

ORIGINAL ARTICLE

Oral administration of *Lactobacillus* strains from Kimchi inhibits atopic dermatitis in NC/Nga miceT.J. Won¹, B. Kim², Y.T. Lim¹, D.S. Song¹, S.-Y. Park³, E.S. Park⁴, D.I. Lee¹ and K.W. Hwang¹¹ Immune Modulation Lab., College of Pharmacy, Chung-Ang University, Dongjak-gu, Seoul, South Korea² CJ Foods R&D Center, CJ CheilJedang Corporation, Guro-gu, Seoul, South Korea³ Pharmacognosy Lab., College of Pharmacy, Dankook University, Chungnam, South Korea⁴ Department of Pathology, College of Medicine, Chung-Ang University, Dongjak-gu, Seoul, South Korea**Keywords**atopic dermatitis, house-dust mite, Kimchi, *Lactobacillus plantarum*, NC/Nga mouse.**Correspondence**Kwang W. Hwang, Immune Modulation Lab., College of Pharmacy, Chung-Ang University, 221 Heukseok-dong, Dongjak-gu, Seoul 156-756, South Korea.
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Abstract**Aims:** Atopic dermatitis (AD) is marked by elevated levels of immunoglobulin E and skin lesions such as oedema and haemorrhage. Kimchi is a Korean fermented food that contains beneficial bacteria for human health. In this study, *Lactobacillus plantarum* CJLP55, CJLP56, CJLP133 and CJLP136 isolated from Kimchi were investigated for their capacity to inhibit AD.**Methods and Results:** The three strains, CJLP55, CJLP133 and CJLP136, suppressed AD-like skin lesions, high serum IgE levels and epidermal thickening. The three strains diminished the accumulation of eosinophils and mast cells into topical inflammatory sites and the enlargement of axillary lymph nodes, which are responsible for the dorsal dermatitis. CJLP55, CJLP133 and CJLP136 decreased production of type 2 cytokines such as IL-4 and IL-5 in lymph node cell culture. CJLP133 and CJLP136 increased IFN- γ secretion, while CJLP55 enhanced IL-10 production.**Conclusions:** The three strains isolated from Kimchi suppress house-dust mite-induced dermatitis in NC/Nga mouse, a representative animal model of human AD.**Significance and Impact of the Study:** These findings suggest that lactobacilli isolated from Kimchi inhibit AD, probably by altering the balance of Th1/Th2 ratio or inducing IL-10 production.**Introduction**

Atopic dermatitis (AD) is a chronic inflammatory diseases and its prevalence has increased steadily in recent decades (Yamamoto *et al.* 2009). In atopic skin, mild to severe itching, rash, oedema, haemorrhage, erosion and desquamation are generally present (Oshio *et al.* 2009). An elevated level of immunoglobulin E (IgE) antibodies and the infiltration of a variety of immune cells, such as lymphocytes, mast cells, eosinophils and neutrophils, are also characteristic features in this disease (Kang *et al.* 2008b; Segawa *et al.* 2008b). Although the cause of AD is complicated, the predominance of the Th2 response over the Th1 response is known to be involved in the pathogenesis and development, as well as various genetic

and environmental factors (Kang *et al.* 2008a). Th2 cells in the skin lesions of AD exhibit increased production of cytokines, IL-4, IL-5, IL-6 and IL-13, which are related to the allergic response. In particular, IL-4 plays a crucial role in IgE synthesis, and IL-5 is responsible for eosinophil recruitment and activation (Gao *et al.* 2004; Kang *et al.* 2006). Moreover, IL-6 induces B-cell differentiation to plasma cells and promotes Ig production (Mutou *et al.* 2007). Therefore, enhancement of Th1-type immunity and suppression of Th2-type immunity might be an effective therapy for the management of AD.

Kimchi is a traditional fermented food in Korea and is made of various vegetables such as Chinese cabbage, radish and cucumber. Because Kimchi contains beneficial

health-promoting like β -carotene, chlorophyll, ascorbic acid and dietary fibre, its intake has been recommended as a means of reducing the risk of chronic diseases in Korea (Nam *et al.* 2009). Diverse bacteria are involved in the process of Kimchi fermentation and the healthful advantages, and one of the major species is *Lactobacillus* (Kang *et al.* 2009b). Recently, numerous reports have shown that ingestion of specific strains of *Lactobacillus* reduces allergic skin symptoms and elevation of serum IgE levels in mice (Segawa *et al.* 2008a; Sunada *et al.* 2008; Watanabe *et al.* 2009), and their ability to inhibit allergic reactions may involve the enhancement of Th1/Th2 balance (Tobita *et al.* 2009). Although the effects of *Lactobacillus* strains isolated from Kimchi on AD have not been intensely studied, we previously found four strains, *Lactobacillus plantarum* CJLP55, CJLP56, CJLP133 and CJLP136, showed that they can modulate Th1/Th2 via stimulation of macrophage *in vitro* (Won *et al.* 2011).

NC/Nga mice spontaneously develop AD-like skin lesions with a marked increase in serum IgE level in air-uncontrolled conventional circumstances, whereas NC/Nga mice maintained under specific pathogen-free (SPF) conditions do not show any clinical signs or IgE hyperproduction (Yamamoto *et al.* 2007). However, when placed in SPF surroundings, repeated application of house-dust mite *Dermatophagoides farinae* (Df) extract can induce atopic skin lesions and high IgE titres in NC/Nga mice similar to those in human patients (Matsuoka *et al.* 2003). In the present study, we examined whether oral administration of *Lactobacillus* strains isolated from Kimchi suppressed the development of skin lesions and IgE elevation in the dust mite-induced AD model in NC/Nga mice. We also investigated the effect of the *Lactobacillus* on infiltration of inflammatory cells into the AD-like skin and cytokine secretion in axillary lymph node cells.

Materials and methods

Materials

MRS broth was obtained from Difco Laboratories (Detroit, MI, USA). Biostir AD cream was purchased from Central Lab Inc. (Seoul, South Korea). Antibody pairs against mouse IgE, IFN- γ , IL-4, IL-5 and IL-10 were from BD Biosciences (San Jose, CA, USA). RPMI1640, foetal bovine serum (FBS) and penicillin/streptomycin were purchased from Mediatech (Manassas, VA, USA). FITC-labelled antibodies against mouse Thy1.2 and CD19 were also obtained from BD Biosciences. All other reagents were from Sigma Aldrich (St Louis, MO, USA).

Animals

Six-week-old female NC/Nga mice were provided by Central Lab Animals Incorporation. Animals were randomized and housed in a temperature-controlled animal room ($24 \pm 2^\circ\text{C}$) under a 12-h/12-h light-dark cycle. They were fed standard laboratory food and water prior to experiments. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the protocol was approved by the Institutional Animal Care and Use Committee of the Laboratory Animal Research Center.

Preparation and oral administration of lactobacilli

Lactobacillus plantarum CJLP55 (KCTC 11401BP, GenBank accession number GQ336971), *Lact. plantarum* CJLP56 (KCTC 11402BP, GenBank accession number FJ455520), *Lact. plantarum* CJLP133 (KCTC 11403BP, GenBank accession number FJ455518), *Lact. plantarum* CJLP136 (KCTC 11404BP, GenBank accession number FJ455519) and *Lactobacillus sakei* CJLS118 (KCTC 13416) were all provided by CJ Foods R&D Center, CJ CheilJedang Corporation, Korea. Lactobacilli were incubated in MRS broth at 37°C for 24 h and lyophilized. The mice were fed a dietary powder containing lyophilized CJLP55, CJLP56, CJLP133, CJLP136 and CJLS118 strains (dose of 1×10^{10} CFU per mouse) for 55 days, including atopic induction. Fresh diet was provided daily according to the schedule summarized in Fig. 1a.

Induction of AD-like skin lesions

Biostir AD cream consists of Df body (Dfb) extracts and ointment base. On day 28 after the first oral administration of lactobacilli, mice were anesthetized with ether and their hair on the back skin was removed using an electric clipper and hair removal cream. Then, 100 mg of Biostir AD cream was painted onto the shaved dorsal surface. For disruption of skin barrier, 150 μl of 4% sodium dodecyl sulfate was topically applied on the surface 3 h before Dfb application. The painting was conducted two times a week for 4 weeks.

Evaluation of skin lesions

On days 27, 34, 41, 48 and 55 after the first feeding of lactobacillus strains, the dermatitis severity in mice applied with Biostir AD cream was evaluated. The severity of erythema/haemorrhage, scarring/dryness, excoriation/erosion and oedema was scored as 0 (none),

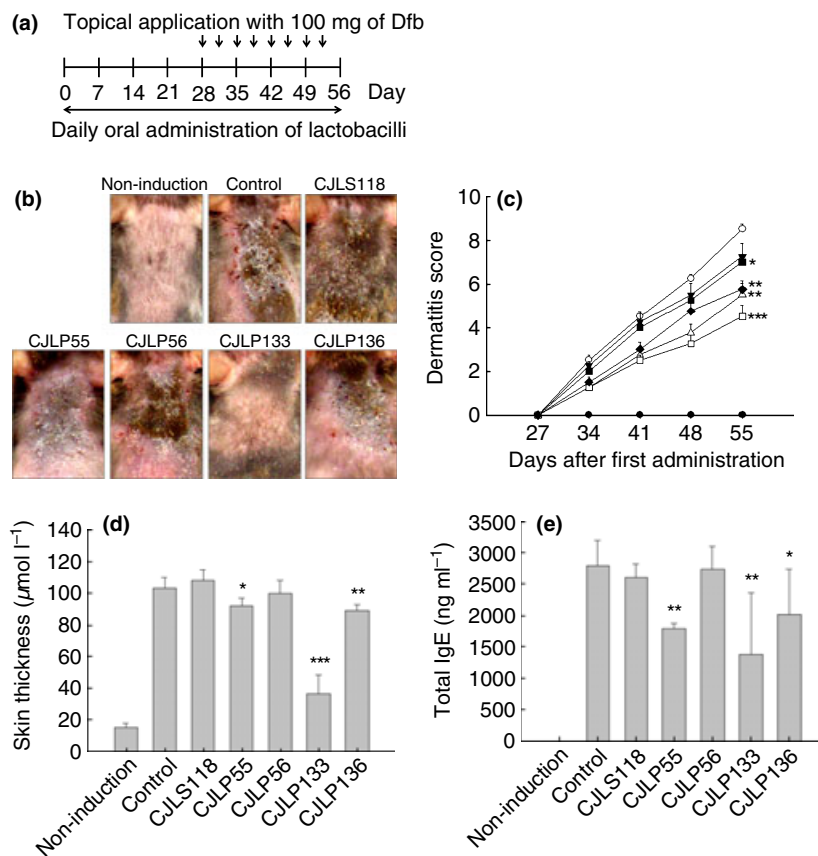


Figure 1 Experimental procedure and effects of the oral administration of lactobacillus strains on dermatitis lesions, skin thickness and serum IgE. (a) Day 0 is defined as the first administration of lactobacillus strains including CJLP55, CJLP56, CJLP133 or CJLP136. (b) Aspects of Dfb-induced dermatitis in NC/Nga mice were taken on day 55. (c) Dermatitis scores were evaluated from day 27 to day 55 once for a week. (d) The dorsal skins were excised, fixed with 10% formalin, embedded in paraffin and stained with haematoxylin and eosin. (e) The concentration of total IgE in collected serum on day 41 was determined by ELISA. Data are shown as mean $\pm$ SD of changes in dermatitis score, skin thickness and total IgE of eight mice ($n = 8$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with control. (—●—) Non-induction; (—○—) Control; (—▼—) CJLS118; (—△—) CJLP55; (—■—) CJLP56; (—□—) CJLP133 and (—◆—) CJLP136.

1 (mild), 2 (moderate) or 3 (severe). Dermatitis score was defined as the sum of these individual scores.

Histological analysis

The dorsal skins of the experimental mice were removed on the final day of the schedule and fixed in 10% phosphate-buffered formalin and embedded in paraffin. The skin sections were stained with haematoxylin and eosin (H&E) for evaluation of oedema. The other sections were stained with toluidine blue or Congo red for detection of mast cells or eosinophils, respectively.

Total serum IgE

For measurement of total serum IgE, blood specimens were obtained from the retro-orbital sinus on days 27, 34, 41, 48 and 55. On day 56, the concentration of total IgE

in the serum was measured by sandwich ELISA using two kinds of rat anti-mouse IgE monoclonal antibody.

Flow cytometric analysis

Axillary lymph nodes and spleens were collected from all mice and then homogenized in RPMI1640 medium. The cell suspension was incubated with FITC-labelled mAb against Thy1.2 or CD19 for 30 min at 4°C. FITC-labelled Armenian Hamster IgG was used as an isotype control antibody. Cell surface expression of molecules was analysed by collecting a minimum of 5000 events in a BD Biosciences FACScan using CELLQUEST software.

Cytokine production

On day 55, all mice were killed and their axillary lymph nodes were isolated. Cell suspensions were prepared at a

concentration of 5×10^6 cells ml^{-1} in RPMI1640 medium containing 10% heat-inactivated FBS, 100 U ml^{-1} penicillin and 100 $\mu\text{g ml}^{-1}$ streptomycin. The lymph node cells were cultured with 10 $\mu\text{g ml}^{-1}$ of Dfb for 48 h at 37°C under 5% CO_2 . After the incubation period, the culture supernatants were collected for the measurement of IFN- γ , IL-4, IL-5 and IL-10 by ELISA.

Statistical analysis

Statistical evaluation of the experiments was performed by Student's *t*-test using SPSS STATISTICS 17.0 (SPSS Inc.,

Chicago, IL, USA). All values are expressed as mean $\pm$ SD. *P*-values <0.05 were considered significant and are indicated by asterisks in the figures.

Results

Effects of oral administration of lactobacilli on dermatitis induction

Figure 1b,c show the effects of CJLP55, CJLP56, CJLP133 and CJLP136 strains on Dfb-induced AD on the dorsal skin. On day 55, severe-grade dermatitis was observed in NC/Nga mice fed with control food or diet containing CJLS118 strain as negative control. Their inflamed skins presented with erythema, scarring/dryness and excoriation, which are the clinical signs of human AD. Moreover, control dietary feeding resulted oedema and epidermal hyperplasia (Fig. 1d). However, oral administration of CJLP55, CJLP133 or CJLP136 suppressed the induction of disease to the level of moderate or mild dermatitis in NC/Nga mice. The antigen-applied regions in these mice remained slightly scarred or dry only on the final day of the experiment. As shown in Fig. 1d, the CJLP133 strain was the most effective suppressor of skin oedema, which means thickening of the epidermis caused by repeated immune response. Although the mice fed CJLP56 manifested lower dermatitis score than the control groups, its dorsal inflammation was evaluated as severe and its skin thickness was not significantly different from control. On the other hand, AD is accompanied by elevated serum IgE levels. As shown in Fig. 1e, total IgE levels in control diet-fed mice were higher than with non-Dfb application on day 41, whereas CJLP55, CJLP133 and CJLP136 feeding significantly decreased the IgE levels. On days 48 and 55, IgE concentration in sera was similar to that on day 41 (data not shown). However, there were no significant differences in serum IgE on days 27 and 34 between mice fed with and without lactobacilli.

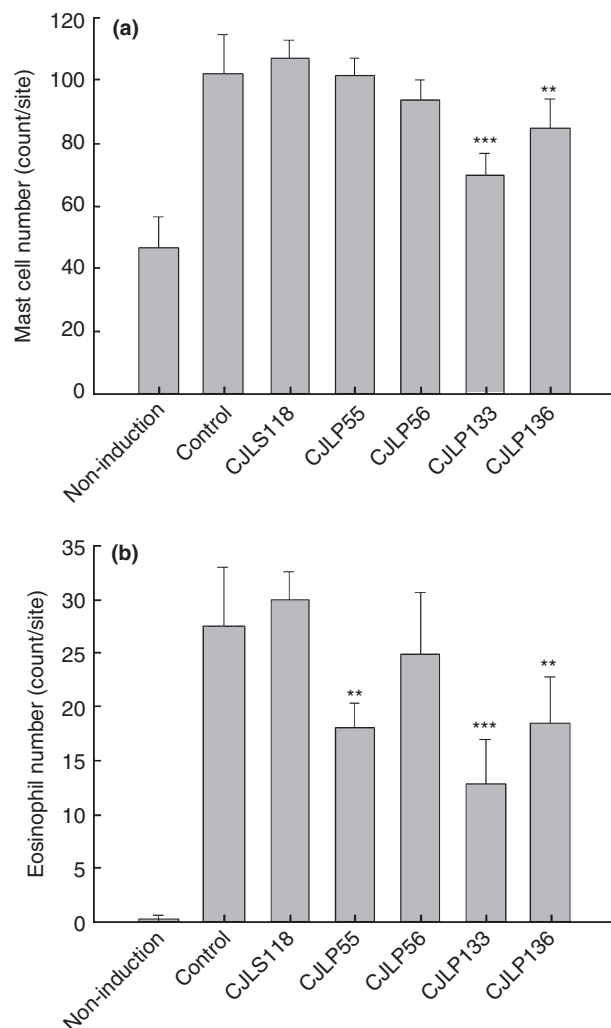


Figure 2 Effects of the administration of lactobacillus strains on topical accumulation of mast cells and eosinophils. The dorsal skins of the NC/Nga mice were stained with Toluidine Blue (a) and Congo Red (b) for mast cells and eosinophils, respectively. The number of cells in 0.025 mm^2 was counted under microscope at a magnification of $\times 400$. Data are shown as mean $\pm$ SD of eight mice. ***P* < 0.01 ; ****P* < 0.001 compared with control.

Effects on local infiltration of mast cells and eosinophils by administration of lactobacilli

Mast cells and eosinophils infiltrate local sites and mainly influence the induction of AD. As shown in Fig. 2, accumulation of mast cells and eosinophils was increased in mice fed the control diet. However, oral administration of CJLP133 or CJLP136 significantly suppressed accumulation of the cells in dorsal inflammatory sites. Histological analysis by Toluidine Blue or Congo Red staining revealed that CJLP55 did not inhibit the infiltration of mast cells, but blocked eosinophil accumulation in the dermis. CJLP56 strain did not decrease the infiltration of both effector cells into local inflamed sites.

Effects on axillary lymph node cells by oral intake of lactobacilli

In the adaptive immune response, a lymphoid organ near the local inflammatory sites generally takes charge of antigen presentation, lymphocyte differentiation and proliferation for rapid and effective elimination of antigen. For these reasons, axillary lymph nodes were enlarged and their cell number was increased in the case of dorsal dermatitis compared with noninduction (Fig. 3). Oral administration of lactobacillus strain CJLP55, CJLP133 or CJLP136 lowered total cell, T cell and B cell numbers and suppressed the lymph node enlargement. However, those cell numbers in splenocytes isolated from mice fed the

four lactobacilli did not exhibit any alteration when compared with control (data not shown).

Effects on cytokine production of lymph node cells by oral administration of lactobacilli

To address whether oral administration of CJLP55, CJLP56, CJLP133 or CJLP136 affected Th1/Th2 balance at the local inflammatory site, axillary lymph node cells isolated from the mice were re-stimulated with Dfb for 48 h *in vitro* and then the cytokine concentration in the culture supernatant was measured. Figure 4a shows that CJLP133 and CJLP136 feeding prompted the production of IFN- γ , representative Th1-type cytokine, to high level

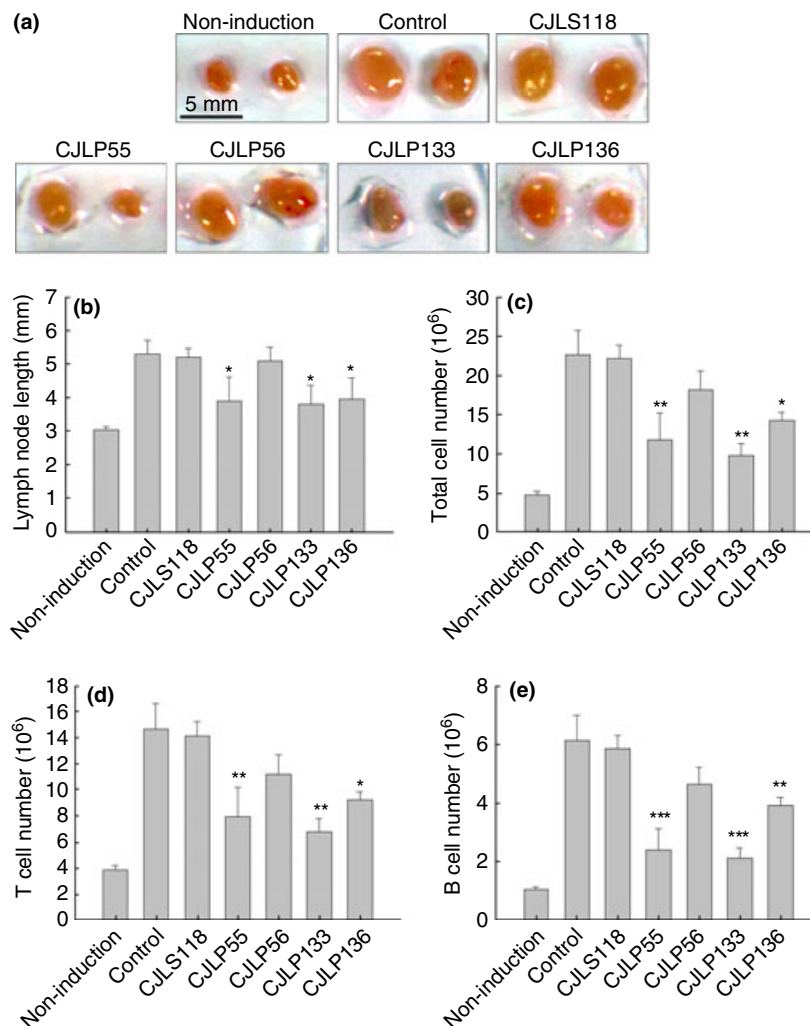


Figure 3 Effects of the ingestion of lactobacilli on axillary lymph nodes. (a) The photographs show the axillary lymph nodes on day 56. (b) The length of axillary lymph nodes was measured on day 56. (c–e) Cell suspensions were obtained from excised lymph nodes and counted for measurement of total cell number. Then the cells were incubated with FITC-labelled anti-Thy1.2 or anti-CD19 for detection of T cells and B cells, respectively. Data are shown as mean $\pm$ SD of eight mice. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with control.

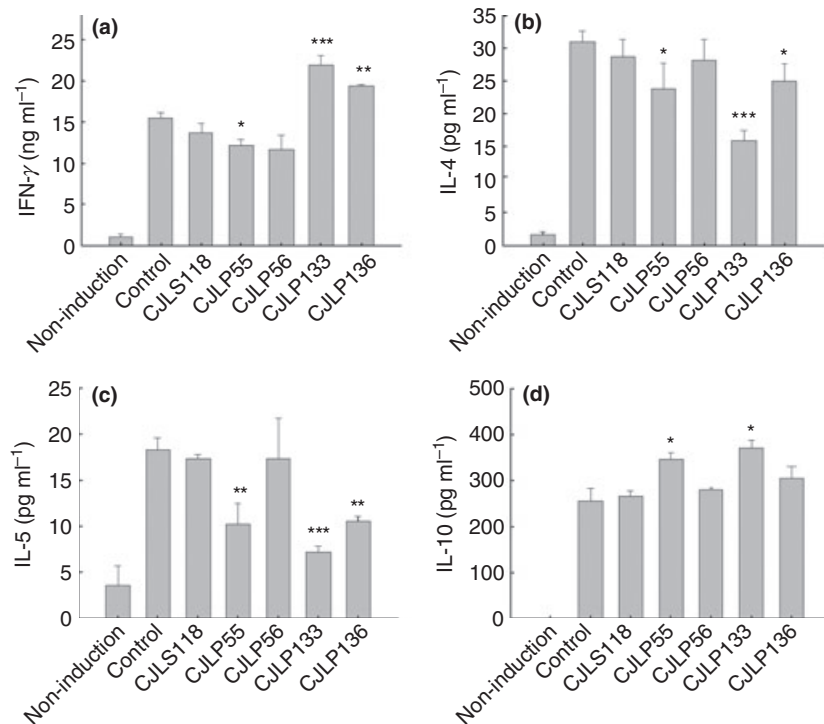


Figure 4 Effects of oral administration of lactobacilli on the production of (a) IFN- γ , (b) IL-4, (c) IL-5 and (d) IL-10 in the draining lymph node cells. On day 56, axillary lymph node cells were purified from lactobacilli-fed NC/Nga mice. The cells were stimulated with $10 \mu\text{g ml}^{-1}$ of Dfb solution for 48 h. Cytokine levels were measured by ELISA. Data are shown as mean $\pm$ SD of three independent experiments. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$ compared with control.

in lymph node cells, while CJLP55 feeding inhibited that. Because IFN- γ generally suppresses T-cell polarization into Th2 cells producing IL-4 and IL-5, ingestion of two potent IFN- γ inducers, CJLP133 or CJLP136, decreased the secretion of Th2-type cytokines in draining lymph node cells; however, CJLP55 strain also inhibited the production of IL-4 and IL-5, although it decreased the secretion of IFN- γ blocking Th2 differentiation (Fig. 4b,c). In the case of immunosuppressive cytokine IL-10, oral stimulation of CJLP55 and CJLP133 enhanced its secretion compared with that of nonbacterial feeding in lymph node cells isolated from AD-induced NC/Nga mice (Fig. 4d). CJLP136 strain did not significantly increase IL-10 production in the cell culture.

Discussion

In this study, we addressed the immunological activity of lactobacilli CJLP55, CJLP133 and CJLP136 isolated from Kimchi that is able to suppress human-like AD in NC/Nga mice. These three strains inhibited clinical signs of Dfb-induced dermatitis lesions, such as redness, bleeding, eruption, and scaling, and decreased the high serum IgE levels and the inflammatory skin thickening. Because

the dermal thickness in mice fed CJLP55, CJLP133 or CJLP136 was lower than in control, it is possible that infiltration of immune cells such as mast cells and eosinophils was reduced in these mice. However, the volume of axillary lymph node, which is responsible for dorsal skin inflammation, was also reduced by oral administration of three lactobacilli in Dfb-induced AD. This result suggests that oral uptake of lactobacillus inhibits the immune response of T and/or B cells, major components of the lymph node, against Dfb antigen invasion, and thus lowering the induced immunological reaction by diminishing the recruitment of major effector cells such as mast cells and eosinophils in atopic hypersensitivity. Furthermore, the decline of serum IgE concentration by lactobacilli suppresses the activation of mast cells and eosinophils, because they express high-affinity receptor for IgE on their surface to induce their activation and degranulation of inflammatory mediators such as histamine and tryptase.

We investigated whether oral administration of CJLP55, CJLP133 or CJLP136 influenced the balance of Th1/Th2 immune response. IFN- γ , secreted by Th1 cells, induces cell-mediated and inflammatory immune response and suppresses polarization immunity towards the type 2

response (Kang *et al.* 2009a). In the present study, the IFN- γ production was elevated in axillary lymph node cells isolated from mice fed CJLP133 or CJLP136, while the concentration of IL-4 and IL-5, Th2 cytokines, was diminished in the culture supernatants. In our previous study, CJLP133 and CJLP136 strains produced a large amount of IL-12, which enhances Th1-type response, on macrophage cell-line J774A.1 *in vitro*, and CJLP133-treated macrophages indeed induced secretion of more IFN- γ and less IL-4 than nonbacterial control in co-cultivation with T cells (Won *et al.* 2011). Hence, the ingestion of CJLP133 or CJLP136 lactobacilli isolated from Kimchi may lead adaptive immunity towards Th1 response in Th2-dominant atopic NC/Nga mice through the activation of IL-12-producing macrophage and restore the skewed-Th1/Th2 balance to its normal condition. The diminished type 2 response in the atopic mice fed CJLP133 or CJLP136 can decline to switch antibody isotype from IgM to IgE produced by B cells and to recruit eosinophils or mast cells to inflamed tissues.

Because of its beneficial effects on Dfb-induced dermatitis lesions and serum IgE levels, CJLP55 is considered an enhancer of Th1 response like CJLP133 or CJLP136. However, oral intake of CJLP55 unexpectedly reduced the production of both Th1- and Th2-type cytokines in axillary lymph node cells, while the production of IL-10, an immunosuppressive cytokine, is enhanced. IL-10 inhibits not only activation and effector functions of T cells, monocytes and dendritic cells but also antigen presentation on dendritic cells (Inoue *et al.* 2007). IL-10 also has the capacity to induce a state of anergy and tolerance in T cells. Therefore, IL-10 induction by CJLP55 in axillary lymph nodes might influence the local immune system and improve the AD-like skin lesions and serum IgE levels. Although a number of immune cells such as T cells, B cells, macrophages and dendritic cells are able to produce IL-10 cytokine, the major source of IL-10 is CD4⁺ CD25⁺ regulatory T (Treg) cells, which have an immunosuppressive function and inhibit the development of both Th1 and Th2 responses (Sawada *et al.* 2007). Recent studies show that oral administration of several lactobacilli and bifidobacteria strains results in the prevention of experimental autoimmune encephalomyelitis (EAE) in mouse model and suppression of allergic response in ovalbumin-sensitized mice through Treg induction in their lymphoid organs (Lavasani *et al.* 2010; Lyons *et al.* 2010). Although exact mechanism used by lactic acid bacteria to induce the recruitment or the differentiation of Treg cells is not clear, ingestion of specific bifidobacteria substrain upregulates the expression of genes involved in metabolism of retinoic acid that can promote Treg cell generation on mouse lymphoid tissue (Lyons *et al.* 2010), and some lactobacilli strains induce

FoxP3⁺ cells in human peripheral blood mononuclear cells *in vitro* (de Roock *et al.* 2010). Although CJLP133 ingestion also increased IL-10 production in the lymph node cells isolated from NC/Nga mice, CJLP133 strongly enhanced the production of IL-12 and IL-10 together on macrophages and dendritic cells in our previous study, while CJLP55 induced mild elevation of IL-12 and IL-10 levels. Thus, our further study would address whether oral administration of CJLP55 induce Treg cells that suppress both type 1 and type 2 immune responses in mouse immunological organs.

Taken together, the results presented in this report demonstrate that CJLP55, CJLP133 and CJLP136 strains isolated from Kimchi inhibit Dfb-induced dermatitis, elevation of serum IgE, topical accumulation of immune cells and enlargement of axillary lymph nodes. CJLP133 and CJLP136 lactobacilli also induced the production of Th1 cytokine IFN- γ for balanced Th1/Th2 response, whereas CJLP55 strain produced IL-10 cytokine, which has a suppressive effect on AD. These results suggest that lactobacilli from Kimchi might be potential candidates for prevention of AD.

Acknowledgement

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