Wnt signaling pathway is another key player during skeletal development. Wnts are strongly associated with osteoblast differentiation but also have different effects depending on the specific family member, on early chondrogenic differentiation during endochondral bone formation [14]. In a series of experiments, Diarra et al. demonstrated that Wnt signaling may determine the phenotypical outcome of arthritis in mouse models [31]. Human TNF transgenic mice typically develop an erosive polyarthritis that shares many similarities with RA. However, when these mice are treated with an antibody directed against Dickkopf-1 (DKK1), a soluble Wnt co-receptor antagonist, bone destruction is inhibited and new bone formation by osteophytes becomes apparent. The inflammatory reaction however remains unchanged. Such observations are not only made in the peripheral joints but also in the sacroiliac joints [32]. Inhibition of DKK1 results in upregulation of osteoprotegerin, inhibiting osteoclast formation. At the same time, bone formation appears directly stimulated. Additional data suggest that functional levels of DKK1 in AS patients are low, although the absolute levels may be increased [33].

6 An Alternative View on the Relationship Between Inflammation and Ankylosis

The cohort observations in patients with AS were further corroborated by data obtained in the DBA/1 model [34]. Treatment with TNF antagonist etanercept had no effect on arthritis or ankylosis suggesting that inflammation and joint remodeling may be largely molecularly uncoupled events. As an alternative or complementary approach we have put forward the entheseal stress hypothesis (Fig. 4) in which we suggests that both inflammation and remodeling have a common trigger but then evolve separately thereby not excluding the potential crosstalk between the pathways [14]. As AS and related SpAs have been strongly associated with the enthesis, we put forward that biomechanical forces and local micro damage to the tissue may play a critical role in the onset of the diseases. In most normal individuals, local homeostatic and repair mechanisms, including minor acute inflammation will be sufficient to restore the tissue but under specific circumstances, for instance in genetically predisposed individuals, inflammation may become a chronic process and new tissue formation may become a pathological rather than a repair process. In the former process cytokines like TNF are essential and their targeting represents an effective therapeutic option. In the latter, BMPs and Wnts may be critical mediators and could be considered as new therapeutic targets.

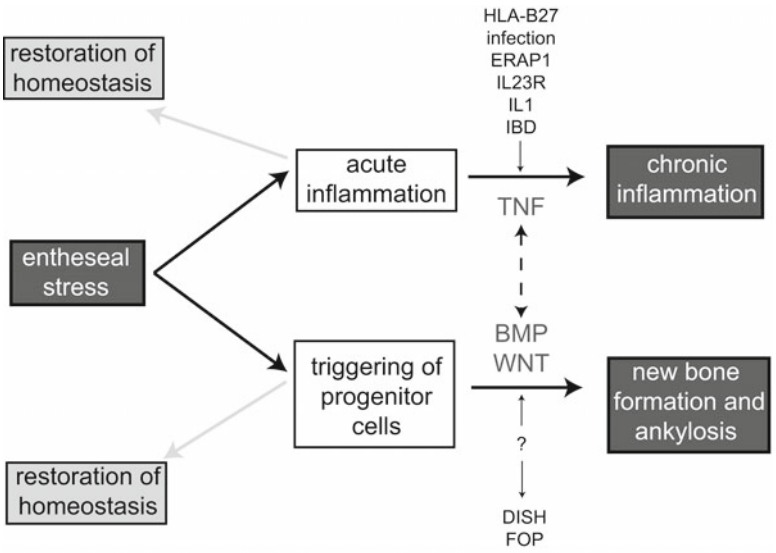

Fig. 4 The entheseal stress hypothesis. The primary event is considered as "entheseal stress." Biomechanical factors and microdamage are likely to play a part in this. Entheseal stress leads to triggering of an acute inflammatory reaction and of progenitor cells. In most instances, the acute events are unnoticed and homeostasis is restored. Under specific circumstances, the acute events can turn into a chronic situation in which both inflammation or ankylosis appears at the forefront. Different pathways regulate chronic inflammation and new tissue formation but these pathways are likely to influence each other. Genetic factors are likely to steer chronic inflammation and new tissue formation. For the latter aspects, clues may be found in other bone forming diseases (*IBD* inflammatory bowel disease, *IL23R* interleukin 23 receptor, *ERAP1* endoplasmic reticulum aminopeptidase 1). This figure is reproduced from Lories et al., Arthritis Research and Therapy 2009, 11(2):221 [14] with permission from the Publisher

The specific anatomic site in which both processes develop may be different. Inflammation develops in the synovium and the bone marrow (osteitis) underlying entheseal sites. The enthesis itself is largely resistant to cell invasion. We have therefore proposed the existence of a functional synovio-entheseal complex to understand the development of inflammation in AS, PsA, and other SpAs [35]. In contrast new bone formation develops from these mechanoprivileged sites [27].

In this context, mesenchymal or stromal cells in the enthesis, bone marrow, and synovium may have a key role in the onset and perpetuation of the inflammation. In a series of elegant experiments in the TNFdARE mice, a mouse model of arthritis and colitis caused by the disruption of a regulator element in the mouse TNFa gene resulting in enhanced endogenous expression, showed that the presence of a TNF receptor on stromal cells is sufficient for the model to develop even when the inflammatory cells cannot respond to the key cytokine [36].

The "chicken and egg" question whether stromal cells rather than inflammatory cells and by extension growth factors or proinflammatory cytokines, provide the

first signals for disease onset in AS remains open. Although the cohort data and animal studies with anti-TNF suggest some degree of uncoupling between inflammation and tissue remodeling, recent evidence obtained in studies on a rare genetic disorder shed additional light on this issue. Fibrodysplasia ossificans progressiva (FOP) is a rare disorder characterized by extensive new bone formation in muscles upon (mild) injury [37]. The disease is often lethal at a young age as an exoskeleton develops with aging. FOP has been associated with activating mutations in the Activin A type I receptor (ACVR1) gene, which is also a BMP receptor [38]. Yu et al. recently engineered a mouse model with overexpression of a constitutively active ACVR1 gene in the muscle [39]. However, to allow a controlled expression of the transgene, an additional removal of a genomic stop-cassette is necessary. Removal of the stop-cassette using an adenovirus overexpressing a cre recombinase enzyme leads to new bone formation in the adenovirus-injected muscle. However, chemical induction of the transgene tamoxifen treatment in contrast is not sufficient to trigger this cascade but requires a nonspecific injection of adenovirus in the target muscle. These experiments suggest that a full cascade only develops after initial microdamage or inflammation even in the presence of a constitutively active system leading to endochondral bone formation. These data are in line with the entheseal stress hypothesis and support its further investigation.

7 Conclusions

Current evidence from patient cohorts and from animal models suggests that inflammation and new bone formation are unique features of some forms of arthritis that also contribute to disability and thus represent a therapeutic challenge. Current strategies based on control of inflammation by targeting cytokines such as TNFa have no specific effect on these disease features despite their overwhelming effect on signs and symptoms. This suggest that inflammation and new bone formation in AS and related SpAs are linked but largely molecularly uncoupled processes.

Further research in AS and related disorders should consider osteoimmunology concepts in the context of microdamage and biomechanical factors contributing to acute and chronic inflammation and also to tissue remodeling. BMP and Wnt signaling pathways have been identified as targets but their modulation may represent specific pharmacological and safety challenges. In addition, further evidence may come from genetic disorders such as FOP and also from more common diseases such as diffuse idiopathic skeletal hyperostosis in which new tissue formation is seen without a clear association with inflammation [40].

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