SYNOVIAL LINING, ENDOTHELIAL AND INFLAMMATORY MONONUCLEAR CELL PROLIFERATION IN SYNOVIAL MEMBRANES IN PSORIATIC AND REACTIVE ARTHRITIS: A COMPARATIVE QUANTITATIVE MORPHOMETRIC STUDY


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SUMMARY

The extent of synovial cell proliferation in situ and its relationship to the destructive potential of rheumatoid arthritis (RA) is a matter of continuing debate. Notably, the situation has not been elucidated in other inflammatory arthritides (i.e. reactive (ReA) and psoriatic (PsA)), which, although they share some histopathological similarities with RA, develop different patterns of joint involvement. In order to estimate the proliferation of synovial cells in situ in PsA and ReA, and to compare this with RA and with ‘non-inflammatory’ joint lesions, we have utilized immunostaining of the Ki-67 antigen complemented with CD68 or Ki-67 double stainings to assess the extent of mononuclear inflammatory cell proliferation. Synovial samples analysed were from 33 patients: RA (n = 8), PsA (n = 13), ReA (n = 6) and six ‘non-inflammatory controls’ (degenerative or traumatic joint lesions). Thickening of the synovial lining (in particular in RA) and perivascular accumulations of mononuclear inflammatory cells, predominantly lymphocytes, were characteristic features in all synovitides. In contrast to the thickened avascular synovial lining in RA, in 5/13 cases with PsA, blood vessels were observed in the lining. The percentage of lining cells expressing Ki-67 antigen was higher in RA (median = 4.7, interquartile range [Q3–Q1] = 3.9, mean [95% CI] = 3.5 [1.7–5.2], P = 0.0063), PsA (median = 1.2, [Q3–Q1] = 1.9, mean [95% CI] = 1.6 [0.7–2.5], P = 0.007) and ReA (median = 1.4, [Q3–Q1] = 2.3, mean [95% CI] = 1.6 [0.1–3.1], P = 0.0235) than in controls (median = 0.1, [Q3–Q1] = 0.45, mean [95% CI] = 0.2 [0.07–0.5]). In this respect, the differences between different forms of the inflammatory arthritides were not statistically significant (P > 0.05). In RA, PsA and ReA, the percentage of labelled cells in the inflammatory mononuclear cell-rich areas was higher than in controls. The percentage of proliferating endothelial cells was also significantly higher in RA, PsA and ReA than in controls. However, in RA, endothelial expression of Ki-67 antigen was often seen in small blood vessels, whereas in PsA, Ki-67 antigen was preferably expressed in the medium to large blood vessels. Synovial lining cells of the monocyte/macrophage lineage (type A synoviocytes), but not stromal fibroblasts, is a prominent feature in RA, the extents to which this, or in situ proliferation of lymphocytes, contribute to the histopathology of PsA, ReA and RA are comparable. Vascular involvement is suggested by the proliferation of endothelial cells in RA, PsA and ReA in an overlapping manner, but, based on topological differences, such a response may represent diverse pathological features, such as angiogenesis, vascular enlargement and reparative responses to injury.

KEY WORDS: Psoriatic arthritis, Reactive arthritis, Rheumatoid arthritis, Cell proliferation, Ki-67 antigen.

Psoriatic (PsA), reactive (ReA) and rheumatoid (RA) arthritides are inflammatory joint disorders characterized by activation of the cellular immune response evolving to synovial inflammation/synovitis [1–6]. However, these arthritides almost always have differences in clinical course and in the pattern of joint damage [5–8]. RA, PsA and ReA represent some overlap histopathologically in that their activated synovial tissue is characterized by the inflammatory cell infiltration and hyperplasia of synovial lining. It is postulated that these features are dependent on cells that have homed from circulation and/or cells that may derive from in situ division/proliferation, and that the extent of these processes may relate directly to the destructive potential of arthritis. Because inflammatory cell recruitment and cell proliferation can be inhibited pharmacologically, their quantitative assessment in different arthritic conditions is an important issue. In this context, a comparatively low proportion of macrophages and unremarkable synovial lining hyperplasia in PsA, as compared with RA, has been suggested to be due to different vascular expression of ELAM-1 [9]. Quantitative similarities in the number of B cells, T cells and T-cell subsets (predominantly CD4, CD45RO+ T cells) in PsA and RA have been associated with the similar expression of ICAM-1 and VCAM-1 [9, 10]. The question of synovial cell proliferation in RA has been addressed in numerous earlier studies [11–21]. The findings appear contradictory, however, and there still seems to be no firm consensus

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as to the extent of synovial lining cell proliferation in RA [22]. Furthermore, as noted elsewhere [22], recent observations on the similar expression of different oncogenes (including c-myc, the oncogene associated with cell proliferation) and oncoproteins in various arthritic conditions [23, 24] have raised the question 'to what extent' are the local expression of oncogenes as well as the in situ proliferation of synovial cells specific to the RA lesion? Thus, characterization of the synovial cell proliferation in situ in other (than RA) inflammatory arthritides seems to be required. A distinct, though not less interesting question, is the proliferation of endothelial cells, a process/step essential for the formation of new blood vessels/angiogenesis, which has been proposed to be an important pathogenetic mechanism promoting PsA and RA [4, 8, 25–27]. However, synovial endothelial proliferation has not been elucidated.

The present study was undertaken to quantify and compare cell proliferation in PsA, ReA and RA synovial membranes. For this purpose, we have employed immunostaining of Ki-67 antigen (a cell cycle-associated antigen expressed in the nuclei of all proliferating cells, but not in resting phase G0 cells) [28]. This was combined with the prior pre-treatment of synovial tissue sections in a microwave oven (microwave oven antigen-retrieval technique) [29].

MATERIALS AND METHODS

Patients and samples

After informed consent of 33 patients, synovial tissue samples (1–2 specimens) were obtained from 29 knees, two hip and two elbow joints at open-joint surgery or diagnostic arthroscopy. Eight of the patients (two men and six women; mean age 46.6 yr, range 31–73) had RA [30] (mean duration of the arthritis 8 yr; range 3–15), 13 (nine men and four women; mean age 37.2 yr, range 7–64) had PsA [31] (mean duration of the arthritis 7.5 yr, range 1–25) and six (two men and four women; mean age 29.8 yr, range 19–53) had ReA [32] (duration of the arthritis 3 days (two cases), 1 yr (two cases), 3 yr (one case), and in one case recurrent arthritis for 12 yr). Specimens from six patients (three men and three women; mean age 41.2 yr, range 28–63) were used as controls; these synovial samples were from joints with osteoarthritis (OA) (N = 2) [33], meniscus lesion (N = 2), distortion of the knee joint (N = 1) and knee chondromatosis (N = 1).

Each of the patients with PsA had psoriatic skin disease. A test for rheumatoid factor was negative in each of the seven PsA patients tested.

Of the patients with ReA, arthritis had been triggered by chlamydial infection in four cases, in one by Salmonella infection, and in one case ReA had developed after pharyngitis (no Salmonella, Yersinia, Campylobacter or chlamydial antibodies were found in the blood). Of ReA patients, five were HLA B27+. All the ReA patients recovered during the follow-up.

Of the 33 patients included in this study, only two patients with PsA had intra-articular steroids during the period less than 3 months (4 weeks and 5 weeks, respectively) prior to synovial biopsy. Of the 33 patients, only one with PsA had previously undergone synovectomy. Of the RA patients, four have been receiving daily non-steroidal anti-inflammatory drugs (NSAIDs) alone, one chloroquine (Delagil®), 200 mg) + NSAID, one steroids (7.5 mg equivalent to prednisolone), one sulphasalazine (1.5 g) + steroids (10 mg equivalent to prednisolone) + NSAID; one of the RA patients had no systemic medication. Of the PsA patients, one has been receiving daily steroids (5 mg equivalent to prednisolone) + NSAID, one sulphasalazine (1.5 g) + NSAID, one allopurinol + NSAID, two NSAID alone, one has been treated with massive doses of steroids due to allergy to sulphasalazine, and six had no systemic medication. One of the PsA patients has been treated with fumarademe (control) + local steroid salve for the skin. Of the patients with ReA, two had no medication, four have been receiving NSAIDs; one of the latter had received antibacterial therapy before synovial biopsy. Of the ‘control’ patients, five have been receiving NSAIDs, and one had no systemic medication.

Immunostaining: Protocol of immunoperoxidase (ABC) technique

Five-micrometre-thick, formalin-fixed, paraffin-embedded sections were deparaffinized in xylene and rehydrated in a graded alcohol series and in distilled water. Endogenous peroxidase activity was inhibited with 0.3% H2O2 in methanol for 30 min, then the sections were washed in distilled water three times for 5 min. As recommended by Dako, and as has been previously utilized [29], antigenic epitopes for Dako rabbit anti-human Ki-67 antigen (affinity-isolated antibody) were disclosed using the microwave antigen-retrieval technique by boiling tissue sections in 10 mM citrate buffer (pH 6.0) twice for 5 min in a microwave with a rotating table at a power of 600 W. After cooling at room temperature for 20 min in citrate buffer, the sections were washed with distilled water, 0.1 M phosphate-buffered saline (PBS), pH 7.4, and serially incubated in: (1) normal goat serum (diluted 1:50; Vector Laboratories, Burlingame, CA, USA) for 45 min, (2) affinity-isolated primary antibody, Dako rabbit anti-human Ki-67 antigen (affinity-isolated antibody) was disclosed using the microwave antigen-retrieval technique by boiling tissue sections in 10 mM citrate buffer (pH 6.0) twice for 5 min in a microwave with a rotating table at a power of 600 W. After cooling at room temperature for 20 min in citrate buffer, the sections were washed with distilled water, 0.1 M phosphate-buffered saline (PBS), pH 7.4, and serially incubated in: (1) normal goat serum (diluted 1:50; Vector Laboratories, Burlingame, CA, USA) for 45 min, (2) affinity-isolated primary antibody, Dako rabbit anti-human Ki-67 antigen (diluted 1:400; Dakopatts A/S, Glostrup, Denmark) overnight at +4°C, (3) biotinylated goat anti-rabbit immunoglobulin G (diluted 1:130; Vector Laboratories) for 45 min, (4) avidin–biotin–peroxidase complex (Vector Laboratories) for 45 min and (5) 3,3′-diaminobenzidine tetrahydrochloride (DAB) (Sigma Chemical Co., St Louis, MO, USA) in 0.006% H2O2 PBS solution. Consecutive tissue sections were left without counterstain or counterstained with haematoxylin. After washing in tap water, sections were dehydrated in alcohol series, cleared in xylene, and mounted in a synthetic mounting medium Diatex (Becker Industriärfab AB, Mårsta, Sweden). Bovine serum albumin, 0.1% in PBS, was used for dilution of serum and antibodies. Between each step (except after incubation with normal goat serum), the slides were washed three times.
times for 5 min in PBS. Omission of the primary antibody, use of normal rabbit IgG instead of specific primary antibodies, and exposure of tissue sections to DAB served as negative staining controls.

**Protocol of ABC–APAAP (alkaline phosphatase–anti-alkaline phosphatase) double staining**

ABC–APAAP double staining was carried out and the colour reactions were described as developed in detail elsewhere [34, 35]. Briefly, 5-μm-thick, formalin-fixed, paraffin-embedded consecutive synovial sections from the same specimens, which have been used for staining of Ki-67, were first treated as for the staining of Ki-67 using the protocol for the ABC technique (described above) up to the step when the slides were rinsed in tap water. Then, the slides were washed with 0.05 M Tris(hydroxymethyl)aminomethane (Sigma Chemical Co., St Louis, MO, USA)-buffered saline (TBS), pH 7.4, and incubated in: (1) normal rabbit serum (diluted 1:50; Dakopatts A/S, Glostrup, Denmark), (2) a monocyte/macrophage marker, mouse anti-human CD68 IgG (dilution 1:50, Dako A/S, Glostrup, Denmark) for 1 h at +22°C, (7) rabbit anti-mouse IgG (dilution 1:50, Dako A/S, Glostrup, Denmark) for 1 h at +22°C, (8) APAAP solution (dilution 1:25, Dako A/S, Glostrup, Denmark) for 1 h at +22°C. (9) Alkaline phosphatase was visualized using 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) and nitroblue tetrazolium (NBT) as substrate and marked and two occasional hyperplasia of the synovial lining. Inflammatory cell infiltrates and peri-vascular accumulations of the inflammatory mononuclear cells were an indistinguishable feature of all chronic synovitides. In RA, the cells mainly with the staining was used in this double-staining procedure. Throughout the APAAP staining, between each incubation step (except before primary antibodies), the slides were washed with TBS three times for 5 min.

The above described double-staining technique was used also to stain Ki-67 antigen (ABC staining) and leucocyte common antigen (ABC, LCA, clones 2B11 and PD7/26, Dako A/S, Glostrup, Denmark) (APAAP staining). In contrast to the many other lymphoid and myeloid cell markers, Dako anti-human LCA (a mixture of 2B11 and PD7/26 antibodies) is particularly recommended for use on routinely processed, paraffin-embedded specimens. It reacts with the epitopes on LCA chains with a molecular mass of 180, 190, 205 and 220 kDa, but is not designed as a CD45 antibody. Dako anti-human LCA (clones 2B11 and PD7/26) mainly labels lymphoid cells and is unreactive with the non-haematopoietic cells (for references, see antibody specification).

**Microscopic evaluation and quantitative assessment of the synovial labelling**

Microscopic examination and cell counting were carried out with a Leitz Diaplan lens system (Wetzlar, Germany). Numbers of cells labelled/stained for Ki-67 antigen were counted separately for 500 consecutive synovial lining cells, 500 endothelial cells and 500 cells in the mononuclear cell-rich areas (in RA, PsA, ReA) or peri-vascular areas (in control samples). The cell counting was performed by two observers (AC and YTK), independently. One of the observers was unaware of the patients’ identities/source of the sample. The estimated averages of the labelling ratios were expressed as percentages [28].

**Statistical analysis**

Statistical analysis was performed with BMDP-PC 7.01 software. Medians plus interquartile ranges (Q3–Q1) as well as means [95% confidence intervals (CI)] were used for data presentation. P values for differences between the groups were calculated using the Mann–Whitney test for unpaired samples.

**RESULTS**

Histological examination of the synovial samples in the present series of ‘controls’, i.e. OA, meniscus lesions, distortion of the knee joint and chondromatosis, and overtly inflammatory conditions, i.e. RA, PsA and ReA, revealed some shared, but also some distinct, histopathological features. In RA, PsA and ReA, thickening of the synovial membrane, due to an increased depth of the synovial lining cells and deposition of extracellular matrix, was a prominent feature, particularly in RA. Out of eight RA cases, six disclosed marked and two occasional hyperplasia of the synovial lining. Out of 13 cases with PsA, three showed no and 10 occasionally mild to moderate hyperplasia. All six cases of ReA had occasionally mild hyperplasia of the synovial lining. Inflammatory cell infiltrates and perivascular accumulations of the inflammatory mononuclear cells were an indistinguishable feature of all chronic synovitides. In RA, the cells mainly with the appearance of lymphocytes often formed large aggregates. Differences were observed in the synovial vasculature/vascularization in PsA and RA. The thickened RA synovial lining was substantially avascular with the blood vessels being situated beneath the lining. In contrast, in 5/13 cases with PsA, increased vasculature and large vessels were also observed close to and/or protruding from the synovial lining. In ReA, the synovial vasculature resembled that seen in control samples. Thus, the cases with PsA and ReA represent the pathomorphological features ascribed to these conditions in some earlier reports [4–6, 8, 36, 37].

Representative examples of immunostaining/expression of Ki-67 antigen in synovial lining, perivascular mononuclear inflammatory infiltrates and vascular endothelium are shown in Figs 1 and 2. Combined assessment of the Ki-67/CD68 (a monocyte/macrophage marker) (Fig. 3) and Ki-67/LCA (clones 2B11 and PD7/26) (Fig. 4) double stainings confirmed that, regardless of the inflammatory condition studied, the absolute majority of the Ki-67 antigen-expressing cells were fibroblast-like cells in the synovial lining and lymphocytes in the inflammatory mononuclear cell-rich areas. Only a few lining cells were co-labelled for Ki-67 antigen and CD68 (Fig. 3B). The majority of
Fig. 1.—Expression of the Ki-67 antigen in synovial membrane. Immunoperoxidase (ABC) staining applied to sections after the microwave oven antigen-retrieval technique; original magnification ×160. (A) Rheumatoid arthritis (RA), haematoxylin counterstain; (B) a consecutive section, without counterstain. (C) Psoriatic arthritis (PsA), haematoxylin counterstain; (D) a consecutive section, without counterstain. (E) Reactive arthritis (ReA), haematoxylin counterstain; (F) a consecutive section, without counterstain. (G) Synovium from the joint with rupture of meniscus, represents a set of non-inflammatory arthropathies, haematoxylin counterstain; (H) a consecutive section, without counterstain.
the Ki-67 antigen-presenting cells in the inflammatory cell-rich areas were positive for LCA, but were not labelled for CD68 (Fig. 3B). Focal infiltrates of and/or a few scattered LCA-positive cells, apparently representing lymphocytes migrating to the joint cavity, were found within the synovial lining in inflammatory arthritides. In fact, these inflammatory cells 'migrating' into the joint cavity were negative for Ki-67 antigen. Endothelial cells expressing Ki-67 antigen were commonly seen in the small blood vessels in RA (Fig. 2A), whereas in PsA they were preferably observed in the medium to large blood vessels (Fig. 2C). Notably, four PsA cases, which were characterized by the most advanced synovial changes, showed comparatively small ratios of proliferating endothelial cells (Fig. 2D), whereas, similarly to ReA (Fig. 2B), relatively high ratios of the proliferating endothelial cells were found in three PsA cases characterized by marked perivascular infiltration and vascular congestion.

Morphometric results/percentages of the nuclei/cells labelled for the Ki-67 antigen in different synovial compartments in the different forms of inflammatory arthritides vs control samples are given in Fig. 5.

The percentage of lining cells expressing Ki-67 antigen in RA (median = 4.7%, [Q3–Q1] = 3.9, mean [95% CI] = 3.5% [1.7–5.2]), PsA (median = 1.2%, [Q3–Q1] = 1.9, mean [95% CI] = 1.6% [0.7–2.5]) and ReA (median = 1.4%, [Q3–Q1] = 2.3, mean [95% CI] = 1.6% [0.1–3.1]) were higher (P = 0.0063, P = 0.007 and P = 0.0235, respectively) than in ‘non-inflammatory control’ (median = 0.1%, [Q3–Q1] = 0.45, mean [95% CI] = 0.2% [0.07–0.5]). In this respect, RA, PsA and ReA did not differ from each other (P > 0.05).

The percentage of labelled cells in the inflammatory mononuclear cell-rich areas was higher in RA (median = 4.4%, [Q3–Q1] = 6.2, mean [95% CI] = 5.5% [1.8–9.3], P = 0.0029), PsA (median = 6.6%, [Q3–Q1] = 7.6, mean [95% CI] = 5.8% [3.4–8.1], P = 0.0084) and ReA (median = 8.7%, [Q3–Q1] = 8.2, mean [95% CI] = 6.5% [2.2–10.9], P = 0.0127) than in the control samples (median = 0.9%, [Q3–Q1] = 0.9, mean [95% CI] = 0.8% [0.3–1.3]) in the control samples, no and/or only occasional perivascular mononuclear cell accumulations were found, although infiltrating inflammatory cells were present in high enough numbers for morphometric calculations). ReA, PsA and ReA did not differ from each other (P > 0.05).

There was a higher percentage of endothelial cells
expressing Ki-67 antigen in synovial membranes in RA (median = 1.0%, [Q3–Q1] = 3.6, mean [95% CI] = 2.1% [0.06–4.3], \( P = 0.0038 \)), PsA (median = 0.4%, [Q3–Q1] = 2.7, mean [95% CI] = 1.2% [0.3–2.1], \( P = 0.0104 \)) and ReA (median = 0.6%, [Q3–Q1] = 2.3, mean [95% CI] = 1.1% [0.2–2.4], \( P = 0.0074 \)) than in the control samples, where the index counted for 500 consecutive endothelial cells was zero. RA, PsA and ReA did not differ from each other (\( P > 0.05 \)).

**DISCUSSION**

The present study compares the proliferation of cells in synovial tissue *in situ* in different inflammatory joint diseases, namely PsA, ReA and RA. Separate assessment of the synovial lining, inflammatory mononuclear cells and vascular endothelium was carried out with the assumption that their labelling for the Ki-67 antigen (a marker for cycling cells) may disclose a different pattern of synovial cell activation in RA, PsA and ReA. The results of the present study indicate that although proliferation of synovial lining fibroblasts is a prominent feature in RA, there may not be any significant differences between their proliferation *in situ* in synovial membranes in RA, PsA and ReA. Also, lymphocyte and endothelial proliferation seem to overlap in PsA, ReA and RA, but topological differences in the endothelial cell responses may represent diverse
pathological features, such as angiogenesis, vascular enlargement and reparative responses to injury.

Proliferation of synovial lining cells was most prominent in RA, intermediate in PsA and ReA, and low in the control samples, with the significant difference being found between inflammatory arthritides and the 'non-inflammatory' controls. It should be noted that in the original study utilizing synovial staining for Ki-67 antigen, the labelling index was very low (0–0.03%) for lining cells in RA [17]. This contrasts with the ratio presented here (median = 4.7%, [Q3–Q1] = 3.9%, mean [95% CI] = 3.5% [1.7–5.2]) which, however, is close to the results reported in other studies utilizing other markers of cell proliferation [12, 19]. This discrepancy may be accounted for by some technical differences. First, we have utilized polyclonal, instead of monoclonal, antibodies [17]. Because polyclonal antibodies recognize several different immunoreactive epitopes, they are not as sensitive to artifacts caused by fixation and sample processing, i.e. the likelihood of false-negative staining is smaller. Second, the microwave oven antigen-retrieval technique was utilized in the present study to reveal hidden immunoreactive epitopes. Finally, we analysed the synovial lining through its whole thickness [19] instead of counting the intimal monolayer only [17]. In addition to the proliferation of the fibroblast-like type B lining cells, chronic synovitis may be characterized by a more prominent migration of macrophage-like type A cells into the lining [38]. Despite existing evidence that monocyte/macrophages are able to proliferate [39, 40], type A synovial lining cells are generally regarded as non-dividing cells. According to the present results on Ki-67 and CD68 or LCA co-expression, it seems that although the contribution of in situ proliferation of the macrophage-like cells to the hyperplasia of synovial lining is little, these cells are able to proliferate. In contrast, this phenomenon was not observed in the mononuclear inflammatory cell-rich areas, where the majority of the proliferating cells were LCA positive, i.e. of lymphoid origin. This suggests that the proliferation of monocyte/macrophages in synovium in arthritis may be related to the maturation/differentiation of monocyte/macrophages into specialized type A synovial cells and also to the 'inflammatory state' of the synovial tissue.

There was a comparatively high, but very similar overall Ki-67 antigen expression in the LCA-positive mononuclear cell-rich areas in RA, PsA and ReA. This corresponds to the quantitative similarities of the immunohistology of these arthritides in this respect [9, 10] and is in keeping with local proliferation of lymphocytes, usually defined as 'antigen-triggered' T cells [3, 41]. Although RA differs from PsA and ReA in the synovial fluid kinetics of CD4+ and CD8+ T cells [8, 42], and is characterized by relatively low expression of T-cell activation markers, namely MHC class II antigen, interleukin-2 and transferrin receptors and gp 40/80 glycoprotein (all are already detectable in the G1 phase of the cell cycle) [1] and [3H]thyidine incorporation (detectable in the S phase of the cell cycle) [21] in the synovial fluid, these differences do not seem to be reflected in the overall proliferation of lymphocytes in synovial tissue.

Endothelial cell proliferation seems to characterize, in addition to RA, also PsA and ReA. It was surprising to find out that the ratio of proliferating endothelial cells in ReA did not differ significantly from that seen.
in RA and PsA, which have been characterized as ‘angiogenesis-dependent diseases’ [4, 8, 25]. Also, the rank order, i.e. RA > ReA > PsA > control samples, of the endothelial proliferation apparently does not fit with the rank order of synovial vascularity, i.e. PsA > ReA > non-inflammatory controls > RA [27]. However, these findings are in agreement with an involvement of angiogenesis in inflammatory arthritides. In RA, endothelial expression of Ki-67 antigen was commonly seen in small and apparently growing vessels, while in PsA proliferating endothelial cells were preferably observed in the medium to large vessels. This suggests that apart from vascular sprouting, endothelial cell activation and proliferation may occur in the context of other vascular events, e.g. degradation and enhanced remodelling of the basement membrane. It is of some interest that overall vascularity is reduced in RA so that one has to speculate that lining hyperplasia/growth rate of inflammatory synovial tissue exceed local proliferation of blood vessels in RA [43]. Because ReA is usually a transient, self-remitting condition, vascular events in ReA seem to be linked to vascular damage [37]. The damage/stimulation accompanied by local release of von Willebrand factor in ReA [27] may link vascular congestion with subsequent activation of platelets to release their constituents (e.g. platelet-derived growth factor-β PDGF-β), which induce reparative proliferation of endothelial cells. Taken together, it may be concluded that proliferation of endothelial cells in RA, PsA and ReA may represent the net effect of pathological processes as diverse as angiogenesis, vascular remodelling and reparative responses to injury. Although the present control samples do not strictly speaking represent normal, non-inflammatory synovial tissue, it still seems clear that cells in all inflammatory arthritides, in all synovial compartments, are activated to proliferate.

ACKNOWLEDGEMENTS

This work was supported in part by the Finnish Academy, Invalid Foundation, grants of the Chancellor of the University of Helsinki and Center for International Mobility (CIMO), Finland; by the Ministry of Health, Lithuania; by the European League Against Rheumatism (EULAR), Switzerland; and by the Uehara Foundation and Nakatomi Foundation, Japan.

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