Integrative Molecular Medicine

Review Article ISSN: 2056-6360

Anti-aging effects of Lactobacilli

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Abstract

Lactic acid bacteria are known the major beneficial bacteria for human health from Dr. Metchnikoff's reports. The action mechanism for aging of lactobacilli remains unclear. In the past decade, some groups have demonstrated the molecular mechanisms of lactobacilli for aging using Caenorhanditis elegans. In this review, we summarize these knowledge.

Anti-aging effects of Lactobacilli

Aging is a complex process characterized by a progressive impairment of the response of organisms to environmental stresses and general metabolic deterioration; however, altering certain processes can prevent aging and it has been shown that lifespan could be increased by the alteration of processes such as dietary restrictions (DR), the insulin like signaling (IIS) pathway, and the oxidative stress pathway. Dietary restrictions, the reduced intake of food without malnutrition, increases the lifespan of many organisms, yeasts as well as mammals [1]. Dietary restrictions increase the lifespan, at least in part, by suppressing activation of pathways involved in growth and nutrient processing, including the target of rapamycin (TOR) pathway. Some important effects of insulin on aging and longevity are hypothesized from both clinical findings and results obtained with experimental animals. Reduction in IIS has been shown to be associated with increased stress resistance and longevity in a range of species. The oxidative stress theory of aging predicts that manipulation which alters the oxidative stress/damage will alter the process of aging. To protect against oxidative stress, eukaryotes possess sophisticated defense systems that cope with elevated ROS levels and promote homeostasis. Proteins that protect against high ROS levels include catalases, superoxide dismutases (SODs), and glutathione peroxidases (GSH-Pxs), and these signaling pathways are known to be strongly evolutionarily conserved. Hallmarks of aging include genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence [2]. To date, many studies have focused on food sources, nutrients, and components that exert inhibitory effects on the hallmarks of aging in worms, flies, mice, and humans.

In 1907, Dr. Metchnikoff first proposed the concept of probiotic bacteria, hypothesizing that lactobacilli were important for promoting human health and longevity [3] and that consumption of lactic-acid-producing bacteria [4], such as the lactobacilli found in yogurt, could be useful for prevention of aging and extension of lifespan. The mechanisms behind the probiotic effects of bacteria, however, are not entirely understood.

Recently, some groups reported the action mechanism by Lactic acid Bacteria (LAB) for longevity by using *Caenorhabditis elegans* (*C.elegans*). *C.elegans* is possibly the most suitable model organism for research on the mechanism of the process for aging. The reason is that it has an evolutionarily conserved metabolism and host defense mechanisms, including insulin/insulin-like growth factor (IGF-1) signaling pathway [5], p38 mitogen-activated protein kinase (p38 MAPK) pathway [6], and the transforming growth factor β (TGF-β) signaling pathway [7]. Moreover, dietary resources, such as bacteria, play an important role in the control of the lifespan of *C. elegans* [8]. Aging in *C. elegans* is a complex process driven by diverse molecular signaling pathways.

Many genes that are differentially regulated in young versus old animals are known or postulated to be regulated by DAF-16 (forkhead box O (FOXO) transcription factor) and SKN-1 (ortholog of mammalian NF-E2-related factor 2 (NRF2)). DAF-16 and SKN-1 play highly conserved roles in regulating stress resistance and longevity genes. Grompone et al. showed that *Latobacillus rhamnosus* CNCM I-3690 exerted a strong antioxidant effect and extended nematode lifespan through the insulin-like pathway DAF-2/DAF-16 [9]. On the other hand, we observed that the feeding *daf-2* (e1368) and *daf-16* (mgDf50) *C. elegans* mutants with *Lactobacillus gasseri* SBT2055 (LG2055) extended their lifespan similarly to that which was observed in wild-type. In contrast, the feeding with LG2055 did not extend the lifespan of *skn-1* mutant worms [10]. SKN-1 plays physiological regulatory roles in multiple processes, including detoxification, metabolism, the immune response, and the oxidative-stress defense.

The maintenance of low ROS levels is critical for normal cell function. Thus, we also investigated whether LG2055 stimulated the host defense system and ROS production. Hoeven *et al.* have shown that ROS released from Ce-Duox1/BLI-3 can activate SKN-1 activity via p38 MAPK signaling [11], with NSY-1 and SEK-1 both able to regulate the p38 MAPK ortholog PMK-1. In response to oxidative stress, PMK-1 phosphorylates SKN-1, which then translocates to the nuclei of intestinal cells and induces the transcription of phase 2 detoxification genes [12]. The p38 MAPK pathway is also known to be crucial for

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Received: May 26, 2016; **Accepted:** June 10, 2016; **Published:** June 13, 2016

stress response and regulation of immunity. Papp *et al.* showed that SKN-1 and PMK-1 were central elements in immunosenescence [13]. Immunosenescence, or the age-dependent decline in immune responsivity, is a critical condition that impedes healthy aging [14]. Therefore, we hypothesize that LG2055 inhibits the accumulation of oxidative damage associated with aging by stimulating the immune system, including p38 MAPK signaling and other pathways. Feeding with LG2055 marginally increased the life span of the tir-1 mutant of *C. elegans* but did not increase the mean lifespan of the *nsy-1*, *sek-1*, or *pmk-1* mutants. We found that feeding with LG2055 effectively stimulated NSY-1-SEK-1-PMK-1-SKN-1 signaling pathway.

Ikeda *et al.* [15] also analyzed whether the LAB could exert probiotic effects on the worm's host defenses and extend lifespan. In their results, although the senescence of the host defense was clearly shown by the survival rate during Salmonella infection of worms, LAB-fed worms were more resistant to the pathogen than those fed OP50 (normal food: *E.coli*). Kim and Mylonakis report that the *Lactobacillus acidophilus* strain NCFM significantly enhances the host defense response of *C. elegans* to Gram-positive pathogens [16].

Immune-stimulating molecules, such as peptidoglycan [17], S-layer protein [18], and expolysaccharide [19,20] exist on the cell surfaces of these bacteria. Therefore, the beneficial efficacy of LAB might be influenced by differences in the species and structures of immune-stimulating molecules. In the future, some other as yet unknown factors could be shown to be critical for the regulation of immunity.

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