High CCL18/PARC Expression in Articular Cartilage and Synovial Tissue of Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We studied the role of CCL18/pulmonary and activation-regulated chemokine (PARC) in rheumatoid arthritis (RA).

Methods. Human cartilage tissues and synovial membranes were obtained from patients with RA and with osteoarthritis (OA). Sera samples were obtained from RA patients, OA patients, healthy controls, and patients with flu, and synovial fluid (SF) from patients with RA and OA. Real-time PCR was performed with RNA from cartilage samples. Immunohistochemical analysis of CCL18/PARC was done with RA and OA cartilage and synovial tissue. Levels of CCL18/PARC in serum and SF were evaluated by ELISA.

Results. CCL18/PARC mRNA was expressed at significantly higher levels in RA cartilage than in OA ($p = 0.0001$) and control ($p < 0.0001$) samples. CCL18/PARC mRNA expression was much higher in RA synovial membrane than OA samples ($p = 0.0001$). All RA cartilage and synovial tissue samples exhibited medium to strong staining for CCL18/PARC. Serum levels of CCL18/PARC were higher in RA patients (156.21 ± 125.73 ng/ml, n = 71) than in OA patients (64.54 ± 40.90 ng/ml, n = 12) and controls (28.04 ± 10.96 ng/ml, n = 20). Levels of CCL18/PARC in RA SF (275.20 ± 228.16 ng/ml, n = 15) were higher than in OA (33.13 ± 14.84 ng/ml, n = 6; $p = 0.0198$). CCL18/PARC levels correlated significantly with rheumatoid factor levels ($r = 0.431$, $p = 0.0040$), but not with matrix metalloproteinase-3, erythrocyte sedimentation rate, and C-reactive protein.

Conclusion. CCL18/PARC was highly expressed in RA articular cartilage and synovial tissue compared with OA samples. Our data indicated that CCL18/PARC levels are not related to the conditions of generalized inflammation, but are related to the pathogenesis of RA. (J Rheumatol 2007;34:266–71)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CCL18/CC CHEMOKINE SYNOVIAL TISSUE
PULMONARY AND ACTIVATION-REGULATED CHEMOKINE CARTILAGE

Rheumatoid arthritis (RA) is a chronic inflammatory disease where the synovial tissue is characterized by heavy infiltration of leukocytes. Chemokines and chemokine receptors have been reported to play an important role in cell migration and positioning of leukocytes within the inflamed rheumatoid synovium. There is now much attention on the specific contribution and role of each chemokine and chemokine receptor in the chronic inflammatory process in the synovial tissue. Loss of functional integrity of articular cartilage due to an imbalance between catabolic and anabolic chondrocyte activity is characteristic of RA as well as osteoarthritis (OA). The biosynthetic and degradative activities of chondrocytes are regulated by extracellular influences that include interactions with the extracellular matrix, mechanical stress, and soluble factors such as cytokines and growth factors. Many investigators have reported that CC and CXC chemokines may also play an important role in OA cartilage degradation[1-3].

Chemokines are chemotactic cytokines that regulate leukocyte migration during inflammatory responses, as well as homeostatic trafficking of lymphocytes and dendritic cells[4,5]. Chemokines are members of a complex superfamily of at least 50 low molecular weight (6–14 kDa) proteins; the importance of these in autoimmune diseases, neoplasia, and cardiovascular diseases has been reported[5]. Their primary structure is characterized by the presence of 4 conserved cysteine residues. Based on the positioning of the 2 NH2-terminal cysteines, the chemokine family can be structurally divided into CC chemokines, CXC chemokines, CX3C chemokines, and C chemokine. Chemokines activate leukocytes via G-protein-coupled receptors, which mediate most of their various biological activities[6].

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Accepted for publication October 13, 2006.

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Among recently discovered chemokines, the CCL18/CC chemokine pulmonary and activation-regulated chemokine (PARC) has been described[7]. CCL18/PARC is structurally most closely related to CCL3/MIP-1α, a well characterized proinflammatory chemokine attracting many leukocytic cell types through binding to at least 2 receptors, i.e., CCR1 and CCR5[6,8-10]. However, its receptors and a mouse equivalent for CCL18/PARC have not been identified yet.

In this study, DNA oligonucleotide microarray analysis was performed to search for differentially expressed genes in RA. Significantly increased levels of CCL18/PARC mRNA, as well as highly abundant protein levels, were found in RA cartilage and synovial tissue compared with OA samples. Little is known about the production levels and the biochemical heterogeneity of this natural protein; we assessed the role of CCL18/PARC in the pathology of RA.

MATERIALS AND METHODS

Patients. Cartilage tissue and synovial membrane samples were obtained from RA and OA patients undergoing total knee replacement (5 RA patients, 5 OA patients), and cartilage tissues from the femoral heads of patients with femoral neck fracture undergoing bipolar hip arthroplasty as controls (5 patients). All cartilage tissue and synovial membrane samples were obtained directly during the surgical procedure and immediately stored in liquid nitrogen. Moreover, we obtained serum samples from RA (n = 71) and OA patients (n = 12), healthy controls (n = 20), and patients with flu (n = 8), and synovial fluid (SF) from RA (n = 15) and OA patients (n = 6).

All samples were collected with the approval of the Ethics Board of the Tokyo Women's Medical University. All RA patients met the 1987 American College of Rheumatology classification criteria[11]. Diagnosis of OA was based on clinical and physical examination along with radiographic findings, typical symptoms, and serologic differences from RA. The patients with femoral neck fracture had no known history of joint disease. All RA patients were receiving treatment that included disease modifying antirheumatic and/or nonsteroidal antiinflammatory drugs, as well as steroids. However, patients treated with biological agents, such as tumor necrosis factor-α blocking agents, were excluded.

Semiquantitative polymerase chain reaction (PCR). Cartilage and synovial tissues were dissected, and total RNA was isolated with Isogen (Nippongene, Tokyo, Japan) and RNeasy Mini Kit (Qiagen KK, Tokyo, Japan). cDNA was synthesized from 1 μg of total RNA, using Superscript II RT (Invitrogen, Carlsbad, CA, USA) and random hexamers in a total volume of 20 μl, according to the instructions of the manufacturer. Primer sequences were designed using Primer Express 1.0 software (PE Applied Biosystems, Foster City, CA, USA) as follows; CCL18/PARC primer: sense primer, GCT CTG CTG CCT CGT CTA TAC C; antisense primer, GGG CTG GTT TCA GAA TAG TCA ACT; glyceraldehyde-3-phosphate dehydrogenase (G3PDH): sense primer, 5'-GGG AAG GTG AAG GTC GGA-3'; antisense primer, 5'-GCA GCC CTG GTG ACC AG-3'. In order to control amplification of genomic DNA, primers were placed within different exons close to an intron-exon boundary, with the probe spanning 2 neighboring exons where possible. Real-time PCR was performed using the ABI Prism 7900HT sequence detection system and SYBR-Green PCR Master Mix following the manufacturer's protocol (PE Applied Biosystems). Conditions for PCR were as follows: 10 min at 95°C, then 40 cycles each consisting of 15 s at 95°C and 1 min at 59°C. Values were calculated based on standard curves generated for each gene. Normalization of samples was determined by dividing copies of CCL18/PARC by copies of G3PDH.

Immunohistochemistry. For immunohistologic analysis of CCL18/PARC distribution, cartilage and synovial tissues from patients with RA and OA were fixed in 4% formaldehyde immediately after surgery and subsequently embedded in paraffin. Tissues were cut into sections 2–5 μm thick. Sections were dewaxed with xylol 3 times for 5 min and hydrated with decreasing concentrations of ethanol (100% for 5 min, 75% for 5 min, and finally distilled water for 5 min). Afterwards, the slides were treated with 3% H_2O_2 in phosphate buffered saline (PBS) to quench endogenous peroxidase. For demasking of CCL18/PARC, sections were subjected to three 5-min heating cycles in citrate buffer using a microwave oven at 560 W. Slides stained for prolyl-4-hydroxylase were covered with the same buffer and incubated 30 min in the microwave oven. Pretreatment for MC tryptase staining involved 5 min incubation with 0.1% pronase (Sigma, St. Louis, MO, USA) in PBS.

All sections were blocked in PBS and 5% goat serum albumin (blocking buffer) for 20 min, and staining was performed with the following primary antibodies at the given dilution in blocking buffer (1 h at room temperature): mouse polyclonal antibodies against CCL18/PARC (R&D Systems, Minneapolis, MN, USA). After 4 washes of 10 min each with PBS, secondary reagents were applied for 30 min at room temperature. Primary antibodies were detected in general using a biotinylated goat antimouse IgG (Biogenex, San Ramon, CA, USA). After extensive washing in PBS as above, sections were incubated with peroxidase-conjugated streptavidin for 30 min at room temperature. Antigen-antibody complexes were visualized by incubation with substrate solution containing 0.5 mg/ml 3-amino-9-ethylcarbazole (Sigma) and 3% H_2O_2 in 0.1 mol/l sodium acetate buffer, pH 5.2, for 5 min at room temperature. Then slides were rinsed in distilled water, counterstained with Mayer's hematoxylin (Merck, Darmstadt, Germany), and mounted in Aquatex (Merck).

Measurement of chemokines in serum and SF. Protein levels of CCL18/PARC in SF and serum of patients with RA and healthy controls were evaluated with the DuoSet ELISA (R&D Systems). The detection limit of the PARC ELISA was 0.01 ng/ml. The specificity of the chemokine ELISA was confirmed by the lack of cross-reactivity with other chemokines and other potentially cross-reactive agents used as inducers. All samples were diluted at least 1/100 and were analyzed in at least 3 independent PARC assays. In addition, all patient samples were analyzed in the same assay to exclude interassay variation. At the same time, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and matrix metalloproteinase-3 (MMP-3) levels were measured. ESR and CRP were measured by standard laboratory techniques. RF was detected by latex fixation test; MMP-3 was measured by ELISA[12].

Statistical analysis. Data were analyzed using StatView for Windows. For correlation analysis, we used the Spearman correlation coefficient. The Mann–Whitney U-test was used to compare variables of the various patient groups. P values < 0.05 were considered statistically significant.

RESULTS

CCL18/PARC mRNA expression in RA cartilage and synovial tissue. As illustrated in Figure 1A, CCL18/PARC mRNA was expressed at significantly higher levels in RA cartilage compared with OA and control cartilage ($p < 0.001$). OA cartilage tissue showed significantly higher expression of CCL18/PARC than in control samples ($p = 0.0085$). As illustrated in Figure 1B, CCL18/PARC mRNA expression was much higher in RA than in OA synovial membrane ($p = 0.0001$).

Distribution of CCL18/PARC in RA and OA tissues. We investigated cellular distribution of the CCL18/PARC protein by immunohistochemistry. All RA cartilage and synovial tissue samples exhibited medium to strong staining for CCL18/PARC (Figure 1C). CCL18/PARC was expressed in all the RA synovium samples with dense staining of the sublining cells. In OA synovial tissue samples, there was weak staining for CCL18/PARC protein within subintimal regions (Figure

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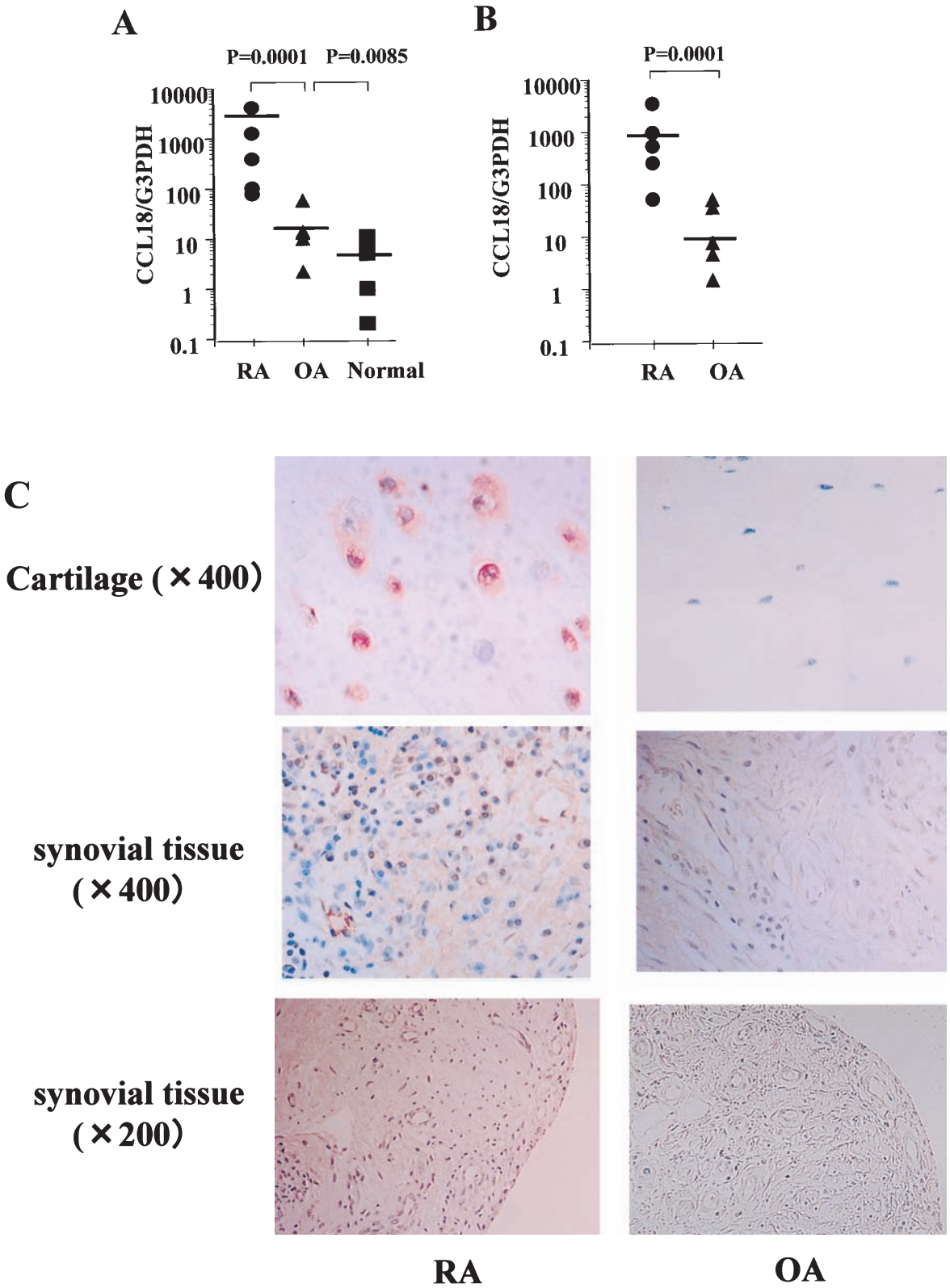

Figure 1. A. Comparative expression of genes for CCL18/PARC in RA, OA, and normal cartilage shows higher expression in RA ($p = 0.001$). Expression of each gene was normalized to the level of G3PDH mRNA. Horizontal bars show the means. B. Comparison of CCL18/PARC mRNA in RA and OA synovial tissue shows higher expression in RA tissue ($p = 0.001$). Expression of each gene was normalized to the level of G3PDH expression. Horizontal bars show the means. C. Immunohistologic analysis of distribution of CCL18/PARC in cartilage and synovial tissue from patients with RA and OA.

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1C). In contrast, signal for CCL18/PARC was undetectable in all OA and normal cartilage samples (Figure 1C).

PARC levels in RA serum. Local overexpression of CCL18/PARC in joints, cartilage, and synovial tissues may be detected in SF and serum from patients with RA. Accordingly, we analyzed the presence of CCL18/PARC in SF as well as serum from patients with RA and OA. In RA serum, significantly high levels of CCL18/PARC (156.21 ± 125.73 ng/ml, n = 71) were detectable, compared to samples from OA patients (64.54 ± 40.90 ng/ml, n = 12) and healthy controls (28.04 ± 10.96 ng/ml, n = 20; Figure 2A). On the other hand, in patients with influenza, in which systemic inflammation occurs and serum CRP was increased, serum levels of CCL18/PARC were as low as those in controls (27.54 ± 1.54 ng/ml, n = 8).

CCL18/PARC was measured in RA and OA SF. The average CCL18/PARC concentrations (275.20 ± 228.16 ng/ml, n = 15) were significantly higher in RA patients than in OA patients (33.13 ± 14.84 ng/ml, n = 6; Figure 2B).

Quantification of serum CCL18/PARC. We then analyzed the correlation between RF concentration and serum CCL18/PARC. As shown in Figure 2C, CCL18/PARC levels correlated significantly with RF levels (r = 0.431, p = 0.0040).

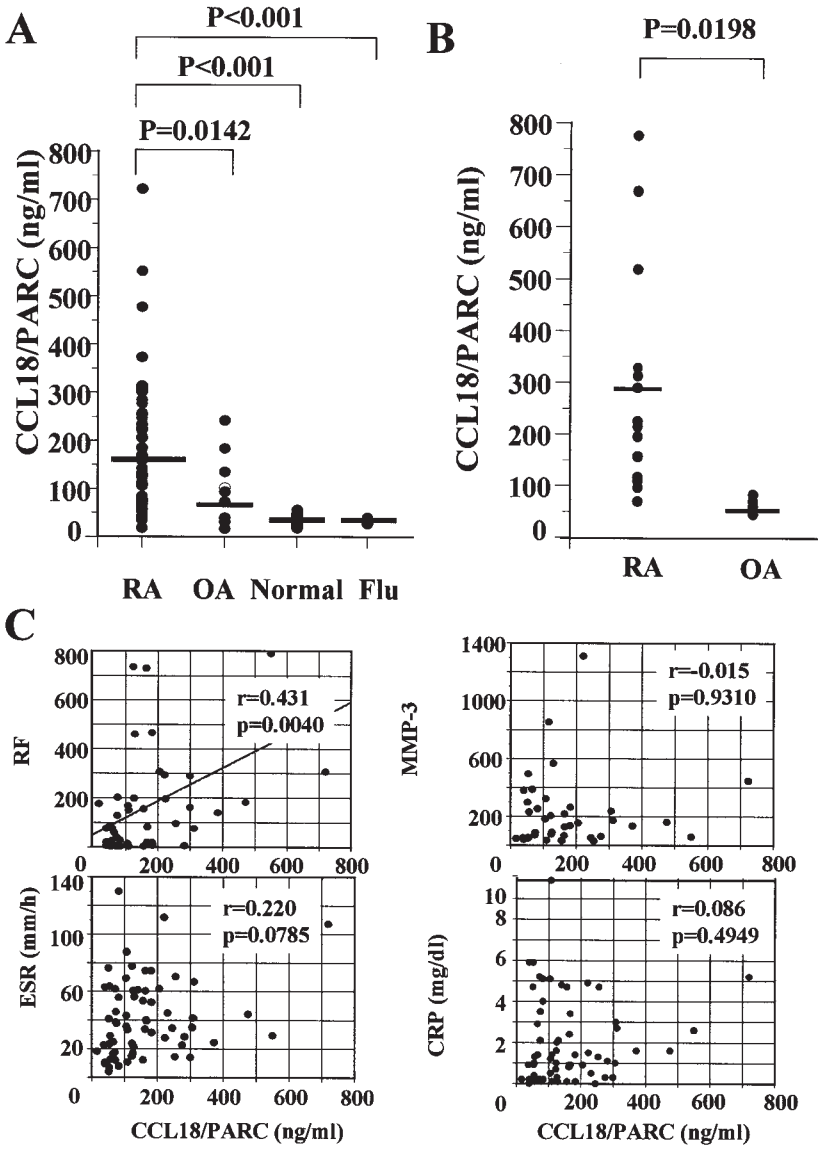

Figure 2. A. CCL18/PARC serum levels were measured by specific ELISA in 71 RA patients, 12 OA, 20 healthy controls, and 8 flu patients, as well as an age matched control group of patients from the same hospital. Horizontal bars indicate median CCL18/PARC concentration for each group. Significance for differences is indicated (Mann-Whitney test). B. CCL18/PARC levels were measured by specific ELISA in RA (n = 15) and OA (n = 6) synovial fluid. Horizontal bars indicate the median CCL18/PARC concentration for each group. Significance for differences is indicated (Mann-Whitney test). C. CCL18/PARC levels were correlated with RF (r = 0.431, p = 0.0040). ESR, CRP, and MMP-3 exhibited no significant correlation with CCL18/PARC levels (CCL18 vs ESR, r = 0.220, p = 0.0785; CCL18 vs CRP, r = 0.086, p = 0.4949; CCL18 vs MMP-3, r = –0.015, p = 0.9310).

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However, assessment of the relationship between MMP-3 and CCL18/PARC levels indicated no significant correlation ($r = -0.015$, $p = 0.9310$; Figure 2C). CCL18/PARC levels also showed no correlations with ESR and CRP levels (CCL18 vs ESR, $r = 0.220$, $p = 0.0785$; CCL18 vs CRP, $r = 0.086$, $p = 0.4949$; Figure 2C).

DISCUSSION

A role for chemokines and their receptors in cartilage degradation has recently been reported[13]. Human chondrocytes can produce CC and CXC chemokines and express chemokine receptors for both chemokine subfamilies. Human chondrocytes express a variety of chemokine receptors, including CCR1, CCR2, CCR3, CCR5, CXCR1, and CXCR2[1-3], which belong to the so-called inducible inflammatory receptors[14]. Interaction of these receptors with the corresponding ligands, which are also produced by chondrocytes themselves, induces the release of matrix-degrading enzymes and the enhancement of extracellular matrix catabolism[1-3]. These observations suggest that the autocrine/paracrine pathway of the chemokines within cartilage may be involved in the control of homeostatic turnover of extracellular matrix. However, since some chemokines and chemokine receptors appear to be overexpressed in RA and OA cartilage, compared with healthy cartilage, the catabolic activity of chondrocytes may become excessive, leading to damage of the cartilage structure.

In our study, levels of CCL18/PARC mRNA and protein were abundant in RA cartilage and synovial tissue compared with OA samples.

CCL18/PARC is either constitutively expressed or induced in monocytes/macrophages and dendritic cells; and chemoattracts T and B lymphocytes[8-10,15-17]. CCL18/PARC has a close structural similarity (64% identical amino acids) to the well characterized CC chemokine MIP-1α and shares its capacity to suppress proliferation of subsets of immature myeloid progenitor cells[18]. To date, CCL18/PARC expression has been reported in unrelated pathologies, such as atherosclerosis[19], hypersensitivity pneumonitis[20], allergic contact hypersensitivity[21], and ovarian carcinoma[22].

For arthritis, there have been 2 reports concerning CCL18/PARC[7,23]. Schutyser, *et al*[7] also reported that CCL18/PARC levels were enhanced 4-fold in RA SF samples compared to those in crystal-induced arthritis and OA; and immunochemistry revealed CD68+ monocytes/macrophages as the main CCL18/PARC-producing cell type in arthritic synovial tissue. Radstake, *et al*[23] assessed the expression of a panel of various chemokines by immature and mature dendritic cells and their regulation by Fc-γ receptor in RA patients and healthy controls. They found evidence for elevated CCL18 expression by RA dendritic cells, and that this expression was at least partly regulated by Fc-γ receptor triggering. They suggested a potential role for chemokines as well as CCL18/PARC-producing dendritic cells in the pathogenesis of RA[23].

We observed that gene expression of CCL18/PARC was significantly higher in RA cartilage than in OA and control cartilage ($p < 0.0001$). Further, there was significantly higher expression of CCL18/PARC in OA cartilage tissue than in control samples ($p = 0.0085$). To our knowledge, there has been no report concerning CCL18/PARC in articular cartilage to date. Further, we observed higher levels of CCL18/PARC mRNA in RA than in OA synovial tissue ($p = 0.0001$). Thus, there was significantly increased expression of CCL18/PARC mRNA not only in cartilage but also in synovial tissue from RA patients compared to OA patients.

We also observed abundant expression of CCL18/PARC in RA cartilage and synovial tissue at the protein level. We investigated cellular distribution of the CCL18/PARC protein. All RA cartilage and synovial tissue samples exhibited medium to strong CCL18/PARC immunostaining. There was weak staining for CCL18/PARC protein within the subintimal regions of OA synovial tissue. In contrast, signal for CCL18/PARC was undetectable in all OA and normal cartilage (data not shown).

Further, we found that serum CCL18/PARC levels were significantly elevated in RA samples compared to OA, control, and flu patient samples. To our knowledge, this is the first study to measure serum CCL18/PARC levels in RA. The CCL18/PARC levels in RA serum were 2.5-fold enhanced compared to OA samples, and 6-fold enhanced compared to influenza and control samples. The level of CCL18/PARC in RA SF was enhanced 8-fold compared to OA SF. Although CRP levels were high in influenza patients, the levels of CCL18/PARC were not elevated. Thus, the elevation of CCL18/PARC does not imply the presence of inflammation. These data indicate that CCL18/PARC may have some role in the pathogenesis of RA.

Next, we assessed correlations between RF, ESR, CRP, and MMP-3 levels and serum CCL18/PARC. Although we found no correlations between serum CCL18/PARC levels and serum ESR, CRP, and MMP-3 levels, there was significant correlation between serum CCL18/PARC levels and RF levels. One of the main questions in RA is whether CCL18/PARC reflects inflammation and/or structural deterioration of the joint, since CCL18/PARC is also secreted by cartilage and synovial tissues. Chemokines promote accumulation of leukocytes at the source of chemokine production in multiple ways; this can be part of a homeostatic process or an inflammatory reaction. Chemokines can be grouped as either constitutive or inflammatory/inducible chemokines, although some may have a dual role depending on how they are produced[5].

We have shown that CCL18/PARC concentrations are not related to conditions of generalized inflammation, but are related to the pathology of RA, as CCL18/PARC levels were correlated with RF levels. The role of RF in the diagnosis of RA has been well documented, but it has suboptimal sensitivity and specificity. Although patients with RF-positive RA generally have more severe disease than those with RF-negative RA, RF is not a reliable predictor of disease severity in

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individual patients. Therefore, we speculated that CCL18/PARC may have a role in the pathogenesis of RA, for example as a triggering factor of immunological dysfunctions such as recruitment of lymphocytes to synovium. Further studies are needed to evaluate the role of CCL18/PARC in the pathogenesis of RA.

In summary, augmented expression of CCL18/PARC was noted in the cartilage, synovial tissues, serum, and synovial fluid of RA patients. High expression of CCL18/PARC may have a relationship with the pathogenesis of RA. However, our data are cross-sectional and were obtained from a small group of patients; further prospective studies in larger populations are required. CCL18/PARC and its downstream signaling pathways could be considered as novel therapeutic targets in RA.

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