Arch. Immunol. Ther. Exp. (2011) 59:89–95
DOI 10.1007/s00005-011-0116-3

REVIEW

Pathogenesis of Joint Destruction in Rheumatoid Arthritis

Shunichi Shiozawa · Ken Tsumiyama · Kohsuke Yoshida · Akira Hashiramoto

Received: 23 June 2010 / Accepted: 20 September 2010 / Published online: 16 February 2011

Abstract Synovial mesenchymal cells, matrix metalloproteinases (MMPs), and osteoclasts are the three major players directly responsible for the pathogenesis of rheumatoid joint destruction. First, synovial mesenchymal cells, internally driven by a transcription factor c-Fos/AP-1, not only directly invade cartilage and bone as a granulation tissue called "pannus" but also release inflammatory cytokine interleukin (IL)-1β. IL-1β induces MMPs and activates osteoclasts. Synovial cells can also present antigen to T cells to drive antigen-specific immune responses. Second, cartilaginous joint matrix can only be degraded after the first attack of collagen fibrils by MMPs, and importantly, most of the MMPs are under the control of c-Fos/AP-1 and IL-1β as well. Third, differentiation of osteoclast is driven internally by NFATc1, where NFATc1 is under the control of TRAF6, c-Fos/AP-1 and osteoclastogenic signaling complex. IL-1β has been shown to induce osteoclastogenesis directly and also indirectly via signaling through RANKL. Therefore, IL-1β and c-Fos/AP-1 influence each other's gene expression and activity, resulting in an orchestrated cross-talk that is crucial to arthritic joint destruction, and thus, blockade of IL-1β and/or c-Fos/AP-1 can be most promising as a therapeutic target, and in fact, a selective inhibition of c-Fos/AP-1 does resolve arthritic joint destruction.

Keywords Rheumatoid arthritis · Joint destruction · c-Fos · c-Fos/AP-1 · IL-1beta

S. Shiozawa · A. Hashiramoto
Division of Rheumatology, Department of Medicine,
Kobe University Graduate School of Medicine,
7-5 Kusunokicho, Chuoku, Kobe 650-0017, Japan

S. Shiozawa (✉) · A. Hashiramoto
The Center for Rheumatic Diseases, Kobe University Hospital,
7-5 Kusunokicho, Chuoku, Kobe 650-0017, Japan
e-mail: shioz@med.kobe-u.ac.jp

S. Shiozawa · K. Tsumiyama · K. Yoshida
Division of Bioregulation, Department of Biophysics,
Kobe University Graduate School of Health Science,
7-10-2 Tomogaoka, Sumaku 654-0142, Japan

S. Shiozawa
Investigator of the Center of Excellence (COE), Kobe, Japan

Introduction

Joint destruction is largely responsible for limiting the activity of daily living of patients with rheumatoid arthritis (RA). We here focus our discussion on the mediators that directly cause joint destruction. Few reviews are available focusing on the mediators of joint destruction while extensive discussions are made on the roles of inflammatory cytokines in RA (Shiozawa and Tsumiyama 2009). The direct mediators of joint destruction are synovial mesenchymal cells, matrix metalloproteinases (MMPs) and osteoclasts: synovial mesenchymal cells directly invade cartilage and bone as a granulation tissue called pannus (Shiozawa et al. 1983a); MMPs directly destroy joint matrix from the surface of cartilage (Kimura et al. 1977) since cartilaginous matrix can only be degraded after the first attack of collagen fibrils by MMP (Pap et al. 2002); osteoclasts induce peri-articular osteoporosis which is an important early manifestation characterising RA (Shimizu et al. 1985) (Fig. 1, schematic representation of the main pathways described in this review).

Synovial Mesenchymal Cell

Normal synovium is composed of one layer of the two types of synovial lining cells with mesenchymal characteristic called

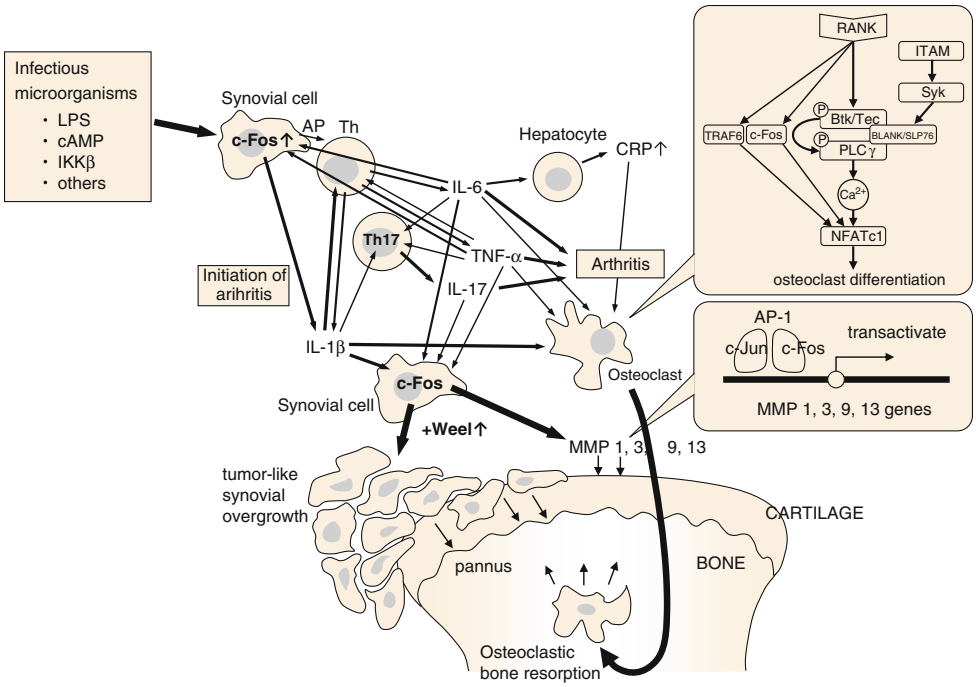

Fig. 1 Synovial cells not only present antigen to T cells (AP) and evoke/aggravate arthritis but also destruct joints as a granulation tissue called pannus. Up-regulation of Wee 1 kinase in conjunction with c-Fos within synovial cell results in a "tumor-like" overgrowth, i.e., proliferation in face of mitosis-arrest, of rheumatoid synovium. c-Fos/AP-1 also transactivates matrix metalloproteinase (MMP) genes and thereby mediating the degradation of cartilage and bone matrices. Further, c-Fos/AP-1 is an important component of the intracellular signalling pathways mediating the effect of interleukin (IL)-1β in osteoclasts. IL-1β is the strongest stimulator of osteoclastic bone resorption

fibroblast-like (type B) and macrophage-like (type A) (Barland et al. 1962; Shiozawa et al. 1992; Shiozawa and Tokuhisa 1992), and a small number of sublining interstitial cells and blood vessels. Synovial fibroblast-like cells degrade cartilaginous matrix as 'pannus' by clinging tightly to the articular surface of cartilage and penetrating deep into cartilage and bone from the bare area between the margin of cartilage and synovial insertion by changing their shape into macrophage-like cells (Kuroki et al. 1993; Shiozawa et al. 1983a; Shiozawa et al. 1992). Importantly, it is noted that the invasive front of rheumatoid pannus is solely composed of the above described synovial mesenchymal cells, but not lymphocytes (Shiozawa et al. 1983a, 1992). Lymphocytes appear somewhat later after the establishment of small blood vessels at cartilage-pannus junction (Shiozawa et al. 1983a).

Such synovial mesenchymal cells are internally driven by up-regulated c-Fos/AP-1 in RA and release interleukin (IL)-1β, an inflammatory cytokine that is *sine qua none* for joint destruction (Asahara et al. 1997; Kawasaki et al. 2003; Kuroki et al. 1993; Shimizu et al. 2000; Shiozawa et al. 1992; Shiozawa and Tokuhisa 1992; Trabandt et al. 1992). Up-regulated c-Fos/AP-1 causes synovial overgrowth (Kawasaki et al. 2003; Shiozawa and Tokuhisa 1992) and osteoporosis (Kuroki et al. 1992; Miyauchi et al. 1994) both typical of RA. Inhibition of c-Fos/AP-1 not only ameliorates arthritis (Shiozawa et al. 1997) but also perfectly resolves arthritic joint destruction (Aikawa et al. 2008). Recent studies show that c-Fos/AP-1 can be so easily up-regulated in response to cAMP, IKKβ and bacterial lipopolysaccharide (Koga et al. 2009), which indicates that c-Fos/AP-1 and IL-1β both can be quickly activated upon encounter with invasive antigen. c-Fos/AP-1 and IL-1β influence each other's gene expression and activity, resulting in an orchestrated cross-talk that is crucial to arthritic joint destruction (Dayer 2003; Hess et al. 2001; Joosten 2010; Karin et al. 1997; Scott and Kingsley 2006; Sirum-Connolly and Brinckerhoff 1991; Sun et al. 2002; Whitmarsh et al. 1995). Both c-Fos/AP-1 and IL-1β are indeed indispensable for arthritic joint destruction (Aikawa et al. 2008; Asahara et al. 1997; Dayer 2003; Horai et al. 2000; Joosten et al. 1999; Kawasaki et al. 2003; Kobayashi et al. 2000; Kuroki et al. 1992; Miyauchi et al. 1994; Probert et al. 1995; Redlich et al. 2002; Shimizu et al. 2000; Shiozawa et al. 1997; Teitelbaum 2004; Trabandt et al. 1992; van den Berg 2002). Invasiveness of rheumatoid synovial mesenchymal cells is far stronger than those of osteoarthritis (Tolboom et al. 2005).

Synovial mesenchymal cells are important not only for arthritic joint destruction but also for the induction of arthritis. Studies have shown that synovial mesenchymal cells can present antigen to T cells (Athanasou et al. 1988; Klareskog et al. 1982; Poulter et al. 1982; Shimizu et al. 1988; Shiozawa et al. 1983b; Tran et al. 2007): the cells behave just as follicular dendritic cells of lymph node and drive B cells to mature into antibody secreting cells (Lindhout et al. 1999; Shimizu et al. 1988; Tiku et al. 1985). Because most intravenously injected antigens reach and pass through the joint space and thus have access to the synovial cells (Schumacher 1973), abnormalities in the recognition of antigens reaching synovium may modify the sequellae of arthritis significantly.

The overgrowth of rheumatoid synovial cells has long been regarded as "tumor-like": the synovial cell with "transforming" appearance containing abundant cytoplasm, large pale nuclei and prominent nucleoli with karyotypic alteration are typical of affected rheumatoid joints and are seen in the experimental animal models of arthritis (Fassbender 1984; Shiozawa et al. 1983a, 1992). This tumor-like overgrowth of rheumatoid synovium comes from up-regulated Wee1 kinase that inhibits mitotic cell division by phosphorylating cdc2 (Kawasaki et al. 2003). Wee1 is transactivated directly by up-regulated c-Fos/AP-1 in RA (Kawasaki et al. 2001, 2003). Up-regulated c-Fos/AP-1 and subsequent increase of Wee1 lead to arrested mitotic cell division in face of heightened cell proliferation, which is the characteristic "tumor-like" overgrowth of rheumatoid synovia (Fassbender 1975). The findings together would highlight the importance of synovial mesenchymal cell and its internal driving force c-Fos/AP-1 and of the inflammatory cytokine IL-1β released from synovial mesenchymal cells.

MMP

How to stop the degradation of bone and cartilage, i.e., to control MMP, has long been the central issue in the research of RA, because collagenous matrix can only be degraded after the first attack of collagen fibrils by MMP (Burrage et al. 2006; Milner et al. 2008). Regulated degradation of extra-cellular matrix by the balance between matrix-degrading MMPs and their physiologic inhibitor TIMPs (tissue inhibitor of metalloproteinases) is essentially important in life not only in the joints but also even the integrity of central nervous system (Beggs and Salter 2008; Chakraborti et al. 2003; Yan and Boyd 2007). TIMP inhibits MMP by binding non-covalently to its enzymatically active site with 1:1 stoichiometry (Murphy and Willenbrock 1995). Its conserved tertially structure predicts that any subtypes of TIMP can inhibit most of MMPs (Will et al. 1996), however, MMPs are active in rheumatoid joints because the amount of MMP exceeds approximately $\times$44 that of TIMPs in RA (Okada 2000; Yoshihara et al. 2000).

Matrix-degrading MMP1 and MMP3 are synthesized in synovial lining cells, MMP2 in subling cells, MMP9 in both lining and sublining cells, and TIMP1, 2 and 3 in synovial tissues (Ahrens et al. 1996; Hembry et al. 1995; Okada et al. 1989; Okada et al. 1990; Pap et al. 2000). MMPs are up-regulated by inflammatory cytokines such as IL-1β or tumor necrosis factor (TNF)-α (Burrage et al. 2006), and indeed, most of the collagenases named MMP1, 8 and 13, gelatinases named MMP2 and 9, stromelysins named MMP3, 10 and 11, matrilysins named MMP7 and 26, and membrane type MMPs named MMP14, 15, 16, 17, 24 and 25 (re-named as MT1, 2, 3, 4, 5 and 6, respectively) are all significantly increased in arthritic joints (Burrage et al. 2006). The collagenases such as MMP1 produced from synovial cells and MMP13 produced from chondrocytes are most important in RA as a rate limiting enzyme that degrades collagenous matrix (Burrage et al. 2006). MMP13 degrades aggrecan in addition to collagen. Gelatinases MMP2 and MMP9 and stromelysin MMP3 degrade non-collagen matrix components in the joints. Among membrane type MMPs, MT1-MMP is most important in RA (Okada 2000; Pap et al. 2000). Another enzymes called ADAMTSs (a disintegrin and metalloproteinase with thrombospondin motifs) mostly degrades aggrecans, and in particular, ADAMTS4 and 5 are responsible for the cleavage of aggrecan in RA (Lohmander et al. 1993; Porter et al. 2004). The ADAM family comprises $\sim$23 members, and is classified according to their enzymatically active sites into ADAM metalloproteinases with transmembrane domain (ADAM1, 8, 10, 12, 13, 15, 17, 19 and 20), ADAMs with thrombospondin motifs (ADAMTS1, 2, 3, 4 and 5), and other inactive nonproteolytic homologues (Table 2 of Okada 2000). ADAM17 acts as TNF-α-converting enzyme and cleaves proTNF-α to release soluble TNF-α.

The activity of MMPs is mainly regulated at the levels of transcription of genes or enzymatic activation of latent enzymes. The transactivation of MMP gene is controlled by the transcription factors such as AP-1, PEA3, Sp-1, β-catenin/Tcf-4 and NF-κB (Yan and Boyd 2007). The majority of MMP promoters, including MMP1, 3, 9, and 13 that are important in arthritis, contains a TATA box at approximately –30 bp and an AP-1 binding site at approximately –70 bp relative to the transcription start point (Chakraborti et al. 2003; Yan and Boyd 2007). Most of the AP-1 sites contain an upstream PEA3-binding site that is often adjacent to, and cooperative with, an AP-1 binding site. Increased transactivation of MMP genes by AP-1 or PEA3 is achieved largely through mitogen-activated protein kinases-mediated phosphorylation, but activated p38 kinases also increase the cellular amount of AP-1 protein indirectly by transactivating *c-jun* and *c-fos* genes (Chakraborti et al. 2003; Yan and Boyd 2007). Thus, c-Fos/AP-1 protein is evidently important in the regulation of MMPs (Asahara et al. 1997; Aikawa et al. 2008; Chakraborti et al. 2003; Kawasaki et al. 2003; Koga et al. 2009; Kuroki et al. 1992, 1993; Miyauchi et al. 1994; Shimizu et al. 2000; Shiozawa et al. 1992; Shiozawa and Tokuhisa 1992; Shiozawa et al. 1997; Trabandt et al. 1992).

c-Fos/AP-1 controls the expression of the inflammatory cytokines and matrix-degrading MMPs, such as MMP1, 3, 9 and 13, important in arthritis via promoter AP-1 binding

motif (Angel et al. 1987; Angel and Karin 1991; Burrage et al. 2006; Schonthal et al. 1988; Gutman and Wasylyk 1990; Hess et al. 2001; Karin et al. 1997; Sirum-Connolly and Brinckerhoff 1991; Sun et al. 2002; Yan and Boyd 2007). Importantly, a selective inhibitor of c-Fos/AP-1 designed and synthesized using 3D pharmacophore modeling based on the crystal structure of the AP-1-DNA complex to inhibit c-Fos/c-Jun heterodimer (Aikawa et al. 2008) inhibits most of the matrix-degrading MMPs, including MMP3, 9 and 13, in a direct fashion. This inhibitor also primarily inhibits IL-1β. While specific inhibition of individual MMPs, such as MMP3, cannot ameliorate collagen-induced arthritis (CIA) possibly owing to compensation by another MMP (Mudgett et al. 1998), broad-spectrum MMP inhibition does successfully reduce clinical severity and perfectly inhibits arthritic joint destruction (Aikawa et al. 2008), which is consistent with the fact that cartilaginous matrix can be readily degraded if two or more MMPs act in concert (Okada 2000).

In conjunction with c-Fos/AP-1, IL-1β is the most important inducer of a variety of MMPs including MMP1, 3, 8, 13 and 14 among inflammatory cytokines (Dayer 2003; Dayer et al. 1985; Gravallese and Goldring 2000; van de Loo and van den Berg 1990; van den Berg 2001; Schett et al. 2008). IL-1β degrades cartilagenous matrix most strongly (Henderson and Pettipher 1989; Schett et al. 2008; van de Loo and van den Berg 1990) and vice versa, MMPs cleave IL-1β into its active forms (Kawasaki et al. 2008). Time course studies in animal experiment show that IL-1β, IL-6 and MMP-3 are initially increased in arthritis (Aikawa et al. 2008; Garnero et al. 2010), and IL-6, and possibly TNF-α, appears activated subsequent to IL-1β in CIA and human synovial cells (Horai et al. 2000; Joosten et al. 1999; Thornton et al. 1999; van de Loo and van den Berg 1990; van den Berg 2002). IL-1β is increased in sera, synovia and joints of patients with RA (Chikanza et al. 1995; Kahle et al. 1992; Koch et al. 1992), and serum levels of IL-1β correlate with its disease severity (Eastgate et al. 1988; Rooney et al. 1990). There are additive effects on the induction of MMPs between IL-1β and other cytokines or growth factors including TNF-α, oncostatin M, FGF and PDGF (Schett et al. 2008). Cartilage damage is fully dependent, even in TNF-triggered arthritis, on IL-1 (van de Loo and van den Berg 1990). IL-1β is 100-fold potent than TNF-α in inducing cartilage destruction in vivo, where IL-1β can act synergistically with TNF-α (Henderson and Pettipher 1989; van de Loo and van den Berg 1990), suggesting that IL-1 is a key link between synovitis and cartilage breakdown.

In contrast, NF-κB indirectly controls MMP1, 3, and 13 by up-regulating the expression of inflammatory cytokines such as IL-1β, TNF-α and IL-6 (Bondeson et al. 1999; Jimenez et al. 1999; Mengshol et al. 2001; van den Steen et al. 2002; Vincenti et al. 1998), since functional NF-κB bining sites are absent within the promoters of MMPs except for the promoter −600 bp of human MMP9 which renders MMP9 gene responsive to TNF-α (Chakraborti et al. 2003; Schett et al. 2008; Yan and Boyd 2007).

Osteoclast

Osteoclastic bone resorption is characteristically seen very early in the disease at the peri-articular areas of the bone of patients with RA (Shimizu et al. 1985; Shiozawa and Kuroki 1994), and can be a very early sign of RA clinically. Molecular studies show that differentiation of osteoclast is facilitated in four ways (Takayanagi 2007; Theill et al. 2002; Walsh et al. 2006). First, RANKL (receptor activator of nuclear factor-κB ligand) binding to RANK activates TRAF6 (TNF receptor-associated factor 6) to stimulate NFATc1 (nuclear factor of activated T cells c1) to differentiate Osteoclasts. Second, RANKL activates c-Fos/AP-1 to stimulate NFATc1 to promote osteoclast differentiation. Third, RANKL phosphorylates Btk/Tek kinase which subsequently phosphorylates PLCγ. Fourth, membrane ITAM (immunoreceptor tyrosine-based activation motif) phosphorylation recruits Syk, leading to the activation of adaptor proteins including BLNK/SLP76, which functions as a scaffold that recruit both Btk/Tec and PLCγ to form osteoclastogenic signaling complex thereby increasing cellular calcium (Shinohara et al. 2008; Takayanagi 2007). This complex is crucial for efficient activation of calcium signaling required for the induction and activation of NFATc1, the key transcription factor for osteoclast differentiation (Koga et al. 2004).

Osteoclastic bone resorption takes place at osteoclast-matrix junction under acidic and hypercalcemic condition (Delaisse and Vaes 1992; Okada 2000). Because of collagenolytic activity with a broad pH optimum and selective expression in osteoclasts, a cysteine proteinase cathepsin K plays a key role in bone resorption. However, cathepsin K may not be the sole agent responsible for bone resorption and MMP9 could also be involved in this process. MMP9 is strongly expressed in the osteoclasts of rheumatoid patients, and has telopeptidase activity against soluble and insoluble type I collagen, and strong gelatinolytic activity. ProMMP9 is activated by acid exposure followed by neutralization, and once activated it is proteolytically active under acidic and hypercalcemic condition. Disruption of cathepsin K signaling results in defective TLR9 signaling in dendritic cells in response to unmethylated CpG DNA, which in turn leads to attenuated induction of T helper 17 cells, indicating an important role of cathepsin K in immune response to antigen (Asagiri et al. 2008; Okada et al. 1995).

While TNF-α inhibits bone formation via Dickkopf-1 and could also contribute to osteoclastic bone resorption via RANKL pathway (Ray et al. 2005; Reunanan et al. 2002; Walsh et al. 2006; Yan and Boyd 2007), TNF-α cannot differentiate osteoclasts directly and helps M-CSF- or RANKL-induced osteoclastogenesis (van de Loo and van den Berg 1990). Instead, IL-1β facilitates osteoclast formation and significantly enhance RANKL-induced osteoclastogenesis (Jiang et al. 2000; Shiozawa and Kuroki 1994; Zwerina et al. 2007). A total lack of chronic erosive arthritis is noted in IL-1β-deficient mice (Gravallese and Goldring 2000), and even the arthritic joint destruction of TNF-α transgenic mice can be totally inhibited by anti-IL-1 receptor antibody in face of still increased serum TNF-α (Probert et al. 1995). Arthritis in IL-1ra-deficient mice is indeed highly progressive (Horai et al. 2000). Synovial mesenchymal cells, internally driven by up-regulated c-Fos/AP-1, release this IL-1β (Aikawa et al. 2008; Shiozawa et al. 1992; Shiozawa and Tokuhisa 1992). Arthritic joint destruction can be perfectly resolved by the use of a specific small-molecule inhibitor of c-Fos/AP-1 designed and synthesized using 3D pharmacophore modeling based on the crystal structure of the AP-1-DNA complex (Aikawa et al. 2008).

Conclusion

A controversy exists regarding the importance of mesenchymal synovial cell and/or lymphocyte in the pathogenesis of RA. It is clear that synovial mesenchymal cells are responsible for joint destruction, while T cell-centered immunity is also important with regards to the response against triggering antigen. However, synovial mesenchymal cells, internally driven by a transcription factor c-Fos/AP-1, have been shown to be important not only for the degradation of cartilage and bone but also for antigen-specific immune response and cytokine release, in particular IL-1β. Synovial mesenchymal cells act in the initiation phase and the final stage of arthritis, i.e., arthritic joint destruction, and the mediators operated in the joints such as c-Fos/AP-1 and IL-1β drive osteoclast and act in concert with osteoclasts to facilitate joint destruction.

References

Ahrens D, Koch AE, Pope RM et al (1996) Expression of matrix metalloproteinase 9 (96-kD gelatinase B) in human rheumatoid arthritis. Arthritis Rheum 39:1576–1587

Aikawa Y, Morimoto K, Yamamoto T et al (2008) Treatment of arthritis with a selective inhibitor of c-Fos/activator protein-1. Nat Biotechnol 26:817–823

Angel P, Karin M (1991) The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim Biophys Acta 1072:129–157

Angel P, Imagawa M, Chiu R et al (1987) Phorbol ester inducible genes contain a common cis element recognized by a TPA-modulated transacting factor. Cell 49:729–739

Asagiri M, Hirai T, Kunigami T et al (2008) Cathepsin K-dependent Toll-like receptor 9 signaling revealed in experimental arthritis. Science 319:624–627

Asahara H, Fujisawa K, Kobata T et al (1997) Direct evidence of high DNA binding activity of transcription factor AP-1 in rheumatoid arthritis synovium. Arthritis Rheum 40:912–918

Athanasou NA, Quinn J, Heryet A et al (1988) The immunohistology of synovial lining cells in normal and inflamed synovium. J Pathol 155:133–142

Barland P, Novikoff AB, Hamerman D (1962) Electron microscopy of the human synovial membrane. J Cell Biol 14:207–220

Beggs S, Salter MW (2008) Taking two cuts at pain. Nat Med 14:243–244

Bondeson J, Foxwell B, Brennan F et al (1999) Defining therapeutic targets by using adenovirus: blocking NF-kappaB inhibits both inflammatory and destructive mechanisms in rheumatoid synovium but spares anti-inflammatory mediators. Proc Natl Acad Sci USA 96:5668–5673

Burrage PS, Mix KS, Brinckerhoff CE (2006) Matrix metalloproteinase: role in arthritis. Front Biosci 11:529–543

Chakraborti S, Mandal M, Das S et al (2003) Regulation of matrix metalloproteinases: an overview. Mol Cell Biochem 253:269–285

Chikanza IC, Roux-Lombrad P, Dayer JM et al (1995) Dysregulation of the in vivo production of interleukin-1 receptor antagonist in patients with rheumatoid arthritis. Pathogenetic implications. Arthritis Rheum 38:64–648

Dayer JM (2003) The pivotal role of interleukin-1 in the clinical manifestations of rheumatoid arthritis. Rheumatology 42(Suppl. 2): ii3–ii10

Dayer JM, Beutler B, Cerami A (1985) Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E2 production by human synovial cells and dermal fibroblasts. J Exp Med 162:2163–2168

Delaisse J, Vaes G (1992) Mechanism of mineral solubilisation and matrix degradation in osteoclastic bone resorption. In: Rifkin BR, Gay CV (eds) Biology and physiology of the osteoclast. CRC Press, Boca Raton

Eastgate JA, Symons JA, Wood NC et al (1988) Correlation of plasma interleukin-1 levels with disease activity in rheumatoid arthritis. Lancet 2:706–708

Fassbender HG (1975) Pathology of rheumatic diseases. Springer-Verlag, Berlin

Fassbender HG (1984) Is pannus a residue of inflammation? Arthritis Rheum 27:956–957

Garnero P, Thompson E, Woodworth T et al (2010) Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. Arthritis Rheum 62:33–43

Gravallese EM, Goldring SR (2000) Cellular mechanisms and the role of cytokines in bone erosions in rheumatoid arthritis. Arthritis Rheum 43:2143–2151

Gutman A, Wasylyk B (1990) The collagenase gene promoter contains a TPA and oncogene-responsive unit encompassing the PEA3 and AP-1 binding sites. EMBO J 9:2241–2246

Hembry RM, Bagga MR, Reynolds JJ et al (1995) Immunolocalisation studies on six matrix metalloproteinases and their inhibitors,

TIMP-1 and TIMP-2 in synovia from patients with osteo- and rheumatoid arthritis. Ann Rheum Dis 54:25–32

Henderson B, Pettipher ER (1989) Arthritogenic actions of recombinant IL-1 and TNF in the rabbit: evidence for synergistic interactions between cytokines in vivo. Clin Exp Immunol 75:306–310

Hess J, Porte D, Munz C et al (2001) AP-1 and Cbfa/Runt physically interact and regulate parathyroid hormone-dependent MMP13 expression in osteoblasts through a new osteoblast-specific element 2/AP-1 composite element. J Biol Chem 276:20029–20038

Horai R, Saijo S, Tanioka H et al (2000) Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in IL-1 receptor antagonist-deficient mice. J Exp Med 191:313–320

Jiang Y, Genant HK, Watt I et al (2000) A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 43:1001–1009

Jimenez MJ, Balbin M, Lopez JM et al (1999) Collagenase 3 is a target of Cbfa1, a transcription factor of the runt gene family involved in bone formation. Mol Cell Biol 19:4431–4442

Joosten LA (2010) Excessive interleukin-1 signaling determines the development of Th1 and Th17 responses in chronic inflammation. Arthritis Rheum 62:320–322

Joosten LA, Helsen MM, Saxne T et al (1999) IL-1 alpha beta blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF-alpha blockade only ameliorates joint destruction. J Immunol 163:5049–5055

Kahle P, Saal JG, Schaudt K et al (1992) Determination of cytokines in synovial fluids: correlation with diagnosis and histomorphological characteristics of synovial fluid. Ann Rheum Dis 51:731–734

Karin M, Liu Z, Zandi E (1997) AP-1 function and regulation. Curr Opin Cell Biol 9:240–246

Kawasaki H, Komai K, Ouyang Z et al (2001) c-Fos/activator protein-1 transactivates wee1 kinase at G1/S to inhibit premature mitosis in antigen-specific Th1 cells. EMBO J 20:4618–4627

Kawasaki H, Komai K, Nakamura M et al (2003) Human wee1 kinase is directly transactivated by and increased in association with c-Fos/AP-1: rheumatoid synovial cells overexpressing these genes go into aberrant mitosis. Oncogene 22:6839–6844

Kawasaki Y, Xu ZZ, Wang X et al (2008) Distinct roles of matrix metalloproteinases in the early- and late-phase development of neuropathic pain. Nat Med 14:331–336

Kimura H, Tateishi H, Ziff M (1977) Surface ultrastructure of rheumatoid articular cartilage. Arthritis Rheum 20:1085–1098

Klareskog L, Forsum U, Kabelitz D et al (1982) Immune functions of human synovial cells: phenotypic and T cell regulatory properties of macrophage-like cells that express HLA-DR. Arthritis Rheum 25:488–501

Kobayashi K, Takahashi N, Jimi E et al (2000) Tumor necrosis factor stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. J Exp Med 191:275–286

Koch AE, Kunkel SL, Chensue SW et al (1992) Expression of interleukin-1 and interleukin-1 receptor antagonist by human rheumatoid synovial tissue macrophages. Clin Immunol Immunopathol 65:23–29

Koga T, Inui M, Inoue K et al (2004) Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis. Nature 428:758–763

Koga K, Takaesu G, Yoshida R et al (2009) Cyclic adenosine monophosphate suppresses the transcription of proinflammatory cytokines via the phosphorylated c-Fos protein. Immunity 30:372–383

Kuroki Y, Shiozawa S, Sugimoto T et al (1992) Constitutive expression of *c-fos* gene inhibits type 1 collagen synthesis in transfected osteoblasts. Biochem Biophys Res Commun 182:1389–1394

Kuroki Y, Shiozawa S, Yoshihara R et al (1993) The contribution of human c-fos DNA to cultured synovial cells: a transfection study. J Rheumatol 20:422–428

Lindhout E, van Eijk M, van Pel M et al (1999) Fibroblast-like synoviocytes from rheumatoid arthritis patients have intrinsic properties of follicular dendritic cells. J Immunol 162:5949–5956

Lohmander LS, Neame PJ, Sandy JD (1993) The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. Arthritis Rheum 36:1214–1222

Mengshol JA, Vincenti MP, Brinckerhoff CE (2001) IL-1 induces collagenase-3 (MMP-13) promoter activity in stably transfected chondrocyotic cells: requirement for Runx-2 and activation by p38 MAPK and JNK pathways. Nucleic Acids Res 29:4361–4372

Milner JM, Patel A, Rowan AD (2008) Emerging roles of serine proteinases in tissue turnover in arthritis. Arthritis Rheum 58:3644–3656

Miyauchi A, Kuroki Y, Fukase M et al (1994) Persistent expression of proto-oncogene *c-fos* stimulates osteoclast differentiation. Biochem Biophys Res Commun 205:1547–1555

Mudgett JS, Hutchinson NI, Chartrain NA et al (1998) Susceptibility of stromelysin 1-deficient mice to collagen-induced arthritis and cartilage destruction. Arthritis Rheum 41:110–121

Murphy G, Willenbrock F (1995) Tissue inhibitors of matrix metalloendopeptidases. Methods Enzymol 248:496–510

Okada Y (2000) Matrix-degrading metalloproteinases and their roles in joint destruction. Mod Rheumatol 10:121–128

Okada Y, Takeuchi N, Tomita K et al (1989) Immunolocalization of matrix metalloproteinase 3 (stromelysin) in rheumatoid synoviocytes (B cells): correlation with rheumatoid arthritis. Ann Rheum Dis 48:645–653

Okada Y, Gonoji Y, Nakanishi I et al (1990) Immunohitochemical demonstration of collagenase and tissue inhibitor of metalloproteinases (TIMP) in synovial lining cells of rheumatoid synovium. Virchows Arch B Cell Pathol Incl Pathol 59:305–312

Okada Y, Naka K, Kawamura K et al (1995) Localization of matrix metalloproteinase 9 (92-kilodalton gelatinase/type IV collagenase = gelatinase B) in Osteoclasts: implications for bone resorption. Lab Invest 72:311–322

Pap T, Shigeyama Y, Kuchen S et al (2000) Differential expression pattern of membrane-type matrix metalloproteinases in rheumatoid arthritis. Arthritis Rheum 43:1226–1232

Pap T, Gay S, Schett G (2002) Matrix metalloproteinases. In: Smolen JS, Lipsky PE (eds) Biological therapies in rheumatology. Taylor & Francis Ltd, London

Porter S, Clark IM, Kevorkian L et al (2004) The ADAMTS metalloproteinases. Biochem J 386(Pt 1):15–27

Poulter LW, Duke O, Hobbs S et al (1982) Histochemical discrimination of HLA-DR positive cell populations in the normal and arthritic synovial lining. Clin Exp Immunol 48:381–388

Probert L, Plows D, Kontogeorgos G et al (1995) The type I interleukin-1 receptor acts in series with tumor necrosis factor (TNF) to induce arthritis in TNF-transgenic mice. Eur J Immunol 25:1794–1797

Ray A, Bal BS, Ray BK (2005) Transcriptional induction of matrix metalloproteinase-9 in the chondrocyte and synoviocyte cells is regulated via a novel mechanism: evidence for functional cooperation between serum amyloid A-activating factor-1 and AP-1. J Immunol 175:4039–4048

Redlich K, Hayer S, Ricci R et al (2002) Osteoclasts are essential for TNF-mediated joint destruction. J Clin Invest 110:1419–1427

Reunanan N, Li SP, Ahonen M et al (2002) Activation of p38 alpha MAPK enhances collagenase-1 (matrix metalloproteinase (MMP)-1) and stromelysin-1 (MMP-3) expression by mRNA stabilization. J Biol Chem 277:32360–32368

Rooney M, Symons JA, Duff GW (1990) Interleukin-1 beta in synovial fluid is related to local disease activity in rheumatoid arthritis. Rheumatol Int 10:217–219

Schett G, Stach C, Zwerina J et al (2008) How antirheumatic drugs protect joints from damage in rheumatoid arthritis. Arthritis Rheum 58:2936–2948

Schonthal A, Herrlich P, Rahmsdorf HJ et al (1988) Requirement for *fos* gene expression in the transcriptional activation of collagenase by other oncogenes and phorbol esters. Cell 54:325–334

Schumacher HR (1973) Fate of particular material arriving at the synovium via the circulation. An ultrastructural study. Ann Rheum Dis 32:212–218

Scott DL, Kingsley GH (2006) Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med 355:704–712

Shimizu S, Shiozawa S, Shiozawa K et al (1985) Quantitative histologic studies on the pathogenesis of periarticular osteoporosis in rheumatoid arthritis. Arthritis Rheum 28:25–31

Shimizu S, Shiozawa S, Shiozawa K et al (1988) The restoration of proliferation and differentiation of peripheral blood mononuclear non-adherent cells into immunoglobulin-secreting cells by autologous synovial adherent cells from patients with rheumatoid arthritis. Virchows Arch B Cell Pathol Incl Mol Pathol 54:350–356

Shimizu K, Kawasaki H, Morisawa T et al (2000) Spontaneous and cytokine regulated c-fos gene expression in rheumatoid synovial cells. Ann Rheum Dis 59:636–640

Shinohara M, Koga T, Okamoto K et al (2008) Tyrosine kinases Btk and Tec regulate osteoclast differentiation by linking RANK and ITAM signals. Cell 132:794–806

Shiozawa S, Kuroki Y (1994) Osteoporosis in rheumatoid arthritis: a molecular biological aspect of connective tissue gene activation. Tohoku J Exp Med 173:189–198

Shiozawa S, Tokuhisa T (1992) Contribution of synovial mesenchymal cells to the pathogenesis of rheumatoid arthritis. Semin Arthritis Rheum 21:267–273

Shiozawa S, Tsumiyama K (2009) Pathogenesis of rheumatoid arthritis and c-Fos/AP-1. Cell Cycle 8:1539–1543

Shiozawa S, Shiozawa K, Fujita T (1983a) Morphologic observation in the early phase of the cartilage-pannus junction: light and electron microscopic studies of active cellular pannus. Arthritis Rheum 26:472–478

Shiozawa S, Shiozawa K, Fujita T (1983b) Presence of HLA-DR antigen on synovial type A and B cells: an immunoelectron microscopic study in rheumatoid arthritis, osteoarthritis and normal traumatic joints. Immunology 50:587–594

Shiozawa S, Tanaka Y, Fujita T et al (1992) Destructive arthritis without lymphocyte infiltration in H2-*c-fos* transgenic mice. J Immunol 148:3100–3104

Shiozawa S, Shimizu S, Tanaka K et al (1997) Studies on the contribution of c-fos/AP-1 to arthritic joint destruction. J Clin Invest 99:1210–1216

Sirum-Connolly K, Brinckerhoff C (1991) Interleukin-1 or phorbol induction of the stromelysin promoter requires an element that cooperates with AP-1. Nucleic Acids Res 19:335–341

Sun Y, Wenger L, Brinckerhoff CE et al (2002) Basic calcium phosphate crystals induce matrix metalloproteinase-1 through the Ras/mitogen-activated protein kinase/c-Fos/AP-1 metalloproteinase 1 pathway. J Biol Chem 277:1544–1552

Takayanagi H (2007) Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nat Rev Immunol 7:292–304

Teitelbaum SL (2004) RANKing c-Jun in osteoclast development. J Clin Invest 114:463–465

Theill LE, Boyle WJ, Penninger JM (2002) RANK-L and RANK: T cells, bone loss, and mammalian evolution. Annu Rev Immunol 20:795–823

Thornton S, Duwel LE, Boivin GP et al (1999) Association of the course of collagen-induced arthritis with distinct patterns of cytokine and chemokine messenger RNA expression. Arthritis Rheum 42:1109–1118

Tiku ML, Theodorescu M, Skosey JL (1985) Immunobiological function of normal rabbit synovial cells. Cell Immunol 91:415–424

Tolboom TC, n Mil AH, Nelissen RG et al (2005) Invasiveness of fibroblast-like synoviocytes is an individual patient characteristic associated with the rate of joint destruction in patients with rheumatoid arthritis. Arthritis Rheum 52:1999–2002

Trabandt A, Aicher WK, Gay RE et al (1992) Spontaneous expression of immediately-early response genes c-fos and egr-1 in collagenase-producing rheumatoid synovial fibroblasts. Rheumatol Int 12:53–59

Tran CN, Davis MJ, Tesmer LA et al (2007) Presentation of arthritogenic peptide to antigen-specific T cells by fibroblast-like synoviocytes. Arthritis Rheum 56:1497–1506

van de Loo AA, van den Berg WB (1990) Effects of murine recombinant IL-1 on synovial joints in mice: measurement of patellar cartilage metabolism and joint inflammation. Ann Rheum Dis 49:238–245

van den Berg WB (2001) Anti-cytokine therapy in chronic destructive arthritis. Arthritis Res 3:18–26

van den Berg WB (2002) Lessons from animal models of arthritis. Curr Rheumatol Rep 4:232–239

van den Steen PE, Dubois B, Nelissen I et al (2002) Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9). Crit Rev Biochem Mol Biol 37:375–536

Vincenti MP, Coon CI, Brinckerhoff CE (1998) Nuclear factor kappaB/p50 activates an element in the distal matrix metalloproteinase 1 promoter in interleukin-1 beta-stimulated synovial fibroblasts. Arthritis Rheum 41:1987–1994

Walsh MC, Kim N, Kadono Y et al (2006) Osteoimmunology: interplay between the immune system and bone metabolism. Annu Rev Immunol 24:33–63

Whitmarsh AJ, Shore P, Sharrocks AD et al (1995) Integration of MAP kinase signal transduction pathways at the serum response element. Science 269:403–407

Will H, Atkinson SJ, Butler GS et al (1996) The soluble catalytic domain of membrane type 1 matrix metalloproteinase cleaves the propeptide of progelatinase A and intiates autoproteolytic activation. Regulation by TIMP-2 and TIMP-3. J Biol Chem 271:17119–17123

Yan C, Boyd D (2007) Regulation of matrix metalloproteinase gene expression. J Cell Physiol 211:19–26

Yoshihara Y, Nakamura H, Obata K et al (2000) Matrix metalloproteinases in synovial fluids from patients with rheumatoid arthritis or osteoarthritis. Ann Rheum Dis 59:455–461

Zwerina J, Redlich K, Polzer K et al (2007) TNF-induced structural joint damage is mediated by interleukin-1. Proc Natl Acad Sci USA 104:11742–11747