Induction of Th1 Cells and Reduction of Th2 Cells in Ovalbumin-immunized BALB/c Mice upon Oral Administration of *Lactobacillus paracasei* K71

Takuya TERADAIRA[1], Takashi HARA[2*], Takehisa KUMAGAI[3] Mariko IGUCHI[3] and Toshio JOH[2]

(Received January 30, 2013)

Summary

Lactobacillus paracasei K71 (*L. paracasei* K71) with stimulatory activity for interleukin-12 (IL-12) production has been isolated from Sakekasu (sake lees), a Japanese traditional fermented food coproduced during sake brewing. Oral administration of *L. paracasei* K71 significantly reduced serum immunoglobulin (Ig) E level in ovalbumin (OVA)-immunized BALB/c mice with type 2 helper T (Th2) polarization. In the present study, we examined the influence of *L. paracasei* K71 on Th1/Th2 cells population in spleen, employing OVA-immunized BALB/c mice. Orally administration of *L. paracasei* K71 resulted in an increase of $CD4^+$ T cells expressing CXCR3 (CD183) and a decrease of CD4+ T cells expressing CCR4 (CD194) in splenocytes, in parallel with a reduction of total and OVA-specific IgE levels in serum. Since Th1 cells and Th2 cells preferentially express CXCR3 and CCR4 respectively, it seems that *L. paracasei* K71 can potentially induce Th1 cells and reduce Th2 cells *in vivo*, leading to down-regulation of IgE synthesis. The splenocytes from *L. paracasei* K71-administrated mice also showed lower IgE production level than those from control mice. These results suggest that *L. paracasei* K71 might be useful for improving Th2-dependent allergic diseases.

Bull.Facul.Agric.Niigata Univ., 65(2):149–155, 2013

Key words : *Lactobacillus paracasei* K71, IgE, Th1/Th2, CXCR3(CD183), CCR4(CD194)

Lactobacilli are used widely in industrial and traditional fermentative food processes. Commensal microorganisms including lactobacilli are intensively exploited for probiotics-containing dairy products. Most bacteria belonging to the genus *Lactobacillus* have a long history of safe use (Salminen *et al*., 1998). It is expected that lactobacilli inhabiting in a variety of food products potentially contribute to health benefits. Certain *Lactobacillus* strains can potentially modulate immune response through the production of interleukin-12 (IL-12), a potent stimulus for interferon-γ (IFN-γ) production, by antigen presenting cells, such as dendritic cells (DCs) and macrophages, leading the population of type 1 helper T (Th1) cells and Th2 cells toward Th1-biased state (Murosaki *et al*., 1998; Shida *et al*., 1998; Fujiwara *et al*., 2004). This effect might be of use in prevention and treatment of allergic diseases. Most of allergic diseases, such as atopic dermatitis, pollinosis and seasonal allergic rhinitis, are associated with elevated production of serum immunoglobulin E (IgE). IgE is produced by plasma B cells, which is mainly regulated by Th2 cells via producing IL-4. IL-4 induces IgE class switching, augments IgE production in B cells and itself promotes Th2 differentiation. It is realized that Th2-biased state participates in clinical condition of allergic diseases (Robinson *et al*., 1996; Platts-Mill, 2001). On the contrary, Th1 cells produce IFN-γ that plays the opposite role to IL-4, and itself promotes Th1 differentiation. Therefore, *Lactobacillus* strains with an ability to induce Th1-biased state via IL-12 production, whereby Th2 responses are weakened, are expected to prevent IgE-mediated allergic diseases (Fujiwara *et al*., 2004; Shida *et al*., 2002; Cross *et al*., 2002; Pochard *et al*., 2002).

Recently, we isolated *L. paracasei* K71, as a potent inducer of IL-12 production, from Sakekasu (sake lees), a Japanese traditional fermented food coproduced during sake brewing. *L. paracasei* K71 exhibited a potential to suppress serum IgE levels in mice given the strain orally (Kumagai *et al*., 2013). This suppression of serum IgE levels could be explained by the modulation of Th1/Th2 balance toward Th1-dominant state in systemic immunity via *L. paracasei* K71-induced IL-12 production. In this study, we focused on the frequency of Th1/Th2 cells in splenocytes from OVA-immunized BALB/c mice upon administration of *L. paracasei* K71.

MATERIALS AND METHODS

Lactobacillus Strain

L. paracasei K71 used in this study were isolated from Sakekasu (sake lees), a Japanese traditional fermented food coproduced during sake brewing, and held at Kameda Seika Co., Ltd. (Niigata, Japan). After cultivation in MRS broth at 37 ℃ for 24 h, the cells of *Lactobacillus* strains were harvested, washed with sterile distilled water and killed by heating at 105 ℃ for 15 min. The resultant heat-killed cells were

[1] Graduate School of Science and Technology, Niigata University

[2] Faculty of Agriculture, Niigata University

[3] Kameda Seika Co., Ltd.

lyophilized and then suspended in distilled water to be used in following experiments.

Mice

Female BALB/c mice at 5 weeks of age were purchased from Charles River Japan (Yokohama, Japan) and were maintained conventionally in plastic cages at about 22 ℃ under a 12-h light-dark cycle. The mice were provided with a standard MF diet (Oriental Yeast, Tokyo, Japan) and allowed *ad libitum* access to autoclaved water throughout the experimental period. This experiment was carried out according to the guidelines laid out by The Ethical Committee for Animal Experiments of Niigata University.

Oral Administration of Lactobacilli and Immunization

The schedule for *in vivo* experiments is summarized in Fig. 1. One mg of heat-killed cells of *Lactobacillus paracasei* K71 in 50 μL sterile water were orally administered to female BALB/c mice (6 weeks of age, n = 6 per group) everyday, in parallel with intraperitoneal immunization with 100 μg OVA and 1 mg $Al(OH)_3$ gel on day 0 and 14. As a control, 50 μL of sterile water, instead of heat-killed cells of *Lactobacillus paracasei* K71, was orally given to mice. For the measurement of total and OVA-specific IgE level, blood were collected from tail bleed every 7 days from day 0 to 28 and sera were separated by centrifugation (10,000 × g) at 4 ℃ for 10 min, and then stored at -80 ℃ before use in measurement. On day 35 to 42, mice were sacrificed and splenocytes were obtained for *ex vivo* IgE production assay and flow cytometry.

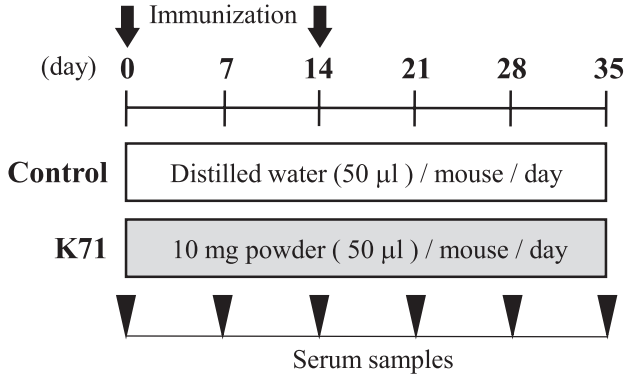

Fig. 1. Experimental schedule for immunization with OVA and administration of *L. paracasei* K71. Female BALB/c mice were immunized by intraperitoneal injection with 100 μg OVA and 1 mg $Al(OH)_3$ gel on day 0, 14. The immunized mice were administrated with or without heat-killed *L. paracasei* K71 orally. Serum samples were collected every 7 days from Day 0 to 35 and splenocytes were obtained on day 35 to 42.

ELISA

For determination of total IgE, sandwich ELISA was employed using anti-mouse IgE antibody (LO-ME-2) (ZYMED, San Francisco, CA, USA) as a primary antibody and biotinylated anti-mouse IgE antibody (LO-ME-3) (Acris, Hiddenhausen, Germany) as a secondary antibody in combination with streptavidin-horseradish peroxidase (HRP) conjugate. OVA-specific IgE levels were also assessed by almost the same sandwich ELISA system using OVA for coating the ELISA plates instead of primary antibody. As HRP substrate, 3,3',5,5'-tetramethylbenzidine (Sigma-Aldrich, St Louis, MO, USA) were used and absorbance at 450 nm was measured using a microplate reader (Model 680, BIO-RAD, Hercules, CA, USA).

***Ex Vivo* Splenocyte Culture**

Spleen from individual mouse was made into single cell suspension containing splenocytes. Red blood cells were removed from splenocytes by incubating with red blood cell lysis buffer (150 mM NH_4Cl, 1 mM $KHCO_3$, 0.1 mM EDTA, pH 7.2). Splenocytes obtained from mice were seeded at 2×10^6 cells/mL in 96-well flat-bottomed culture plates and cultivated with 100 μg/mL OVA in RPMI-1640 containing 10 % (vol/vol) heat-inactivated fetal bovine serum, 100 U/mL penicillin and 100 μg/mL streptomycin, under a humidified atmosphere of 5 % CO_2 at 37 ℃. Following cultivation for 14 days, culture supernatants were collected to measure the amount of total IgE by ELISA.

Flow Cytometry

After removing red cells by incubating with red blood cell lysis buffer, splenocytes were washed and resuspended in phosphate buffered saline (PBS) containing 0.1% BSA. Subsequently, cells were stained with FITC-conjugated anti-CD3 mAb (Beckman coulter, Miami, USA), PE-conjugated anti-CD4 mAb (Beckman coulter), PerCP-conjugated anti-CD183 (CXCR3) mAb (Biolegend, San Diego, CA, USA) and APC-conjugated anti-CD194 (CCR4) mAb (Biolegend). After staining, the cells were analyzed by FACSCalibur (BD Biosciences, San Jose, CA, USA). A minimum of 10,000 events in the lymphocyte gate were collected and data analysis were performed using CellQuest software (BD Biosciences). Appropriate isotype-matched, irrelevant mAbs served as negative control.

Statistical Analysis

Data are represented as the mean ± standard deviation (SD). Statistical differences between the means of administrated and control groups were tested using one-way analysis of variance (ANOVA) and Fisher's protected least significant difference (PLSD). A p-value of less than 0.05 was considered statistically significant.

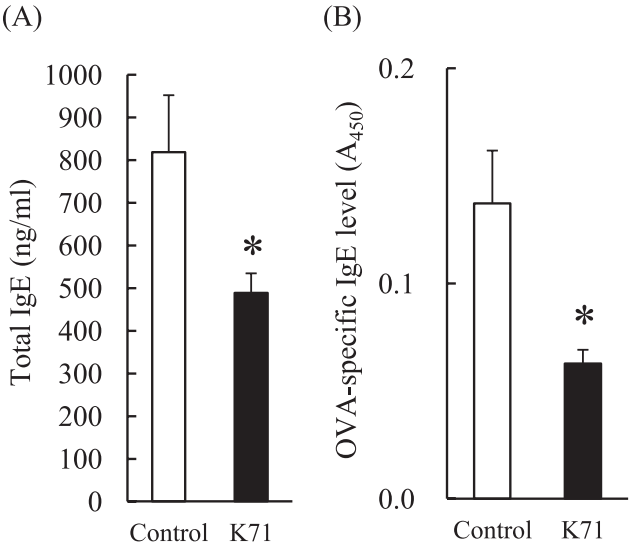

Fig. 2. Serum IgE levels in OVA-immunized mice. Lyophilized powder of heat-killed *L. paracasei* K71 was suspended in sterile water and administrated orally to mice at 1 mg/mouse/day. Total IgE (A) and OVA-specific IgE (B) levels in serum on day 35 were determined by ELISA. Data represent mean ± SD of six mice per group (n = 6). $^*p < 0.05$ compared with control (OVA-immunized mice without *L. paracasei* K71).

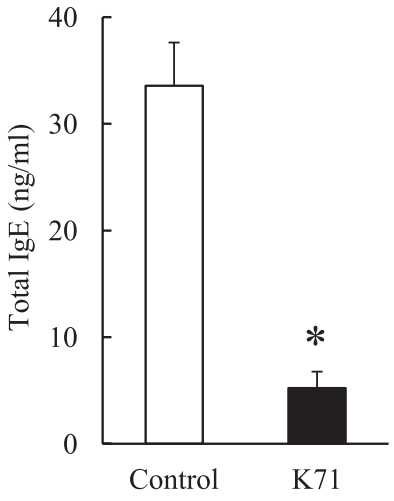

Fig. 3. *Ex vivo* IgE production in splenocyte culture. Splenocytes from OVA-immunized BALB/c mice were cultured with OVA (100 μg/ml) for 14 days. Total IgE in culture supernatants were determined by ELISA. Data represent mean ± SD (n = 6). $^*p < 0.05$ compared with control (OVA-immunized mice without *L. paracasei* K71).

RESULTS

Serum IgE levels

L. paracasei K71 was administered orally to OVA-immunized mice at 1 mg/day/mouse and the sera were collected every 7 days during the experiment. The concentrations of total IgE and the levels of OVA-specific IgE in serum on day 35 were shown in Fig. 2. OVA-immunization without administration of *L. paracasei* K71 resulted in gradual elevation of both total and OVA-specific IgE levels in serum during the experimental period. Administrated *L. paracasei* K71 exhibited the ability to reduce total and OVA-specific IgE level in serum with statistical significance ($P < 0.05$).

Ex vivo IgE production by splenocytes

After confirming decreased levels of total and OVA-specific IgE in serum by oral administration of *L. paracasei* K71, splenocytes from individual mouse were collected on day 35 to 42 and stimulated with OVA in culture for 14 days. Fig. 3 shows the concentration of total IgE in culture supernatants of splenocytes. Concentration of total IgE was significantly lower in culture supernatants of splenocytes from GABA-administrated mice than those in control mice ($P < 0.05$). IgE in culture supernatants of splenocytes without OVA were below the limits of detection (data not shown). In accordance with serum IgE level described above, the IgE production level in splenocytes was significantly lower in the *L. paracasei* K71-administrated mice compared to that in the control mice.

CD183 and CD194 expression in helper T cells

It has been revealed that helper T cell phenotypes are accompanied by certain cell surface markers, particularly chemokine receptors. CXCR3 (CD183), the receptor for IP-10 (CXCL10), I-TAC (CXCL11) and Mig (CXCL9), is highly expressed on Th1 cells and down-regulated on Th2 cells. In contrast, CCR4 (CD194), the receptor for TARC (CCL17) and MDC, is preferentially found on Th2 cells but on Th1 cells. Orally administrated *L. paracasei* K71 showed increased percentage of CXCR3-expressing helper T ($CXCR3^+CCR4^-CD3^+CD4^+$) cells concomitant with decreased percentage of CCR4-expressing helper T ($CXCR3^-CCR4^-CD3^+CD4^+$) cells in splenocytes (Fig 4). It seems that *L. paracasei* K71 can potentially induce Th1 cells and reduce Th2 cells *in vivo*. Although we cannot totally exclude the possibility that Th1 and/or Th2 cells are in part contained among $CXCR3^+CCR4^+$ double-positive T cells, most of which must be within populations of naive helper T cells (Th0) cells and fewer polarized T cells than Th1 and Th2 cells (Kim *et al*., 2001). Almost no significant changes between the percentages of helper T ($CD3^+CD4^+$) cells in splenocytes from *L. paracasei* K71-administrated mice and control mice were detected (data not shown).

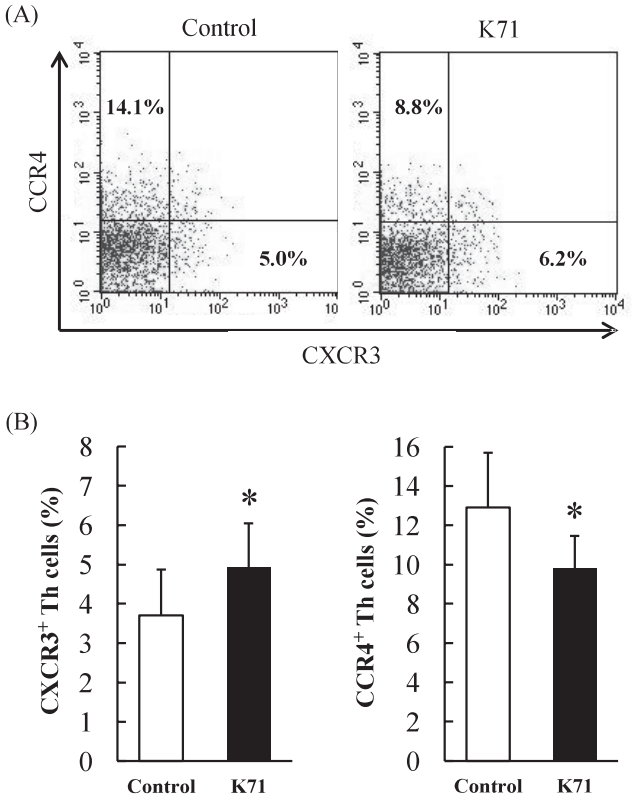

Fig. 4. Frequency of helper T cells expressing CXCR3 and CCR4 in splenocytes. Typical flow cytometry plots (A) and percentages (B) of CXCR3 and CCR4 expressing cells in helper T ($CD3^+CD4^+$) cells from mice administrated with or without heat-killed *L. paracasei* K71 were depicted. Data represent mean ± SD (n = 6). $^*p < 0.05$ compared with control (OVA-immunized mice without *L. paracasei* K71).

DISCUSSION

Considerable attention has been given to immunomodulatory activities of lactobacilli. Previously, *in vitro* study revealed that *L. casei* Shirota killed by heating induced IL-12 and IFN-γ production, but inhibited IL-4 production in splenocytes (Shida *et al*., 1998). The same cytokine production pattern concomitant with decreased serum IgE levels was observed in splenocytes from OVA-immunized BALB/c mice given heat-killed cells of *L. casei* Shirota orally (Matsuzaki *et al*., 1998). It has also been found that oral administration of heat-killed *L. paracasei* KW3110 (Fujiwara *et al*., 2004) and *L. gasseri* OLL2809 (Sashihara *et al*., 2006) selected by their IL-12-inducing and IL-4-repressing activity through *in vitro* experiments showed repression of serum IgE levels in OVA-immunized Balb/c mice, with increased IL-12, but not IFN-γ, and decreased IL-4 production in splenocytes. Thus, there have been numerous experimental evidences that indicate certain *Lactobacillus* strain with stimulatory activity for IL-12 production is potentially effective in lowering serum IgE levels in murine models (Matsuzaki *et al*., 2000; Sashihara *et al*., 2006; Segawa *et al*., 2008). Recently, we demonstrated that *L. paracasei* K71, isolated from Sakekasu as a potent inducer of IL-12 production, suppress serum IgE levels in mice given the strain orally (Kumagai *et al*., 2013). It is possible that administrated *L. paracasei* K71 can modulate the imbalance between Th1 and Th2 cells through induction of Th1 cells in systemic immunity, leading to suppression of IgE production. However, there is almost no available information concerning the change in Th1/Th2 cells population in mice upon oral administration of lactobacilli. Therefore, we investigated the frequency of Th1 and Th2 cells, as well as IgE production, in splenocytes from OVA-immunized BALB/c mice given *L. paracasei* K71 orally.

A number of groups have reported that adhesion molecules and chemokines selective for Th1 and Th2 cells are involved in the differential recruitment of these two subsets (Springer, 1994; Yoshie *et al*., 1997). In this context, differential expressions of certain chemokine receptors in Th1 and Th2 cells have been identified intensively. Previous studies provide evidence that Th1 cells preferentially express CXCR3 (CD183), while Th2 cells selectively express CCR4 (CD194) (Sallusto *et al*., 1998; Bonecchi *et al*., 1998; Yamamoto *et al*., 2000). It is also recognized that, IFN-γ, a Th1 cytokine, is required for the induction of CXCR3 expression and function, while expression and functionality of CCR4 are generated depending on IL-4, a Th2 cytokine (Nakajima *et al*., 2002; Morimoto *et al*., 2005). Based on their different CXCR3 and CCR4 expression pattern, the populations of Th1 and Th2 cells in splenocytes were measured by flow cytometry.

When administrated with *L. paracasei* K71, OVA-immunized BALB/c mice exhibited reduced total and OVA-specific IgE levels in serum than those in control mice (Fig. 2). Furthermore, *ex vivo* IgE production level by splenocytes from mice given *L. paracasei* K71 orally was decreased significantly (Fig. 3). The reduction of serum IgE levels by administrated *L. paracasei* K71 could be explained by the decrease of IgE production in the splenocytes. Furthermore, we have demonstrated that the balance of Th1 ($CXCR3^+CCR4^-CD3^+CD4^+$) cells to Th2 ($CXCR3^-CCR4^+CD3^+CD4^+$) cells were upreguleted by orally administrated *L. paracasei* K71 (Fig. 4). In line with our previous *in vitro* study, *L. paracasei* K71 exhibited strong potential to induce Th1 cells and reduce Th2 cells *in vivo*. It may explain in part the beneficial effects of *L. paracasei* K71 in the treatment of Th2-dependent allergic diseases through promoting Th1 cells to improve Th1/Th2 balance, leading to lower serum IgE level.

In human clinical trials, *L. paracasei* K71 was found to ameliorate the symptoms in atopic dermatitis patients (Moroi *et al*., 2010). Further examination concerning immunomodulatory effects of *L. paracasei* K71 on symptoms in NC/Nga mice, which are accepted as a suitable model for human atopic dermatitis, are now on going in our research

group. In the present study, we demonstrated a potential use of *L. paracasei* K71 in promoting Th1 cells *in vivo*. Besides anti-allergic effect, *L. paracasei* K71 may have different immunological functions, such as improving effects against infectious diseases, through enhancing Th1-immunity.

ACKNOWLEDGMENT

This work was supported in part by the grant from Regional Innovation Research and Development Operation, Kanto Bureau of Economy, Trade and Industry.

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Lactobacillus paracasei K71投与によるオボアルブミン感作したBALB/c マウスにおける Th1細胞増加と Th2細胞減少

寺平拓也[1]・原　　崇[2]*・熊谷武久[3]・井口真理子[3]・城斗志夫[2]

（平成25年 1 月30日受付）

要　約

Lactobacillus paracasei K71（K71株）は、IL-12産生促進作用を有する乳酸菌として日本酒の酒粕より分離された。Th2優位の状態にある BALB/c マウスにオボアルブミン感作し、このマウスに K71株を経口投与すると、血中 IgE レベル亢進を顕著に抑制した。本研究では、OVA 感作した BALB/c マウスを用い、脾臓における Th1／ Th2バランスに及ぼす K71株の影響について検討した。K71株を経口投与すると、血中の総 IgE および OVA 特異的 IgE レベル亢進を抑制すると同時に、脾臓における CXCR3（CD183）陽性 $CD4^+$T 細胞の増加と CCR4（CD194）陽性 $CD4^+$T 細胞の減少が確認された。K71株投与群マウス脾臓細胞は、対象群マウス脾臓細胞より IgE 産生能が低下していた。Th1および Th2細胞はそれぞれ CXCR3と CCR4を特徴的に発現することから、K71株は生体内で Th1細胞の増加と Th2細胞の減少を促し、IgE 産生の抑制に繋がることが伺える。以上の結果は、Th2型免疫応答が関与するアレルギー疾患の改善に K71株が有効であることを示唆する。

新大農研報, 65(2):149-155, 2013

キーワード：*Lactobacillus paracasei* K71, IgE, Th1/Th2, CXCR3（CD183）, CCR4（CD194）

[1] 新潟大学自然科学研究科

[2] 新潟大学農学部

[3] 亀田製菓株式会社

* 代表者：harata@agr.niigata-u.ac.jp