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RESEARCH REVIEW

Health Benefits of Lactic Acid Bacteria Isolated from Kimchi, with Respect to Immunomodulatory Effects

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Abstract Kimchi is a traditional Korean fermented vegetable product, which is fermented by various lactic acid bacteria (LAB), including the genera *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Weissella*. While the immunomodulatory effects of LAB isolated from dairy products are relatively well established, little is known about whether kimchi LAB are capable of modulating a variety of host immune responses. Recent studies have shown that several kimchi LAB that show probiotic properties regulate the balance of T-helper cell response by inducing macrophage activation and enhance the differentiation and activation of regulatory T cells, resulting in the alleviation of allergies and atopic dermatitis in animal models. In this review, current knowledge will be discussed about the beneficial effects of kimchi LAB, including the effects of different strains on immunological functions, and the potential use of kimchi LAB strains as immunomodulators in various immunological settings for therapeutic purposes.

Keywords: kimchi, lactic acid bacteria, immunomodulatory effect

Introduction

Kimchi, which is a type of traditional fermented food in Korea, is fermented by various lactic acid bacteria (LAB) originating from soil or ingredients of kimchi. More than 100 different species of LAB are involved in kimchi fermentation, such as the genera *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Weissella*, and novel species of LAB are still being identified (1,2). LAB not only improve the shelf-life of kimchi, but also contribute desirable tastes and flavors (3). LAB constitutes a major part of the commensal microbial flora of the human gastrointestinal tract and reinforce the host defense systems by inducing mucosal immune responses (4). A number of reports have shown that LAB and their fermented products are effective at preventing gastric mucosal lesion development, protecting the host from intestinal pathogen infections, and enhancing innate and adaptive immunity (5). Since kimchi is naturally fermented by a variety of LAB and kimchi LAB have been shown to modulate the host's immune responses, kimchi has been placed in the spotlight as a rich source of beneficial LAB. In this review, we describe the immunomodulatory effects of LAB strains isolated from kimchi as compared with those of other LAB strains isolated from humans and other fermented foods.

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Immunomodulation by LAB from human and other fermented foods

After the first immunological study was reported in 1976 showing that the cell membrane and cell wall components of LAB originating from the oral cavity were able to stimulate immune responses (6), there were no further studies on the immunomodulation by LAB for some time. Then, intensive research started after a study by Hatcher and Lambrecht in 1993, which reported that cell-free extracts of *Lactobacillus acidophilus* enhanced the phagocytic activity of the macrophage cell line J774 (7).

Modulation of innate immunity Innate immunity is not only the first immunological barrier against pathogens, but also plays a pivotal role in the development of adaptive immunity. Macrophages and dendritic cells (DCs) acting as antigen-presenting cells (APCs) are involved in innate immunity by producing proinflammatory cytokines in response to stimuli, and natural killer (NK) cells also participate in innate immunity. In particular, several LAB strains, including the genera *Lactobacillus*, *Lactococcus*, and *Pediococcus*, have been found to enhance the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, and that of immune-stimulating cytokines such as IL-6, IL-12, and interferon (IFN)-γ in response to macrophages and DCs. They were also shown to increase the surface expression of MHC molecules and co-stimulatory molecules such as CD40, CD80, CD86, and ICOS (8-11). According to the study of Koizumi *et al.* (12), bone marrow-derived DCs from toll-like receptor 2 (TLR2) and TLR4 knockout mice showed impaired IL-12 production in response to LAB, suggesting that TLR molecules expressed on DCs are essential for the activation of DCs upon interaction with LAB. Moreover, recent study has shown that the cell wall components of LAB are capable of acting as TLR ligands, supporting the above findings (13).

NK cells are effector lymphocytes that play an important role in controlling certain types of tumors and infections, since they have natural cytotoxic activity (14). Several LAB strains can enhance NK cell proliferation and function. Tsai *et al.* (15) reported that mice fed *Lactobacillus paracasei* subsp. *paracasei* NTU 101 showed an increased proportion of mature DCs and an enhanced level of cytotoxic activity of NK cells compared with mice fed a control diet. Surprisingly, these immunomodulatory effects were sustained after the termination of *L. paracasei* subsp. *paracasei* NTU 101 feeding, suggesting that a *L. paracasei* subsp. *paracasei* NTU 101 strain may contribute to modulate immunity for as long as it survives in the mouse intestine. Similar results have been reported by Kosaka *et al*. (16). Stimulation of mouse splenocytes with *Lactococcus lactis* subsp. *cremoris* FC strain *in vitro* augments the number of IFN-γ-producing NK cells. In mice fed yogurt fermented by *Lactobacillus casei* Shirota, increased production of IL-12 by APCs was shown to occur, which also resulted in the enhancement of the cytotoxic activity of NK cells (17-19). In mice that were transplanted with the teratocarcinoma cell line F9, administration of cytoplasmic fractions of *L. casei* and *Bifidobacterium longum* extended the survival of mice by increasing the cytotoxic activity of NK cells (20). Cheon *et al.* (21) also reported that *L. acidophilus* La205 enhances the cytotoxic activity of NK cells by increasing granule exocytosis by NK cells. Another study showed that oral administration of heat-killed *Lactobacillus plantarum* 06CC2 isolated from Mongolian dairy products enhanced NK cell activity in the bronchoalveolar lavage fluid of influenza-infected mice, consequently prolonging their survival (22). These studies imply that LAB may be useful for controlling cancers and virus infections by activating the cytotoxic function of NK cells.

Modulation of adaptive immunity Adaptive immunity is a specific immune response that consists of cell-mediated responses and antibody responses, which are mediated by T and B cells, respectively. In general, APCs trigger adaptive immunity by presenting a specific antigen to T cells. In particular, the balance of T cell subtypes involved in the adaptive immune response is important for immune homeostasis. An imbalance between T-helper 1 (Th1) and Th2 cells can result in allergic responses, inflammation, and autoimmune diseases (23). Different LAB strains have effects on modulating adaptive immunity by controlling Th responses. Gut-derived LAB were found to induce $CD4^+$ T cell responses, with different LAB strains differentially inducing the Th1, Th2, Th17, and regulatory T (Treg) $CD4^+$ T cell subtypes (24). *L. lactis* W19, *Streptococcus thermophilus* W67, and *B. lactis* W52 specifically enhanced the mRNA expression of T-bet, GATA3, and Foxp3, transcriptional factors expressed in $CD4^+$ Th1, Th2, and Treg cells, respectively (24). *Streptococcus thermophilus* ST28 strain was shown to have a suppressive effect on Th17 responses by enhancing Th1 cytokine (IFN-γ) secretion (25). Several *Lactobacillus* strains also enhanced IFN-γ production by splenic T cells (26). *L. plantarum* NRIC1832 enhanced IL-10 production by $CD4^+$ T cells (27), and *L. paracasei* BB5 and *L. rhamnosus* BB1 increased the proportions of $CD4^+$ and $CD8^+$ Treg cells in mouse spleen and induced the apoptosis of $CD4^+$ Th2 cells (28). *L. plantarum* NRIC0380 showed an inhibitory effect against β-lactoglobulin-specific immunoglobulin E (IgE) production by facilitating $CD4^+CD25^+Foxp3^+$ Treg cell differentiation (29).

Two types of DCs, plasmacytoid DCs (pDCs) and myeloid DCs (mDCs), are present in the body and have different roles in modulating immunity (30). TLR7 or TLR9 expressed on pDCs interact with nucleic acids derived from virus and bacteria, leading to the induction of type I IFN production by pDCs (31). Several LAB are also capable of activating pDCs, resulting in type I IFN secretion. According to the study of Jounai *et al.* (13), interestingly, only spherical LAB, such as *Lactococcus*, *Streptococcus*, *Leuconostoc*, and *Pediococcus*, could trigger a TLR9-mediated signaling cascade (13). However, administration of *B. infantis* 35624 strain induced Treg cell differentiation by enhancing TLR2- and TLR6-mediated IL-10 production via interactions with both mDCs and pDCs (32), suggesting that unlike spherical LAB, rod-shaped LAB may be

Table 1. Various immunomodulatory effects exhibited by different lactic acid bacteria isolated from kimchi

LAB	Immunomodulatory effects		Symptoms improvement	References
	Innate immunity	Adaptive immunity		
Lactobacillus brevis FSB-1	Induce proliferation and activation of macrophages	Enhance proliferation of bone marrow cells		(38)
Lactobacillus plantarum CJLP133	Up-regulate expression of costimulatory molecules on macrophages	Adjust Th1/Th2 balance	Reduce hypersensitive reaction caused by Th2 cells	(11)
Lactobacillus plantarum CJLP243		Enhance IFN-γ secretion and lymphocyte proliferation		(45)
Lactobacillus sakei proBio65		Induce Foxp3$^+$ Treg differentiation Inhibit IgE and Th2 cytokine production	Alleviate atopic dermatitis	(42,45)
Lactobacillus plantarum K8		Inhibit IgE and Th2 cytokine production	Alleviate atopic dermatitis	(44)
Lactobacillus plantarum	Enhance NO production by peritoneal macrophages	Enhance intestinal secretory IgA production		(36)
Lactobacillus casei and *Bifidobacterium longum*	Enhance NK cell activity	Stimulate total T cells		(20)
Lactococcus lactis JCM 5805	Induce activation of pDC resident in intestinal draining mesenteric lymph nodes	Induce CD4$^+$CD25$^+$Foxp3$^+$ Treg differentiation		(13)
Lactococcus lactis subsp. *cremoris* ATCC 19257	Induce IL-12 and IL-18 production in DCs Stimulation of IFB production in NK cells			(16)
Bifidobacterium infantis 35624		Induce Foxp3$^+$ Treg differentiation		(32)

capable of activating both types of DCs. Table 1 shows the immunomodulatory effects of different LAB strains on innate or adaptive immune responses and the related potential health benefits.

Immunomodulation by kimchi and LAB isolated from kimchi A number of studies have demonstrated the involvement of dietary intake of kimchi in innate and adaptive immunity through research on animal models. A study by Park *et al.* (33) demonstrated that treatment of methanol extracts from onion kimchi induced enhanced proliferation of mouse spleen cells, while also causing increased nitric oxide (NO) production in macrophages (33). Kim and Lee (34) also reported that rats fed freeze-dried kimchi that had been fermented for 3 and 6 weeks at 4°C exhibited more elevated proliferation of the splenocytes than control rats given unfermented kimchi (34). A similar study showed that kimchi extracts accelerated the growth of murine splenocytes, thymocytes, and bone marrow cells, suggesting that kimchi may have an effect on the differentiation of immune cells (35). As cells of the innate immune system, macrophages act upon the sensing of external stimuli, such as pathogenic infections, to cause enhanced phagocytosis, pinocytosis, and production of lysozyme and cytoplasmic granules. Treatment with fermented kimchi extracts was reported to enhance the phagocytosis of murine macrophages against *Candida albicans* (36).

A series of studies have also reported immunomodulatory effects of the LAB isolated from kimchi. Chae *et al.* (37) examined the effect of the LAB homogenate on various aspects of the immune response. The mice fed the *L. plantarum* homogenate displayed the following effects: (i) increased proliferation of both the splenocytes and Peyer's patch cells; (ii) promoted production of NO by macrophages; (iii) elevated levels of intestinal IgA; (iv) elevated serum levels of both TNF-α and IL-2; and (v) enhanced production of specific IgG. These results imply that intake of *L. plantarum* homogenate modulates both systematic and mucosal immunity, as determined by the increased cytokine levels detected in the blood (37). Cellular components of *Lactobacillus brevis* FSB-1 isolated from kimchi were also capable of potentiating immunomodulation. Cellular fractions (cell wall and cytosol preparation) of *L. brevis* FSB-1 were found to induce the activation of macrophages, whereas all cellular fractions did not display any direct action on the proliferation of bone marrow cells (38). Strong complement activation was also exhibited particularly by the cytosol fraction of *L. brevis* (38). A similar study examined the immunomodulatory effects of cellular fractions of *L. acidophilus* DDS-1 isolated from kimchi. Treatment of the cytosol fraction of *L. acidophilus* DDS-1 enhanced proliferation of murine Peyer's patch cells at a comparable level to lipopolysaccharide, used as the positive control, whereas the cell wall fraction was found to have weak immunomodulatory activity.

However, the levels of proliferation by macrophage treated with each of the two fractions were higher than those in the positive control group (39). A recent study showed that *L. plantarum* HY7712 isolated from kimchi restored immune responses impaired by aging, such as NK cell activity, toward a youthful level of function by activating the TLR2/NF-κB signaling pathways in a γ-irradiated mouse model (40). Several LAB isolated from kimchi are capable of skewing Th effector response from Th2 toward Th1, thus modulating balance of Th1/Th2 responses. Won *et al.* (11) demonstrated the ability of *L. plantarum* from kimchi to polarize Th activity toward Th1, consequently suppressing the Th2 responses. These findings indicated that the kimchi LAB might modulate the Th1/Th2 balance by regulating macrophage function in the hypersensitive immune response induced by Th2 cells (11).

A similar study has been reported by Park *et al.* (41), in which several *L. sakei* strains isolated from kimchi were found to induce the production of a Th1 cytokine by ovalbumin-sensitized mouse splenocytes. In addition, the *L. sakei* wikim-100 strain strongly inhibited the release of a Th2 cytokine, suggesting that *L. sakei* wikim-100 modulates the Th1/Th2 balance (41). These studies imply that dietary supplementation with certain LAB, including those found in kimchi, may be useful to alleviate Th2-mediated allergies such as atopic dermatitis.

It has been found that probiotics have beneficial effects on the treatment of human inflammatory bowel diseases (IBDs), as they have the ability to promote the differentiation and activation of Treg cells, while also leading to enhanced secretion of immunosuppressive cytokines such as IL-10 by Treg cells in the intestine (32). Lim *et al.* (42) demonstrated that *L. sakei* proBio65 isolated from kimchi is able to induce the production of IL-10 by mesenteric lymph node cells. Intriguingly, the population of $Foxp3^+$ Treg cells was also found to be increased by this kimchi isolate (42). Like the other LAB strains that were capable of inducing Treg differentiation through activation of the TLR2 and TLR6 signaling pathways (32,43), kimchi LAB may also be employed as therapeutics for the control of inflammatory illnesses, such as atopic dermatitis and IBDs (42).

Alleviation of immune disorders Several LAB were found to have anti-allergic effects by suppressing the synthesis of specific IgE, resulting in the alleviation of allergic symptoms in animal models (5). Treatment with extracts of the kimchi LAB isolate also showed the suppressive activity of atopic dermatitis, which is mediated by the hyper-production of IgE in serum. Specifically, supplementation of *L. plantarum* K8 extracts alleviated atopic dermatitis-like symptoms by lowering the serum IgE levels and production of Th2 cytokines, such as IL-4 and IL-5, in an animal model of atopic dermatitis (44). Mice fed *L. sakei* proBio65 also exhibited rapid recovery from allergic dermatitis, which was mediated by modulating the levels of both IgE and IL-4 (45,46). A recent study has shown that *L. plantarum* SY11 and *L. plantarum* SY12 are capable of significantly decreasing NO production, and down-regulated Th2-associated cytokines, cyclooxygenase-2, TNF-α, and inducible nitric oxide synthase (47).

Pathogen infection-preventing effects Probiotic bacteria not only modulate host immune responses, but also improve the balance of the intestinal microflora. The ingestion of probiotics leads to the development of favorable gut microbiology conditions which suppress the harmful microorganisms while favoring beneficial microorganisms, ultimately leading to enhancement of gut health (48). Several studies have shown that a number of kimchi LAB are capable of protecting host from enteropathogenic bacterial infections. A study by Park *et al.* (45) reported that *L. sakei* proBio65 showed a broad spectrum of antimicrobial activity against various enteropathogens, including *E. coli*, *Salmonella enterica* serovar Typhimurium, and *Shigella flexneri*, while also strongly inhibiting the growth of *Staphylococcus aureus*, a factor known to be involved in atopic dermatitis (45). Recent study has shown that several lactobacilli isolated from kimchi which had immune modulatory properties displayed strong antagonistic effects against intestinal pathogens, including *E. coli*, *S. aureus*, *Yersinia enterocolitica*, *S.* Typhimurium, and *Listeria monocytogenes* (26). While the protective role of kimchi LAB has not yet been investigated in a pathogenic infection model, it is expected that they will contribute to protection of the host against enteropathogenic bacterial infections, since kimchi LAB strains were demonstrated to have direct microbicidal functions and ability to enhance the production of IL-12 and IFN-γ (26,45), essential Th1 cytokines for the clearing of pathogen-infected cells via immune response. Further studies are needed to confirm the protective effects of kimchi LAB through use of appropriate animal models.

Conclusion

Kimchi is the most popular side dish in Korea and an

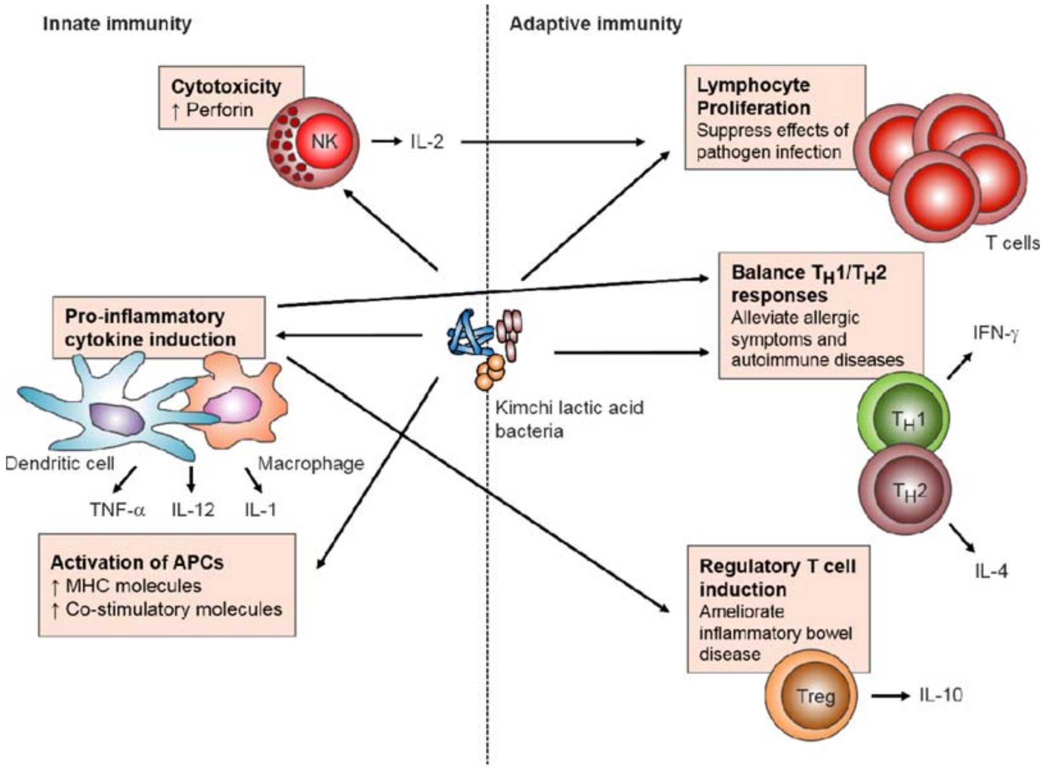

Fig. 1. Immunomodulatory effects of lactic acid bacteria isolated from kimchi. Lactic acid bacteria confer health benefits by inducing either innate or adaptive immune response.

attractive source for nutrition and LAB intake. In particular, kimchi LAB activity during the fermentation of kimchi provide desirable flavors, the extension of shelf-life, and more importantly, contributes to health-beneficial features of kimchi. Various LAB are involved in kimchi fermentation, including strains different from those found in dairy products. Some of these LAB have immunomodulatory effects that are strain-specific. Kimchi LAB not only modulate the function of NK cells and the balance of Th1/Th2 responses by inducing macrophage and DC activation via TLR signaling pathways, but also enhance the differentiation and activation of Treg cells, resulting in the alleviation of allergies and atopic dermatitis. As each LAB shows a different immunological function, it could be possible to make functional kimchi products by adding selected LAB strains as a starter. Therefore, further extensive studies on how kimchi LAB modulate intestinal (mucosal) immunity, activate systemic immunity, and protect the host from various immune disorders must be performed to elucidate their health benefits.

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