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Roles of myeloperoxidase and GAPDH in interferon-gamma production of GM-CSF-dependent macrophages

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Abstract

Interferon (IFN)-gamma is highly expressed in atherosclerotic lesions and may have an important role in atherogenesis. Myeloperoxidase (MPO), the most abundant protein in neutrophils, is a marker of plaque vulnerability and a possible bridge between inflammation and cardiovascular disease. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has also been implicated in the pathogenesis of atherosclerosis. The present study investigated the role of neutrophil activation in atherosclerosis. Adherent macrophages were obtained from primary cultures of human mononuclear cells. Expression of IFN-gamma protein by GM-CSF-dependent-macrophages was investigated by enzyme-linked immunosorbent assay after stimulation with MPO. GM-CSF enhanced macrophage expression of the mannose receptor (CD206), which is involved in MPO uptake. MPO increased IFN-gamma production by GM-CSF-dependent macrophages in a concentration-dependent manner. Pretreatment of macrophages with small interfering RNA (siRNA) for CD206 or extracellular signal-regulated kinase (ERK)-2 attenuated IFN-gamma production,

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while siRNA for ERK-1 did not. GAPDH is known to bind to adenylate/uridylate (AU)-rich elements of RNA and may influence IFN-gamma protein expression by binding to the AU-rich element of IFN-gamma mRNA. Interestingly, pretreatment with siRNA for GAPDH significantly reduced IFN-gamma production by macrophages, while it did not affect TF protein expression. In conclusion, MPO upregulates IFN-gamma production by GM-CSF-dependent-macrophages via the CD206/ERK-2 signaling pathway, while silencing GAPDH reduces IFN-gamma production.

Keywords: Biological sciences, Immunology

1. Introduction

Myeloperoxidase (MPO) has emerged as a potential participant in the development of atherosclerosis. Extracellular release of MPO after neutrophil activation is a marker of plaque vulnerability and MPO has been proposed as a bridge between inflammation and cardiovascular disease since elevated circulating levels of MPO are associated with an enhanced risk of major adverse cardiac events [1].

Interferon (IFN)-gamma also is a key regulator of immune function that is highly expressed in atherosclerotic lesions and may have a significant role in atherogenesis. However, the influence of IFN-gamma on atherogenesis is complex, with both pro-atherogenic and anti-atherogenic actions being identified. It has been reported that IFN-gamma induces arteriosclerotic changes in the absence of immunocytes by acting on vascular smooth muscle cells (VSMCs) to potentiate growth-factor-induced mitogenesis [2].

Atherosclerotic lesions contain a large number of immune cells, particularly macrophages and T cells [3]. Activation of macrophages and T cells by pro-inflammatory stimuli causes switching of metabolism towards glycolysis and away from oxidative phosphorylation [4,5]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a multifunctional protein, and its expression and activity can be affected by disease states and/or experimental manipulation. Expression of GAPDH has been reported to be altered in certain tumors, as well as in proliferating and differentiating cells [6]. While GAPDH was long considered to be a classical glycolytic enzyme exclusively involved in cytosolic energy production, extra-glycolytic functions of GAPDH have been described, including regulation of protein expression via RNA binding [7]. RNA elements rich in adenine and uracil residues (AU-rich elements) bind with specific proteins that either direct the RNA to degradation or not, and GAPDH is a non-canonical AU-rich RNA- binding protein [7]. This suggests that GAPDH may play a role in regulating RNA expression and cytokine production. Removal of the AU-rich element from interferon (IFN)-gamma has been reported to promote chronic elevation of circulating serum IFN-gamma

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levels [8]. Regulation of mRNA decay is a major control point in gene expression. The expression of a particular mRNA is controlled by specific interactions between its structural elements and RNA-binding proteins that can be general or mRNA-specific [9]. AU-rich elements are one of the most common factors regulating RNA expression in mammalian cells [10]. An AU rich element in the 3' noncoding region promotes rapid degradation of mammalian cytokine and proto-oncogene mRNAs [11].

Atherosclerosis is a chronic and progressive inflammatory disease characterized by accumulation of lipids and fibrous plaques in the intimal layer of the walls of large arteries. Macrophages play a pivotal role in both the initiation and the progression of atherosclerosis [12, 13]. There is increasing evidence that plaque macrophages have a dynamic role and that both macrophage numbers and their expression of the inflammatory phenotype influence plaque fate. GM-CSF may be involved in the pathogenesis of atherosclerosis and other chronic inflammatory diseases since it is found in atherosclerotic plaques and promotes aortic lipid accumulation. A key component of chronic inflammation in atherosclerotic plaques is persistent influx of mononuclear phagocytes, which are the major leukocyte population in atherosclerotic lesions [14]. When cultured with GM-CSF, murine macrophages undergo differentiation into low-density lipoprotein (LDL)-rich foam cells [15].

We previously reported that IFN-γ mRNA expression by monocytes was increased after exposure to neutrophil extracellular traps in the Transwell assay. In addition, MPO significantly increased IFN-gamma protein production by monocytes compared with HNE, proteinase-3, and cathepsin G [16]. MPO is a ligand cleared by the mannose receptor (CD206) and macrophages express CD206. Therefore, this study was performed to investigate the effect of either MPO or GAPDH on IFN-gamma production by GM-CSF-dependent macrophages.

2. Materials and methods

2.1. Ethics statement

Human peripheral blood samples were obtained from healthy volunteers and this study was approved by the Institutional Review Board of Kumamoto Health Science University. Written informed consent was obtained from all of the volunteers.

2.2. Chemicals and reagents

Myeloperoxidase (MPO) was purchased from Athens Research and Technology (Athens, GA). All reagent solutions were negative for endotoxin by the Endospecy test [17].

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2.3. Isolation of adherent monocytes from peripheral blood mononuclear cells

Lymphocyte thawing medium (BBLYMPH1) was obtained from Zen-Bio, Inc. (Research Triangle Park, NC). Peripheral blood mononuclear cells (PBMCs) were isolated as described previously [18]. Briefly, heparinized blood samples were obtained from nonsmoking healthy volunteers and were diluted 1:1 with pyrogen-free saline. PBMCs were isolated immediately after blood collection by using Lymphoprep gradients (Axis-Shield PoC As, Norway) and were suspended in BBLYMPH1 and incubated for 3 h. For isolation of monocytes from PBMCs by adherence to plastic, cells (1×10^6 per well) were distributed into 12-well plates (Corning Inc. Costar, NY, USA) and allowed to adhere in a 5% CO_2 incubator at 37 °C for 2 h, followed by washing 3 times with warm phosphate-buffered saline (PBS) to remove nonadherent cells. Then the monocytes thus obtained were cultured in complete medium consisting of RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum (FCS) and 10×10^3 μg/L gentamicin at 37 °C in humidified air with 5% CO_2. Adherent monocytes were recovered with a cell scraper and the purity of these cells was evaluated by FACS analysis after staining with a phycoerythrin-conjugated mouse anti-human CD14 monoclonal antibody (Life Technologies, Staley Road Grand Island, NY). The monocytes were also evaluated by trypan blue staining and counting under a Zeiss microscope (Jena, Germany). Only $CD14^+$ monocytes with >85% purity were used for each experiment.

2.4. Differentiation of adherent monocytes into macrophages

Adherent monocytes (1×10^6 cells/mL) were seeded into 12-well tissue culture plates containing RPMI-1640 medium with 10% FCS and 4 mM L-glutamine, and were incubated in the presence of recombinant human GM-CSF (10×10^3 ng/L; Tocris Bioscience, Bristol, UK) [19]. On days 3 and 6 of culture, the cells were washed and fresh medium containing GM-CSF was added. After further incubation until day 9, the cells were utilized as GM-CSF-dependent macrophages [20].

2.5. Enzyme-linked immunosorbent assay (ELISA) for interferon (IFN)-gamma

Monocytes (1×10^6 cells) and GM-CSF-dependent macrophages (1×10^6 cells) were stimulated with MPO (0, 20, 50, or 100×10^3 mU/L) for 6 h and IFN-gamma protein levels in whole-cell lysates were determined by ELISA (Santa Cruz Biotechnology, Santa Cruz, CA) with an anti-IFN-gamma monoclonal antibody.

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2.6. Western blotting for the mannose receptor (CD206)

On days 0, 1, 3, 5, 7, and 9 of culture, CD206 protein was detected in GM-CSF-dependent macrophages (1×10^6 cells) by western blotting. Equivalent amounts of whole-cell lysates were subjected to electrophoresis and the products were transferred to polyvinylidene difluoride membranes. The membranes were incubated with 0.5×10^3 μg/L mouse anti-human CD206 IgG (Santa Cruz Biotechnology), washed, and incubated with alkaline phosphatase-conjugated goat anti-mouse IgG (Santa Cruz Biotechnology) diluted to 1:4000. Then the membranes were incubated with chemiluminescent enhancer (Immun-Star, Bio-Rad, Hercules, California) and exposed to XAR film (Kodak, Rochester, NY). After the film was developed, bands were quantified with a densitometer and ImageQuant software (Molecular Dynamics, Sunnydale, CA). Human whole cell lysate was utilized as a positive control (Santa Cruz Biotechnology).

2.7. Transfection with small interfering RNA (siRNA)

siRNA duplexes (siRNAs) of extracellular signal-regulated kinase (ERK)-1, ERK-2, and CD206 were purchased from Santa Cruz Biotechnology. Transfection of siRNAs (50 nM) into GM-CSF-dependent macrophages on days 7 and 8 of culture was performed according to the manufacturer's protocol for Lipofectamine™ RNAiMAX (Life Technologies). siRNA for GAPDH was utilized as a negative control.

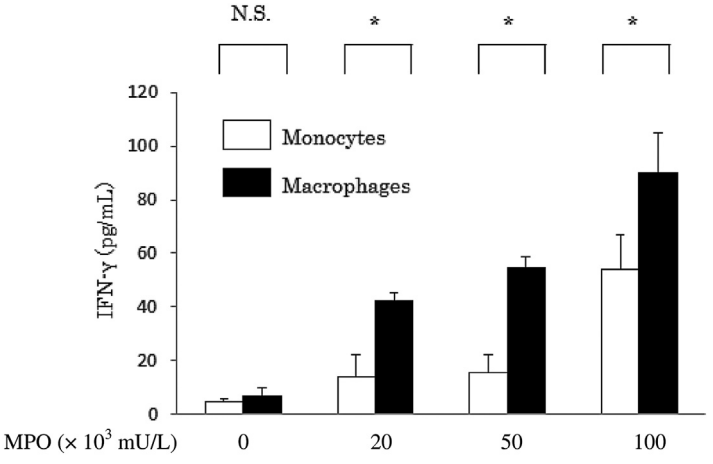

Fig. 1. IFN-gamma protein levels in monocytes and GM-CSF-dependent macrophages after stimulation with myeloperoxidase (MPO). Monocytes (1×10^6 cells) and GM-CSF-dependent macrophages on day 9 of culture (1×10^6 cells) were stimulated with MPO (0, 20, 50 or 100×10^3 mU/L) for 6 h. Whole-cell lysates of GM-CSF-dependent macrophages contained significantly higher levels of IFN-gamma than lysates of monocytes and the effect of MPO was concentration-dependent. IFN: interferon, GM-CSF: granulocyte-macrophage colony-stimulating factor, MPO: myeloperoxidase.

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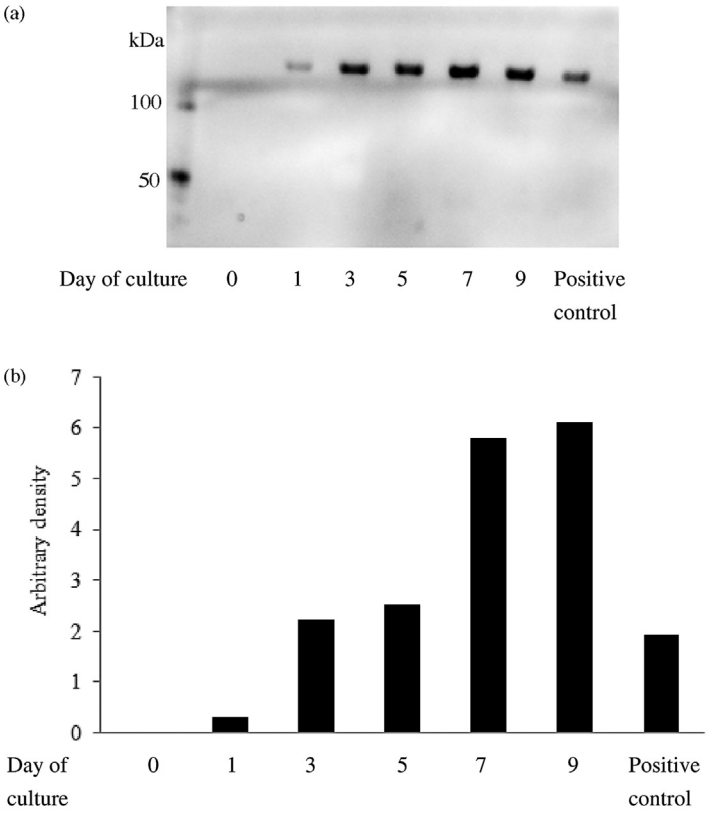

Fig. 2. Western blotting for CD206. CD206 expression by GM-CSF-dependent macrophages (1×10^6 cells) on day 0, 1, 3, 5, 7, and 9 of culture was detected by western blotting. CD206: mannose receptor (cluster of differentiation 206), GM-CSF: granulocyte-macrophage colony-stimulating factor. Data were obtained by using samples from three volunteers in each group and a representative result is shown as arbitrary density units. (a) Representative blot. (b) Arbitrary density data. Human whole cell lysate was utilized as a positive control.

On day 9, transfected cells (1×10^6) were stimulated with MPO (50×10^3 mU/L) for 6 h and then IFN-gamma protein levels in whole-cell lysates were determined by ELISA (Abcam Inc.) with an anti-IFN-gamma monoclonal antibody. The tissue factor protein level in whole-cell lysates was also determined by ELISA (Abcam Inc.) with an anti-tissue factor monoclonal antibody as an unrelated control.

2.8. Statistical analysis

Results are expressed as the mean ± SE. Analysis of variance and the *t*-test for independent mean values were used to assess differences between multiple groups and differences between two groups, respectively. When the F ratio was found to be significant, mean values were compared by a post hoc Bonferroni test. A probability (P) value <0.05 was considered to indicate significance in all analyses.

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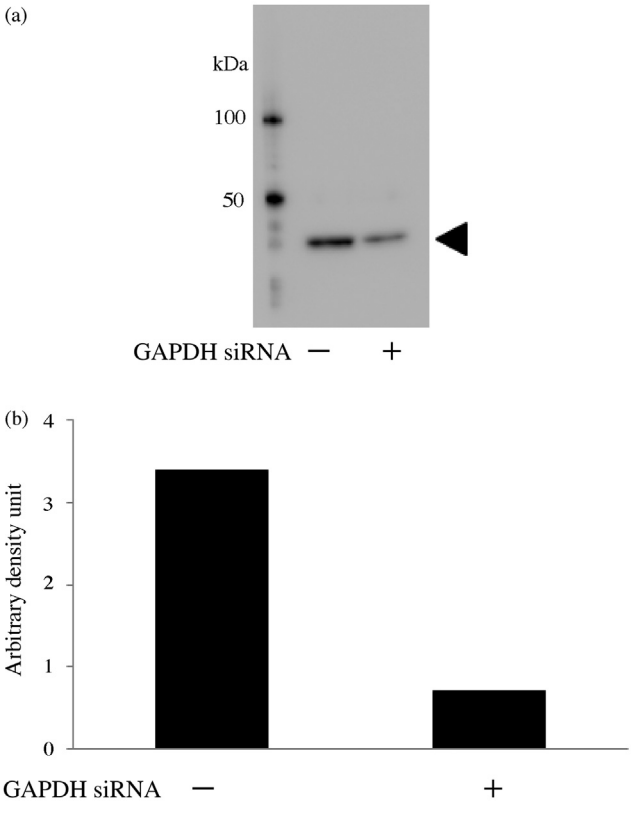

Fig. 3. Western blotting for glyceraldehyde 3-phosphate dehydrogenase (GAPDH). GAPDH protein was detected by western blotting in whole-cell lysates of GM-CSF-dependent macrophages (day 9) with or without transfection of siRNA for GAPDH. GAPDH: glyceraldehyde 3-phosphate dehydrogenase. Data were obtained by using macrophages from three volunteers in each group and a representative result is shown as arbitrary density units.

3. Results

Incubation with MPO resulted in a concentration-dependent increase of IFN-gamma production by GM-CSF-dependent macrophages. IFN-gamma protein levels were also significantly higher in macrophages than in monocytes (Fig. 1). Western blotting showed that expression of mannose receptor (CD206) protein by GM-CSF-dependent macrophages increased a time-dependent manner during culture (Fig. 2). Transfection of macrophages with siRNA for GAPDH reduced the level of GAPDH protein detected by western blotting (Fig. 3). Transfection with siRNA for extracellular signal-regulated kinase-2 (ERK-2) attenuated IFN-gamma production after stimulation with MPO, but siRNA for ERK-1 did not affect it. Transfection with siRNA for CD206 also significantly reduced IFN-gamma production. Interestingly, IFN-gamma production by GM-CSF-dependent macrophages stimulated with MPO was significantly attenuated after transfection with the siRNA for GAPDH. In contrast, tissue factor (TF) expression was not affected by silencing of GAPDH with siRNA (Fig. 4).

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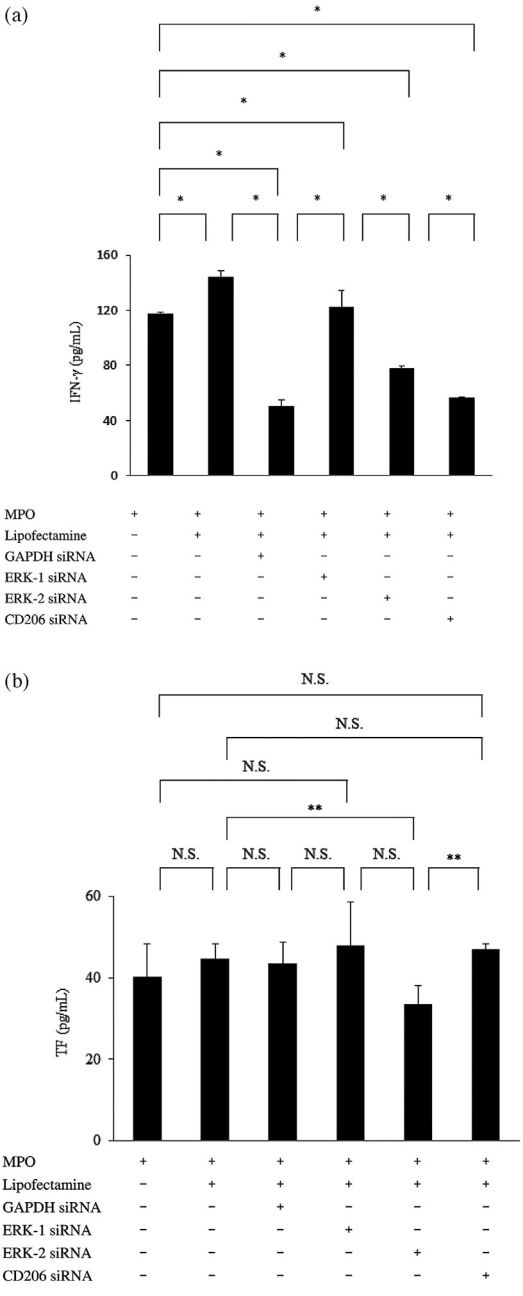

Fig. 4. Effect of small interfering RNA (siRNA) on IFN-gamma production. IFN-gamma protein levels in whole-cell lysates of GM-CSF-dependent macrophages (day 9) transfected with siRNAs for GAPDH, ERK-1, ERK-2, or CD206 were determined by ELISA after stimulation with MPO (50×10^3 mU/L) (a). In addition, tissue factor (TF) protein levels in whole-cell lysates of GM-CSF-dependent macrophages (day 9) transfected with siRNAs for GAPDH, ERK-1, ERK-2, or CD206 were determined by ELISA after stimulation with MPO (50×10^3 mU/L) (b). ERK: extracellular signal-regulated kinase, CD206: mannose receptor (cluster of differentiation 206), GAPDH: glyceraldehyde 3-phosphate dehydrogenase, GM-CSF: granulocyte-macrophage colony-stimulating factor), TF: tissue factor. Data were obtained by using macrophages from three volunteers in each group and are represented as the mean ± SE. *P<0.01; **P<0.05; N.S., not significant.

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4. Discussion

The present study demonstrated that stimulation of GM-CSF-dependent macrophages with MPO resulted in significant elevation of the IFN-gamma protein level compared with that in monocytes. This study also clearly demonstrated that expression of CD206 by cultured GM-CSF-dependent macrophages increased over time. Furthermore, we found that MPO stimulated IFN-gamma production, while it was significantly reduced by pretreatment with siRNAs for CD206 or GAPDH. Our findings suggest that GAPDH may influence atherosclerosis through stabilizing IFN-gamma production by macrophages.

CD206 has been shown to be essential for the production of both pro-inflammatory and anti-inflammatory cytokines. Furthermore, CD206 is an important pattern recognition receptor of the innate immune system [21] and it might interact with other pattern recognition receptors to mediate intracellular signaling [22, 23]. Moreover, C-type lectins have a direct effect on signaling pathways, including activation of mitogen-activated protein kinases (MAPKs) and nuclear-factor kappa B (NF-kB) [24]. In the present study, MPO stimulated IFN-gamma production by GM-CSF-dependent macrophages, while it was significantly attenuated by transfection of siRNA for CD206. The MAPKs are serine/threonine protein kinases that regulate diverse cellular programs by relaying extracellular signals and they include the extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino (N)-terminal kinases 1/2/3 (JNK1/2/3), p38 isoforms (alpha, beta, gamma, and delta), and ERK5 [25]. The ERK cascade is a central pathway involved in transmitting signals from many extracellular agents to regulate cellular processes, with ERK1 and ERK2 being dual-specificity protein kinases that control cell growth and differentiation. In the present study, siRNA for ERK-2 attenuated IFN-gamma production by GM-CSF-dependent macrophages after stimulation with MPO, while ERK-1 siRNA had no effect.

We utilized siRNA for GAPDH as a negative control. Unexpectedly, we found that pretreatment of macrophages with siRNA for GAPDH significantly attenuated IFN-gamma production after stimulation with MPO. GAPDH is generally thought of as an enzyme that only has an important role in glycolysis, and is used as a housekeeping gene for measurement of equal loading in many experiments. Interestingly, it has been reported that GAPDH binds to the adenylate/uridylate-rich (AU-rich) element of the 3' untranslated region of macrophage colony-stimulating factor RNA [26]. AU-rich elements are one of the most common determinants of RNA expression in mammalian cells [27] and are often targeted for rapid mRNA degradation [28, 29]. In addition, Chang et al. [30] reported that GAPDH directly regulates IFN-gamma protein expression in $CD4^+$ T cells and that this interaction takes place at the 3'UTR, where binding of GAPDH prevents translation of the mRNA sequence. Thus,

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GAPDH is a multifunctional protein that binds mRNAs to regulate stability as part of its repertoire [31]. In the present study, silencing GAPDH did not affect TF production, although TF mRNA contains AU-rich elements. Thus, we demonstrated a differential effect of GAPDH on IFN-gamma or TF production by macrophages that requires further investigation. We found that transfection of macrophages with siRNA for GAPDH resulted in a decline of IFN-gamma production. Both GAPDH and heat shock protein 70 have been reported to bind to the AU-rich element of IFN-gamma [32, 33]. In contrast, TF production was not affected by transfection with siRNA for GAPDH, suggesting that GAPDH is involved in regulating the immune and inflammatory responses of macrophages.

5. Conclusion

The present findings suggested that GAPDH may have a role in regulating the production of IFN-gamma by macrophages.

Declarations

Author contribution statement

Rui Yamaguchi: Conceived and designed the experiments, wrote the paper.

Takatoshi Yamamoto, Arisa Sakamoto: Performed the experiments.

Yasuji Ishimaru: Analyzed and interpreted the data.

Shinji Narahara, Hiroyuki Sugiuchi: Contributed reagents, materials, analysis tools or data.

Yasuo Yamaguchi: Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

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Additional information

No additional information is available for this paper.

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