Is there a final common pathway for arthritis?

Charles J Malemud[†] *&*
Mark E Schulte

[†]*Author for correspondence*
Case Western Reserve University School of Medicine, Department of Medicine, Division of Rheumatic Diseases and Department of Anatomy, University Hospitals Case Medical Center, 2061 Cornell Road, Cleveland, OH 44106-5076, USA
Tel.: +1 216 844 7846;
Fax: +1 216 844 2288;
cjm4@cwru.edu

A well-accepted view holds that the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA) differs. However, recent evidence has also indicated that similar focal and systemic alterations exist in RA and OA, leading us to postulate that there may well be a 'final common pathway' for arthritis. Thus, synovial tissue and articular cartilage responses to activated T and B cells, NF-κB and AP-1 activation, proinflammatory cytokines, growth hormone, chemokines, matrix metalloproteinases and hydrolytic cathepsins often act concurrently and synergistically to generate RA and OA pathology in which articular cartilage destruction is uncoupled from cartilage repair. However, there are also several critical areas in which RA and OA differ. These include the prominent involvement of synovial tissue angiogenesis and fibrin deposition in RA and, most notably, in the timing and extent of subchondral bone responses. Thus, irreversible bone erosion occurs in RA, whereas subchondral bone sclerosis with synovial joint remodeling is typically characteristic of OA.

Despite the well-accepted view that the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA) differs, recent and often compelling evidence has shown that there are remarkable similarities in synovial tissue and articular cartilage pathophysiologic responses when comparisons are made between the two joint disorders [1–4]. For example, a real-time PCR analysis of OA chondrocyte mRNA showed that many upregulated proinflammatory cytokine genes that contribute to OA articular chondrocyte dysfunction and extracellular matrix (ECM) protein degradation, which include IL-1β, IL-6, IL-8 and TNF-α as well as proinflammatory soluble mediators, such as NO and prostaglandin E2 (PGE2) [2], are also elevated in RA synovial tissue and fluid [5]. Furthermore, there is a strong correlation between the types of matrix metalloproteinases (MMPs) and other hydrolytic enzymes in OA and RA synovial joints [4,6–9]. In addition, proinflammatory cytokines detected in OA and RA tissues play a similar critical role in activating transcription factors, such as NF-κB and AP-1. Moreover, similarities exist between OA [2,10–13] and RA [8,12,14] in the repertoire of SAP/MAPK signaling pathways that regulate cytokine, chemokine and MMP gene expression.

Taken together, the strength of the current literature has led us to postulate that there may well be a 'final common pathway' for arthritis that contributes to chondrocyte dysfunction, synovial tissue activation and progressive articular cartilage and bone destruction.

Our extensive literature search focused mainly on peer-reviewed basic and clinical research published since 2002 where comparisons were made between immune- and inflammatory-mediated pathophysiologic responses of synovial tissue, articular cartilage and bone in RA and OA. Where appropriate, qualitative and quantitative differences that contribute to differences in the pathophysiology of RA and OA are also discussed.

Markers of disease activity that are similar in OA & RA

Overview

The prevailing view is that RA and OA constitute pathologic musculoskeletal processes that can be subdivided into early, middle and late phases based on the extent to which autoantibodies and markers of inflammation first appear, as well as the degree to which articular cartilage and subchondral bone alterations occur. For example, individuals who presented with only arthroscopic evidence of minimal cartilage damage or fibrillation (i.e., early OA) actually had elevated numbers of inflammatory cells, new blood vessel formation, and higher expression of COX-1 and -2, IL-1β, TNF-α and NF-κB compared with OA patients undergoing joint arthroplasty (i.e., late OA) [15], but synoviocytes isolated from subjects with either early or late OA synovial tissue produced similar levels of PGE2 *in vitro* in response to various cytokines. Although such general similarities do exist in synovial fluid analyses in RA and OA, where

Keywords: chemokine, cytokine, growth hormone, immune response, inflammation, matrix metalloproteinase, osteoarthritis, rheumatoid arthritis

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proinflammatory markers, such as IL-1β, TNF-α and inducible NO synthase (iNOS), were found in great abundance, it is important to note that Melchiorri *et al.* showed that the cell sources responsible for producing these proinflammatory cytokines and iNOS differed when RA and OA tissue samples were compared [16]. Thus, this study found that in OA, articular chondrocytes were the main source of IL-1β, TNF-α and iNOS, whereas in RA, synovial lining cells, infiltrating lymphocytes and endothelial cells were where the highest levels of IL-1β, TNF-α and iNOS were found.

Transcription factors

NF-κB

There is no stronger evidence that similarities exist between OA and RA than the involvement of the transcription factor NF-κB [12,16–18]. NF-κB activation critically regulates the inflammatory response that ultimately leads to the progressive and irreversible loss of ECM proteins from articular cartilage.

The evidence for NF-κB [17–20] and the inflammasome [20] playing a crucial role in autoimmune inflammation in general, and in various forms of inflammatory arthritis, such as juvenile chronic arthritis, adult-onset Still's disease and RA, is persuasive. In further support of the important role of NF-κB in mediating cartilage degradation, recent findings by Benito *et al.* showed that NF-κB1 (i.e., p50) expression was highest at sites of joint erosion in RA [21].

IL-1β-TNF-α-mediated NF-κB activation is also considered a critical step in inducing chondrocyte apoptosis [22] as well as in regulating inflammation in OA [12]. In fact, suppression of NF-κB by the small-molecule inhibitor RO100 significantly suppressed IL-6, MMP-1 (i.e., collagenase-1) and MMP-3 (i.e., stromelysin-1) expression by OA synovial tissue-derived fibroblasts *in vitro* without altering cell viability or tissue inhibitor of metalloproteinase (TIMP)-1 levels [23]. This effect was also mimicked by treating OA synovial fibroblasts with either an IL-1β- or a TNF-α-neutralizing antibody. Moreover, administration of an adenoviral vector containing an NF-κB-silencing RNA suppressed inflammation as well as the progression of cartilage destruction in a rat partial medial meniscectomy model of OA [24], suggesting the possibility that further development of NF-κB inhibitors might provide a novel therapeutic strategy for inhibiting synovial tissue-mediated inflammation in OA [12,25].

Enzyme markers

Matrix metalloproteinases

Individuals with rapidly destructive hip OA, a type of OA that mainly affects elderly women, had significantly elevated serum MMP-1, -3 and -9 (i.e., 92-kDa gelatinase) and TIMP-1 levels when compared with the MMP/TIMP levels in subjects with a more indolent form of OA [26]. Moreover, the MMP and TIMP repertoire among the individuals with the destructive form of hip OA resembled the serum MMP and TIMP pattern in RA [27].

Of note, SDF-1, working through its receptor, CXCR4, was also found at comparable levels in OA and RA sera and, furthermore, surgical synovectomy significantly reduced SDF-1 levels in both RA and OA [28]. Additional studies went on to show that SDF-1 also increased MMP-9 and -13 (i.e., collagenase-3) expression by chondrocytes in a dose-dependent manner [28], suggesting that SDF-1 should be added to the growing list of receptor-mediated cytokines that increase MMP gene expression in RA and OA.

Although immunohistochemical evidence showed that MMP-9 was found in a large percentage of OA chondrocytes, more OA chondrocytes contained MMP-2 (i.e., 72-kDa gelatinase) than MMP-9 [29,30]. These results confirmed an earlier study, which showed that 69% of synovial tissue isolated from the acetabulum of OA patients who were undergoing total joint replacement only contained MMP-2, whereas only 13% of these synovial tissues contained other MMPs, including MMP-1, -2, -3 and -9 [31]. Of note, this MMP pattern found in advanced hip OA was consistent with the MMP-9:-2 synovial fluid ratio found in RA [32]. However, quantitative analyses later revealed that the molar ratios of the total MMP:TIMP levels were approximately 5.2-fold higher in RA synovial fluid compared with OA synovial fluid [33] and, furthermore, that serum MMP-1, -3 and -9, as well as TIMP-1 and -2, were also at higher levels in RA compared with OA [34]. These results indicated that one of the fundamental differences between OA and RA is in the amount, rather than the types, of activated MMPs and/or TIMPs.

In addition to significant levels of MMP-9 and -2 produced by OA synoviocytes and chondrocytes *in vitro* [8], OA synovial fluid was also found to contain significant amounts of MMP-9, as well as neutrophil gelatinase-associated lipocalin (NGAL), which was isolated from a high-molecular-weight complex containing MMP-9 [35]. Using a variety of analytical methods, this study

showed that high-molecular-weight MMP-9 on SDS/PAGE and Western blots was actually a complex of NGAL and MMP-9. Further studies went on to show that the apparent role of NGAL in OA synovial fluid was to preserve activated MMP-9 by preventing its autodegradation. Relating these results from studies on OA synovial fluid to RA, it should be noted that prior studies had demonstrated that elevated NGAL levels correlated with inflammatory responses as evidenced by the capacity of NGAL to sequester neutrophil chemoattractants, particularly *N*-formylated tripeptides and, possibly, LTB4, as well as by its role in regulating the production of platelet-activating factor [36], all of which are associated with the development of RA pathology [37,38].

Recently, Barksby *et al.* showed that MMP-10, an MMP that is structurally related to MMP-3 and has been implicated in the 'superactivation' of procollagenases, was immunolocalized to both RA and OA synovial tissue, as well as to chondrocytes derived from arthritic cartilage [39].

ADAMs

The enzyme protein family ADAMs has been implicated in cartilage remodeling in experimental murine OA. In that regard, Böhm *et al.* showed that aged ADAM15-null 129/SvJ mice exhibited accelerated OA pathology compared with their wild-type counterparts and, moreover, ADAM15 overexpression in the chondrocytic cell-line T/C28a4 resulted in enhanced chondrocyte viability [40]. By contrast, ADAM15 was found to be overexpressed in human RA synovium [41]. Furthermore, *ADAM15* gene upregulation by VEGF-165 was blocked by a specific VEGF receptor-2 antagonist, SU14980, suggesting that ADAM15 is an important mediator in the VEGF-stimulated neo-angiogenesis response in RA [37,42]. Thus, this result apparently distinguished a role for ADAM in RA from its putative role in experimental OA [40]. However, additional studies are needed to elucidate a role for ADAM15 in human OA.

Hydrolytic cathepsins

Comparable levels of the hydrolytic enzyme cathepsin K was found in RA and OA fibroblast-like synoviocytes (FLSs) [43], but cathepsin K protein levels in the interstitial and perivascular regions of RA synovium were two- to five-fold higher in RA compared with OA. By contrast, cathepsin S was confined to $CD68^+$ macrophage-like synoviocytes, interdigitating cells and blood vessel endothelial cells, but neither OA nor RA FLSs expressed cathepsin S. Although IL-1β and TNF-α stimulated FLS cathepsin K gene expression, there were no differences in the cathepsin K gene response between RA and OA FLS strains after treatment with IL-1β or TNF-α. This finding suggests that cathepsin K expression by OA or RA FLSs in response to IL-1β or TNF-α *in vitro* is apparently independent of any other influences that synovial cell infiltrates in OA or RA joints could have in altering cathepsin K gene expression *in vivo*.

Growth hormone–IGF-I–somatostatin paracrine axis

Denko and Malemud postulated that growth hormone (GH) dysfunction was part of OA pathogenesis [44,45]. They hypothesized that GH production by the pituitary in OA individuals was elevated and the subsequent transport of GH to synovial joints via its sequestration by erythrocytes [46] was a potential mechanism leading to elevated synovial fluid GH levels in OA. However, despite the confirmatory results of several studies showing elevated serum and synovial fluid GH levels with low IGF-1 in OA (reviewed in [45]), the significance of these GH–IGF-1 paracrine axis aberrations in OA remain conjectural. Of note, more recent studies showed that elevated serum and synovial fluid GH in OA was unlikely to be caused by a generalized suppression of somatostatin synthesis since serum somatostatin levels in primary hand and hip OA or secondary hip OA were generally not reduced, with the one possible exception that reduced serum somatostatin levels were found in patients with knee OA aged over 55 years [45]. In addition to, and in keeping with, several reports of impaired pituitary–hypothalamic axis function in RA (reviewed in [45]), recent evidence also showed that the serum GH:somatostatin ratio was skewed upwards in RA, but serum IGF-I levels did not differ from those found in the normal control group [47]. Furthermore, in the RA subjects, prednisone therapy did not alter these results. Thus, the significance of some common abnormalities in the GH–IGF-1 paracrine axis in OA [45] and RA [44,45,47] remain to be further explored.

Cytokines

IL-10

Some controversy remains with regards to the significance of IL-10 levels and the meaning of perturbations in IL-10 levels in RA. IL-10 was originally identified as the most potent of the anti-inflammatory cytokines produced within

the RA milieu [48], but recent studies have indicated that IL-10 may also play an important proinflammatory role in RA [49].

By contrast, there are far too few studies that would point to a significant pathophysiologic role for IL-10 in OA, although, recently, Botha-Scheepers *et al.* showed that TNF-α and IL-10 levels, but not IL-1β or IL-1 receptor antagonist protein levels, were strongly correlated with progression of joint-space narrowing in the knee in OA when the analysis was adjusted for age, sex and BMI [50].

However, from a genetic perspective, an association between an IL-10G microsatellite polymorphism and idiopathic knee OA was found in individuals of Greek descent [51]. Furthermore, an IL-10 SNP, including the SNP found at -2849 in the IL-10G promoter, was associated with distal interphalangeal OA in a Dutch cohort, but elevated or reduced IL-10 receptor gene expression did not appear to be associated with the susceptibility of Dutch subjects to develop distal interphalangeal OA [52]. Thus, IL-10 polymorphisms may play a significant role in increasing the relative risk for certain individuals who will develop OA.

Some immunologic markers that are common to OA & RA

Overview

The clinical benefit received by many patients with inflammatory arthritis that occurs after modulation of distinctive immunologic pathways with the so-called biologic response-modifying drugs has drawn attention to the complexity of interactions between multiple immunologic pathways in regulating inflammatory arthritis. Unfortunately, the available molecular targets for promoting immune modulation have rarely led to a complete resolution of inflammation and subsequent joint damage. This has spawned attempts to target potential final common pathways that initiate immunologic events that generally precede inflammation. As stated above, there are similarities between RA and OA inflammatory phenotypes, but additional commonalities exist in the immunologic cascades that lead to inflammation and synovial joint destruction. However, the targeting of immunologic pathways, while common in RA therapy [5], has yet to be developed for OA. Given the less than ideal response of many patients with inflammatory arthritis to current biologically based therapies, coupled with their associated immunosuppressive effects and the absence of targeted immune-based therapy for those patients with OA, continued identification of novel immunologic targets for RA and OA intervention is worthy of further consideration.

Arthritogenic autoantigens

The K/BxN mouse arthritis model showed that the chronic erosive polyarthritis with pannus formation was similar to human RA synovial tissue. In this animal model, the cause of arthritis was correlated with autoantibody production to glucose-6-phosphate isomerase (GPI) [53]. This finding led to renewed interest into whether specific autoantibodies were a causative factor in initiating inflammatory arthritis.

Although a pathologic role for GPI in the pathogenesis of human RA has yet to be determined, other antigens, such as those that produce antibody responses to heat-shock proteins, collagen, heavy-chain binding protein and CCP have also been suggested as possible RA-causing agents [54,55].

Recent evidence also suggested that a specific immune response was associated with the pathogenesis of OA [56–58]. Cartilage components, including chondrocytes, proteoglycans and collagens, have all been found to be immunogenic [58]. Thus, studies by Xiang *et al.*, using a proteomics approach, revealed that there were autoimmune profiles with unique arthritogenic autoantigens common to both RA and OA patients [59]. Interestingly, a relatively common autoantigen, triosephosphate isomerase, was found in patients with OA, but was rarely seen in patients with RA. Of note, triosephosphate isomerase is a glycolysis pathway enzyme, as is GPI, the antigen involved in murine K/BxN arthritis autoimmunity [53,55]. In addition, it appears that a temporal association exists between antigen-induced autoantibody production and disease onset. Thus, Du *et al.* studying patients with both early and late OA, showed that autoantibody production occurred preferentially during early OA (Kellgren–Lawrence radiographic grades II and III) compared with late OA (Kellgren–Lawrence radiographic grade IV) [57]. Furthermore, they found serum antibodies to CILP in 18.3% of OA patients but only 1.5% of controls, whereas serum antibodies to YKL-39, osteopontin and CCP were detected in 6.6, 8.1 and 5.1% of OA patients, respectively, and 0% of the control group. In addition, this autoantibody repertoire rarely overlapped in a single OA patient, suggesting a specific immune response to a distinct antigen in each

case. Thus, autoantibody prevalence to various arthritis-related proteins in early-stage knee OA appears to support autoantibody involvement in early OA cartilage degeneration. This result is similar in many respects to the findings in RA, in which serum rheumatoid factor and/or CCP autoantibodies often appear before the onset of clinically symptomatic disease. Taken together these results suggest that, although the specific inciting arthritogenic event leading to activation of the inflammatory cascade in RA and OA may differ, a similar preclinical immunologic defect may nonetheless be causative.

Chemokines & chemokine receptors

Chemokines and their associated receptors play a critical role in angiogenesis and in the recruitment of inflammatory cells into synovial tissue. Over 50 chemokines have been discovered and new data are continually being accumulated on their complex interactions [60]. In addition, their role in the pathogenesis of arthritis and their potential as a possible therapeutic target can not be discounted [58,61–63].

Chemokines are expressed by many cells within the synovium, including endothelial cells, synovial fibroblasts, macrophages and lymphocytes. Among the chemokines, CXCR3, CCR1 and CCR5 appear to be particularly attractive for further study because they are upregulated in the synovium of both OA and RA patients [61]. In that regard, Haringman *et al.* examined chemokine receptor expression in patients with RA, OA or reactive arthritis and found significant expression of the chemokine receptors CCR1, CXCR4 and CCR5 in all three forms of arthritis [64]. Based on chemokine expression data, the results of this study suggested that novel therapies directed at inhibiting chemokine activity might not only be a potential treatment for patients with RA, but could also have efficacy for other inflammatory joint disorders, including OA, because this approach would be directed at a final common pathway. A recent Phase I trial demonstrated 'proof of concept' in this regard by showing a decrease in synovial fluid macrophage recruitment with blockade of CCR1 [62]. Interestingly, the results of studies by Desmetz *et al.* showed that the density of cell-surface CCR5 expression determined the intensity of T-cell migration towards synoviocytes with higher CCR5 expression and, furthermore, that the density of synoviocyte CCR5 expression remained constant over time within a given individual, but varied between individuals, which may explain some of the heterogeneity in clinical presentation among individual patients with all forms of inflammatory arthritis [65,66].

T cells & T-cell subsets

The association of RA with certain *HLA* alleles, the prominence of T-cell synovial infiltrates and the role of T-cell-derived cytokines in the inflammatory cascade has confirmed the central and essential role of T cells in RA immunopathogenesis [67,68]. The role of T cells in OA pathogenesis is less well accepted, but growing evidence supports their importance there as well [69].

Previous studies of HLA associations in OA have been conflicting, although recent analysis by Merlotti *et al.* [70] and Riyazi *et al.* [71] showed associations between certain *HLA-B* and *HLA-DR* alleles in patients with primary hand OA, suggesting a role for *HLA* haplotypes in the pathogenesis of primary OA.

Evidence for the role of regulatory T cells (Tregs; i.e., $CD4^+$, $CD25^+$, Tr1 and Th3), which act as immunomodulatory suppressor cells in arthritis, has also recently come to light [72]. Tregs function as suppressors of inflammation and it was hypothesized that chronic inflammation was caused by an imbalance between inflammatory and anti-inflammatory mechanisms in which Tregs play a major role [72]. Although Tregs were found in the synovium and peripheral blood of patients with inflammatory arthritis, their activity appears to be altered or depressed [73].

Several mechanisms have been suggested to cause Treg dysfunction in RA, including the effects of TNF-α and numerous other cytokines and growth factors, such as TGF-β, on the development of these cells [74], as well as the influence of molecular weight changes in hyaluronic acid within inflamed joints [75]. Since the cytokine profile and inflammatory characteristics of synovial fluid are not unique to RA, it is not unreasonable to suggest that dysfunction of Tregs may also play a seminal role in OA inflammation. However, at the present time, the role of Treg networking in OA pathogenesis and/or disease progression has yet to be elucidated.

IL-17

IL-17 is a T-cell-derived cytokine expressed in the synovium of RA and OA patients. IL-17 was established as an important mediator of VEGF

production as well as VEGF-mediated synovial neo-angiogenesis, synovial tissue inflammation and cartilage degradation [76–78].

IL-17 is produced by Th17 cells, which represent a distinct T-cell lineage subset from the Th1 and Th2 T-cell subsets [79,80]. The development of a murine model of arthritis with features similar to human RA in which Th17 cells played a central role thus challenged the view that RA was predominantly a Th1-mediated disease [81]. Although conflicting results have been presented for the role of Th17 cells in human RA, IL-17 has been shown to act synergistically with IL-1 and TNF-α to enhance the effects of these proinflammatory cytokines [81,82].

In addition to its putative role in driving arthritis pathology, IL-17 was also shown to be a powerful stimulator of osteoclast differentiation through the receptor activator of RANKL pathway so that IL-17 potentially plays an important role in subchondral bone destruction in RA [83]. Indeed, treatment of murine collagen-induced arthritis with a murine anti-IL-17 reduced joint inflammation, cartilage destruction and bone erosion [84]. However, similar studies in animal models of OA have yet to be performed and, for that matter, the role of IL-17 and/or Th17 cells in OA has yet to be clarified.

B cells

A growing understanding that B cells play a critical role in inflammation has emerged. The positive response of patients with certain inflammatory conditions to targeted peripheral B-cell-depleting therapy has solidified B cells as a major target for further investigation in RA [85]. Initially it was thought that B cells contributed to RA disease pathogenesis only through their capacity to produce autoantibodies, but now it has become clear that B cells play a central role in cytokine production and cell trafficking, as well as by acting as 'professional' antigen-presenting cells in the RA-inflamed synovium [86]. In this way, B cells have been implicated in maintaining and perpetuating inflammation in RA tissue.

In keeping with previously published results by Benito *et al.* [15], Da *et al.* confirmed the presence of significant inflammatory- and immune-cell infiltrates in OA synovial tissue [87]. Of particular importance was the finding that almost half of the patients that were evaluated showed synovial tissue B-cell infiltrates in clinically inflamed OA joints, as well as lymphoid follicles and plasma cells in the most severe cases. This study also presented evidence for B-cell clonality, where B cells with antigen-driven somatic hypermutations, as assessed by a genetic analysis of the IgH variable (V[H]) region, were found. In all of the five OA cases examined, sequencing of the *VH* gene CDR3 region revealed clonal or oligoclonal B-cell expansion. Expanded B-cell clones showed evidence of clustered somatic mutations, which occurred primarily in the CDR region with a high replacement:silent ratio (>2.9). This finding indicated that these B-cells were probably derived from postgerminal centers that were positively selected for by their antigen receptor. Furthermore, in all five OA samples, VDJ junction-deduced peptide sequences from the clonally expanded B-cells showed that the nucleotide sequences of the dominant B-cell clone(s) possessed individual patterns of VH, DH and JH combination. Thus, these results suggest a potential role for B-cell clonality in perpetuating synovial inflammation in OA and that B-cell migration to, and proliferation in, OA synovial tissue is a 'selective' rather than a 'random' event. However, these results should be interpreted with some caution, since this B-cell clonal analysis was performed only on B cells derived from OA patients with the most severely inflamed joints. Therefore, whether these hypermutated B-cells play a pivotal role in the pathogenesis of all patients with OA or only in that OA subset with an advanced inflammatory phenotype remains to be determined.

Lipid mediators

There is no doubt that lipid mediators, such as PGE2, LTB4 and the platelet aggregating factor TXA2, actively participate in the pain and edema common to OA and RA, as well as influencing the levels of proinflammatory markers of arthritis [88]. Lipid mediators have also been shown to play a crucial role in altering cartilage homeostasis as well as regulating apoptosis and angiogenesis in arthritic tissues [89]. However, direct comparison studies of RA and OA synovial tissue or cartilage that examine the rates of synthesis of PGE2 via COX-1 and/or COX-2 are few in number. Indeed, studies of lipid mediators and their role in arthritis appear to focus mainly on quantitative variations between tissue samples and the cells where COX-2 is induced rather than defining functional or mechanistic differences that would discriminate between the roles of COX-1/-2 in OA versus RA [89]. In that regard, medical therapy of OA and RA with NSAIDs is commonly employed to treat both forms of arthritis [1,89].

Disease markers that may distinguish OA from RA

IL-16

A recent study by McFadden *et al.* [90] showed that IL-16 may contribute to the selective expansion of Tregs [68,72] as well as *de novo* expression of the Treg FoxP3$^+$ transcription factor. Therefore, IL-16 may be important for stimulating immune suppression in RA. The question as to whether IL-16 gene-expression regulation differs in RA and OA was studied by assessing IL-16 gene transcription in dermal and synovial fibroblasts from RA and OA patients [91]. In doing this, Weis-Klemm *et al.* found that cAMP-dependent protein kinase activation induced by the plant diterpene forskolin was primarily involved in upregulating IL-16 in OA fibroblasts, whereas protein kinase C activation was primarily responsible for upregulating IL-16 in RA fibroblasts. However, neither the addition of IL-1β nor TNF-α changed the level of IL-16 gene transcription by RA and OA fibroblasts [91].

IFN-β

If IFN-β is a modulator of inflammation in RA and OA, it should be abundant in FLSs or other cell types associated with the inflamed synovial membrane. To address this possibility, van Holten *et al.* employed anti-IFN-β immunostaining and digital image analysis to distinguish between CD55$^+$ FLSs, CD68$^+$ macrophages and CD83$^+$ dendritic cells from patients with RA, OA and reactive arthritis [92]. They showed that IFN-β was especially prominent in RA FLSs and less so in RA macrophages and dendritic cells. Significantly less IFN-β was found in OA or reactive arthritis FLSs, suggesting that the IFN-β protein was a specific marker for RA.

HIF

VEGF and PD-ECGF, also known as thymidine phosphorylase, are expressed in both RA and OA synovium [93]. Because HIF-1α is a critical factor in the regulation of VEGF gene transcription [42], Giatromanolaki *et al.* employed an immunohistochemical analysis to compare the expression of HIF-1α and its isoform, HIF-2α, in RA and OA synovium with non-arthritic synovial tissue [94]. HIF-1α and HIF-2α were overexpressed in both RA and OA synovium compared with synovium derived from non-arthritic subjects. In addition, HIF expression correlated with well-developed microvessels as well as microvascular density, high expression of PD-ECGF and VEGF/KDR expression. However, expression of VEGF/KDR was consistently more prominent in RA compared with OA, suggesting that the HIF-α plays a relatively minor role in the new blood vessel formation that may be associated with synovial-tissue activation in OA.

Coagulation pathway & tissue factor

Activation of the coagulation and tissue factor (i.e., fibrinolysis) pathways appears to play a prominent role in fibrin deposition associated with arthritis. So *et al.* found that tissue factor activity and levels of thrombin-antithrombin-II and thrombin-activated fibrinolysis inhibitor were significantly higher in RA synovial fluid compared with OA synovial fluid, the tissue factor activity being strongly correlated with serum C-reactive protein levels and synovial fluid leukocyte counts [95]. Thus, increased thrombin-activated fibrinolysis inhibitor levels may account for the prominent fibrin deposition common to RA synovial tissue compared with OA synovial tissue, as well as with the more severe joint inflammation scores in RA when assessed by histological analysis [96].

Wnt & FRP

Wnt and its endogenous inhibitor, secreted FRP, along with β-catenin, play a prominent role in growth-plate morphogenesis, neo-angiogenesis and skeletal development [97], and elevated levels of Wnt may be an important signal in the regulation of synoviocyte activation in RA [98]. With regard to the latter, Imai *et al.* investigated whether Wnt/FRP was related to the prominent vascular changes associated with RA and to what extent differential Wnt/FRP expression occurred in RA and OA synovial tissue [99]. As measured by *Wnt10B* mRNA expression, Wnt10B was most frequently associated with RA synovial tissue, whereas the three isoforms of FRP, namely FRP1, FRP2 and FRP4, were more prominent in OA synovium. Wnt10B-expressing cells most strongly correlated with the level and retention of inflammatory cells within the synovium as well as with elements of tissue fibrosis that were more prominent in RA than in OA. In addition, MT1MMP, an activator of pro-MMPs [97], was upregulated by Wnt and colocalized with cells expressing both Wnt10B and β-catenin.

With respect to the tissue localization of Wnt in RA and OA, Nakamura *et al.* showed that Wnt7b was present in articular cartilage and synovium in both RA and OA, in bone in RA, and in the osteophytic spurs and bone marrow in OA tissue samples [100]. As expected, elevated levels of TNF-α, IL-1β and IL-6 were found in RA

synovium compared with OA synovium but, more importantly, Wnt7b-transfected normal synoviocytes showed elevated levels of TNF-α, IL-1β and IL-6. Thus, overexpressed Wnt7b may be critical for modulating the level of pro-inflammatory cytokines. Of note, Diarra *et al.* recently showed that inhibition of DKK-1, a regulatory molecule of the Wnt pathway, reversed the bone-destructive lesions of inflammatory murine arthritis to the bone-forming pattern of OA and, furthermore, that TNF-α was an important inducer of DKK-1 [101].

Fak/Pyk2

The nonreceptor tyrosine kinase Fak family, including Pyk2, mediate intracellular signaling involving growth factor receptors and adhesion-mediated integrin, clustering to form a network with the proteins paxicillin, vinculin and talin [102]. The Fak/Pyk2 signaling pathway has been implicated in fostering cell adhesion, osteoclast-mediated bone resorption and angiogenesis [103], all of which are prominent features in the pathogenesis of RA, but not in OA. To assess whether or not there were intrinsic differences between Fak and Pyk2 activation in RA and OA, Shahrara *et al.* examined RA and OA synovial tissue-lining cells and showed that both contained more activated (i.e., phosphorylated) Fak (p-Fak) compared with synovial tissue from normal donors [104]. However, RA synovial-lining cells and peripheral blood differentiated macrophages contained more p-Pyk2 and p-Src than their OA counterparts. p-Pyk2 was mainly expressed by synovial-lining cells but not by peripheral blood macrophages at baseline. Of note, both p-Pyk2 and p-Src levels increased when these cells were treated with IL-1β or TNF-α *in vitro*. Thus, differential phosphorylation of Fak and Pyk2 in RA versus OA synovial tissue may account, in part, for differences in the adhesion and retention of inflammatory cells when the two arthritic disorders are compared.

Subchondral bone

Overview

Although significant changes in subchondral bone are common to both RA and OA, there is compelling evidence to indicate that subchondral bone alterations in RA and OA occur by mechanisms that lead to profoundly different pathologic consequences for the two disease processes.

Subchondral bone changes in OA

In OA, articular cartilage degeneration occurs concomitantly with sclerosis of subchondral bone and bone thickening [105]. This event is likely related to the upregulation of bone matrix proteins, since it was found that OA sera contained elevated Type I collagen *N*-propeptide and Type I collagen levels [106]. Thus, subchondral bone thickening and concomitant joint stiffening in OA, while regarded as a secondary phenomenon by some investigators [107], also result in increased mechanical stress over articular cartilage and continuous joint remodeling. Furthermore, formation of Type I collagen homotrimers in OA subchondral bone during joint remodeling [108] could cause dysfunction of newly synthesized bone as well as hypomineralization.

In addition to subchondral bone thickening, the recently described bone marrow edema-like (BME) lesions in OA subchondral bone were found to be associated with accelerated cartilage damage and worsened histological cartilage scores [109]. Although recent evidence showed that BME size fluctuated in patients with familial OA over a 2-year follow-up, the increase (40%) or decrease (20%) in the BME lesion score in this OA study group was not associated with changes in the Western Ontario and McMaster Universities OA index, pain and function score [110], suggesting that changes in the BME lesion score were not predictive of OA pain and disability levels. Thus, the long-term effects of changes in the number and size of BME lesions on the rate of OA progression remains to be fully elucidated.

Subchondral bone changes in RA

In contrast to subchondral bone changes in OA, which generally involve heightened osteoblast activity and increased bone thickness, subchondral bone alterations in RA result in aggressive, focal bony erosions in affected joints, with associated synovitis. Furthermore, experimental studies in the mouse indicated that conversion of bone marrow-derived osteoclast progenitor cells to osteoclasts correlated with administration of TNF-α and proliferation of the osteoclast precursor pool [111].

In RA, bone erosion is mediated by activated osteoclasts acting through the RANK and its ligand, RANKL, which stimulates osteoclastic differentiation from osteoclast progenitor cells [112,113]. In support of this view, RANK/RANKL was found to be prominently expressed at the

pannus–bone interface [114] and RANK/RANKL was recently found to be strongly upregulated by proinflammatory chemokines such as CCL20 (i.e., macrophage inhibitory protein-3α) and its receptor, CCR6 [115], along with other proinflammatory cytokines within the RA milieu. Conversely, osteoprotegerin, the endogenous inhibitor of RANKL (and therefore of osteoclast differentiation) was primarily expressed by cells remote from pannus. Thus, it was suggested that because osteoprotegerin expression was largely confined to a location away from subchondral bone, it was likely to have limited suppressive activity on osteoclast-mediated bone destruction in RA [114].

Recent evidence has indicated that lymphoid aggregates containing tartrate-resistant acid phosphatase-positive and cathepsin K-positive osteoclasts also accumulate in RA synovial tissue and bone marrow, where they can adhere to subchondral bone and may therefore contribute to irreversible bone loss in RA [116]. However, at this juncture, no functional evidence exists to suggest that subchondral bone marrow infiltrates contribute to subchondral bone damage, nor has it been ascertained whether the presence of lymphoid aggregates results from an epigenetic phenomenon linked to the presence of RA bone erosions.

Conclusion

Several critical cellular events appear to be common to RA and OA, suggesting the possibility that there does indeed exist, to some extent, a final common pathway for arthritis (Table 1). First and foremost in this proposed scheme is the significant upregulation of three major proinflammatory cytokines, IL-1β, TNF-α and IL-6, whose role is twofold: to upregulate MMP gene expression and MMP activity, which results in cartilage ECM protein degradation, and to suppress chondrocyte-mediated compensatory synthesis of ECM proteins. A second facet of this scheme that appears to be of importance in both joint diseases is the initiation and perpetuation of a synovial joint inflammatory response, perhaps arising from the generation of arthritogenic autoantigens that activate T- and B-cell immune responses. A third component common to RA and OA during the disease process is synoviocyte activation as part of the inflammatory response, which appears to accelerate articular cartilage destruction. Finally, cartilage destruction in RA and OA both appear to involve activation of the SAP/MAPK pathway and the transcription factors NF-κB and AP-1, which are crucial for increasing MMP gene expression and for differentially regulating survival and apoptosis of chondrocytes and synoviocytes.

The current literature also points out where specific markers of RA and OA disease progression allow one to discriminate between the two forms of arthritis (Table 2). These arthritis discriminators include the interplay between VEGF and synovial tissue angiogenesis, coagulation pathway components, the presence of FAK/Pyk2 and the generation of significant subchondral bone erosions as a result of RANKL/RANK-mediated osteoclast activation, all of which are more specific and prominent in RA than in OA.

Table 1. Similar biomarkers in rheumatoid arthritis and osteoarthritis.

Biomarker	Type(s)	Activity	Ref.
Cytokines	TNF-α, IL-1, IL-6	↑ MMP	[1,3,7,8]
		↓ ECM synthesis	[3,27]
		Apoptosis induction	[3,22,116]
		↓ Treg activity	[75]
MMPs	-1, -2, -3, -9	Degrade ECM	[7,8,29,30]
	-10	Activate pro-MMP	[35,97]
Cathepsins	K, S, L	Degrade ECM	[43]
Autoantigens	CILP, TPI, GPI	T- and B-cell activation	[54–59]
Transcription factors	NF-κB, AP-1	↑ Inflammation	[12,18–21]
		↑ MMP	[8]
		↑ Apoptosis	[22]
SAPK/MAPK	p38, JNK, ERK	↑ Inflammation, cytokine gene expression, apoptosis	[10–14,19]

ECM: Extracellular matrix; GPI: Glucose-6-phosphate isomerase; MMP: Matrix metalloproteinase; TPI: Triosephosphate isomerase; Treg: Regulatory T cell.

Table 2. Biomarkers that distinguish rheumatoid arthritis from osteoarthritis.

Biomarker	Type	Activity	Ref.
Growth factors	VEGF/KDR	↑ Angiogenesis	[93]
Fibrin	TAFI, TAT-II	↑ Inflammation	[96]
Skeletogenesis	Wnt10B, Wnt7b, FRP1, 2, 4	↑ Inflammation, ↑ cytokines	[97–101]
NRTK	FAK/Pyk2	↑ Cell adhesion	[102–104]
Bone	RANKL/RANK	↑ Resorption	[112–114]

NRTK: Nonreceptor tyrosine kinase; TAFI: Thrombin-activated fibrinolysis inhibitor; TAT: Thrombin-antithrombin.

Future perspective: strategies designed to regulate immune responses & inflammation

The significant role played by proinflammatory cytokines in RA and OA pathophysiology resulted in the development of disease-modifying biologics designed to inhibit the upstream activation of signaling pathways that were dependent on the biological activity of these cytokines [60,117–119]. But because OA is generally considered a focal, rather than a systemic, musculoskeletal disturbance, intravenous or subcutaneous administration of anti-TNF-α or anti-IL-1 biologics for treating OA has received little support [120,121]. However, intra-articular administration of anakinra (IRAP®, Amgen, CA, USA), Orthokine® (Orthogen AG, Düsseldorf, Germany) and IGF-1 have shown some promise in OA clinical trials [117,122,123]. A comprehensive review of the use of anakinra in adult RA clinical trials by Burger *et al.* indicated that anakinra, while showing efficacy and tolerability in these patients, produced weaker effects on clinical outcome measurements (i.e., ACR20–70 responses) of RA disease activity compared with anti-TNF-α therapies [124].

Another potential avenue for future arthritis therapy that has at least demonstrated 'proof of principle' *in vitro* involves employing a NSAID, such as aceclofenac (i.e., 2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetic acid) [125], a derivative of phenylacetic acid, to increase human chondrocyte IRAP synthesis [126] in an attempt to neutralize elevated levels of IL-1β found in RA and OA synovial fluid. In addition to increasing IRAP, aceclofenac also decreased chondrocyte nitric oxide production, which is a critical soluble mediator of synovial joint inflammation [3] and a potent inducer of chondrocyte apoptosis [22].

The upregulation of MMP and ADAMTS (ADAM with a thrombospondin motif) genes has been shown to drive both RA and OA joint destruction [8,127–129]. Thus, a renewed interest might emerge for developing MMP and/or ADAMTS protein mimetic inhibitors with suitable bioavailability and efficacy profiles that, when orally administered to animals prior to, and after, initiating experimentally induced arthritis, they suppress inflammation and cartilage damage. Of note, however, were the results of a recent clinical trial involving subjects with mild to moderate knee OA in which MMP inhibitor, PG-116800, administered by oral dosing, did not provide clear benefit and produced so many unfavorable adverse side effects involving the hands and shoulders that its continued development for use in OA was considered to be contraindicated [130].

Chemical modification of MMP synthesis *in vivo* may also prove worthy of further study. Of note, recent studies conducted in the rat collagen-induced arthritis model of human RA showed that vanadate (i.e., bis[maltoato]oxovandadium), when administered subcutaneously together with the reducing agent *N*-acetyl cysteine, suppressed established arthritis by inhibiting MMP-3 and -1 through the modulation of AP-1 activity [131].

Gene-therapy strategies have also been tested in arthritis animal models and some studies have actually been conducted on human OA and RA patients (reviewed in [132]). These experimental protocols have largely targeted those proteins thought to be critical in driving the progression of synovial inflammation, angiogenesis, and cartilage and bone alterations in RA and OA.

Recent studies suggested that a loss of immune tolerance, together with the appearance of autoantigens and proliferation of autoreactive T and B cells, appears to play a central initiating role in both RA and OA pathogenesis [67–69]. Therefore, in the future, an ideal OA and RA therapy might target this initial complex immune-mediated event that could lead to suppression of inflammation with the additional effect of perhaps restoring tolerance to self antigens. In this regard, Tregs appear to be an

attractive target for intervention, whether through induction of Treg production, restoration of existing Treg function or a combination of both. Of note, recent studies reported by Nadkarni *et al.* demonstrated that RA therapy with infliximab (Centocor, PA, USA) promoted the production of Tregs *in vivo*, whereas *in vitro*, infliximab induced the differentiation of $CD62L^-$ Tregs from $CD4^+CD25^+$ cells, isolated from RA patients, in a TGF-β-dependent manner [133]. In addition, Bollyky *et al.* showed that Treg suppressor function could be improved after treatment with high-molecular-weight hyaluronan, suggesting that Tregs might be a suitable target for arthritis intervention via viscosupplementation [75]. However, to date, no experimental *in vitro* or *in vivo* drug therapy has been developed to specifically counteract the suppressed function of Tregs in RA [134].

Chemokines, including CCR1, CX3CL1/fractaline and CCL2, have been targeted as potential therapies in RA, but initial experimental and human studies have yielded variable and somewhat conflicting results [62,135,136]. Of note, Nanki *et al.* showed that anti-CX3CL1/fractaline monoclonal antibody treatment significantly lowered the arthritis score, while also reducing synovial inflammation and bone erosion in murine collagen-induced arthritis [135]. However, in a more recent clinical trial, Haringman *et al.* did not report any clinical benefit when human anti-CCL2 was administered to RA patients, and no synovial tissue or peripheral blood RA biomarker levels were altered [136]. The fact that upregulation of synovial tissue chemokine expression is not unique to RA suggests that chemokine targeting could also be considered in future therapeutic drug development for OA [61], but only if supportive results for antichemokine therapy are first obtained in OA animal models.

Finally, there are currently no experimental or clinical studies that have evaluated specific T- or B-cell-targeted therapy for OA. However, it stands to reason, given the similarities between the histological appearance of articular cartilage changes in RA and OA and the inflammatory joint milieu in a small subset of patients with the aggressive inflammatory OA phenotype (which appears to resemble RA), that therapy targeted at T and/or B cells might provide additional clinical benefit to these OA patients. However, a difficulty will still remain in identifying this particular OA subset prior to the appearance of significant joint damage,

Executive summary

Inflammation

- Proinflammatory cytokines that have been shown to contribute to chondrocyte dysfunction and extracellular matrix degradation in osteoarthritis (OA) are also involved in the pathogenesis and synovial tissue dysfunction in rheumatoid arthritis (RA).
- Clear similarities exist between OA and RA in the quality, but not the quantity, of synovial-cell infiltrates, as well as cytokine, chemokine and cartilage degradative enzyme profiles.
- IL-17, a proinflammatory cytokine produced by the distinct Th17 cell subset, is found in inflamed synovial tissue in RA and OA, and may regulate the new blood vessel development that is required for bone remodeling.

Growth hormone–IGF-1–somatostatin

- Perturbations have been reported in the growth hormone–IGF-1–somatostatin paracrine axis in RA and OA.

Angiogenesis

- Evidence has shown that many similarities exist between the joint milieu in RA and OA synovial tissue. However, clear differences exist between RA and OA, including the level of VEGF production and synovial blood vessel development, the involvement of the coagulation pathway and tissue-factor synthesis, and Fak/Pyk2 activation.

Immunoregulation

- Arthritogenic autoantigens, although unique to either OA or RA, appear to play a central role in the pathogenesis and perpetuation of the inflammatory response in both types of arthritis.
- Autoantibody production in RA and OA appears to occur early in the disease process, suggesting a preclinical immune defect and the potential for early recognition for those patients at risk for developing clinical symptoms.
- Regulatory T-cell activity, which plays a critical role in the generation of self tolerance and immune modulation, is suppressed in inflamed RA synovial tissue and other chronic synovial joint inflammatory states, which could now include OA.

Chemokines

- Similar types of chemokines are present in RA and OA synovial tissue. The recent development of monoclonal antibodies targeted at chemokines has shown some promise as a therapeutic strategy in experimental autoimmune arthritis, and may well be tested in OA animal models.

when the potential benefits of systemic therapy would outweigh the sustained immunosuppression that might be achieved by targeting T- and B-cell activity. In addition, in moderate to end-stage OA, cartilage destruction is generally limited to one or only a few joints, making OA amenable to surgical intervention or intra-articular drug administration rather than systemic immunomodulatory drug therapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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Affiliations

- *Charles J Malemud, PhD*
  Case Western Reserve University School of Medicine, Department of Medicine, Division of Rheumatic Diseases and Department of Anatomy, University Hospitals Case Medical Center, 2061 Cornell Road, Cleveland, OH 44106-5076, USA
  Tel.: +1 216 844 7846
  Fax: +1 216 844 2288
  cjm4@cwru.edu
- *Mark E Schulte, MD, Fellow in Rheumatology*
  Case Western Reserve University School of Medicine, Division of Rheumatic Diseases, University Hospitals Case Medical Center, 2061 Cornell Road, Cleveland, OH 44106-5076, USA
  Tel.: +1 216 844 7821
  Fax: +1 216 844 2288
  mark.schulte@UHhospitals.org