

3 Pathophysiology of musculoskeletal disease

3.6 Synovial pathology

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Macroscopic appearances of synovitis in rheumatoid arthritis

The gross pathologic changes that are characteristic of rheumatoid arthritis (RA) result from chronic synovial inflammation (Tak and Bresnihan 2000). Typically, the surface of the synovium becomes hypertrophic and oedematous, with an intricate system of prominent villous fronds that expand into the joint cavity. The macroscopic appearances of synovitis may be readily quantified at arthroscopy (Veale et al. 1999), which provides easier access to human synovial tissue. This has produced new opportunities for those engaged in the study of arthritis (Bresnihan et al. 2000). Synovial tissue can now be selected from many sites within large and small joints, even in the earliest phases of disease, enhancing studies of aetiology, prognosis, and response to treatment (Bresnihan and Tak 1999). Contemporary imaging modalities, such as magnetic resonance imaging and ultrasonography, possess the capability of further characterizing and quantifying macroscopic synovial inflammation, joint effusion, cartilage integrity, and bone erosion (Backhaus et al. 2001; Peterfy 2001).

Microscopic appearances of synovitis in RA

The synovium in RA is hypertrophic and oedematous. There is marked hyperplasia of the lining layer, and accumulation of many cell populations, including T-cells, plasma cells, B-cells, macrophages, neutrophils, mast cells, natural killer (NK) cells, and dendritic cells in the sub-lining layer (Tak 2000) (Fig. 1).

The lining layer

The dominant cellular components of the lining layer are fibroblast-like synoviocytes (FLS) and macrophages. These cell populations release an array of proinflammatory cytokines and their inhibitors, which may promote further intraarticular perturbations. There is abundant production of matrix metalloproteinases (MMPs), cysteine proteases, and other tissue degrading mediators, which accumulate in the synovial fluid and augment joint damage by directly interacting with exposed cartilage matrix. These features are present very early in the disease course. Increased lining layer macrophage accumulation and perivascular mononuclear infiltration were prominent in tissue obtained days after the onset of symptoms (Schumacher and Kitridou 1972), and in the clinically uninvolved joints (Soden et al. 1989), of patients with RA. CD68+ macrophage accumulation in the synovium was more prominent in symptomatic joints (Pando et al.

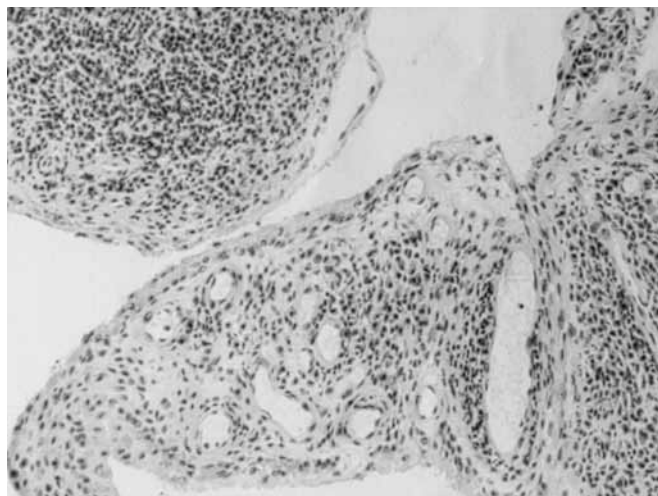


Fig. 1 Chronic inflammation in RA synovial membrane. Villous formation can be observed. Many blood vessels are seen, through which inflammatory cell populations have infiltrated the synovial sublining layer (haematoxylin and eosin; magnification $\times 100$).

2000), and the pre-clinical cellular infiltration of synovium, as well as tumour necrosis factor α (TNF α) and interleukin-1 β (IL-1 β) expression, observed in RA was similar in rhesus monkeys developing experimental arthritis (Kraan et al. 1998). Abundant protease gene expression has also been observed in synovial tissue obtained only 2 weeks after the onset of symptoms, emphasizing the very early potential for joint destruction in RA (Cunnane et al. 1999). The intensity of some of these quantifiable immunohistologic features in the synovial lining layer may reflect the degree of joint damage (Yanni et al. 1994; Mulherin et al. 1996). This suggestion was highlighted in a recent study, which demonstrated that high levels of MMP-1 mRNA expression in the lining layer distinguished patients with more rapidly progressive erosive RA (Cunnane et al. 2001).

It remains to be clarified which factors account for the specific architecture of the lining layer and the interaction between FLS and intimal macrophages. The abundant expression of the transmembrane receptor CD97 on macrophages in the lining layer and the expression of its ligand, CD55, on FLS suggest that macrophages and FLS could interact functionally through CD97/CD55 binding (Hamann et al. 1999). Other molecules, including adhesion molecules and CD40 and its ligand CD40L may also be involved.

The sub-lining layer

T-cells and plasma cells are prominent in the synovial sub-lining layer. Lymphocyte aggregates are observed in 50–60 per cent of patients with RA. These aggregates can be surrounded by plasma cells. In addition, macrophages and lymphocytes infiltrate the areas between the lymphocyte

aggregates. In some patients, areas with granulomatous necrobiosis are apparent (Klimiuk et al. 1997). These areas are characterized by regions with fibrinoid necrosis lined by a collar of epithelioid histiocytes and granulation tissue. Fibrin deposition and fibrosis can be observed. The macrophages often constitute the majority of inflammatory cells in the synovial sub-lining layer. Local disease activity is particularly associated with their number and with the expression of cytokines, such as TNF α and IL-6 (Tak et al. 1997; Kraan et al. 1998). The synovial sub-lining macrophages produce a variety of mediators of joint destruction (Kontinen et al. 1999; Onodera et al. 2000).

Large numbers of T-cells are also present in the synovial sub-lining. There are two basic patterns of T-cell infiltration (Firestein and Zvaifler 1990). First, perivascular lymphocyte aggregates can be found, which consist predominantly of CD4+ cells in association with B-cells, few CD8+ cells, and dendritic cells (Fig. 2). The second pattern of T cell infiltration is the diffuse infiltrate of T-cells scattered throughout the synovium. A subset of the CD4+ T-cells in synovial tissue is activated. A possible biologic effect of activated perivascular T-cells in the synovium is the activation of migrating macrophage populations through direct cell contact. This mechanism is known to stimulate macrophage production of cytokines and MMPs *in vitro* (Vey et al. 1992; Lacraz et al. 1994). A factor in human serum, identified as apolipoprotein A-1 (apo A-1), was recently shown to inhibit contact-mediated stimulation of monocytes by activated T-lymphocytes *in vitro* (Hyka et al. 2001). It was speculated that apo A-1 may play an important

role in modulating T-lymphocyte-mediated effects in both acute and chronic inflammation. Many of the T-cells in synovial tissue are, on the other hand, in a state of hyporesponsiveness (Firestein and Zvaifler 1990; Maurice et al. 1997). Interdigitating dendritic cells, which are potent antigen presenting cells, are located in proximity to CD4+ T-cells in the lymphocyte aggregates and near the intimal lining layer (Duke et al. 1982; Thomas and Lipsky 1996; Pettit et al. 2000).

B-cells constitute a small proportion of the total amount of lymphocytes in the synovial sub-lining layer. However, numerous plasma cells may be present throughout the synovium, sometimes exceeding the number of infiltrating T-cells. A considerable number of the plasma cells synthesize and secrete rheumatoid factors and other autoantibodies (Hakoda et al. 1993; Otten et al. 1993). Follicular dendritic cells are observed in the same areas in proximity to proliferating B-cells. They are thought to play a crucial role in isotype switching and final differentiation of B-cells towards plasma cells or memory B-cells (Krenn et al. 1996; Schroder et al. 1996).

Granzyme positive NK cell and cytotoxic T-cells are present in both the synovial lining layer and in the synovial sub-lining. In line with the increased infiltration of granzyme positive cells in the synovium (Tak et al. 1993; Muller-Ladner et al. 1995; Smeets et al. 1998), there are markedly elevated levels of soluble granzymes in the synovial fluid and plasma of RA patients (Tak et al. 1999). Granzyme B could contribute to cartilage loss by degrading resident aggrecan (Froelich et al. 1993). Only few neutrophils are found in rheumatoid synovial tissue. However, large numbers of neutrophils traffic through the synovial lining layer into the synovial fluid. These cells are activated and contain a variety of proteinases and other enzymes, which might be of primary importance in destruction of the joint (Moore et al. 1999; van Meurs et al. 1999).

Mast cell sub-populations were found to expand in RA synovial tissue and an association between the intensity of infiltrating mast cells producing both tryptase and chymase, particularly in the superficial synovial layer, and impairment of function have been described (Gotis-Graham and McNeil 1997). This observation is noteworthy as mast cells produce proteolytic factors, which can degrade proteoglycans. Synovial tissue from patients with relatively early RA was characterized by infiltrating mast cells producing tryptase only, suggesting that the synovial mast cell phenotype may alter as RA progresses (Gotis-Graham et al. 1998). However, the interpretation of this observation remains unclear, as it may be explained by differences in levels of disease activity.

TNF α and IL-1 β production is prominent in the synovial lining layer and in some sub-lining layer cell populations at non-CPJ (CPJ stands for cartilage-pannus junction) sites (Tak and Bresnihan 2000). Using techniques that are highly specific for the detection of cytokine-producing cells, TNF α -producing cells were prominent in the lining layer of most, but not all, RA tissue samples (Ulfgren et al. 1995). TNF α -producing cells were also present to a lesser degree in the sub-lining interaggregate areas and in the lymphoid aggregates. The impressive therapeutic effects of TNF α -blockade in RA may result from inhibition of the pathogenetic effects of TNF α produced by synovial tissue macrophages. Cells that are immunoreactive for IL-1 and IL-1Ra are also present in the lining and sub-lining layers (Deleuran et al. 1992a; Ulfgren et al. 1995) (Fig. 3). The distribution of IL-1Ra gene expression and protein production in RA differs from that in osteoarthritis, being notably less in the lining layer of RA synovium (Firestein et al. 1992). This observation is consistent with a relative deficiency of IL-1Ra production by RA synovial macrophages (Firestein et al. 1994). Taken together, studies of non-CPJ synovium from patients with late-stage RA suggest that TNF α , IL-1 α , IL-1 β , their inhibitors, and receptors are produced by most, but possibly not all, tissue samples. However, it is possible that the detection of cytokine production might depend on the site of biopsy. This was examined in multiple samples using reverse transcriptase PCR. TNF α was expressed in all samples from all biopsy sites, but at very low levels in the tissues of some. IL-1 β was expressed in all samples from most sites (Kirkham et al. 1999). These observations are consistent with the findings at the CPJ and suggest that either synovial tissue TNF α or IL-1 β production may be minimal or absent in some patients (Klimiuk

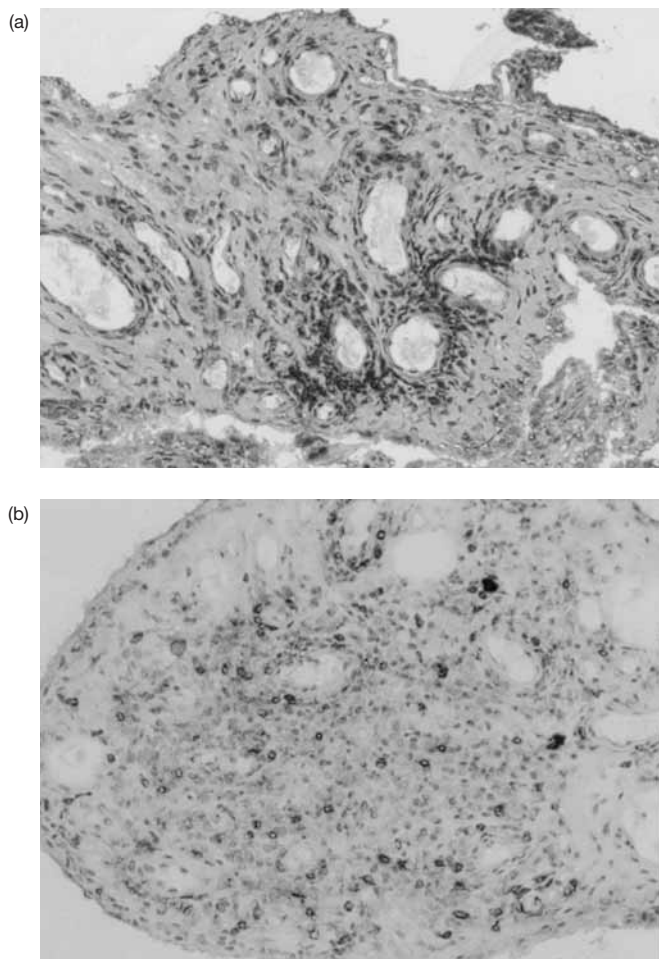


Fig. 2 Perivascular CD4+ T-cells in RA synovial membrane (a) CD8+ T-cells are scattered sparsely throughout the synovial sublining layer. (b) immunoperoxidase; magnification $\times 100$.

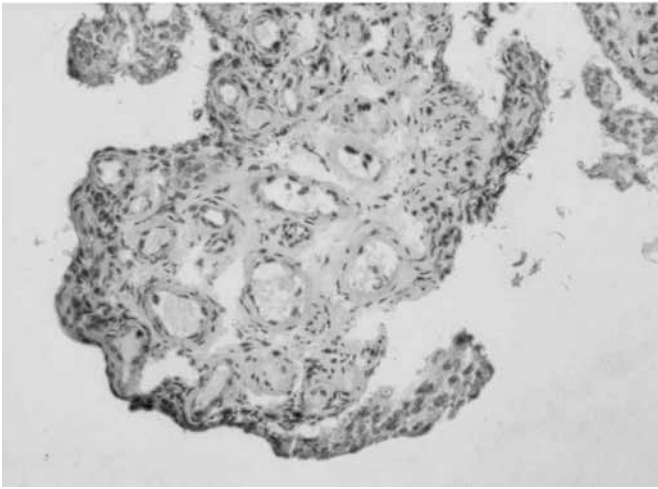


Fig. 3 Mononuclear cells producing interleukin-1 β . Positively-stained cells (predominantly macrophages) accumulate in synovial lining layer, and in the sub-lining layer (immunoperoxidase; magnification $\times 100$).



Fig. 4 Prominent proliferating blood vessels in the synovial sub-lining layer. Immunoreactive vascular endothelium is highlighted using an anti-factor VIII monoclonal antibody (immunoperoxidase; magnification $\times 100$).

et al. 1997; Tak et al. 1997). This is compatible with the heterogeneity of disease expression and response to treatment which is characteristic of RA.

IL-18 is a novel cytokine that is closely related to the IL-1 family in both structure and function (Okamura et al. 1998; Dinarello 1999). It induces both TNF α and IL-1 β gene expression and protein synthesis, as well as MMP and iNOS gene expression by chondrocytes *in vitro*. It could, therefore, contribute to cartilage matrix degradation. IL-18 is produced by macrophages, chondrocytes, osteoblasts, and other cell populations. IL-18 mRNA and protein production have been described in RA synovial tissues (Gracie et al. 1999; Yamamura et al. 2001). It was predominantly expressed by synovial tissue macrophages within and adjacent to lymphocytic aggregates and, less prominently, by lining layer macrophages.

IL-15 in RA synovial tissue has been co-localized to macrophages, including lining layer macrophages, and sub-lining layer T-cells, and NK cells (McInnes et al. 1996; Thurkow et al. 1997). Inflamed synovial tissue also produces increased amounts of many other cytokines, colony stimulating factors and chemokines, which can modulate synovial cell functions (Dayer and Arend 1997). The role of many cytokines in the complex pathogenesis of joint degradation in RA remains to be clarified. The chemokines are a family of chemoattractant proteins which participate in the chemotaxis of cells to sites of inflammation. In RA, monocyte chemoattractant protein-1 (MCP-1), a member of the C-C sub-family, is constitutively expressed by lining layer macrophages and is upregulated in FLS by IL-1 β or TNF α (Koch et al. 1992). Synovial MCP-1 production appears to be important in maintaining the accumulation of tissue macrophages.

There has been extensive analysis of proteolytic enzyme production by synovial tissue samples and primary synoviocyte cultures selected from non-CPJ sites in established RA (Tak and Bresnihan 2000). These studies have demonstrated MMP-1, MMP-3, and tissue inhibitor of metalloproteinase (TIMP) mRNA in the lining layer cells, including both macrophage and FLS populations, and in some sub-lining layer cell populations. Other MMPs, including MMP-9 (gelatinase B), have also been demonstrated in RA synovial tissue (Ahrens et al. 1996). The tissue distribution of MMP-9 was localized to sites of synovial inflammation, particularly the lining layer, endothelium, and tissue macrophages. MMP-13 has been cloned from RA synovial tissue (Wernicke et al. 1996). MMP-13 mRNA and protein was demonstrated in lining layer FLS and not in macrophages in most late-stage RA tissue samples. It seems likely that the degree of cartilage and bone degradation will depend on excessive MMP activity over the inhibitors in the synovium, especially within the pannus. In addition to MMPs, cathepsin B and cathepsin L production by synovial lining layer cells has also been demonstrated (Keyszer et al. 1995; Keyszer et al. 1998).

Synovial tissue is rich in blood vessels (Koch 1998; Walsh 1999) (Fig. 4). Angiogenesis is a complex process and a central feature in synovial inflammation and pannus formation. There are many regulators, including inhibitors, of angiogenesis that are produced and released by the human synovium. Angiogenic factors that have been demonstrated in RA synovium and implicated in the pathogenesis of progressive joint damage include VEGF, basic fibroblast growth factor, hepatocyte growth factor, IL-1, TNF α , IL-8, TGF α and TGF β , angiogenin, and platelet-derived endothelial growth factor. Important inhibitors of angiogenesis produced by RA synovium include thrombospondin, TGF β , TNF α , IFN γ , TIMP-1 and TIMP-2, and leukaemia inhibitory factor. In RA, evidence of angiogenesis and vascular regression may be observed in different microscopic foci of the same synovial samples. Angiogenesis may augment inflammation as newly formed blood vessels express increased levels of cell adhesion molecules such as E-selectin, which facilitate the migration of inflammatory cells. In turn, inflammatory cells generate angiogenic factors which further increase angiogenesis. Angiogenesis permits continuing growth of the proliferating synovial pannus. Migrating endothelial cells produce proteases which may degrade adjacent cartilage and bone. However, the direct contribution of proliferating blood vessels to tissue destruction may be small compared to that of the FLS, macrophages, and other proteolytic enzyme-producing cells which accumulate at the CPJ.

The cartilage–pannus junction

The characteristic pattern of juxta-articular cartilage and bone erosion readily distinguishes RA from other forms of chronic arthritis (Resnick et al. 1997). Joint erosion results, at least in part, from the invasion of articular cartilage and adjacent sub-chondral bone by proliferating pannus (Fig. 1). However, joint erosion may also result more directly from bone-derived cells, particularly osteoclasts (Goldring and Gravallese 2000). The process of joint erosion is distinct from degradation or dissolution of the cartilage surface, which results from the direct effects of enzymes and other synovial cell products that accumulate in the synovial fluid.

In some patients with long-standing RA the CPJ tissue, examined at the time of surgery, may be relatively acellular (Kobayashi and Ziff 1975; Bromley and Woolley 1984). More typically, CPJ tissue contains several cell populations (Fig. 1) (Tak and Bresnihan 2000). FLS and macrophages are the dominant populations in the majority. Numerous clusters of macrophages and FLS are frequently observed at the leading edge where synovial tissue penetrates the degrading cartilage (Fig. 2(a)). It is not known if these cells are pre-activated cells which continue to advance from

the proliferative lining layer, cells which migrate through tissue channels from the bone marrow, or cells that are derived from the peripheral circulation. Synovial tissue adjacent to the CPJ in early RA demonstrates prominent cellular infiltration, with apparent preferential accumulation of macrophage populations compared to non-CPJ tissue (Youssef et al. 1998).

Both FLS and macrophages in the synovial lining layer and at the CPJ exhibit features which suggest a high level of activation (Firestein 1996; Burmester et al. 1997; Bresnihan and Youssef 2002). The functional properties of FLS in RA have been determined mostly from studies utilizing primary synoviocyte cultures or tissue samples selected from non-CPJ sites. Activated FLS exhibit many features of transformed cells and demonstrate increased cell adhesion molecule expression, proliferative and invasive activity, oncogene expression, and the release of proteolytic enzymes and cytokines (Firestein 1996). Activated synovial tissue macrophages demonstrate increased expression and transcription of IL-1 β , TNF α , and C-C monokine chemoattractant protein-1 (MCP-1). Synovial tissue macrophages are multifunctional cells that incorporate biologic activities which may be destructive or protective (Firestein 1996; Burmester et al. 1997).

There is some evidence to suggest that the cell populations at the CPJ may undergo local functional modulation. Macrophages close to the CPJ were compared to those at sites distant from the CPJ with respect to the presence of myeloid-related proteins (MRP), which are myeloid differentiation markers on infiltrating tissue macrophages in inflammatory lesions (Youssef et al. 1999). Striking differences were observed. MRP8, MRP14, and the heterodimer MRP8/14 were expressed on lining layer macrophages adjacent to the CPJ but only in patients with active disease. Minimal or absent MRP staining was observed in sections from non-CPJ sites. These observations were consistent with altered macrophage differentiation at the site of maximal cartilage destruction during active phases of disease.

Other cell populations, including lymphocytes, plasma cells, and neutrophils may participate in the pathogenesis of joint destruction at the CPJ (Mohr and Menninger 1980; Kobayashi and Ziff 1995) (Fig. 1). Chondrocyte-derived cells are also known to appear in the proliferating pannus (Allard et al. 1987). Chondrocytes, when stimulated by TNF α or IL-1 β , can produce proteolytic enzymes and cause cartilage matrix degradation (Borden et al. 1996). In addition, a morphologically distinct cell type that shares some of the characteristics of chondrocytes and FLS has been described at the CPJ (Zvaifler et al. 1997). It was suggested that this cell population, designated pannocytes, may represent an earlier stage of mesenchymal cell differentiation. Their role in joint destruction remains to be determined. A similar cell type, which expressed MMP-1, cathepsin B, and cathepsin L, has been cloned from an RA pannus lesion (Xue et al. 1997).

Mast cells have been identified at the site of cartilage erosion in RA (Bromley et al. 1984). Mast cell subsets can be defined according to their capacity to produce tryptase, or tryptase and chymase (Tetlow and Woolley 1995a). Local accumulations of mast cells were observed in approximately 50 per cent of late-stage RA synovial tissue samples selected from the CPJ (Tetlow and Woolley 1995b). Evidence of cell activation was present in most.

One mechanism implicating mast cells in joint damage may relate to the abundant production of vascular endothelial growth factor (VEGF), which enhances angiogenesis and could promote the growth of synovial pannus (Yamada et al. 1998). However, the exact role of mast cells in matrix degradation remains unknown and, in some experimental models, cartilage degradation and fibroblast invasion occurs in their absence (Geiler et al. 1994; Wang et al. 1997).

Osteoclasts at the CPJ also have a critical role in bone erosion (Goldring and Gravallesse 2000). The calcitonin receptor (CTR) has been identified as a specific marker that distinguishes osteoclasts from other haematopoietic and bone cells (Chang et al. 1992; Ashton et al. 1993). Joint tissues obtained from the pannus-bone and pannus-cartilage interface in late-stage RA demonstrated strong osteoclast-specific CTR mRNA expression in multinucleated cells in the resorption lacunae of calcified cartilage and immediately adjacent sub-chondral bone (Gravallesse et al. 1998). The multinucleated cells were also positive for tartrate-resistant alkaline phosphatase (TRAP) mRNA and TRAP enzyme activity. The important role of osteoclast

precursors in the pathogenesis of joint erosion was further highlighted by the demonstration of osteoclast differentiation factor (ODF) (also known as osteoprotegerin ligand (OPG-L)) expression by both fibroblasts and activated T lymphocytes derived from the synovial tissues of patients with RA (Gravallesse et al. 2000). The balance between osteoprotegerin and ODF/OPG-L production appears to be critical in the regulation of osteoclast activation (Lacey et al. 1998). Moreover, in murine adjuvant arthritis, it has been demonstrated that T-cell activation can lead to OPG-L production and subsequent bone loss (Kong et al. 1999).

TNF α and IL-1 β are prominent in the pathogenesis of RA (Arend and Dayer 1995). Both are produced predominantly by macrophages, which accumulate maximally adjacent to the CPJ (Youssef et al. 1998; Youssef et al. 1999). Some TNF α -positive cells were identified adjacent to the CPJ in specimens from patients with long-standing erosive RA (Chu et al. 1991a; Chu et al. 1992). In contrast, in patients with relatively early RA (symptoms <18 months), all tissue samples from the CPJ demonstrated quantifiable TNF α -producing cells, suggesting that TNF α -producing macrophages accumulate at the CPJ early in the disease course and become less prominent for unknown reasons during the later phases. Both the p55 and p75 TNF receptors (TNF-R) are also present in abundance at the CPJ, especially by those cells invading cartilage (Deleuran et al. 1992a). Both receptors are expressed on a variety of cell types including fibroblasts, macrophages, and chondrocytes, supporting the view that a wide range of cells at the CPJ are potential targets for TNF α .

IL-1-producing macrophages have also been demonstrated at the CPJ in late-stage erosive RA (Chu et al. 1992). CPJ tissue from patients with long-standing disease (duration 6–29 years) demonstrated IL-1 α - and IL-1 β -producing cells in the majority, but not in all (Ulfgren et al. 2000). In patients with relatively early RA (<18 months), IL-1 α - and IL-1 β -producing cells were present at the CPJ in all, and measurements of the areas occupied by cytokine-producing cells suggested that considerably more IL-1 α - and IL-1 β -producing cells than TNF α -producing cells are present at the CPJ, especially in the earlier phases of RA. The apparent predominance of IL-1 β -producing cells at the CPJ in these studies is consistent with quantitative analysis of gene expression in long-standing RA (Firestein et al. 1990). However, further study of this issue will need to apply strict criteria to the selection of biopsy material in relation to disease activity, medication, and other clinical parameters. The type I IL-1 receptor (IL-1RI) was also demonstrated in abundance on a variety of cell populations at the CPJ (Deleuran et al. 1992b). As expected, cells producing IL-1 receptor antagonist (IL-1Ra) were less prominent at the CPJ than IL-1 α -producing cells.

The production of several other cytokines and their inhibitors has also been demonstrated at the CPJ in advanced RA, including IL-6 (Chu et al. 1992b; Ulfgren et al. 2000), TGF β (Chu et al. 1991b), IFN- γ , and GM-CSF (Chu et al. 1992b). In contrast to the increased production of many cytokines at the CPJ, cells producing IL-8, a potent chemoattractant, were notably more prominent at non-CPJ sites (Deleuran et al. 1994). The relative influence of each of the pro- and anti-inflammatory mediators in matrix degradation at different disease stages is likely to be complex and requires considerable further analysis.

Cellular invasion and degradation of cartilage and sub-chondral bone is mediated in part by the secretion of proteolytic enzymes (Tak and Bresnihan 2000). Proteolytic mechanisms may be divided into extracellular pathways, which involve the MMPs and serine proteinases, active at neutral pH, and the intracellular pathways, which involve the cysteine and aspartate proteinases, active at a low pH (Nagase and Okada 1997). In RA synovial tissue, the MMPs and cysteine proteinases have been widely studied. The abundant production of MMP-1, which can digest collagen types I, II, III, VI, and X and gelatins, at sites of joint erosion was first demonstrated in late-stage RA using immunofluorescent techniques (Woolley et al. 1997). The large number of MMP-1-producing cells at the CPJ were subsequently identified as predominantly fibroblasts, although some chondrocytes close to the CPJ were also noted to express MMP-1 RNA and protein, confirming the capacity of chondrocytes to both degrade and synthesize cartilage matrix (Trabandt et al. 1992). The predominance of MMP-1 over MMP-13

production at sites of cartilage erosion by both synoviocytes and chondrocytes has also been demonstrated (Tetlow and Woolley 1998). MMP-13 gene expression in FLS at the CPJ was demonstrated and, in primary synoviocyte cultures, it was upregulated two- to four-fold following treatment with IL-1 β or TNF α (Schulz et al. 1999).

The cysteine proteases degrade major cartilage components including proteoglycans, collagen types I, II, IX, and XI and basement membrane components (Nagase and Okada 1997). In advanced RA, cathepsin B was demonstrated in most, but not all, synovial tissue samples selected from the CPJ and was localized to FLS at the invading front, and to the intimal and sub-intimal layers of adjacent tissue (Trabandt et al. 1991). Abundant macrophage cathepsin L expression was also observed at sites of cartilage erosion, suggesting a role in the pathogenesis of joint damage (Iwata et al. 1997). Cathepsin K has been implicated in osteoclast-mediated bone resorption (Inoaka et al. 1995; Drake et al. 1996) and cathepsin K mRNA was demonstrated at sites of articular destruction (Hummel et al. 1998). Not surprisingly, some of the cathepsin K positive cells were osteoclast precursors. However, cathepsin K mRNA, was also expressed in large numbers of FLS at the CPJ, and in areas adjacent to lymphocytic infiltration, strongly suggesting that it may not only contribute to matrix degradation but also facilitate the movement of mononuclear cells through perivascular interstitial tissue. Chondrocytes in RA cartilage also release the first component of complement C1s, which has collagenolytic activity and may participate in the degradation of cartilage matrix (Nakagawa et al. 1999).

Synovitis in other chronic inflammatory polyarthropathies

There are some similarities between RA and other categories of chronic polyarthritis, which are summarized below. Several categories of arthritis such as granulomatous diseases, crystal-related arthropathies, and infectious diseases, which are often mono- or pauci-articular and have specific inflammatory characteristics, are not considered in this chapter.

Ankylosing spondylitis

Synovial tissue from the sacroiliac joints of patients with ankylosing spondylitis (AS) demonstrate both mononuclear cell infiltration and islands of early ossification (Braun et al. 1995). Mononuclear cell infiltrates, which include lymphocytes, macrophages, and fibroblasts, are seen in synovium, and in adjacent cartilage and bone. Pannus formation similar to RA has been described. There is evidence to suggest that the primary site of inflammation is the enthesis, where ligament, tendon, or the joint capsule is inserted into bone. It is not clear how the inflammatory cell populations migrate to sacroiliac joint structures. It has been suggested that they may migrate from proliferating blood vessels, or directly from the bone marrow. Increased vascularity is seen in the early enthesitis lesion (McGonagle et al. 2002). Sacroiliitis is also characterized by TNF α , TGF β 2, IFN- γ , IL-4, and, IL-12 mRNA expression (Braun et al. 1998).

The manifestations of synovitis in the peripheral joints in AS are indistinguishable from RA in many respects. However, some quantitative differences have been described. Firstly, the cellularity of the lining layer appeared to be less in AS than in RA. Secondly, more intense mononuclear cell infiltration has been described in AS, but this observation has not been highlighted in all published studies (Kidd et al. 1989). Finally, large B-cell aggregates may be prominent in the peripheral joints of some patients with AS. Rheumatoid granulomas do not occur in AS. It has been suggested that the enthesis may be the primary site of inflammation in peripheral joints in AS (McGonagle et al. 1998).

Psoriatic arthritis

There are similarities between the manifestations of synovitis in psoriatic arthritis (PsA) and AS. In both, the cellularity of the lining layer is less than RA. Similarly, synovial tissue macrophages are more numerous in RA

synovium than in PsA (Veale et al. 1993). Vascular changes are a dominant feature in PsA. For example, a comparison of synovial tissue obtained from patients with PsA and RA demonstrated that the number of blood vessels per square millimetre quantified microscopically in PsA tissue was almost double the number seen in RA. In addition, a distinct macroscopic pattern of blood vessel formation has been highlighted in PsA (Reece et al. 1999). Thus, under direct vision at arthroscopy, PsA and reactive arthritis synovium were characterized by the presence of tortuous, bushy vessels, and RA by straight, branching vessels.

Juvenile idiopathic arthritis

The synovial response to inflammation in children with juvenile idiopathic arthritis (JIA) is similar to adults with RA (Cassidy and Petty 1990). Macroscopically, villous formation is characteristic. Microscopically, there is increased cellularity of the synovial lining layer. In the sub-lining layer, vascular endothelial hyperplasia is prominent, associated with macrophage, lymphocyte, and plasma cell infiltration. Pannus formation is usual, leading to progressive erosion of adjacent cartilage and bone. The histopathologic manifestations of synovial inflammation in polyarticular and pauci-articular disease are indistinguishable.

Systemic lupus erythematosus

Synovitis in systemic lupus erythematosus is usually milder than RA. Vascular proliferation, perivascular mononuclear cell infiltration, and lining layer hypercellularity, consisting of both fibroblast-like synoviocytes and macrophages, are observed to varying degrees (Labowitz and Schumacher 1971). Deposition of fibrin-like material along the synovial surface and throughout the synovial membrane is characteristic. Features of synovial vasculitis, with infiltration of vessel walls and obliteration of the vascular lumen, is observed occasionally.

Osteoarthritis

Osteoarthritis (OA) is widely regarded as being primarily a degenerative disorder of articular cartilage. However, a considerable degree of synovial inflammation, often indistinguishable from RA, may be observed in many OA biopsy samples (Goldenberg et al. 1982; Kennedy et al. 1988). Well-developed lymphoid follicles and significant numbers of plasma cells are not seen in OA synovium.

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