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Short review

Protective effects of lactic acid bacteria on influenza A virus infection

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Abstract: Gut microbiota is essential to regulate the whole body metabolism and the immune system of the host animals. Lactic acid bacteria have as a major characteristic to produce lactic acid from glucose. As probiotics, lactic acid bacteria provide many beneficial effects on human health by regulating the gut microbiota or the cell function. Recently, we have reported that oral administration of a probiotic strain, *Lactobacillus gasseri* SBT2055 (LG2055) induced IgA production by increasing the population of IgA+ B cell in Peyer's patch and propria mucosae of small intestine in mice. Furthermore, we demonstrated that oral administration of LG2055 increased the survival rate of mice infected with influenza A virus and decreased the ratio of body weight losses. The virus titer was significantly decreased and the amount of inflammatory cytokine, IL-6 in the lung tissue was reduced by LG2055 administration. The expression of antiviral genes in the lung tissues was increased by LG2055. Therefore, LG2055 administration is shown to be effective for the protection against influenza A virus infection by inhibition of viral replication through the induction of antiviral genes expression. In the future, the constituents of LG2055 to have the effects on the induction of antiviral genes should be clarified for the development of novel influenza drugs.

Keywords: lactic acid bacteria; probiotics; influenza A virus; IgA; IFN; anti-viral gene

1. Introduction

Influenza A viruses are negative sense, single-stranded RNA viruses carrying eight segmented RNA as its genome and cause highly contagious respiratory illness, influenza [1,2]. Infection of influenza A virus caused several pandemic diseases, and almost annual epidemics "seasonal flu", or lethal infectious diseases culminating in severe pneumonia. Higher risk groups, such as older adults,

very young children and patients with chronic diseases cause serious illness or death by the viral infection. Therefore, to develop the effective drugs or vaccines for treatment or prevention of influenza is very important for a lot of people. For the regulation of the immune system, gut microbiota is very important especially, to prevent infectious diseases or immune disorders such as inflammatory diseases [3]. Recently, probiotics, and lactic acid bacteria become famous as good candidates to prevent or treat influenza by regulation of the gut microbiota and the immune system. Probiotics, live microorganisms, when administered in adequate amounts, provide the beneficial effects on human health. For example, lactobacilli and bifidobacteria are used as health-promoting microbes in the human gastrointestinal tract [4]. Certain microorganism including these bacterial strains prevented the intestinal infections of pathogens by reducing the duration of diarrhea, or inflammatory bowel syndromes [5]. In addition, several probiotics are effective for enhancement of the effects of vaccination against influenza viruses [6,7]. Recently, we had reported that oral administration of *Lactobacillus gasseri* SBT2055 (LG2055) was effective to inhibit the replication of influenza A virus through augmentation of the expression of antiviral genes in the lung of mice [8]. LG2055 is a probiotic lactic acid bacterium, and its oral administration to mouse dams prevented rotavirus infection in their pups [9]. In addition, LG2055 induced TGF-β expression in dendritic cells and subsequently IgA production by B cells in the small intestine [10]. Therefore, LG2055 administration prevents virus infection by produced IgA. Especially in the lumen of the intestinal tract, secretory IgA has a function as significant barriers to exclude pathogens from mucosal surfaces [11]. Furthermore, there is a possibility that produced IgA is flowed into the serum or bronchoalveolar lavage fluid (BALF) after LG2055 administration and protects the lung from the influenza A virus infection.

2. Enhancement of the Vaccine Efficacy

Lactobacillus fermentum (CECT5716) for co-adjuvant capability by the immunologic effects was tested in human clinical trial [6]. Proportion of natural killer cells was increased by CECT5716 administration at two weeks after vaccination. Antigen specific immunoglobulin A, total immunoglobulin M and also the response of T-helper type 1 were increased by the administration. Furthermore, it decreased the incidence of the illness during 5 months after the vaccination. *Lactobacillus GG* (LGG) also improved the influenza vaccine immunogenicity as shown by the randomized double-blind pilot study [7]. Against the H3N2 influenza A virus, 84% people of the LGG administration group versus 55% people of the placebo group had a protective titer on day 28th after the vaccination.

Recently, in elderly person, aged 65–85 years, *Lactobacillus plantarum* CECT7315/7316 was shown to improve the immune responses to the vaccination [12]. The levels of virus-specific IgA and IgG antibodies were increased by the consumption during 3 months after the vaccination of influenza vaccine (A/Wisconsin/67/2005 (H3N2), A/Solomon Islands/3/2006 (H1N1) and B/Malaysia/2506/2004). These results demonstrate that the lactic acid bacteria are useful to enhance the effects of influenza vaccine. In the future, beneficial effects of the probiotics should be studied and they could be applied for the enhancement of vaccines.

3. Beneficial Effects on the Prevention of Influenza

The consumption of only probiotics or lactic acid bacteria is reported to be effective for the prevention of influenza virus infection. Administration of heat-killed *Lactobacillus plantarum* L-137 (HK-LP) stimulated the macrophage or dendritic cells to produce T helper (Th) 1 cytokines [13]. Oral administration of HK-LP significantly prolonged the survival time of the mice infected with H1N1 influenza virus A/FM/1/47. In addition, daily intragastric administrations after viral infection (H1N1 influenza virus A/PR8/34), *Lactobacillus plantarum* CNRZ1997 was demonstrated to have functions alleviating clinical symptoms, and inhibiting significantly virus proliferation in lungs (daily administered 1.0×10^9 cfu) [14]. In addition, *Lactococcus lactis ssp. lactis* JCM5805 has been shown to activate plasmacytoid dendritic cells in both murine and human species. By a randomised placebo-controlled double-blind experiment for 213 volunteers, divided into two groups, which received either yogurt made with JCM5805 or a placebo beverage daily for 10 weeks, in the JCM5805 group, the cumulative incidence days of "cough" and "feverishness" were significantly decreased compared with the placebo group. Amount of IFN-α elicited by A/H1N1 tended to be higher in the JCM5805 group compared with the placebo group [15]. It is suggested that JCM5805 administration prevents the pathogenesis of an influenza-like illness by IFN-α-mediated response.

We had previously shown that lysozyme-treated *Enterococcus faecalis* FK-23 (LFK), isolated from human intestinal tract, reduced the mortality in the mice infected with the influenza virus A/PR8/34 [16]. Furthermore, we demonstrated that administration of the water-soluble fraction (SLFK) of LFK significantly improved the survival rate of the mice compared to the control after the viral infection [17]. The mRNA expression level of the anti-inflammatory cytokine interleukin-10 (IL-10) was enhanced by SLFK administration in lung tissues. Oral administration of SLFK protected mice after influenza virus infection by activation of the anti-inflammatory response.

Recently, we have shown that oral administration of LG2055 increases the survival rate of mice infected with the A/PR8/34 virus [8]. The virus replication in the lung is significantly decreased by LG2055 administration after the virus infection. In addition, LG2055 administration enhances the mRNA expression level of the antiviral genes, myxovirus resistance 1 (Mx1), and 2'–5' oligoadenylate synthetase 1A (Oas1a) in the lung [8]. The expression of Mx1 and IFN-β mRNAs are strongly induced in macrophage-like cell, RAW264.7 by LG2055 treatment. These results suggest that the oral administration of LG2055 is efficient to inhibit the virus replication through up-regulation of the antiviral genes expression of the macrophage in the lung.

On the other hand, especially, IgA antibodies are very critical to prevent influenza virus infection in mucosal tissues, including the upper respiratory tract. Production of secretory IgA by IgA+ plasma cells, differentiated from IgA+ B cells depends on the commensal bacteria in the gastrointestinal tract. This differentiation is induced by the intestinal dendritic cells (DCs), stimulated by their antigens incorporated through M cells. Recently, we reported that oral administration of LG2055 induced IgA production by increasing IgA+ cell population in Peyer's patch lamina propria of the murine small intestine [10]. TLR2 signal was shown to be critical for IgA production by LG2055 in the bone marrow derived dendritic cells (BMDCs) by co-culture with B cells. In addition, LG2055 induced BMDC to produce TGF-β, BAFF and IL-6, critical for IgA secretion from B cells [10]. Among these cytokines, TGF-β was critical for the production of BAFF, IL-6, IL-10, and TGF-β itself in LG2055-stimulated BMDC. Therefore, it was suggested that LG2055 stimulated

BMDC to produce TGF-β and TGF-β is essential for BMDC to induce BAFF and IL-6 production. Induction of IgA production by LG2055 should be important for the control of the intestinal microflora and the protection from pathogenic viruses and bacteria.

4. Conclusion

In summary, administration of lactic acid bacteria is effective to inhibit the influenza A virus infection by different mechanisms depending on the strain such as regulation of natural killer cell population or T-helper type 1 response, and production of virus-specific IgA and IgG. Furthermore, administration of LG2055 induced the expression of anti-viral genes to inhibit the viral replication, inflammatory responses, and secretion of cytokines to produce IgA by B cells in mice.

Conflict of Interest

The author has no conflict of interest to declare in this paper.

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