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Ⅴ．研究成果の刊行物・別冊
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Interleukin-18 induces serum amyloid A (SAA) protein production from rheumatoid synovial fibroblasts

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Abstract

Interleukin-18 (IL-18) is a novel proinflammatory cytokine that was recently found in synovial fluids and synovial tissues from patients with rheumatoid arthritis (RA). To investigate the role of IL-18 in rheumatoid synovitis, the levels of IL-18 and serum amyloid A (SAA) were measured in synovial fluids from 24 patients with rheumatoid arthritis (RA) and 13 patients with osteoarthritis (OA). The levels of IL-18 and SAA in the synovial fluids were elevated in RA patients. In contrast, the levels of IL-18 in synovial fluids from OA patients were significantly lower compared to those of RA patients. SAA was not detected in synovial fluids from OA patients. The expression of *SAA* mRNA in rheumatoid synovial cells was also examined. *SAA4* mRNA, which was constitutively expressed by rheumatoid synovial cells, was not affected by IL-18 stimulation. Although acute phase SAA (A-SAA, *SAA1+2*) mRNA was not detected in unstimulated synovial cells, its expression was induced by IL-18 stimulation. By immunoblot, we demonstrated that IL-18 induced the SAA protein synthesis from rheumatoid synovial cells in a dose-dependent manner. These results indicate a novel role for IL-18 in rheumatoid inflammation through the synovial SAA production.

Keywords: Amyloidosis; Interleukin-18; Rheumatoid arthritis; Serum amyloid A; Synovial cells

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Introduction

The serum amyloid A (SAA) isoforms protein are precursors of amyloid A (AA) protein, a major component of the fibrous deposits in amyloidosis associated with chronic inflammatory diseases such as rheumatoid arthritis (Steel and Whitehead, 1994). SAA is an acute phase reactant synthesized by the liver in response to inflammatory cytokines and secreted in the plasma (Uhlar and Whitehead, 1999). SAA protein gene family consists of 4 members, which are divided into two classes, acute phase and constitutive SAA (Sipe, 1999). Although acute phase SAA encoded by the two genes, *SAA1* and *SAA2*, is induced by inflammatory stimuli up to 1000-fold, the constitutive *SAA4* is only inducible to a small degree (Steel et al., 1993). There is a evidence suggesting that the human *SAA3* is a pseudogene (Sellar and Whitehead, 1994). Like other acute phase proteins, SAA is synthesized in the liver, however, extrahepatic A-SAA synthesis has been confirmed, for example, in vascular smooth muscle cells and synovial cells (Meek et al., 1994; Kumon et al., 1999). Furthermore, multiple functions such as chemotaxis and collagenase induction have been assigned to SAA (Xu et al., 1995; Brinckerhoff et al., 1989). IL-18, a member of the IL-1 cytokine family, is also highly expressed in the RA synovium and is implicated in the pathogenesis of RA as a proinflammatory cytokine (Gracie et al., 1999). The present study was undertaken to assess whether IL-18 is associated with the synovial inflammation of RA. We examined the concentrations of IL-18 and SAA in synovial fluids from RA patients as well as in vitro effects of IL-18 on rheumatoid synovial cells.

Material and Methods

Patients

Patients who presented to Nagasaki University Arthritis Clinics were included in the study. Synovial fluids were obtained from 24 patients with RA diagnosed according to the 1987 revised criteria American Rheumatism Association and 13 patients with osteoarthritis (OA). Synovial fluids were removed for therapeutic purpose. The synovial fluids obtained from the study subjects were collected and stored at −20 °C.

Reagents

Recombinant human IL-18 was purchased MBL (Nagoya, Japan). The endotoxin levels were less than 0.1 ng per 1 μg of recombinant human IL-18. Human anti-SAA polyclonal antibodies were kindly provided by Dr N. Kubota (Eiken Chemicals Ltd, Tochigi, Japan)

IL-18 and SAA measurements

IL-18 and SAA were measured using specific enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The IL-18 ELISA kit was purchased from MBL and the SAA ELISA kit was purchased from Eiken Chemicals (Tochigi, Japan). The detection limits of the assay were as follows: 12.5 pg/ml for IL-18, 1 μg/ml for SAA.

Isolation of synovial cells

The experimental protocol was approved by the local ethics committee, and a signed informed consent was obtained from each participant prior to commencement of the study. Synovial tissue samples were obtained from patients with RA and OA during synovectomy. Synovial membranes were minced aseptically and then dissociated enzymatically with collagenase (4.0 mg/ml, Sigma) in RPMI 1640 for 4 hr at 37 °C. The obtained cells were plated on culture dishes and allowed to adhere. In order to eliminate non-adherent cells from synovial cells, the plated cells were cultured for 18 hr with RPMI 1640 supplemented with 10% fetal bovine serum (FBS) at 37 °C in humidified 5% CO_2 in air. The cells were then washed thoroughly with phosphate-buffered saline (PBS) solution. Adherent synovial cells were removed by adding trypsin-EDTA followed by washing the cells with PBS containing 2% FBS. The collected synovial cells were used at the third or fourth passages for subsequent experiments. Synovial cell preparations (fibroblast-like synovial cells) were less than 1% reactive with monoclonal antibodies CD3, CD20, and CD68 (Coulter Immunology, FL) and anti-human von Willebrand factor (Immunotech, Marseilles, France), indicating that these preparations were almost free of mature T lymphocytes, B lymphocytes, monocytes / macrophages, and vascular endothelial cells. Isolated synovial cells were cultured with RPMI 1640 media containing 10% FCS. For the experiment, medium was discarded and the cells were incubated with serum-free RPMI 1640 containing IL-18 (MBL).

RNA preparation and RT-PCR assay

RT-PCR analysis for SAA mRNA expression was performed according to the method of Kumon et al. (1999). Total cellular RNA was extracted from synovial fibroblasts using guanidium thiocyanate and phenol (RNAzol B, Cinna/Biotek Labs Int. Inc., Friendswood, TX). First-strand cDNA was synthesized by reverse transcription at 45 °C for 45 min in a 50 μl reaction mixture containing 1 μg of total RNA and MuLV reverse transcriptase (Gibco BRL, Gaithersburg, MD). After denaturing at 99 °C for 5 min followed by cooling at 5 °C, the cDNA was amplified using PCR. Two microliters of denatured cDNA was amplified a 20 μl final volume containing 1 U Taq DNA polymerase (Gibco, BRL), 1 μM of each primer, Taq polymerase buffer, 1.5 mM $MgCl_2$, and 1.5 mM of each dNTP. PCR was performed in a thermal cycler (Perkin Elmer Cetus, Foster City, CA) using a program of 31 cycles of 95 °C for 1 min, 51 °C for 1 min, and 72 °C for 1 min with a final 10 min extension at 72 °C. The amplified products were subjected to electrophoresis on 2% agarose gel.

The following specific primers were used for SAA1 + 2 (Kumon et al., 1999):

5′-CGAAGCTTCTTTTCGTTCCTT-3′ (forward), 5′-CAGGCCAGCAGGTCGGAAGTG-3′ (reverse). Predicted size of the fragment is 300 bp.

For SAA4: 5′-TTTCAAGGAGGCTCTCCAAG-3′ (forward), 5′-CCATTCCTCAGCTTTCTCGT-3′ (reverse), Predicted size of the fragment is 276 bp.

For IL-18Rα(Tanaka et al., 2001); 5′-CCCAACGATAAGAAGGAACGC-3′ (forward), 5′-TGTC-TGTGCCTCCCGTGCTGGC-3′(reverse), Predicted size of the fragment is 419 bp.

For IL-18Rβ (Tanaka et al., 2001); 5′-AACACAACCCAGTCCGTC-3′(forward), 5′-AACATCAG-GAAATAGGCTGAG-3′(reverse), Predicted size of the fragment is 291 bp.

For β-actin; 5′-GACGAGGCCCAGAGCAAGAGAG-3′ (forward), 5′-ACGTACATGGCTGGGG-TGTTG-3′(reverse), Predicted size of the fragment is 284 bp.

Immunoprecipitation and immunoblot analysis

Synovial cell-conditioned media were centrifuged at 800 g for 5 min and supernatants (0.5 ml) were pre-cleared with protein-A-Sepharose 4B (50 μl, Pharmacia, Uppsala, Sweden) for 30 min and centrifuged at 6000 g for 5 min. The pre-cleared supernatants were incubated with 5 μl of anti-SAA antibodies for 1 hr. Collection of immunocomplex was performed using protein-A Sepharose 4B (Pharmacia) for 30 min. Laemmli sample buffer (2%SDS 10% glycerol 100 mM DTT 60 mM Tris[PH6.8]) was added and boiled for 10 min. Supernatants were loaded on 14% polyacrylamide gels. The fractionated proteins were transferred to nitrocellulose membrane (pore-size: 0.2 μ, Bio-Rad, Hercules, CA) and incubated with anti-SAA antibodies (1:2000 dilution) for two hours at room temperature. The filter was rinsed and incubated with donkey anti-rabbit IgG conjugated with horseradish peroxidase (Amersham, Arlington Heights, IL) and developed using an enhanced chem-iluminesence (ECL) system (Amersham). The blots were exposed to films.

Statistical analysis

Samples with values below the detection limit for the assay were regarded as negative and assigned a value 0. The data are expressed as the mean ± standard deviations (SD) of the number patients indicated. The statistical significance of differences between 2 groups was deter-

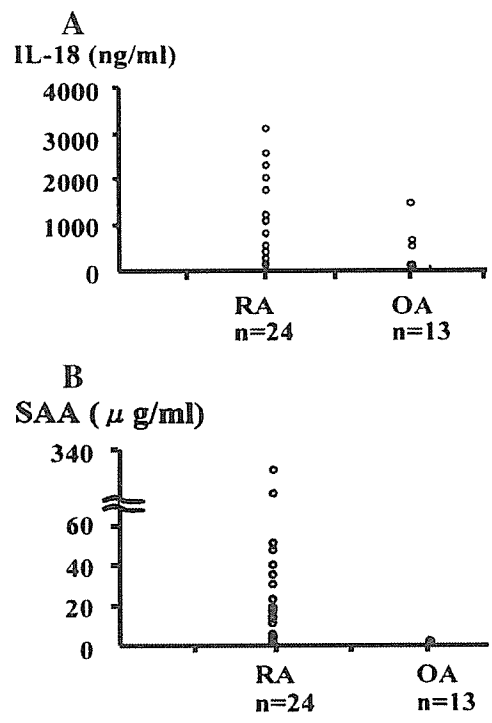

Fig. 1. Concentrations of IL-18 (A) and SAA (B) in the synovial fluid of rheumatoid arthritis (RA) and osteoarthritis (OA) patients, measured in triplicate by enzyme-linked immunosorbent assay. n = numbers of samples tested.

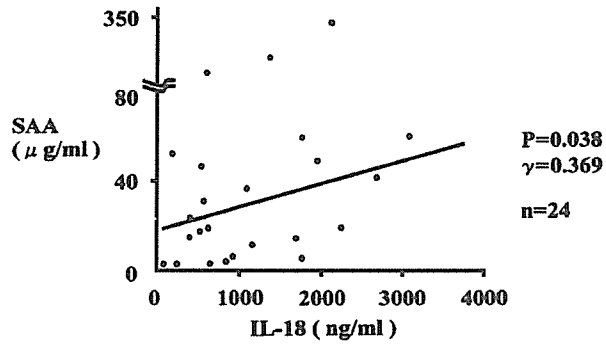

Fig. 2. Correlation between IL-18 and SAA levels in the synovial fluids of RA patients The correlation coefficient was analyzed by Peason's correlation coefficient test.

mined by Student's t-test. The correlation coefficient was obtained by Peason's correlation coefficient test.

Results

Increased IL-18 and SAA levels in the synovial fluids of RA patients

Concentrations of IL-18 in synovial fluid samples from RA and OA patients were measured by specific ELISA. As shown in Fig. 1A, the levels of IL-18 in the synovial fluids from RA patients (mean ± SD 1171.8 ± 879.5 ng/ml) were significantly higher ($p < 0.001$) than those of OA patients (mean ± SD 37.9 ± 126.6 ng/ml). We also measured the SAA concentrations of synovial fluids by means of specific ELISA using same samples. As shown in Fig. 1B, synovial SAA levels of RA patients were markedly elevated (mean ± SD 44.6 ± 68.1 μg/ml). These measurements of SAA in rheumatoid synovial fluids were similar to previous studies (Sukenik et al., 1998). On contrast, those of OA patients were below the detection limits (<2.5 μg/ml).

To investigate the relevance of IL-18 and SAA, concentrations of IL-18 were compared with those of SAA. The results suggested a possible correlation between these two values (Fig. 2). Therefore, SAA overproduction in the synovium appears to be linked to the IL-18 elevation observed in RA patients.

Fig. 3. Expression of IL-18 receptor (IL-18Rα and IL-18Rβ) mRNA in rheumatoid synovial cells. Total RNA was extracted from rheumatoid synovial cells isolated from 2 patients with RA (RA1, RAA2) and IL-18Rα and IL-18Rβ mRNA was detected by TR-PCR. Rheumatoid synovial cells constitutively expressed IL-18R mRNA.

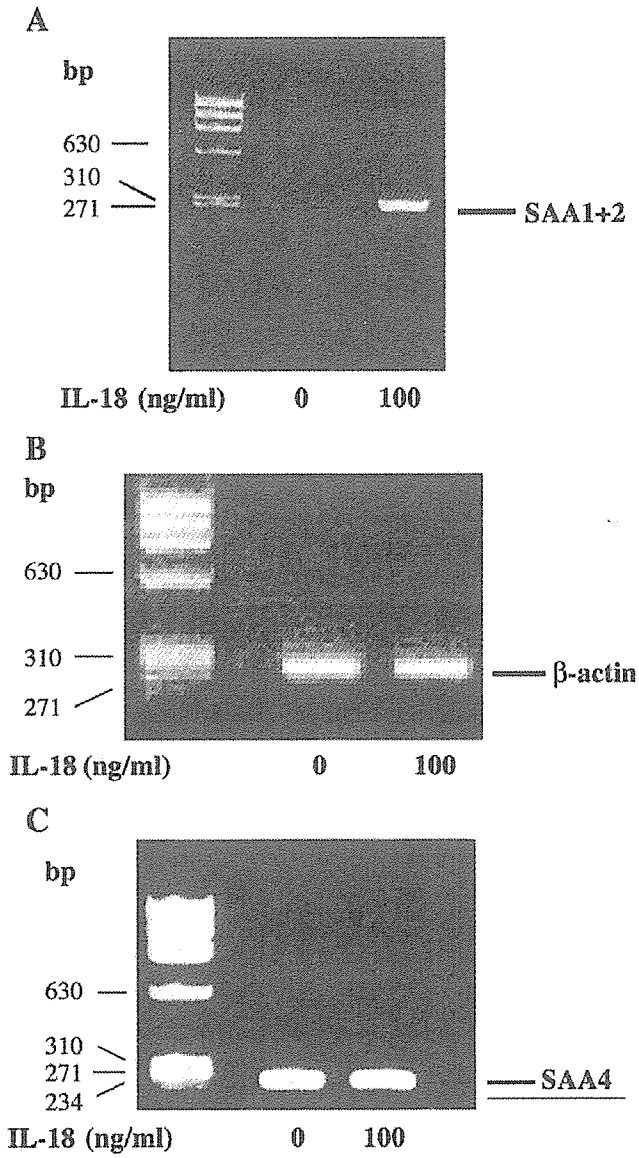

Fig. 4. **A**. A-SAA mRNA expression of IL-18-treated synovial cells. Rheumatoid synovial cells cultured with or without 100 ng/ml of IL-18 for 6 hr. Total RNA was extracted and amplified by RT-PCR using gene-specific primers. SAA1 + 2 mRNA was induced in IL-18-treated synovial cells. **B**. β-actin mRNA expression of IL-18treated synovial cells. Rheumatoid synovial cells incubated with or without 100 ng/ml of IL-18 for 6 hr. Total RNA was extracted and amplified by RT-PCR using gene-specific primers. **C**. C-SAA mRNA expression of IL-18treated synovial cells. Rheumatoid synovial cells incubated with or without 100 ng/ml of IL-18 for 6 hr. Total RNA was extracted and amplified by RT-PCR using gene-specific primers. The density *SAA4* mRNA bands were not different between control and IL-18-treated synovial cells. (control: 1.0 IL-18 treatment :0.93. The density of *SAA4* mRNA band was measured by densitometer. The density of *SAA4* mRNA band of untreated cells was assigned the value of 1.0 and that of IL-18-treated cells was calculated as relative units).

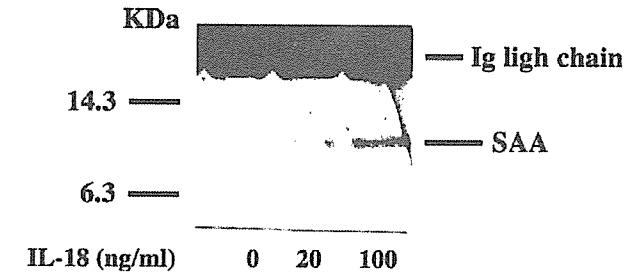

Fig. 5. SAA protein synthesis by IL-18-treated synovial cells. Rheumatoid synovial cells were cultured with IL-18 for 24 hr. The culture supernatants were removed and immunoprecipitated using ant-SAA antibodies. The immunoprecipitants were analyzed by anti-SAA immunoblot. Ig light chain indicated the light chain of immunoglubulin G that was used for immunoprecipitation.

SAA mRNA induction in IL-18-stimulated synovial cells

In order to investigate the relationship between IL-18 and SAA in rheumatoid synovium, we decided to analyze the acute phase SAA (A-SAA) mRNA expression in rheumatoid synovial cells. First, we checked the expression of IL-18 receptor in rheumatoid synovial cells. As shown in Fig. 3, IL-18Rα and IL-18Rβ mRNA were detected in rheumatoid synovial cells. SAA1 and SAA2 isoforms (A-SAA) have been identified as an acute phase reactant, and shown to be induced by proinflammatory cytokines. Next, we analyzed the *SAA1+2* mRNA expression in rheumatoid synovial cells by means of RT-PCR. As shown in Fig. 4A, *SAA1+2* mRNA was induced in IL-18-stimulated synovial cells not in unstimulated synovial cells. *SAA1+2* mRNA induction was confirmed after 6 hours of IL-18 stimulation and sustained for 24 hours (data not shown). In contrast, β-actin mRNA expression was not modulated with or without IL-18 stimulation (Fig. 4B). Constitutive-SAA (C-SAA, *SAA4*) mRNA was expressed in RA synovial cells, and were not changed by IL-18 stimulation (Fig. 4C).

SAA protein synthesis in IL-18-treated RA synovial cells

In order to further substantiate the results obtained by RT-PCR, we investigated the effects of IL-18 on de novo synthesis of SAA. We performed the immunoprecipitation of the supernatants of IL-18 treated synovial cells. RA synovial cells-conditioned media (0.5 ml) were immunoprecipitated using anti-SAA antibodies. The immunoprecipitants were fractionated by 14% polyacrylamide gels and analyzed by anti-SAA immunoblot. An immunoblot analysis of a sample of the SAA immunoprecipitates from IL-18-stimulated synovial cell-conditioned media showed an induced SAA band at 12 Kda (Fig. 5).

Discussion

IL-18 is a member of IL-1 cytokine family that was originally identified as an IFN-γ inducing factor (Akira, 2000). Similar to IL-12, IL-18 stimulates Th1 differentiation and enhances natural killer cell cytotoxicity (Dinarello, 1999). It was demonstrated that RA synovial tissues showed increased expression of IL-18 mRNA expression and increased IL-18 protein synthesis as well as IL-18 receptor

expression (Gracie et al., 1999). In the present study, we investigated the role of IL-18 in rheumatoid synovitis. We demonstrated that the proinflammatory cytokine IL-18 and SAA are markedly elevated in the synovial fluids of RA patients but not in those of OA. Furthermore, we examined the effects of IL-18 on A-SAA mRNA in rheumatoid synovial cells and demonstrated that A-SAA mRNA induction and SAA protein synthesis was confirmed in IL-18-treated RA synovial cells.

Although the major site of SAA production during inflammation is the liver, SAA is produced by vascular smooth muscle cells, and synovial cells (Meek et al., 1994; Kumon et al., 1999) . Recent reports suggest a new role of SAA in the development of inflammation. SAA can induce chemotaxis of neutrophils and matrix metalloproteinases (MMPs) induction, a key process involved in tissue destruction that occurs in rheumatoid cartilage (Xu et al., 1995; Brinckerhoff et al., 1989). We previously reported that SAA can induce matrix metalloproteinases, an important proteinase for rheumatoid joint destruction, from synovial cells (Migita et al., 1998). These evidences indicate that IL-18-mediated SAA synthesis could be implicated in chronic inflammatory diseases. IL-18-mediated SAA synthesis in rheumatoid synovium could be involved in the synovial inflammations through the synthesis of cartilage-degrading matrix metalloproteinases. More recently, Maury et al. (Maury et al., 2000) measured the circulating levels of IL-18 in patients having RA with or without amyloidosis and they showed the levels of IL-18 were significantly higher in patients with amyloidosis than in those without amyloidosis. Taken together, our data may suggest that IL-18 may be involved in amyloidogenesis through the perpetuation of rheumatoid synovitis as well as the production of amyloid precursor protein, SAA during inflammatory process.

In conclusion, we demonstrated for the first time the association between IL-18 and SAA in rheumatoid synovial fluids. Furthermore, IL-18 induced SAA synthesis from RA synovial cells. These data support the concept of IL-18 as an inducer of proinflammatory SAA and suggest a possible role of IL-18 in amyloidogenesis.

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