and quantify the inflammatory activity of the disease.[6] This is important, because 44% of patients in clinical remission have histologically proven inflammatory activity[1 2] and blood inflammatory markers are still limited.[9] In addition, [^{18}F]FDG-PET is useful in assessing the effectiveness of different treatments during follow up[6] and could be used in randomised controlled trials. However, [^{18}F]FDG-PET should be compared with more standardised techniques, such as angiography, VMR, computed tomography, or Doppler ultrasound to obtain firm support for its value in clinical practice.

The accuracy of [^{18}F]FDG-PET for diagnosing TA has been estimated as 94% and false positives are not found in normal patients aged under 40.[6] In our patients PET was the only technique with a positive result for diagnosing TA and showed good correlation with disease activity. Our experience also confirms previous reports of relapsing TA after tapering the corticoid dose,[2 9] even though methotrexate was started after diagnosis.

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Interleukin (IL) 1α, IL1β, IL receptor antagonist, and IL10 polymorphisms in psoriatic arthritis

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Interleukin (IL) 1 is a potent proinflammatory cytokine that occurs as IL1α and IL1β. The biological activity of IL1α and IL1β is initiated by binding with type 1 IL1 receptor and is inhibited by IL1 receptor antagonist (ILRa).[1] IL10 is an anti-inflammatory cytokine that suppresses macrophage production of cytokines and enhances soluble cytokine receptor release.[2] These cytokines have been implicated in the pathogenesis of psoriatic arthritis (PsA), as increased expression of IL1 and IL10 has been observed in the synovial fluid and synovial membrane of patients with PsA in comparison with patients with osteoarthritis.[3] Given the proposed function of these cytokines in autoimmune disease, we set out to examine the role of polymorphisms in IL1α, IL1β, ILRa, and IL10 in the Newfoundland PsA population.

This study was approved by the ethics committee at the Memorial University of Newfoundland. In this study, PsA was defined as an inflammatory arthritis in patients with psoriasis and the absence of other causes for inflammatory arthritis. Patients and controls were genotyped for the following single nucleotide polymorphisms (SNPs): IL1α (−889; rs1143634), IL1β (+3953; rs1800587), and IL10 (−1082; rs1800896) using the Sequenom MassArray platform. All primers were designed using SpectroDESIGNER software. For ILRa (accession No AF387734), an 86 bp variable number tandem repeat was determined by a polymerase chain reaction.

Two hundred and twenty six patients with PsA and 95 matched controls were studied. The mean age of the patients with PsA was 54.0 years; 108 (48%) were women. All genotypes satisfied the Hardy-Weinberg equilibrium. χ^2 Tests were used to examine the relationship between the minor allele frequencies of the candidate genes and PsA. The minor allele frequencies for patients with PsA and controls were for IL1α (T) 0.24 *v* 0.31 (odds ratio 0.7 (95% confidence interval 0.4 to 1.2)) respectively; for IL1β (T) 0.24 *v* 0.25 (0.9 (0.5 to 1.6)); for ILRa (two repeats) 0.27 *v* 0.24 (1.1 (0.7 to 2.0)); and for IL10 (A) 0.47 *v* 0.49 (0.9, (0.5 to 1.6)). Thus none of the polymorphisms examined were significantly associated with PsA in the Newfoundland population.

There is a paucity of association studies of IL1 and IL10 in PsA. In studies with an admixed white population Ravindran *et al* noted an increased frequency of the IL1α −889 polymorphism among patients with PsA but observed no difference for IL1β +3953 and IL1 receptor R1 +970 genes.[4] Another study demonstrated no association between IL1β +3953 and IL1Ra gene polymorphisms in patients with PsA nor with IL10 SNPs (−1082 and −592) and PsA.[5]

Newfoundland has a white founder population known to exhibit homogeneity comparable to that of the Hutterites.[6] A potential advantage in studying this population is the detection of small to modest genetic effects, as a result of an enhanced signal to noise ratio. In our study no association was found between polymorphisms in IL1α (−889), IL1β (+3953), IL10 (−1082), and ILRa in the Newfoundland founder population. Thus, these polymorphisms are unlikely to have a major role in the Newfoundland PsA population.

We cannot, however, rule out the possibility that an association with other SNPs exists in these genes. Furthermore, we also acknowledge that because our sample size is limited we are unlikely to detect small differences in allele frequencies.

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Production of anti-CCP antibodies and matrix metalloproteinase-3 by human rheumatoid arthritis synovial tissues using SCID mice

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The diagnosis of rheumatoid arthritis (RA) remains imprecise, particularly early in the course of the disease. Up to now, rheumatoid factor (RF) has been used as a typical marker for RA; however, RF has a low specificity because it also occurs in many inflammatory diseases as well as in healthy people. It has recently been shown that autoantibodies directed toward cyclic citrullinated peptides (anti-CCP) are potentially important serological markers for diagnosis and prognosis in RA.[1]

The proteolytic pathways associated with cellular interactions also seem to have an important role in joint cartilage destruction of RA. Matrix metalloproteinase-3 (MMP-3) is secreted by fibroblasts and synovial cells,[2] and it has been shown to be increased in RA serum, not only in the late stage but also in the early stage of the disease. Therefore, MMP-3 is a useful marker for predicting bone damage in early RA.[3]

In many early cases of RA, patients will not always fulfil the American College of Rheumatology criteria. Therefore, it is important to detect the point at which disease-specific autoantibodies and proteinases appear in RA serum. In this study we directly investigated the production of anti-CCP and MMP-3 using a severe combined immunodeficiency (SCID) mutant mouse, into which human RA synovial tissue was transferred.

SCID mice are a well known model for analysing the developmental mechanism of T and B cells. We previously developed SCID mice (CB.17/Icr; Charles River Japan, Tokyo, Japan) in which human RA synovial tissue was grafted (SCID-HuRAg), and we evaluated them as models for RA.[4 5] The histological features of RA were observed in all SCID-HuRAg mice and these mice induced the production of human antibodies. Proliferative synovial fibroblasts and infiltration of inflammatory cells were also seen in the pannus.

The serum levels of anti-CCP and human MMP-3 of SCID-HuRAg mice were examined weekly after implantation. Non-implanted SCID mice sera were used as controls. Figure 1 shows representative results of independent experiments from two patients. The mean (SD) anti-CCP and MMP-3 levels in the serum of the patients were 702 (26.9) U/ml and 321 (12.0) ng/ml, respectively. Human, not mouse, MMP-3 appeared in mouse serum shortly after implantation and decreased immediately. On the other hand, anti-CCP increased gradually and reached a plateau from the fifth week. It is reported that anti-CCP are produced locally in the inflamed synovial tissue from RA.[6 7] Therefore we think it is reasonable that the surviving, activated human B cells can produce autoantibodies, and the proliferative synovial fibroblasts around the engrafted tissue can produce MMP-3, and that producing autoantibodies spontaneously takes much longer than inducing enzyme. In our previous report, both human RF and interleukin 6 were also detected in these mice sera[4] and not in mice with tissue implants from osteoarthritis synovia (data not shown).

MRL-lpr/lpr mice develop an autoimmune syndrome resembling human systemic lupus erythematosus.[8] Anti-CCP were present in these mice and (NZW × B6)F_1-hbcl-2 transgenic mice, which have defects in the regulation of B cell apoptosis.[9] However, these animals showed not only antibody reactivity against the citrullinated peptide cfc1-cyc peptide, but also against the non-citrullinated control peptide; therefore, Vossenaar *et al* reported that the antibodies in these mice are not citrulline specific, and citrulline-specific autoantibodies are present only in human patients with RA and not in animal models of autoimmune disease.[10]

We think that the main problem is that citrulline-specific autoantibodies detected by both groups were of mouse origin. On the contrary, all the target cells within SCID-HuRAg mice which we used were of human origin, having migrated from the implanted tissue, and anti-CCP and MMP-3 were of human origin, too.

In conclusion, we showed the point at which disease-specific autoantibodies and proteinases appear in RA. SCID-HuRAg mice will be worth using in the study and development of new drugs for RA.