

## Inhibitory mechanisms of NK92 cell cytotoxicity by IL-17 stimulation

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Invasion of lymphocytes and other immunocompetent cells have been confirmed in inflamed periodontal tissue such as occurs with chronic periodontitis. Local immune responses by NK cells and other immunocompetent cells are considered a factor in the progression of periodontal disease. Although IL-17 participates in various cells and is involved in various inflammatory pathologies, the effect of IL-17 on NK cells is not clearly understood. In a previous study, we reported that IL-17 stimulation (50, 100, 200 ng/mL) suppresses the cytotoxicity of NK92 cells. In this study, we investigated mechanisms of intracellular signal transduction pathways that suppress the cytotoxicity of IL-17 stimulated NK92 cells. We confirmed that NK92 cells expressed sufficient IL-17RA to induce intracellular signaling transduction and cell function by FACS analysis. We confirmed that an even lower concentration of IL-17 (10, 20 ng/mL) suppresses the cytotoxicity on NK92 cells in our model. In this study, we examined the phosphorylation of MAPKs (ERK, JNK and p38) and GSK3- $\beta$  in NK92 cells stimulated with IL-17 (10, 20 ng/mL) for 5 min. The phosphorylation of ERK and JNK were not altered in the absence or presence of IL-17 stimulation. Phosphorylation of p38 was observed even in the absence of IL-17. However, phosphorylation of p38 in the absence of IL-17 was suppressed by IL-17 stimulation. GSK 3- $\beta$  was slightly phosphorylated in the absence of IL-17, while this phosphorylation was increased in the presence of IL-17. These results suggest that suppressing phosphorylation of p38 and increasing phosphorylation of GSK3- $\beta$  may affect the intracellular signaling mechanism that suppresses the cytotoxicity of IL-17 stimulated NK92 cells. (J Osaka Dent Univ 2017 ; 51 : 105-113)

**Key words :** Interleukin-17 (IL-17) ; Natural killer (NK) cells ; Cytotoxicity

## INTRODUCTION

Periodontitis is a common chronic inflammatory disease that results in tooth loss and the destruction of periodontal tissues such as gingiva, cementum, the periodontal ligament and alveolar bone. Invasion of lymphocytes and other immunocompetent cells have been confirmed in inflamed periodontal tissue such as that in chronic periodontitis. Local immune responses by natural killer (NK) cells and other immunocompetent cells are considered a factor in the progression of periodontal disease. Human NK cells are a population of granular lymphocytes that are 5-15% of the lymphocytes in the peripheral blood.<sup>1-4</sup> NK cells participate in the innate

immune system through the prompt secretion of cytokines and chemokines, and have the ability to lyse virally infected cells and tumor cells without prior sensitization. NK cells express two functional types of receptors, killer-cell activating receptors (KAR) and killer-cell inhibitory receptors (KIR). The final outcome of NK cell activity results from a balance between KAR and KIR.<sup>5-7</sup>

Cytotoxicity is a major function used by the immune system to eliminate a variety of tumor cells and virus infected cells.<sup>8, 9</sup> NK cells mediate the destruction of target cells using two principal mechanisms: the perforin-dependent granule exocytosis pathway and the Fas ligand/Fas pathway. The granular exocytotic pathway has the function of de-

stroying target cells by NK cells or cytotoxic T lymphocytes (CTLs), and utilizes the lytic mediators perforin and several proteases (e.g., granzymes) existing in cytoplasmic granules.<sup>10</sup> This mechanism induces both necrosis and apoptosis of target cells,<sup>11</sup> and activation receptors on NK cells such as CD2, CD16 and integrin are involved in activating this mechanism.<sup>12, 13</sup> Our group previously reported that crosslinking of CD2 enhances spleen tyrosine kinase (Syk) activity and phosphatidylinositol 3-kinase (PI 3-K) activity, which result in increased protein tyrosine phosphorylation and granular exocytosis in the NK like cell line, NK 3.3 cells.<sup>14</sup> In addition, cytokines such as interleukin (IL)-2 and IL-12 are critical regulators of NK cell activation and their effects include increasing lytic activity and stimulation of interferon (IFN)- $\gamma$  production and proliferation.<sup>15-20</sup>

IL-17 (also called IL-17A or CTLA 8), a proinflammatory cytokine, was first described and cloned in 1993.<sup>21</sup> Since the discovery of IL-17, five other members of this family IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F have been identified based on amino acid sequence homology.<sup>21-27</sup> IL-17 was thought to be a representative cytokine released by Th17 cells. Recent studies have reported that IL-17 can also be produced by a wide range of innate immune cells, such as iNKT cells, NK cells, macrophages and neutrophils.<sup>28-30</sup> It participates in both innate and adaptive immune responses and plays a crucial role in host defense against microbial infections, as well as in the pathogenesis of allergies, autoimmune diseases, obesity and tumors. IL-17 has been reported to be highly upregulated at inflammatory tissue sites of autoimmune diseases and amplifies the inflammation through synergy with other cytokines, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).

Thus, although IL-17 is active in various cells and is involved in various inflammatory pathologies, its effects on NK cells are not clearly understood. In a previous study, we reported that IL-17 stimulation may suppress the cytotoxicity on NK92 cells. In this study, we investigated the intracellular signal transduction pathway mechanisms that suppress the cy-

totoxicity on NK92 cells.

## MATERIALS AND METHODS

### Reagents and antibodies

Recombinant human IL-17 was purchased from PeproTech (Rocky Hill, NJ, USA). We used as primary antibodies anti-IL-17RA (Rb 07), anti-Mouse IgG, anti-phospho p38 (E10), anti-p38  $\alpha/\beta$  (A-12), anti-phospho c-Jun N-terminal kinase (JNK), and anti-JNK (D-2), which were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Anti-phospho extracellular signal-regulated kinase (ERK) (E10), anti-ERK, anti-phospho glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) (5B3), and anti-GSK-3 $\beta$  (3D10) were used as primary antibodies. They were purchased from Cell Signaling Technology (Danvers, MA, USA). Alexa Fluor 488 chicken anti-goat IgG (H + L) was used as a secondary antibody. It was purchased from Invitrogen (Eugene, OR, USA). Horseradish peroxidase (HRP)-conjugated secondary antibodies (Anti-mouse IgG and Anti-rabbit IgG) were obtained from Merck KGaA (Darmstadt, Germany). Immobilon Western HRP Substrate (Merck KGaA) was used for chemiluminescent detection in western blotting on proteins that were transferred to polyvinylidene difluoride (PVDF) membranes (Merck KGaA).

### Cells and cell culture

The NK92 cell line was obtained from American Type Tissue Collection (ATCC, Rockville, MD, USA). NK92 cells were maintained in Alpha Minimum Essential Medium ( $\alpha$ -MEM) (Wako Pure Chemical Industries, Osaka, Japan) supplemented with 2 mM L-glutamine (Wako Pure Chemical Industries), 0.2 mM inositol (Merck KGaA), 0.02 mM folic acid (Merck KGaA), 1.5 g/L sodium bicarbonate (Wako Pure Chemical Industries), 0.1 mM 2-mercaptoethanol (Wako Pure Chemical Industries), 100 U/mL recombinant IL-2 (Primmune, Kobe, Japan), 12.5% horse serum (Thermo Fisher Scientific, Waltham, MA, USA) and 12.5% fetal bovine serum (Thermo Fisher Scientific). NK92 cells were incubated at 37°C under 5% CO<sub>2</sub>.

### Fluorescence-activated cell sorting (FACS) analysis

For detecting IL-17RA on NK92 cells, the cells were incubated at 4°C for 1 h with anti-IL-17RA (Rb 07) antibody or anti-Mouse IgG, and then washed to remove excess amounts of the antibodies. The cells were then resuspended and incubated with Alexa Fluor 488 chicken anti-goat IgG (H+L) at 4°C for 30 min in the dark, and then washed and analyzed using a BD FACSVerse (BD Biosciences, Mountain View, CA, USA).

### Cytotoxicity assay

The K562 cell line was obtained as the target cell from American Type Tissue Collection. For cytotoxicity assays, target cells (K562) were labeled with calcein-AM (Thermo Fisher Scientific) for 30 min at 37°C. The target cells (10,000 per well) and effector cells (NK92 cells) were then plated onto 96-well plates at the effector to target cell (E:T) ratio of 20:1 and stimulated with IL-17 (10, 20 ng/mL). The cells were incubated for 4 h at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. After incubation, supernatants were transferred to new wells and fluorescence was measured using a SpectraMax M5 (Molecular Devices, Sunnyvale, CA, USA). Assays were performed in triplicate and data were expressed as percent lysis of total cells.

### Western blot analysis

NK92 cells were stimulated with IL-17 (0, 10, 20 ng/mL) for 5 min. The reaction was terminated by the addition of 800 µL of ice-cold α-MEM. Then, we added lysis buffer solution (1% Triton X-100, 25 mM Tris/HCL (pH 7.4)), 5 mM ethylenediaminetetraacetic acid (EDTA) and 1 mM phenylmethylsulfonyl fluoride (PMSF)), and boiled the solution at 98°C for 3 min to prepare it for electrophoresis. Equal amounts of each sample were then subjected to 8% SDS/PAGE and transferred to PVDF membrane. Gels were run at 185 V for 90 min. The membrane was blocked with 10% Blocking One (Nacalai Tesque, Kyoto, Japan) in TBS-T at 4°C overnight.

It was then treated with primary antibody (anti-

phospho p38 (E10), anti-phospho JNK, anti-phospho ERK (E10) or anti-phospho GSK-3β (5B 3)) for 1 h, and washed with TBS-T for 10 min three times. The membrane was further treated with secondary antibody (HRP-conjugated anti-mouse IgG or HRP-conjugated anti-rabbit IgG) for 30 min, and washed with TBS-T for 10 min three times. After incubation with the antibody, phosphorylated proteins were detected by Immobilon Western Chemiluminescent HRP Substrate for 2 min. The images were analyzed using a VersaDoc 5000 (Bio-Rad, Hercules, CA, USA). The membranes were stripped and reprobed with antibody (anti-p38 α/β (A-12), anti-JNK (D-2), anti-ERK or anti-GSK-3β (3D10)). The results revealed that comparable amounts of proteins were applied from lysates obtained from NK92 cells subjected to each treatment.

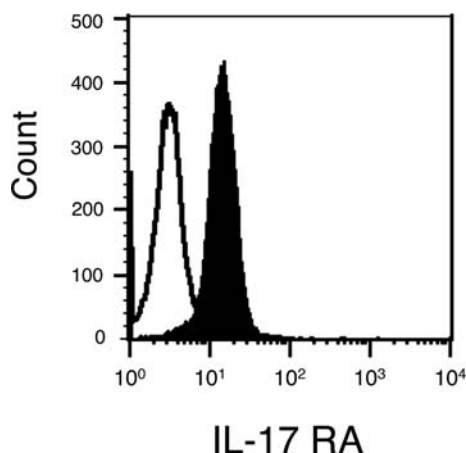
## RESULTS

### Expression of IL-17RA on NK92 cells

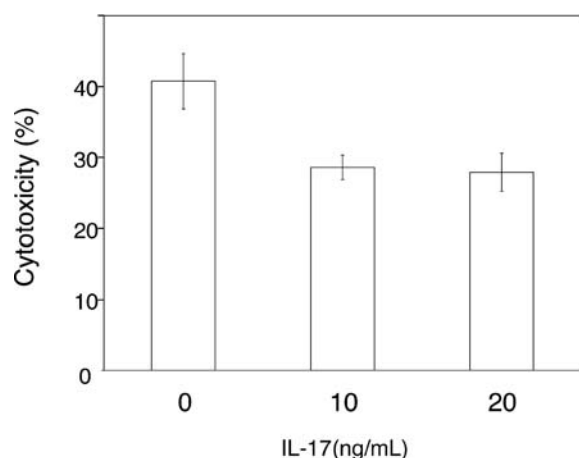
Expression of cell-surface antigens was measured by FACS analysis. The NK92 cells were then stained with primary antibody (anti-IL-17 RA antibody or anti-Mouse IgG) and secondary antibody (Alexa Fluor 488 chicken anti-goat IgG (H+L)), and BD FACSVerse was used to assess the expression of IL-17RA. The levels of IL-17RA cell-surface expression on NK92 cells are shown in Fig. 1 (closed histogram). The majority of NK92 cells expressed IL-17RA, which is one of the IL-17 receptors. Its expression was confirmed on the NK92 cells (Fig. 1). Staining with a negative control antibody (anti-Mouse IgG) is shown as an open histogram for ease of comparison.

### Effect of IL-17 on NK92 cell cytotoxicity against K562 cells

In order to investigate the effect of IL-17 on the cytotoxicity of NK92 cells, target cells (calcein-AM labeled K562 cells) and effector cells (NK92 cells) were plated onto 96-well plates at an E:T ratio of 20:1 and stimulated with IL-17 (10, 20 ng/mL). The cocultures of NK92 cells and K562 cells were incubated at 37°C in 5% CO<sub>2</sub> for 4 h. After incuba-



**Fig. 1** Expression of IL-17 RA on the surface of NK92 cells. NK92 cells were stained with mAb specific for anti-IL-17RA, followed by incubation with Alexa Fluor 488 goat anti-mouse IgG (H+L). The levels of IL-17RA cell-surface expression on NK92 cells are shown as a closed histogram. Staining with a negative control antibody is shown as an open histogram for ease of comparison.



**Fig. 2** IL-17 suppression of cytotoxicity against K562 cells on NK92 cells. NK92 cells ( $2 \times 10^5$ /well) were stimulated with various concentrations of IL-17 and cultured with calcein AM labeled K562 cells ( $1 \times 10^4$ /well) for 4 h. After incubation, supernatants were transferred to new wells and fluorescence was measured using a microplate spectrofluorometer. Assays were performed in triplicate and data were expressed as percent lysis of total cells.

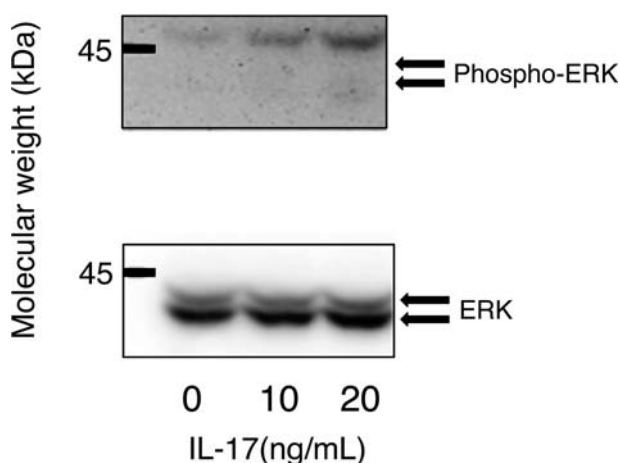
tion, the supernatants were transferred to new wells and fluorescence was measured using a microplate spectrofluorimeter, SpectraMax M5. Cytotoxicity was observed at 40.8% in unstimulated cells used as a control. IL-17 stimulation at 10 ng/mL and 20 ng/mL showed a decrease in cytotoxicity (10 ng/

mL : 28.6%, 20 ng/mL : 27.9%) compared to the control. IL-17 stimulation suppressed the cytotoxicity against K562 cells on NK92 cells.

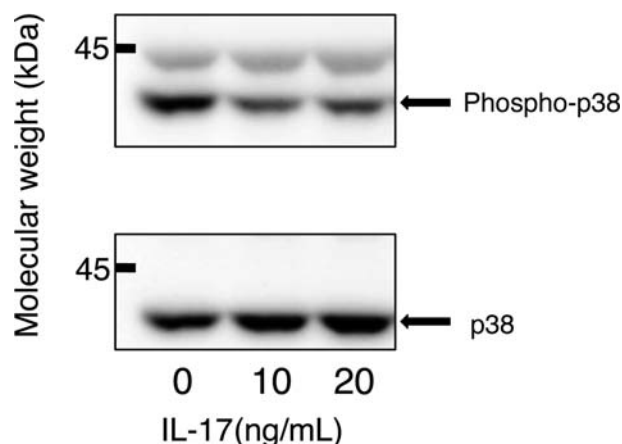
### Effect of IL-17 stimulation on mitogen-activated protein kinase (MAPK) signaling pathway in NK 92 cells.

MAPKs have been implicated in the production of cytokines and downstream signaling events by providing the essential link between receptor signals and nuclear gene transcription. MAPKs play a part in the regulation of key cellular processes including gene induction, cell survival/apoptosis, proliferation and differentiation as well as cellular stress and inflammatory responses.<sup>31</sup> IL-17 exerts its inflammatory effects by inducing the expression of proinflammatory genes such as chemokines, cytokines and matrix metalloproteinases (MMPs). Although IL-17 is known to activate MAPKs, how it affects the cytotoxicity of NK cells is not well understood. There are three major classes of MAPKs in mammals, ERK, JNK and p38. We examined the phosphorylation of these three in NK92 cells stimulated with IL-17 (10, 20 ng/mL) for 5 min.

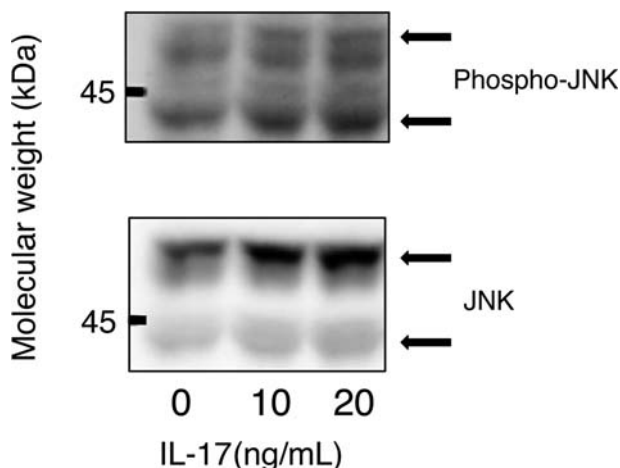
First, we investigated the effects of IL-17 on the phosphorylation of ERK in NK92 cells. Phosphorylation of ERK could not be confirmed in unstimulated NK92 cells. Furthermore, we could not confirm phosphorylation of ERK even when IL-17 was stimulated (Fig. 3 upper panel). To ensure that equal amounts of ERK were obtained from the lysates, the membranes were stripped and reprobed with anti-ERK antibody. The results revealed that equal amounts of ERK were created by lysates obtained from each sample (Fig. 3 lower panel). Next, we investigated the effects of IL-17 on the phosphorylation of JNK in NK92 cells. When NK92 cells were stimulated in the absence of IL-17, JNK was constitutively phosphorylated a small amount. In the presence of IL-17 the phosphorylation of JNK could only be observed at a level comparable to the phosphorylation in the absence of IL-17 (Fig. 4 upper panel). To ensure that equal amounts of JNK were obtained from the lysates, the membranes were stripped and reprobed with anti-JNK antibody.



**Fig. 3** Effect of IL-17 stimulation on phosphorylation of ERK in NK92 cells. NK92 cells were stimulated with IL-17 (0, 10, 20 ng/mL) for 5 min. Detergent-soluble proteins were resolved by SDS-PAGE, and immunoblotted with anti-phospho ERK mAb (upper panel). To ensure that equal amounts of ERK were obtained from the lysates, the membranes were stripped and reprobed with anti-ERK mAb (lower panel). IL-17 stimulation did not affect phosphorylation of ERK in NK92 cells.



**Fig. 5** Effect of IL-17 stimulation on phosphorylation of p38 in NK92 cells. NK92 cells were stimulated with IL-17 (0, 10, 20 ng/mL) for 5 min. Detergent-soluble proteins were resolved by SDS-PAGE, and immunoblotted with anti-phospho p38 mAb (upper panel). To ensure that equal amounts of p38 were obtained from the lysates, the membranes were stripped and reprobed with anti-p38 mAb (lower panel). IL-17 stimulation reduced phosphorylation of p38 in NK92 cells.



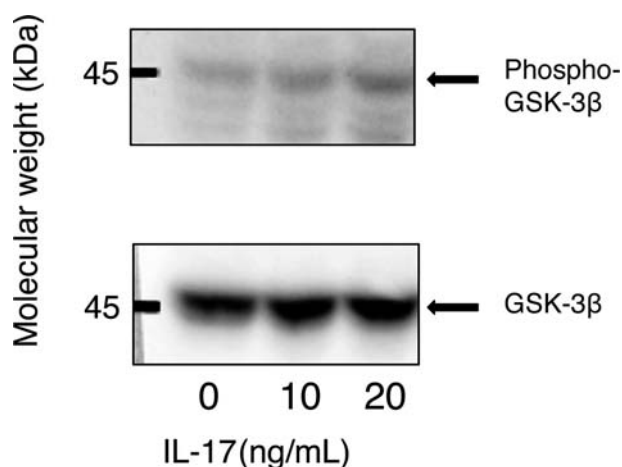
**Fig. 4** Effect of IL-17 stimulation on phosphorylation of JNK in NK92 cells. NK92 cells were stimulated with IL-17 (0, 10, 20 ng/mL) for 5 min. Detergent-soluble proteins were resolved by SDS-PAGE, and immunoblotted with anti-phospho JNK mAb (upper panel). To ensure that equal amounts of JNK were obtained from the lysates, the membranes were stripped and reprobed with anti-JNK mAb (lower panel). IL-17 stimulation did not affect phosphorylation of JNK in NK92 cells.

The results revealed that equal amounts of JNK were created by lysates obtained from each sample (Fig. 4 lower panel). Finally, we investigated the effects of IL-17 on the phosphorylation of p38 of NK92 cells. When NK92 cells were stimulated in the

absence of IL-17, p38 was constitutively phosphorylated. However, in the presence of IL-17 the phosphorylation of p38 was reduced compared with that in the absence of IL-17 (Fig. 5 upper panel). To ensure that equal amounts of p38 were obtained from the lysates, the membranes were stripped and reprobed with anti-p38 antibody. The results revealed that equal amounts of p38 were created by lysates obtained from each sample (Fig. 5 lower panel). These results suggest that the reduction of p38 phosphorylation was involved in the suppression of cytotoxicity in NK92 cells.

#### IL-17 increased phosphorylation of GSK-3 $\beta$ in NK92 cells

CCAAT-enhancer binding protein (C/EBP) sites are essential for IL-17-dependent induction of genes encoding IL-6, various chemokines, acute-phase proteins, and other inflammation-related genes.<sup>32</sup> The activation of C/EBP $\beta$ , one of the C/EBP family, is mediated through ERK and GSK-3 $\beta$  dependent mechanisms. In this study, we examined the phosphorylation of GSK-3 $\beta$  in NK92 cells stimulated with IL-17. A little phosphorylation of GSK-3 $\beta$  was confirmed in unstimulated NK92 cells. In addition,



**Fig. 6** Effect of IL-17 stimulation on phosphorylation of GSK-3 $\beta$  in NK92 cells. NK92 cells were stimulated with IL-17 (0, 10, 20 ng/mL) for 5 min. Detergent-soluble proteins were resolved by SDS-PAGE, and immunoblotted with anti-phospho GSK-3 $\beta$  mAb (upper panel). To ensure that equal amounts of GSK-3 $\beta$  were obtained from the lysates, the membranes were stripped and reprobed with anti-GSK-3 $\beta$  mAb (lower panel). IL-17 stimulation increased phosphorylation of GSK-3 $\beta$  in NK92 cells.

stimulation by IL-17 increased phosphorylation of GSK-3 $\beta$  compared with the absence of IL-17 (Fig. 6 upper panel). To ensure that equal amounts of GSK-3 $\beta$  were obtained from the lysates, the membranes were stripped and reprobed with anti-GSK-3 $\beta$  antibody. The results revealed that equal amounts of GSK-3 $\beta$  were created by lysates obtained from each sample (Fig. 6 lower panel). These results suggest that the increase in phosphorylation of GSK-3 $\beta$  was involved in the suppression of cytotoxicity in NK92 cells.

## DISCUSSION

IL-17 is a novel pro-inflammatory cytokine that is involved in host defense. IL-17 family cytokines, which are characterized by the homology to the prototype member IL-17, are a subset of cytokines with diverse functions in the immune system. This family of cytokines contains six members, IL-17, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. IL-17 is the fundamental member in this family, and the most investigated cytokine.<sup>28</sup> It has been shown to target various tissues under different inflammatory conditions and participate in the pathogenesis of

multiple autoimmune diseases,<sup>33-35</sup> allergic disorders,<sup>36</sup> tumor formation<sup>37</sup> and host defense.<sup>36, 38</sup> For example, increased IL-17 levels have been observed in various inflammation models including rheumatoid arthritis and periodontitis.

IL-17 receptor families consist of five subtypes (IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE),<sup>39</sup> all of which share sequence homology. IL-17RA is ubiquitously expressed on a wide range of tissues and cell types. After stimulation with IL-17, IL-17RA initiates the activation of downstream signaling pathways to induce the production of pro-inflammatory molecules. Members of the IL-17 family are also homodimeric and have been shown to bind and signal through both homodimeric and heteromeric counterstructures.<sup>40</sup> IL-17RA and IL-17RC form a heterodimeric receptor complex for mediating the signals of IL-17 and IL-17F.

First, we examined by FACS analysis the expression of IL-17RA, one of the IL-17 receptors, that is expressed on NK92 cells. We confirmed that NK92 cells expressed sufficient IL-17RA to induce intracellular signaling transduction and cell function. This suggests that IL-17 has an effect on NK92 cells. In a previous study, we reported that IL-17 (50, 100, 200 ng/mL) stimulation suppresses the cytotoxicity of NK92 cells. Furthermore, in this study we confirmed that an even lower concentration of IL-17 (10, 20 ng/mL) suppresses the cytotoxicity of NK92 cells in our model. However, molecular mechanisms involved in the suppression of IL-17-mediated NK92 cytotoxicity have not been fully elucidated. In this report, we investigated intracellular signal transduction pathway mechanisms that suppress cytotoxicity of NK92 cells by IL-17 stimulation.

When IL-17 binds to the IL-17RA and IL-17RC heterodimeric receptor complex, NF-kappaB activator 1 (Act1) is recruited to the IL-17RA through SEFIR. TNF receptor associated factor 6 (TRAF6) then binds to Act1, and therefore indirectly interacts with the IL-17R complex. Act1 functions as an adaptor for the recruitment of TRAF6. Act1 and the TRAF6 complex activates several downstream signaling pathways. IL-17 can upregulate the expres-

sion of a variety of proinflammatory chemokines and cytokines through activation of transcription factors. IL-17 can also post-transcriptionally stabilize mRNAs induced by TNF- $\alpha$ .<sup>28, 41</sup> All of the IL-17-stimulated pathways lead to the activation of transcription factors such as C/EBPs, NF- $\kappa$ B and AP1 to induce gene expression of proinflammatory chemokines and cytokines, antibacterial peptides and MMPs. However, exactly how IL-17 contributes to the activation of these pathways is complex and poorly understood.

A typical event induced by pro-inflammatory mediators is activation of the MAPK signalling pathway, which leads to the activation of AP1. IL-17 is known to induce activation of various MAPKs. In our model, phosphorylation of ERK and JNK was not altered in IL-17 stimulated NK92 cells. ERK phosphorylation was not observed in NK92 cells regardless of whether there was IL-17 stimulation. Even with no stimulation, JNK was constitutively phosphorylated a small amount. However, no change in the phosphorylation level of JNK was observed with IL-17 stimulation. Like JNK, phosphorylation of p38 was observed even in the absence of IL-17. However, in the presence of IL-17 the phosphorylation of p38 was reduced compared with that in the absence of IL-17. These results seem to indicate that the ERK and JNK of MAPKs were hardly involved in the suppression of cytotoxicity of NK92 by IL-17 stimulation. However, in p38 of the MAPKs, it appears that suppression of p38 phosphorylation stimulated by IL-17 may be involved in suppression of cytotoxicity of NK92 cells.

C/EBP sites are essential for IL-17-dependent induction of genes encoding IL-6, various chemokines, acute-phase proteins, and other inflammation-related genes.<sup>32, 42</sup> IL-17 stimulation also triggers the dual phosphorylation of C/EBP $\beta$  at Thr188 and Thr179 by ERK and GSK3- $\beta$ , respectively.<sup>21, 43</sup> The dual phosphorylation of C/EBP $\beta$  inactivates itself, resulting in the suppression of IL-17-mediated downstream gene induction.<sup>21, 32</sup> The two phosphorylation events are probably activated through different signalling pathways, as they require different domains in the IL-17R.<sup>32, 42</sup> Under our present experimental

conditions, phosphorylation of ERK in NK92 cells was not observed in the presence or absence of IL-17. On the other hand, GSK3- $\beta$  was slightly phosphorylated in the absence of IL-17, and this phosphorylation was increased in the presence of IL-17. These results suggest that the increase in phosphorylation of GSK3- $\beta$  was involved in the suppression of cytotoxicity in NK92 cells.

We confirmed that IL-17 stimulation suppresses the cytotoxicity of NK92 cells against K562 cells. Our results indicate that two signaling pathways may be involved in the suppression of cytotoxicity by IL-17 stimulation. The first one is a signaling pathway in which transcription factor AP-1 may be suppressed by suppressing phosphorylation of p38 of the MAPKs. The other is a signaling pathway in which transcription factor C/EBP $\beta$  may be suppressed by increasing phosphorylation of GSK3- $\beta$ . This suggests that the involvement of these two signaling pathways may have suppressed cytotoxicity of NK92 cells stimulated by IL-17. However, the signaling pathway for suppressing cytotoxicity of NK92 cells stimulated by IL-17 is complicated and its exact pathway has yet to be elucidated.

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