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Role of Lactic Acid Bacteria and Their Exosomes in Anti-Food Allergy

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Abstract. Food allergies, a pressing health concern with worldwide ramifications, have attracted immense attention in recent decades. A promising solution to this enduring issue lies in the prophylactic and therapeutic benefits offered by lactic acid bacteria (LAB) fermented products. These bacteria exhibit remarkable abilities, not only assisting in alleviating allergy symptoms but also in reducing the likelihood of allergies by intricately regulating the host's immune system. Through the process of fermentation hydrolysis, LAB modifies the antigenicity of food proteins, altering their linear epitopes and higher structural configurations. Additionally, they secrete epigenome modulators, release anti-inflammatory cytokines, and fortify the intestinal barrier, collectively contributing to the reduction of allergic reactions. The emerging role of LAB and their exosomes in combating food allergies presents an innovative and intriguing path for future research endeavors and therapeutic applications.This review summarizes the research achievements of lactic acid bacteria products in combating food allergies through two main approaches.

Keywords: Lactic acid bacteria; Food allergy; Fermentation; Immune regulation.

1. Introduction

Food allergy is a kind of immune response that is caused by a person's immune response to the allergen in food. In the past decades, people's attention on food safety has been increasing, and food allergy as an important food safety problem has attracted people's attention. Various methods have been studied to reduce food sensitization. At present, heating, high pressure, enzymatic hydrolysis, molecular modification and other methods have been used. Lactobacillus is a kind of probiotics, through fermentation can produce a variety of functional peptides and active substances, while reducing the sensitization of food. However, the anti-allergenic effects of different lactic acid bacteria vary, and the mechanism by which lactic acid bacteria reduce food allergy is still unclear. Therefore, the research progress of lactic acid bacteria in reducing and resisting food allergy was reviewed in this paper, aiming to provide ideas for further research and development of anti-allergic fermented food.

2. Lactic acid bacteria fermentation against food allergySection Headings

Fermentation is a traditional food processing technique that extends the shelf life of food while giving it a specific flavor [1]. Lactic acid bacteria are heterotrophic microorganisms that rely on peptidases, proteases, and transport systems to hydrolyze proteins into peptides and amino acids for growth.Their sensitivity-sensitive capability is that they can induce an IGE-type response, which is initiated on a molecular scale by an 8-12-amino acid (epitope) immuno-activated oligopeptides. There are two kinds of antigens: (i) linear epitope, which is associated with the consecutive amino acids of the protein sequence; and (ii) conformational epitope, which is composed of discrete amino acids in the 3D structure of the protein.Lactic acid bacteria fermentation affects both linear and conformational epitopes of proteins, and thus has the potential to reduce immunogenicity [1].

2.1. Changing the linear epitopes of antigens reduces sensitization

During the fermentation process of lactobacillus, proteases and peptidases are produced, leading to the hydrolysis of antigens. This hydrolysis results in the fragmentation of linear epitopes, thereby reducing their antigenic potential. Key allergens in milk proteins, such as α-whey protein (α-LA), α-casein (α-CN, including αS1 and αs2-CN), β-casein (β-CN), and β-lactoglobulin (β-LG), are known to cause allergic reactions.

The combined fermentation of Lactobacillus Swisseri and Streptococcus thermophilus has been observed to significantly decrease the antigenicity of α-LA and β-LG proteins. As fermentation time increases, the content of free amino groups rises, indicating a gradual enhancement in the hydrolysis of milk protein. This reduction in antigenicity can be attributed to the enzymatic cleavage of epitopes on whey protein by proteases generated during hydrolysis [2]. Further studies have revealed that fermentation leads to the cleavage of numerous allergic epitopes, thus reducing the IgE binding capacity of α-CN, α-LA, and β-LG. This, in turn, diminishes the immune response in vitro [3]. Zhao et al. discovered that the primary allergic epitopes of α-CN and β-LG undergo cleavage during fermentation, leading to the destruction of linear epitopes and a decrease in the antigenicity of the milk protein.

Plant proteins derived from grains and legumes also serve as significant protein sources, albeit with potential allergenic properties. Wheat, lupine, mustard, sesame, soybeans, and their derivatives are known allergens. Research suggests that 2S storage proteins, present in seeds, often exhibit allergenic characteristics, with the exception of lentils[1]. Currently, efforts are being made to reduce the allergenicity of soybean protein, wheat protein, and peanut protein through lactic acid bacteria fermentation.

Yang et al. discovered that initiating solid state fermentation of soybean meal with a starter culture composed of Bacillus subtilis, Lactobacillus casei, and yeast could influence allergenics in both laboratory and living organism tests. This process decomposed soy protein into polypeptides with lower molecular weights, effectively dismantling β-conglycinin and glycinin allergy epitopes and subsequently reducing the human IgE binding capacity [2].

However, it's crucial to recognize that even as the proteolysis level rises with prolonged fermentation, the antigenicity doesn't always decrease. This is because enzymes further hydrolyze the protein into even smaller peptides and amino acids, potentially revealing previously concealed or linear epitopes [5].

2.2. Destruction of the antigen's higher structure reduces sensitization

In addition to directly cutting hydrolysis into small molecular peptides and amino acids, lactic acid bacteria can also reduce sensitization by altering the higher structure (secondary or tertiary structure).

For milk proteins, jiang,Rui et al. found that fermentation may significantly affect the modification of βstructure in proteins and lead to the expansion and relaxation of secondary and tertiary structures [6][7]. Subsequent studies by zhao et al. found that theαhelix is converted intoβsheets andβturns during fermentation, and the protein conformation becomes more loose, which may make the sensitized linear epitopes of the antigen protein more easily exposed during fermentation and thus hydrolyzed by proteases [8].

For peanut protein, Zhou Yang studied the effect of Bacillus subtilis and Bacillus natto on reducing the sensitization of peanut protein by fermentation, and found that Bacillus subtilis could reduce the IgE binding capacity of the sample to 0, while Bacillus natto could only reduce the IgE binding capacity of the raw material by 48% [9]. On the basis of their research, Pi et al. selected Bacillus natto with better enzyme production to ferment peanut and treated it with high-pressure steam sterilization before fermentation. It was found that autoclave-assisted fermentation of Bacillus natto resulted in peanut protein degradation, protein conformation change,αhelix reduction, etc., which markedly declined the IgE binding property of raw peanut and changed the particle size of peanut protein.

Soybean ranks among the top eight sources of food allergens in both the United States and Europe. Lactic acid bacteria fermented soy triggers acidic gelation of proteins and improves the texture and functional properties of soy products, and Swiss lactic acid bacteria effectively reduced soy immune reactivity by 100%. Due to structural changes such as allergen degradation and increased surface hydrophobicity andβ-chain content, the sensitization of soybean protein after fermentation by Lactobacillus plantarum was reduced by 83.8% to 94.8%. Fermentation has been successful in reducing allergic reactions in many soy products, such as soybean meal, soybean paste, soy milk, and soy protein. Wang reports that LAB's ability to trigger the formation of acidified soy protein gels leads to network formation or molecular rearrangement that exposes or destroys soy allergen epitopes and leads to overall changes in soy allergenicity. Soybean protein isolate (FSPIs) was fermented in four concentrations (0.2% to 5.0% w/v) of lactic acid bacteria solution (LAB), resulting in different matrix structures (non-gel, NG, weak gel, WG, medium gel, MG and hard gel), MG/WG digestives obtained during early and middle duodenal digestion (D-5 and D-30) have been found to have greater immunoreactivity reduction efficacy than NG in reducing immune reactivity, to 1.9% - 68.3% [10].

The incidence rate of wheat allergy was about 0.1%, and it was mainly caused by wheat proteins through IgE or non-ige hypersensitivity reactions. However, the exact mechanism was not clear. Enzyme proteolysis has little effect on reducing wheat protein sensitivity because it disrupts the function activities of gluten proteins, thus affecting sensory properties of wheat foods. Therefore, fermentation of proteins using strains of lactic acid bacteria is a key method to reduce the sensitization of these proteins. Studies have shown that the immune reactivity of LAB-fermented wheat and rye flour to human IgE is reduced, but not completely [11].

In conclusion, the prehydrolysis of food protein through lactic acid bacteria production is an effective method to change the immune reactivity of protein. During hydrolysis, protease cleaves linear epitopes and causes rapid collapse of conformational epitopes, but the degree of hydrolysis depends on the site of action and reaction time of the enzyme.However, there is no direct relationship between the molecular weight of the peptides in the hydrolysis products and their residual sensitization, and the sensitization potential of lactic acid bacteria is strain specific, which may be caused by the different action sites of the secreted enzymes.

3. Immunomodulatory effects of lactobacilli exosomes

The metabolites of lactic acid bacteria, epigenome, also have many components that can play an immunomodulatory role. Among them, probiotics can also produce bacteriocins, eliminate competitive pathogens and regulate host immunity [12]. Hao H. et al. showed that Lactobacillus plantarum Q7 secreted by Lactobacillus plantarum has activity against pathogenic bacteria related to intestinal inflammation such as Staphylococcus aureus, listeria monocytogenes, and Escherichia coli.Proteobacteria, the primary phylum of pathogenic bacteria, plays a pivotal role in fostering the overproduction of pro-inflammatory cytokines, thereby contributing to the pathogenesis of IBD. Remarkably, Q7-EVs have demonstrated their effectiveness in alleviating colitis by decreasing the population of enteritis-inducing proteobacteria and enhancing the intestinal flora of mice [13].

The health-promoting properties of probiotics are primarily attributed to the production of extracellular vesicles (EVs). These EVs possess remarkable immunomodulatory effects. EVs are nanoparticles surrounded by lipid bilayers released by cells, responsible for transporting various macromolecules such as lipids, polysaccharides, proteins, and nucleic acids. This transport mechanism enables long-distance delivery of nutrients, protection against environmental stressors, and communication during microbial-host interactions. Crucially, these vesicles play a pivotal role in the "communication" between probiotics and their host. They regulate the host immune response by modulating the signaling pathways involved, which is linked to their ability to modulate various cytokines, chemokines, and antibodies [14]. Li M et al. have demonstrated that EVs secreted by Lactobacillus plantarum enhance the expression of host immune genes, providing protective benefits to the host.By leveraging their immunomodulatory and communication capabilities, probiotics and their extracellular vesicles offer a promising approach in allergy prevention and treatment.

Recent studies suggest that electric vehicles (EVs) exert immunomodulatory effects through two key mechanisms. Firstly, they stimulate dendritic cells (DCs) via toll-like receptors, particularly TLR2 and TLR4, triggering immune responses. These activated DCs then facilitate the transformation of Th0 cells into regulatory T cells (Tregs), which secrete anti-inflammatory cytokines, including interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-22 (IL-22). This process suppresses the expression of pro-inflammatory cytokines. Secondly, EVs interact with intestinal epithelial cells, enhancing the expression of tight junction proteins and modulating cytokine secretion. This reinforcement of the intestinal barrier prevents antigenic translocation and subsequent inflammation, while maintaining homeostasis of hydrolysis. Consequently, EVs effectively mitigate inflammatory responses [15].

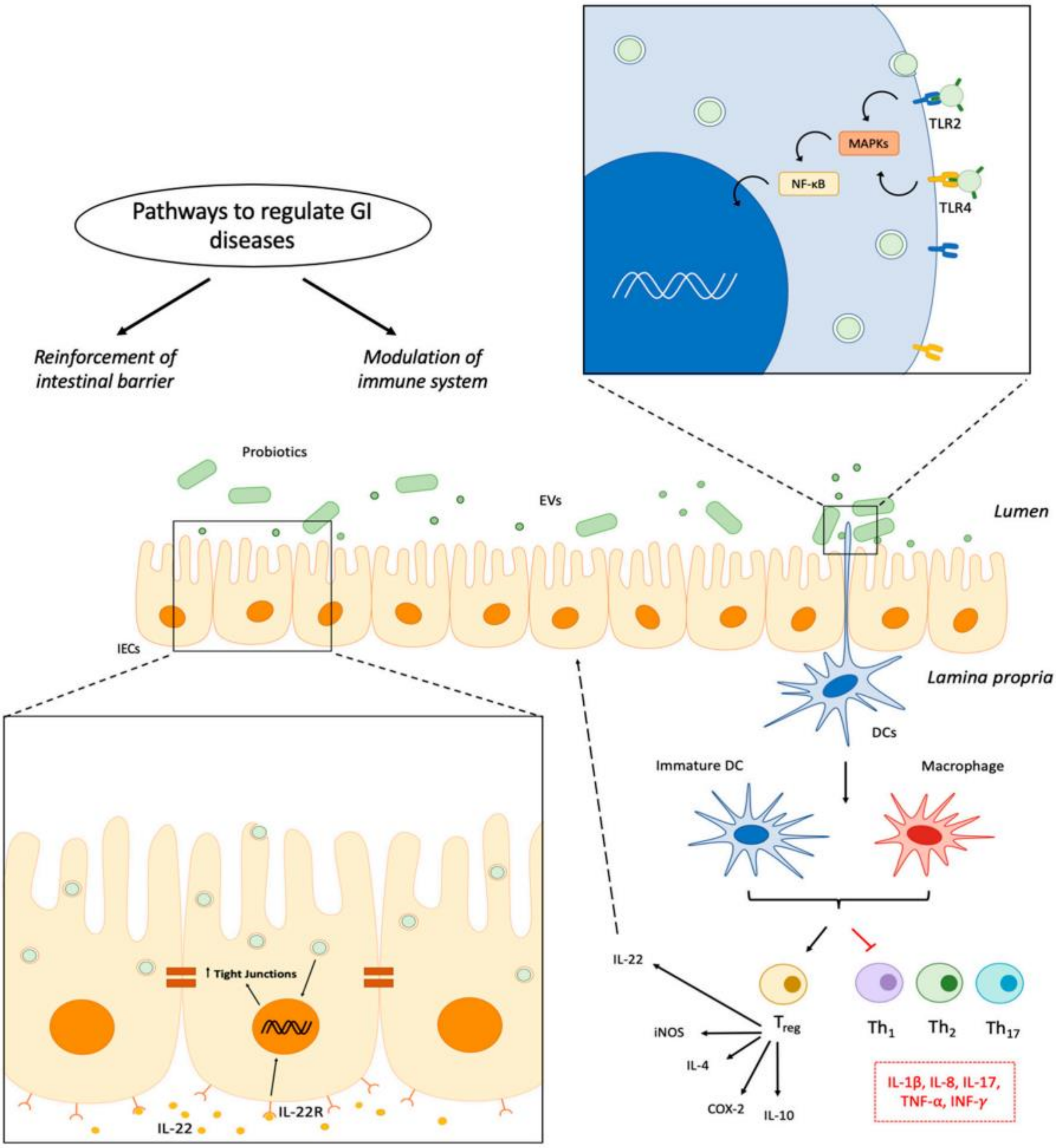

Figure 1. The main mechanism of immune regulation by lactic acid bacteria EV [15]

4. Conclusion

Over the past decades, numerous studies have consistently demonstrated the beneficial effects of lactic acid bacteria on human health. Nevertheless, the exploration of their anti-sensitization effects, including those of their exosomes, remains nascent. Yet, our thorough examination of the available literature reveals a noteworthy surge in interest and understanding regarding the application of lactic acid bacteria in allergy prevention and treatment over the last ten years. Incorporating lactic acid bacteria-fermented products or probiotic supplements into one's diet offers a gentle yet effective approach to combatting allergies, and we eagerly anticipate future groundbreaking discoveries in these fascinating areas.

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