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Allograft inflammatory factor-1 stimulates chemokine production and induces chemotaxis in human peripheral blood mononuclear cells

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ABSTRACT

Allograft inflammatory factor-1 (AIF-1) is expressed by macrophages, fibroblasts, endothelial cells and smooth muscle cells in immune-inflammatory disorders such as systemic sclerosis, rheumatoid arthritis and several vasculopathies. However, its molecular function is not fully understood. In this study, we examined gene expression profiles and induction of chemokines in monocytes treated with recombinant human AIF (rhAIF-1). Using the high-density oligonucleotide microarray technique, we compared mRNA expression profiles of rhAIF-1-stimulated $CD14^+$ peripheral blood mononuclear cells ($CD14^+$ PBMCs) derived from healthy volunteers. We demonstrated upregulation of genes for several CC chemokines such as CCL1, CCL2, CCL3, CCL7, and CCL20. Next, using ELISAs, we confirmed that rhAIF-1 promoted the secretion of CCL3/MIP-1α and IL-6 by $CD14^+$ PBMCs, whereas only small amounts of CCL1, CCL2/MCP-1, CCL7/MCP-3 and CCL20/MIP-3α were secreted. Conditioned media from rhAIF-1stimulated $CD14^+$ PBMCs resulted in migration of PBMCs. These findings suggest that AIF-1, which induced chemokines and enhanced chemotaxis of monocytes, may represent a molecular target for the therapy of immune-inflammatory disorders.

1. Introduction

Allograft inflammatory factor-1 (AIF-1) is a cytokine that was originally identified and cloned from rat heart allogeneic grafts undergoing chronic transplant rejection [1]. AIF-1 is a 17 kDa, interferon γ-inducible, Ca^{2+}-binding EF-hand protein that is encoded within the major histocompatibility complex (MHC) class III genomic region [1–3]. AIF-1 is thought to be involved in the regulation of cell cycle progression and cellular activation status [4].

Previously, it was reported that AIF-1 was highly upregulated in various autoimmune diseases and inflammatory disorders such as psoriasis, lichen planus, and systemic sclerosis. The main cell types expressing AIF-1 in these affected skins are macrophages and Langerhans cells [5,6].

We recently showed that mice expressed AIF in infiltrating mononuclear cells and fibroblasts in thickened skin of scleroderma-tous graft-vs.-host disease (GVHD) and in synovial tissues in rheumatoid arthritis (RA). Recombinant human AIF-1 (rhAIF-1) induced the proliferation of cultured synovial cells and the migration and proliferation of dermal fibroblasts [7]. Moreover, in patients with RA, rhAIF-1 increased IL-6 production by synovial fibroblasts and peripheral blood monocytes (PBMCs) and by dermal fibroblasts [8]. In addition, AIF-1 plays a role in the activation of macrophages, T-lymphocytes and vascular smooth muscle cells (VSMCs), and endothelial cells that participate in atherogenesis and the vascular response to injury [4,9,10].

Chemokines are small, chemoattractant cytokines that play key roles in the accumulation of inflammatory cells at the site of inflammation. Therefore, chemokines and chemokine receptors are considered to be therapeutic targets in several chronic inflammatory disorders such as RA [11]. The relationship between AIF-1 and chemokines is not clear. Recently, microarray techniques have become available that allow characterization of the mRNA

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expression pattern of a large number of genes. In this study, using the GeneChip system for comprehensive analysis, we identified the specific gene expression profiles of $CD14^+$ peripheral blood mononuclear cells ($CD14^+$ PBMCs) stimulated by rhAIF-1. Then, we examined cytokine production by ELISAs and their functions by using cell migration assay.

2. Materials and methods

2.1. Preparation of recombinant human AIF-1 (rhAIF-1)

Human *AIF1* cDNA was amplified from human peripheral blood lymphocyte cDNA (BD Bioscience Clontech, Palo Alto, CA) using PCR. The forward and reverse primers were 5′-GTG GAT CCA TGA GCC AAA CCA GGG ATT T-3′ (containing a BamHI site) and 5′-CAC TCG AGT CAG ATA GGG CTT TCT TGG CT-3′ (containing a XhoI site). The DNA fragment obtained was inserted in the BamHI/XhoI sites of pGEX-4 (Amersham Biosciences, Piscataway, NJ) in frame. To express AIF-1 as a glutathione *S*-transferase fusion protein, the protein was purified with a glutathione-*S*-transferase purification system (Amersham Biosciences) and affinity chromatography with anti-rhAIF-$1_{113–129}$ antibody.

To investigate the effect of AIF-1 on chemotaxis and cytokine induction, rhAIF-1 was treated with Detoxi-Gel Endotoxin Removing Gel (Pierce, Rockford, IL, USA). Endotoxin detection was performed using *Limulus* amoebocyte lysate analysis (Wako Pure Chemical, Osaka, Japan) and treated AIF protein was confirmed to contain less than 0.1 ng/μg of endotoxin.

2.2. Preparation of anti-human AIF-1_{53-71} and AIF-$1_{113-129}$ antibodies

Two synthetic peptides that corresponded to residues 53–71 and 113–129 of human AIF-1 (AIF-$1_{53–71}$ and AIF-$1_{113–129,}$ respectively) as deduced from the nucleotide sequence of the human *AIF1* gene, were obtained with an additional cysteine residue at the N-terminus (Biologica, Nagoya, Japan). Following purification by reverse phase high-performance liquid chromatography, the synthetic peptide (purity > 90%) was coupled to keyhole limpet hemocyanin with *N*-(ε-maleimidocaproyloxy) succinimide (Sigma–Aldrich). The carrier-conjugated peptide was then emulsified with Freund's complete adjuvant (Difco Laboratories, Detroit, MI) and injected subcutaneously (0.5 mg/injection) into rabbits. The rabbits were immunized six times at ten day intervals. Blood samples were collected ten days after the last injection and the specific antibody in the sera was purified using an AIF-1 peptide-coupled cyanogen bromide-activated Sepharose affinity column. The antibodies reacted with proteins from abdominal adipose tissue and PBMCs that were identical in molecular size of purified recombinant human AIF-1.

2.3. Isolation and stimulation of $CD14^+$ PBMCs

PBMCs were isolated from healthy volunteers ($n = 5$; age: 34 ± 2) using Ficoll–Paque density gradients (GE Healthcare Bio-Sciences, Sweden). Human monocytes were purified from the cells using the MACS (Miltenyi Biotec, Germany) system, a direct magnetic labeling technique using anti-human CD14 microbeads (Miltenyi Biotec, Germany), according to the manufacturer's protocol (Daiichi Pure Chemicals Japan).

All subjects in this study provided written informed consent to participate. The study was approved by the Ethical Committee of Kyoto Prefectural University of Medicine (Kyoto, Japan).

2.4. Preparation of biotin-labeled complementary RNA (cRNA) and hybridization to microarrays

$CD14^+$ PBMCs were seeded in 92-mm dishes at a concentration of 2×10^5 cells/mL/dish in a volume of 10 mL of serum-free RPMI1640, then incubated with PBS or rhAIF-1 (100 ng/mL). After incubation at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h, total RNA was extracted using a Qiagen RNeasy kit (Qiagen, Valencia, CA, USA). Preparation of cRNA and target hybridization was performed according to the Affymetrix GeneChip® technical protocol (Affymetrix, Santa Clara, CA, USA). Briefly, double-stranded cDNA was prepared from 1 μg of total RNA using Life Technologies Superscript Choice system (Life Technologies, Inc., Gaithersburg, MD, USA) and an oligo-(dT) 24 anchored T7 primer. Biotinylated RNA was synthesized from the double-stranded cDNA by in vitro transcription using 3′-Amplification Reagents for IVT Labeling (Affymetrix kit). Transcription products were purified using a Qiagen RNeasy column (Qiagen). After biotinylation, the in vitro transcription products were fragmented for 35 min at 94 °C in a buffer composed of 200 mmol/L Tris acetate (pH 8.1), 500 mmol/L potassium acetate and 150 mmol/L magnesium acetate. Human Genome® U133 plus 2.0 (Affymetrix, Santa Clara, CA, USA) was hybridized with the biotinylated products (0.05 μg/μL per chip) for 16 h at 45 °C using the manufacturer's hybridization buffer. After washing the arrays, the hybridized RNA was detected by staining with streptavidin–phycoerythrin SSPE, 0.01% Tween-20, pH 7.6, 2 mg/mL acetylated BSA and 10 mg/mL streptavidin–phycoerythrin (Molecular Probes, Carlsbad, CA, USA). Microarrays were scanned using a specially designed confocal scanner (GeneChip® Scanner 7G; Affymetrix).

2.5. Induction of IL-6, CCL1, CCL2/MCP-1, CCL3/MIP-1a, CCL7/MCP-3, and CCL20 /MIP-3a, and production by $CD14^+$ PBMCs by rhAIF-1

$CD14^+$ PBMCs from healthy volunteers ($n = 5$) were incubated with serum-free RPMI-1640 medium (Nissui Pharmaceutical) containing zero, one, ten, or 100 ng/mL of rhAIF-1 or 10 ng/mL of LPS from *Escherichia coli* (Sigma–Aldrich, MO, USA). After incubation at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h, the culture supernatants were recovered and stored at −80 °C until assay. IL-6, CCL1, CCL2/MCP-1, CCL3/MIP-1α, CCL7/MCP-3 and CCL20/MIP-3α concentrations were measured using commercial ELISA kits (IL-6 and CCL2/MCP-1: eBioscience CA USA) (CCL1: Antigenix America Inc., NY, USA) (CCL3/MIP-1a, CCL7/MCP-3, and CCL20/MIP-3α: R&D systems, MN, USA) according to the manufacturer's instructions. The absorbance was measured with a microplate reader (MPRA4, TOSHO, Tokyo, Japan).

3. Cell migration assays

We prepared culture supernatants of $CD14^+$ PBMCs (1×10^6/mL, $n = 6$) that had been incubated with serum-free RPMI-1640 medium (Nissui Pharmaceutical) with or without of 1, 10, or 100 ng/mL rhAIF-1. After incubation at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 12 h, the culture supernatants were harvested, stored at −80 °C, and used as lower chamber liquids. Then, we examined human PBMC migration induced by the culture supernatants using cell culture inserts and (Control Cell Culture Inserts in two 24-well plates, pore size 3.0 μm, BD Bioscience, USA). Human PBMC suspensions (5×10^6 cells/mL) were placed in the upper chamber ($n = 6$). Culture supernatants (400 μL) were added to lower chambers filled with the culture supernatants as mentioned above or CCL3/MIP-1α (50 ng/mL) in serum-free RPMI-1640 medium. The chambers were placed in a 37 °C humidified atmosphere of 5% CO_2 in air for 90 min. Migratory PBMCs

extended protrusions towards chemoattractants and ultimately passed through the pores of the polycarbonate membrane. We assessed chemotactic response both by counting the number of migratory PBMCs under the optical microscope and by Chemotactic Index which was calculated by dividing the number of migrated cells in each chamber by that in the chamber added CCL3/MIP-1α (50 ng/mL).

3.1. Statistical analysis

Array data analysis was carried out using Affymetrix GeneChip Operating Software (GCOS) version 1.4. GCOS analyzed image data and computed an intensity value for each probe cell. Briefly, mismatched probes acted as specificity controls that allowed the direct subtraction of both background and cross-hybridization signals. To quantitatively determine RNA abundance, the average difference values (i.e., gene expression levels) representing the perfect match–mismatch for each gene-specific probe family was calculated and the fold-changes in average difference values were determined according to Affymetrix algorithms and procedures. Hierarchical clustering analysis of the gene expression profiles of 118 genes was performed using GeneSpring software 7.3.1 (Agilent Technologies, Inc., Santa Clara, CA, USA). The differences were analyzed by Wilcoxon signed-rank test in ELISA and by Mann–Whitney U and Kruskal–Wallis tests in Cell migration assay.

4. Results

4.1. Upregulated genes following stimulation of CD14$^+$ PBMC by rhAIF-1

We compared mRNA expression profiles of monocytes with and without rhAIF-1 stimulation, using CD14$^+$ PBMCs derived from five healthy volunteers. We used the Human Genome U133 plus 2.0 array (Affymetrix), which contained about 55,000 probes. Comparison of the gene expression levels from vehicle- and rhAIF-1-treated CD14$^+$ PBMCs enabled the identification of 10^5 genes demonstrating greater than twofold alterations after AIF-1 stimulation. Using hierarchical clustering analysis of the gene expression profiles, we narrowed the expression of genes to 56 gene probe sets in terms of "inflammatory diseases". That probe set contained several chemokines. They included major CC chemokine genes such as *CCL1*, *CCL2/MCP-1*, *CCL3/MIP-1α*, *CCL7/MCP-3* and *CCL20/MIP-3α*. Among them, *CCL2/MCP-1*, *CCL7/MCP-3* and *CCL20/MIP-3α* genes were strongly upregulated after rhAIF-1 stimulation (Fig. 1).

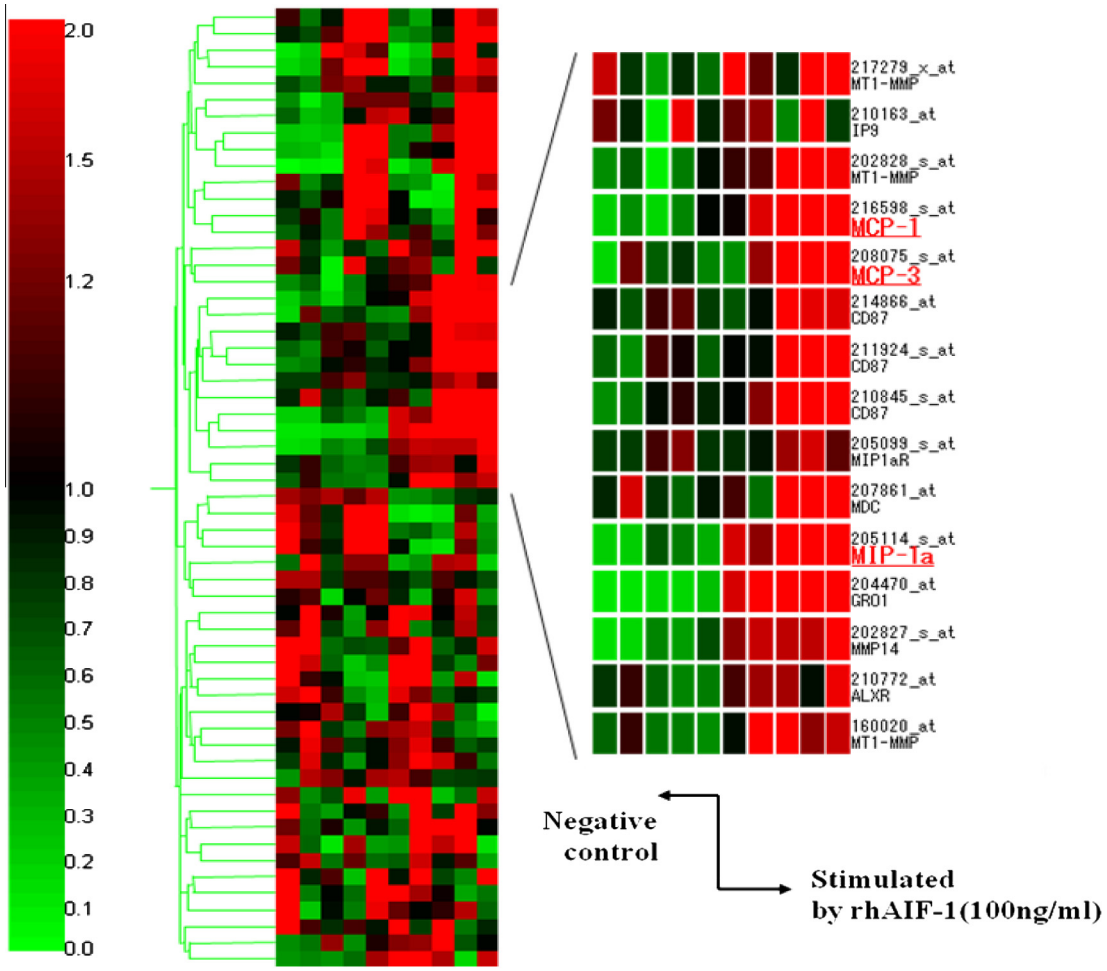

Fig. 1. Gene cluster analysis of peripheral blood CD14$^+$ mononuclear cells with and without rhAIF-1 stimulation. Starting with CD14$^+$ PBMCs stimulated by rhAIF-1 (100 ng/mL), we used hierarchical clustering analysis of the gene expression profiles of approximately 10,000 genes. We identified the expression of 58 genes associated with "proinflammatory cytokines" (at left). The data were analyzed by applying a hierarchical-tree algorithm to the normalized intensities. Upregulated genes are indicated by red shades and repressed genes by green. For one example, we picked up a region where gene expression was increased strongly after rhAIF-1 stimulation (at right). Among them, genes for CC chemokines such as CCL2/MCP-1, CCL3/MIP-1α and CCL7/MCP-3 were included in the region.

4.2. IL-6 and chemokine secretion from CD14$^+$ PBMCs after rhAIF-1 stimulation

From the results of the mRNA expression profiles of CD14$^+$ PBMCs stimulated by rhAIF-1 ($n = 5$), we examined the expression of IL-6, CCL1, CCL2/MCP-1, CCL3/MIP-1α, CCL7/MCP-3 and CCL20/MIP-3α proteins following rhAIF-1-stimulation. As shown in Fig. 2, the concentrations of IL-6 and CCL3/MIP-1α in the culture supernatant significantly increased after stimulation by human rAIF-1 for 24 h ($P < 0.05$). Expression of CCL1, CCL2/MCP-1, CCL7/MCP-3 and CCL20 /MIP-3 increased a very small amount (data not shown).

4.3. PBMC migration induced by cultured media from rhAIF-1-stimulated CD14$^+$ PBMCs

CD14$^+$ PBMCs were stimulated with rhAIF-1 (zero, one, ten, or 100 ng/mL) in RPMI, for 12 h. The supernatants were collected and used for cell migration assays. PBMCs ($n = 6$) were cultured for 90 min, and were attracted by the rhAIF-1-stimulated culture supernatant. The migrated cell counts were increased by culture supernatants from CD14$^+$ PBMCs stimulated with 100 ng/mL rhAIF-1 compared to RPMI ($P < 0.05$, Fig. 3). There was no significant difference in the number of the migratory cells between 100 ng/mL rhAIF-1 and 50 ng/mL CCL3/MIP-1α as reference control. We confirmed that culture supernatants from rhAIF-1 stimulated CD14$^+$ PBMCs induced the chemotaxis of PBMCs (Table 1).

5. Discussion

In this study, we used a high density oligonucleotide microarray technique for mRNA expression profiling of CD14$^+$ PBMCs to investigate the cellular response of PBMCs to rhAIF-1 stimulation. We identified upregulated expression of several CC chemokine and cytokine genes. They included CC chemokine genes such as *CCL1*, *CCL2/MCP-1*, *CCL3/MIP-1α*, *CCL7/MCP-3* and *CCL20/MIP-3α*. Then, we used ELISAs to confirm that rhAIF-1 promoted the secretion of CCL3/MIP-1α and IL-6 by CD14$^+$ PBMCs. However, secretions of CCL1, CCL2/MCP-1, CCL7/MCP-3 and CCL20/MIP-3α were at very low levels. Finally, we demonstrated that the cultured media from rhAIF-1-stimulated CD14$^+$ PBMCs enhanced migration of PBMCs.

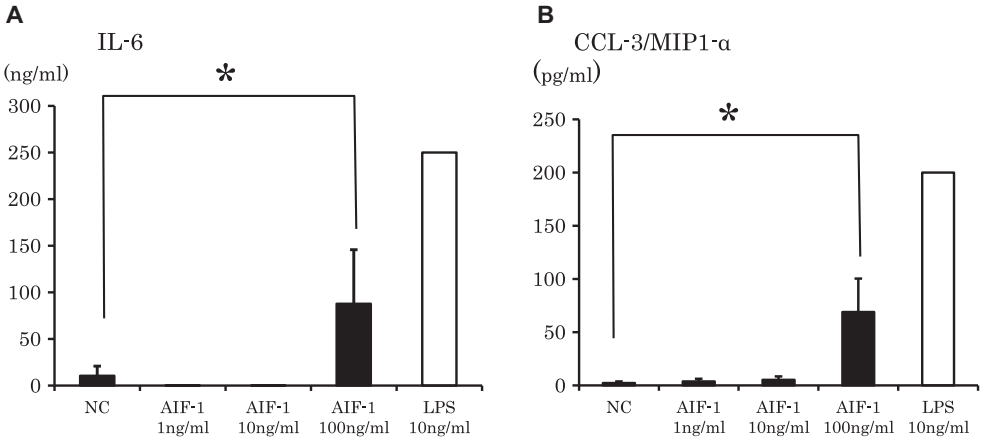

Fig. 2. Induction of IL-6 (A) and CCL3/MIP-1α (B) secretion from CD14$^+$ PBMC stimulated by rhAIF-1. Human CD14$^+$ PBMC ($n = 5$) were stimulated with serum-free RPMI-1640 medium containing 0, 1, 10 or 100 ng/mL rhAIF-1 or 10 ng/mL of LPS. Concentrations of IL-6 and CCL3 in the supernatant were measured with an ELISA at 24 h. Each bar represents the mean ± SE. The difference was analyzed by Wilcoxon signed-rank test. (*$P < 0.05$). NC: negative control.

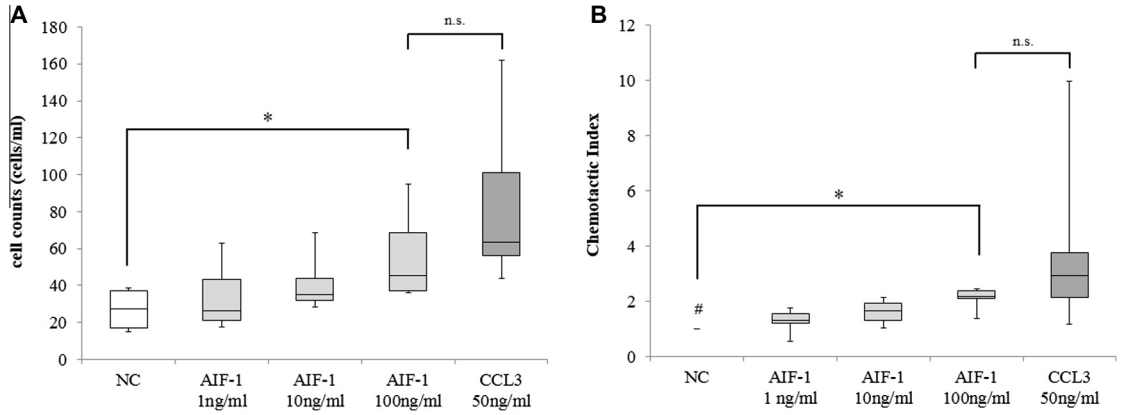

Fig. 3. PBMC migration was stimulated by culture supernatants from cells treated with rhAIF-1. Culture supernatants were prepared from human CD14$^+$ PBMC ($n = 6$) that had been incubated with serum-free RPMI-1640 medium with or without of 1, 10, or 100 ng/mL rhAIF-1 for 12 h. These culture supernatants or 50 ng/mL CCL3 were added to lower chambers, and PBMCs were applied to the surface of the polycarbonate membranes at 5×10^6 cells/mL. Cell migration into the lower chamber significantly increased with culture supernatants from human CD14$^+$ PBMC stimulated with 100 ng/mL of rhAIF-1 for 90 min. The difference was analyzed by Mann–Whitney U and Kruskal–Wallis tests in Cell migration assay (*$P < 0.05$). The *Y*-axis indicates the number of cells that migrated into the lower chamber (A) and Chemotactic Index (B). On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles. There was no significant difference in the number of the migratory cells between 100 ng/mL rhAIF-1 and 50 ng/mL CCL3/MIP-1α as reference control. NC (normal control) indicates culture supernatants incubated with serum-free RPMI-1640 medium containing no rhAIF-1. #The index of NC is 1.0. The other medians were calculated as the ratio on the basis of NC.

Table 1
Fold-changes of expression of "chemokine genes" after rhAIF-stimulation of isolated $CD14^+$ PBMCs. Signals and ratios were determined according to Affymetrix algorithms and procedures.

Probe set ID	AIF signal	NC signal	Ratio	Gene title
206365_at	499.7	27.9	13.00	CCL-1
216598_s_at	1325.1	237.0	4.00	CCL-2
205114_s_at	47689.5	5122.8	9.19	CCL-3
204103_at	48797.1	6007.6	8.00	CCL-4
1405_i_at	130.7	9.8	9.85	CCL-5
208075_s_at	195.1	69.5	2.00	CCL-7
214038_at	753.5	283.7	3.48	CCL-8
210133_at	26.5	54.8	0.57	CCL-11
216714_at	213.7	105.2	2.14	CCL-13
210390_s_at	3128.5	110.2	25.99	CCL-14, CCL-15
207354_at	122.5	56.5	2.64	CCL-16
207900_at	37.2	40.1	0.71	CCL-17
32128_at	888.7	334.4	2.14	CCL-18
210072_at	237.2	384.1	1.15	CCL-19
205476_at	7638.8	67.7	45.25	CCL-20
204606_at	92.6	416.7	0.22	CCL-21
207861_at	153.0	124.2	1.23	CCL-22
210548_at	580.0	28.5	16.00	CCL-23
221463_at	5081.6	694.9	6.50	CCL-24
206988_at	104.1	41.2	1.74	CCL-25
223710_at	64.2	128.2	0.38	CCL-26
230327_at	211.9	213.4	1.32	CCL-27
224240_s_at	358.6	629.9	0.93	CCL-28

T cells that secrete AIF-1 upregulate the proliferation of VSMCs [12]. Moreover, LPS-stimulated macrophages expressed AIF-1 and secreted interleukin IL-6, IL-10 and IL-12p40 [13]. Thus, *AIF-1* gene expression is involved in specific inflammatory signaling pathways related to T cell activation. Moreover, rhAIF itself can induce chemotaxis and proliferation as well as IL-6 production in synovial fibroblasts from patients with RA and in normal human fibroblasts [7,8]. IL-6 and AIF-1 concentrations in synovial fluid were significantly elevated in patients with RA compared with patients with osteoarthritis. There was a positive correlation between the synovial fluid levels of AIF-1 and IL-6. In this study of $CD14^+$ PBMCs, rhAIF-1 induced expression of chemokine-related genes and enhanced secretion of CCL3/MIP-1α, together with IL-6 and small amounts of other chemokines. It is reported that CCL3/MIP-1α induced chemotaxis in monocytic cells by more than 1 ng/mL [14]. Actually, we applied CCL3/MIP-1α as reference control at 0.5, 5, 50, 150 ng/mL in PBMC migration, but the chemotaxis was induced at a concentration of more than 50 ng/mL CCL3/MIP-1α (data not shown). We assume that the difference of the cells and the assay system we adopted may be a cause of this matter. As a result, these secreted molecules could induce chemotaxis of PBMCs. CCL3/MIP-1α is produced by a variety of immune cells such as monocytes and macrophage, and orchestrates acute and chronic inflammatory responses by recruiting proinflammatory cells [15]. CCL3/MIP-1α is considered one of the most important molecules in RA pathology [11,16].

Chemokines expressed in joints can recruit leukocytes and stimulate both fibroblast-like synoviocytes (FLS) and chondrocytes to release inflammatory mediators, including cytokines and MMPs, leading to cartilage degradation and pannus formation. Furthermore, chemokines enhance cell proliferation and angiogenesis, leading to synovial hyperplasia. Chemokines released by leukocytes and FLS, or by the chondrocytes themselves, can induce autocrine/paracrine stimulation of these cells, leading to joint destruction [11].

IL-6 is a pleiotropic cytokine with multiple biological effects on immune regulation, haematopoiesis, inflammation, and oncogenesis [17]. These finding suggest that AIF-1 could be involved with various immune-inflammatory reactions by inducing IL-6 and chemokines in $CD14^+$ PBMCs.

In conclusion, we found that AIF-1 upregulated several CC chemokine genes, leading primarily to release of CCL3/MIP-1α that could induce PBMC migration towards inflamed tissue. Although further work is needed to clarify the molecular mechanism of action of AIF-1, we suggest that AIF-1 may represent a molecular target for the therapy of immune-inflammatory disorders.

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