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REVIEW

Probiotic bacteria as modulators of cellular senescence: emerging concepts and opportunities

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ABSTRACT

Probiotic bacteria are increasingly gaining importance in human nutrition owing to their multi-faceted health beneficial effects. Studies have also shown that probiotic supplementation is useful in mitigating age-associated oxi-inflammatory stress, immunosenescence, and gut dysbiosis thereby promoting health and longevity. However, our current understanding of the process of aging suggests a strong interrelationship between the accumulation of senescent cells and the development of aging phenotype, including the predisposition to age-related disorders. The present review studies the documented pro-longevity effects of probiotics and highlights how these beneficial attributes of probiotics could be related to the mitigation of cellular senescence. We present a perspective that to fully understand and comprehend the anti-aging characteristics of probiotic bacteria; it is imperative that probiotics or their synbiotic amalgamation with plant polyphenols, be studied under the purview of cellular senescence, that may ultimately help devise probiotic-based anti-senescence strategies.

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Introduction

Human aging is a stochastic, deleterious and progressive phenomenon that renders elderly prone to increasing morbidity and mortality. However, aging itself is not a disease and several attempts have been made to understand its origin, causes and effects considering both genetic and epigenetic factors.[1] Amongst these, the free radical theory of aging has gained considerable attention as it emphasizes that the underlying cause of organismal aging is related to the cellular accumulation of harmful and partially reduced metabolites of molecular oxygen due to dysfunctions in various metabolic processes.[2,3] Since then, different extensions of the original theory have been proposed including the recent concept of 'oxi-inflamm-aging' that highlights the role of immune cells as chief sources of chronic oxidative and inflammatory stress which ultimately contribute to the accelerated rate of aging of organisms.[4] Another landmark observation by Hayflick[5] propagated the notion that aging could be associated with the inherent tendency of somatic cells to resist proliferation or undergo 'senescence' after a finite number of divisions in vitro. While this phenomenon was subsequently attributed to gradual telomere attrition (replicative senescence); it is now understood that senescence can be accelerated and induced in cells through different extrinsic as well as intrinsic insults such as oxidative and genotoxic stress,[6,7] oncogenic activation,[8] or irradiation.[9] In particular, the accumulation of reactive oxygen species (ROS) has been implicated as an important mediator of different aspects of cellular senescence due to their ability to not only disrupt cellular oxidative and inflammatory homeostasis but to also accelerate telomere attrition.[10-15] However, Hayflick's observations were initially dismissed as mere in vitro artifact and the connection between limited cell proliferative capacity and aging largely remained controversial.[16,17] This scenario now appears to be changing as convincing data are emerging which not only confirm the in vivo presence of senescent cells, but that their gradual accumulation directly contributes to organ dysfunction and the characteristic-aged phenotype.[18-20] Another recent report substantiates this fact wherein an in vivo bystander effect of senescent

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cells has been identified that acts as a potential trigger of the initiation of senescent-cell accumulation.[21] It is also pertinent to note here that senescent cells are not only characterized by the loss of proliferative capacity but also show several unique-associated features such as high metabolic activity,[22] activation of nutrient-sensing pathways such as mammalian target of rapamycin (mTOR),[23] and the development of senescence-associated secretory phenotype (SASP), which is a complex milieu of pro-inflammatory cytokines and growth factors that can contribute to inflammatory damage in nearby cells.[24,25] Therefore, it is not surprising to contemplate that elimination of senescent cells or enabling their delayed development could be a potent way of targeting several age-associated disorders, including the hallmark diseases of twenty-first century, i.e. cancer and diabetes. In this context, a breakthrough study has shown that life-long removal of cells expressing a biomarker of cellular senescence-p16^{Ink4a}, delayed the onset of age-related pathologies in several tissues such as adipose, skeletal muscle, and eye while late-life clearance of p16^{Ink4a} cells also attenuated the progression of already established age-related disorders.[26] Similarly, in another recent work, it was observed that targeting senescent cells could alleviate the symptoms of obesity-induced type II diabetes thereby providing a novel perspective on the therapeutic applications of senescent cells.[27] Overall, it seems plausible that even during aging, healthier cellular functions can be maintained by inhibiting the development or selective removal of senescent cells, which may result in a lower rate of incidences of tumorigenesis and inflammatory disorders.

The emerging deleterious impact of accumulating senescent cells on aging and associated disorders has accelerated the need for identification of modulators of cellular senescence that may improve or maintain cellular functions during aging. In this context, nutritional interventions could play an important role, as several bioactive phytomolecules have been identified which target different aspects of cellular senescence and SASP.[28-30] Lactic acid bacteria mediated modulation of human health and longevity was first highlighted by Metchinkoff[31] in 1907. The term 'probiotic' however was coined by Lilly and Stillwell[32] in 1965 and presently probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[33] A plethora of research has established that gut microbiome plays a critical role in influencing several facets of human health including metabolic regulation and energetic homeostasis,[34,35] immune stimulation,[36,37] gut barrier integrity[38,39] as well as neurological behavior.[40,41] Dietary supplementation of probiotic microorganisms is known to influence the composition, diversity, and functions of the gut microbiome and probiotics have been documented for several health beneficial effects to the host through diverse mechanisms.[42-44] In the context of aging, evidence is emerging that probiotic bacteria are useful modulators of age-related pathologies and morbidity. This has been especially affirmed in cases such as gastrointestinal health[45-47] and immunosenescence[48-50] wherein probiotic supplementation has shown potential as natural alleviators of these deleterious aspects of aging. However, the role of probiotics as modulators of cellular senescence per se is only beginning to be understood. The present review describes the known anti-aging effects of probiotics and discusses evidences and mechanisms suggesting how probiotics could be useful in mitigating the progression and severity of cellular senescence in an attempt to advocate the development of probiotic-based anti-senescence therapies.

Cellular senescence relates causes and effects of aging

Some of the most dangerous and hallmark disorders known to humanity in the 21st century are deeply related to aging. However, *why* and *how* we age have remained the most enduring of questions-both philosophically and scientifically. In this regard, recent advances in geroscience have led to a functional and provable hypothesis suggesting that microscopic damage in the wake of accumulating senescent cells in tissues and organs gradually manifests as an observable aged phenotype and various associated morbidities.[51] However, cellular senescence is not exclusively a deleterious process, but is thought to have evolved as an important barrier to tumorigenesis[52] and has also been shown as an

important regulator of wound healing in tissues.[53] The SASP in senescent cells of young organisms provides inflammatory signals that help attract immune cells enabling the removal of senescent cells, while growth signals in SASP stimulate proliferation in nearby cells to allow subsequent replacement of senescent cells.[54] However, as we age, this delicate balance is seemingly perturbed and senescent cells begin to accumulate in tissues resulting in chronic inflammatory stress thorough persistent SASP which now induces a pro-inflammatory and pro-tumorigenic micro-environment characteristically indicative of antagonistic pleiotropy[55] (Figure 1). The apparent age-related increase in senescent-cell burden reflects either an enhanced rate of senescent-cell production due to accumulating oxidative damage in cellular macromolecules including in the replicatively sensitive telomeric regions of the DNA,[14,15] and/or decreased senescent-cell clearance by the immune system. In the latter aspect, senescent cells are considered to be highly immunogenic targets due to the upregulation of certain ligands that are recognized by immune cells such as natural killer (NK) resulting in their specific clearance.[56,57] However, the immune system itself is known to undergo multi-faceted age-associated changes (immunosenescence) including impaired immune surveillance[58] and reduced cytotoxic ability[59] which may directly hinder the efficiency of immune cell-mediated clearance of senescent cells and thus enabling their gradual accumulation. This notion has been recently substantiated when it was observed that mice deficient in perforin-mediated cell cytotoxicity exhibited higher senescent-cell tissue burden, chronic inflammation and also suffered from multiple age-related disorders suggesting that impaired immune surveillance can accelerate the accumulation of senescent cells and aging phenotype.[60]

Apart from cell cycle inhibition, perturbations in oxidative and inflammatory pathways are

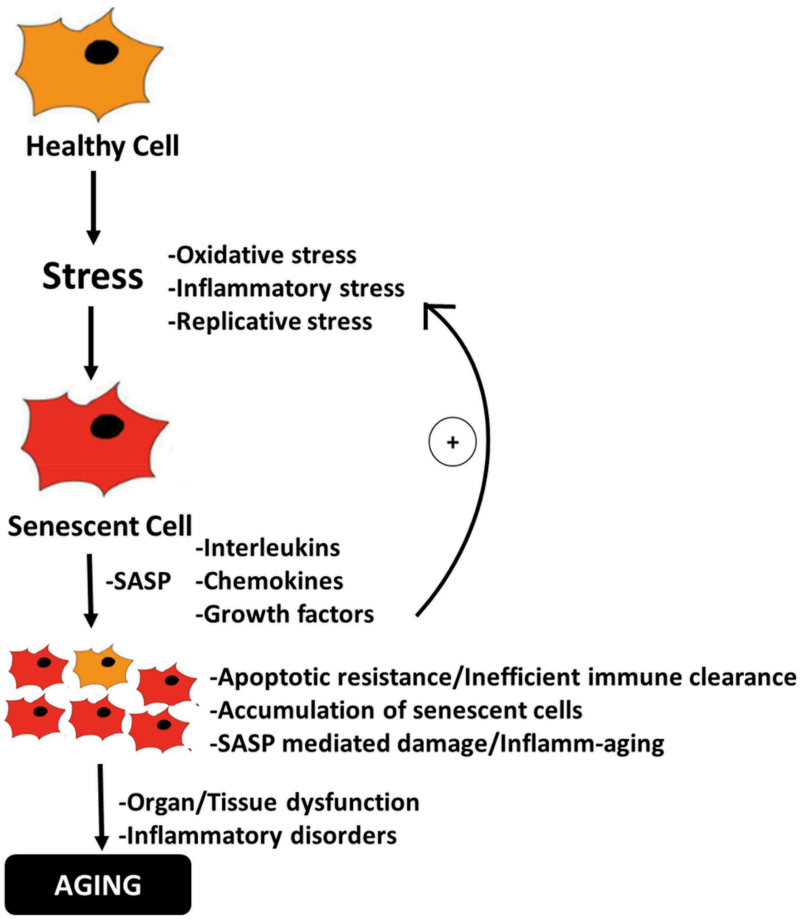

Figure 1. Schematic diagram depicting the role of senescent cells in driving the process of aging. Oxi-inflammatory stress contributes to the development of senescent cells which gradually accumulate and promote inflamm-aging, resulting in tissue and organ dysfunctions and pro-tumorigenic environment characteristic of aging-phenotype.

amongst the most discernible features of cellular senescence that are common to different cell types. Therefore, not surprisingly, it has been shown that the application of non-lethal stressors in vitro can initiate a cell senescence program with characteristics similar to replicative senescence.[13,61] In fact, chronic oxidative and inflammatory stress and decrease in antioxidant potency can augment the development of ROS-mediated molecular and eventual DNA damage[4] which is often followed by the induction of DNA damage response (DDR)[62] and downstream activation of cell cycle inhibitory pathways ($p53/p21^{WAF1}/p16^{INK4a}$)[13,63,64] ultimately resulting in senescence. Although the inhibition of cell cycle is desirable to prevent the division of unhealthy cells; however, senescent cells are known to resist apoptosis by dysregulating pro-apoptotic and anti-apoptotic pathways (Bax/Bcl-2)[65] thereby resulting in their enhanced survival and gradual accumulation in tissues and organs (Figure 1). In contrast to replicative senescence, which is an inherent cellular feature, oxidative stress-induced induction of senescence is more dynamic and presents an added modifiable opportunity that can be targeted to prevent or deaccelerate senescence. Considering this, it can be envisaged that various natural antioxidants, or even putative probiotics with strong antioxidant capacity, could be important regulators of oxidative stress-induced senescence and aging. Indeed, it has been shown that different phytomolecules can influence diverse aspects of senescence including suppression of both replicative or stress-induced senescence, development of SASP or even induction of apoptosis in senescent cells (senolytics).[28] Further, given the key role of immunosenescence in dysregulating immune cells mediated surveillance and clearance of senescent cells; strategies aimed at augmenting specific immune cells functions during aging may also contribute to the delayed accumulation of senescent cells as well as SASP.

Probiotic bacteria and healthy aging

Studies pertaining to age-related changes in the gut microbiome have shown that gut dysbiosis is related to the development of age-associated pathologies that may reduce longevity.[66] Gut dysbiosis can disrupt the host nutrient signaling pathways and metabolism[67] which are presumed to have negative effects on host health ultimately contributing to the pathology of various age-associated disorders.[68] Studies have also shown that interventions of dietary probiotics are useful in improving elderly health by preventing diarrheal diseases,[69] improvement in inflammatory disorders,[70] prevention of recurring infections,[71] and colon cancer.[72] Here, we present evidence indicating that probiotic bacteria can also intervene and modulate different aspects of cellular senescence and SASP that may contribute to observed improvements in organ functions as well as enhancement in longevity.

Probiotics enhance lifespan in model organisms

Probiotic supplementation has shown promising results in improving the longevity of experimental animals. In this regard, Matsumoto and Kurihara[73] first hypothesized that probiotic bacteria may extend lifespan by inducing production of small metabolites called polyamines, that act via suppression of inflamm-aging. Subsequently, using the probiotic strain *Bifidobacterium animalis* subsp. *lactis* LKM512, Matsumoto et al.[74] observed a higher survival rate and reduced incidence of skin ulcers and tumors in probiotic fed mice as compared to control. Authors also noted that LKM512 administration downregulated the expression of aging-associated and inflammation-associated genes in 21 months old animals which were comparable to 10 months old untreated (younger) mice. Another report by Zhao et al.[75] observed that feeding probiotic *Lactobacillus salivarius* strain FDB89 to the nematode *Caenorhabditis elegans* (*C. elegans*) extended lifespan by 11.9% as compared to control nematodes in a dietary restriction-dependent manner. Similarly, Grompone et al.[76] observed that *Lactobacillus rhamnosus* CNCM I-3690 enhanced lifespan in *C. elegans* by about 20% and transcriptomic analysis of *C. elegans* fed with this strain showed that apparent increase in the nematode lifespan was correlated with differential expression of the DAF-16/insulin-like pathway. Using the probiotic *Bacillus licheniformis*, Park et al.[77]

observed enhanced longevity in *C. elegans* via modulation of expression of genes associated with host serotonin signaling. Nakagawa et al.[78] observed that feeding of *Lactobacillus gasseri* SBT2055 (LG2055) to *C. elegans* enhanced the survival rate of nematodes by strengthening the resistance to oxidative stress and by stimulating the innate immune response signaling including p38MAPK signaling pathway. Authors also observed that amounts of mitochondria were significantly increased by LG2055 feeding in comparison to the control. Similarly, Park et al.[79] observed that *Lactobacillus fermentum* strain JDFM216 improved resistance of *C. elegans* to foodborne pathogens and enhanced nematode lifespan mediated by a nuclear hormone receptor family and PMK-1 signaling. In a recent report by Westfall et al.,[80] it was observed that a novel probiotic and synbiotic formulation combinatorially extended longevity in male *Drosophila melanogaster* through the mechanisms of gut-brain-axis communication. Both the probiotic and synbiotic formulations rescued markers of metabolic stress by managing insulin resistance and energy regulatory pathways and further ameliorated aggravation in inflammation, oxidative stress and the loss of mitochondrial complex integrity.[80] In another recent work, it was reported that feeding of *Lactobacillus fermentum* MBC2 to *C. elegans* enhanced the lifespan and attenuated age-related markers such as pumping rate, lipofuscin accumulation, and body bending in nematodes.[81]

Probiotics as suppressors of age-associated oxi-inflammatory stress

Dysregulation in the processes pertaining to maintenance of redox and inflammatory homeostasis is central to the etiology of senescence as well as to the pathogenesis of various age-related predispositions to inflammatory disorders. It is thus not surprising that the preservation of oxi-inflammatory cellular environment has shown potential as modulators of age and associated disorders. In this context, Lin et al.[82] observed that oral administration of *L. plantarum* AR113 and AR501 improved the antioxidant status of d-galactose-induced oxidative stress in aging mice and alleviated liver damage and abnormal activities of superoxide dismutase, glutathione peroxidase, and catalase to normal levels, while also enhancing gene expression of nuclear factor erythroid-2-related factor 2 and antioxidant genes such as glutathione reductase, glutathione S-transferase and NAD(P)H quinone oxidoreductase 1. Zhao et al.[83] further observed that administration of *L. plantarum* strains protected against d-galactose induced oxidative damage and gut dysbiosis in aging mice and inferred that the protective effects of *L. plantarum* strain on the host microbiota could be one of the mechanisms of their resistance to age-related oxidative stress. Similarly, a recent study by Hor et al.[84] demonstrated that administration of probiotic *Lactobacilli* strains improved gut dysbiosis, modulated the metabolism of amino acids such as urocanic acid, citrulline, cystamine, and 5-oxoproline as well as antioxidant capacity in d-galactose senescence-induced aging rats thereby highlighting the potential of probiotics as anti-aging therapeutics through healthy gut modulation. In a similar report by Lew et al.,[85] the administration of different *Lactobacillus* strains to a high-fat diet and d-galactose-induced model of aging rats led to strain-specific effects on gut microbiota diversity and composition, short-chain fatty acids production as well as higher fecal contents of compounds related to amino acid or carbohydrate metabolism. Jeong et al.[86] observed anti-inflammaging effects of probiotic *Lactobacillus brevis* OW38 in aged mice. Authors reported that oral administration of *Lactobacillus brevis* OW38 significantly reduced the LPS level in colon fluid and blood, while also inhibiting the expression of inflammatory markers, such as myeloperoxidase, tumor necrosis factor (TNF), interleukin (IL)-1β, and activation of NF-κB. An interesting report by Lee et al.[87] observed gender-specific beneficial effects of an anti-inflammatory probiotic strain *Lactobacillus reuteri* BM36301 on aging C57BL/6 mice. Authors observed that males treated with the probiotic bacteria experienced less weight gain and higher testosterone level while females treated with the same bacteria maintained lower serum TNF-α as well as healthy skin with active folliculogenesis and hair growth. Pan et al.[88] observed that calorie restriction caused changes in the gut microbiome of mice wherein a selective increase in *Lactobacilli* species was observed that

correlated with decreased markers of systemic inflammation and circulating microbial antigens. One of the isolates, *Lactobacillus murinus* CR147, downregulated interleukin-8 production in TNF-α-stimulated Caco-2 cells and significantly increased the lifespan and the brood size of the *C. elegans* indicating that proliferation of *Lactobacillus murinus* in calorie-restricted mice causatively contributed to the attenuation of aging-associated inflammation. Previously, we have also observed that supplementation of probiotic *Lactobacillus rhamnosus* to aged mice suppressed an age-associated increase in systemic inflamm-aging markers as evident by a decrease in circulatory TNF-α and MCP-1 proteins along with enhanced antioxidant capacity in liver and RBCs as compared to control.[70] Together, these observations provide evidence that probiotic bacteria can mitigate age-associated cellular oxidative and inflammatory stress that can ultimately help alleviate cell senescence and rate of occurrence of inflammatory disorders in the elderly.

Probiotic-mediated suppression of immunosenescence: potential against cell senescence?

Immunosenescence is an umbrella term that describes the characteristic remodeling of different aspects of the immune system which contribute to age-related disorders.[4,89,90] Emerging evidence is now suggesting that impaired surveillance and antigenic uptake by immune cells during aging could directly contribute to the inefficient clearance of senescent cells and associated increase in senescent-cell burden in tissues.[58,60] Studies in both experimental animals and human subjects have shown that probiotic bacteria can alter some of the deleterious aspects of immunosenescence. For instance, in a study by Gill et al.,[48] it was observed that consumption of *Lactobacillus rhamnosus* HN001 or *Bifidobacterium lactis* HN019 by healthy elderly subjects for three weeks enhanced the numbers and activity of NK cells. Similarly, consumption of *Lactobacillus gasseri* TMC0356 enhanced splenic NK cell activity and expression of IL-2 and IFN-α/β receptor 1 in lung cells of senescence-accelerated mice.[91] We have also observed that consumption of probiotic *Lactobacillus fermentum* in aged swiss albino mice attenuated markers of inflamm-aging, improved neutrophil functions and enhanced resistance to infectious *E. coli* as compared to control.[50] Spaiser et al. reported that consumption of a probiotic mixture enhanced circulatory IL-10 levels and reduced inflammatory cytokine profile in older adults.[92] Miyazawa et al.[93] observed that consumption of heat-killed *Lactobacillus gasseri* increased the number of $CD8^+$ T cells and reduce CD28 expression loss in $CD8^+$ T cells of the elderly subjects. Vidal et al.[94] reported that supplementation of *Lactobacillus paracasei* NCC2461 in aged mice improved specific adaptive immune response as evident with higher IgG2a levels after antigenic challenge. Consumption of probiotic *Bacillus subtilis* CU1 enhanced fecal and salivary secretory IgA concentrations in elderly subjects that decreased the frequency of respiratory infections as compared to placebo.[95] A recent report also suggests that supplementation of fermented milk containing probiotic *Lactobacillus casei* DN-114001 to aged mice improved macrophage functions, NK cell activity and proliferative index as compared to control.[96] However, despite these encouraging observations, studies exploring the role of probiotic treatment in the augmentation of immune surveillance and the subsequent clearance of senescent cells are lacking. It is also pertinent to note that although immunosenescence is a recognized age-associated immunological disorder; however, it should not be confused with cell senescence, as immunosenescence encompasses a variety of changes that are unrelated to cell senescence.[97] Whether or not probiotics can influence the senescence of immune cells per se is also not investigated and therefore, probiotics mediated modulation of the immune system vis-à-vis immune surveillance and immune cell senescence represents an exciting area for exploring probiotic-based therapeutics during aging.

Probiotics as modulators of cellular senescence

Evidences presented in this manuscript thus far suggest that probiotics can attenuate age-associated inflamm-aging, immunosenescence and oxidative stress that may promote longevity. Although these disorders are intimately linked with the macro-phenotype of senescent cells; however, studies directly relating the observed anti-aging or healthy aging effects of

probiotics with the progression and development of cellular senescence per se are very rare. Jeong et al.[98] initially showed that administration of *Lactobacillus pentosus* var. *plantarum* C29 to aged Fisher rats prevented senescence of colon tissue as evident by suppression of senescence markers viz. p16 and p53 along with the inhibition of activation of NF-κB and mTOR pathway providing evidence of anti-senescence and SASP inhibitory effects of probiotics. Similarly, the application of probiotic mixture IRT5 ameliorated age-dependent onset of colitis in Fisher rats and suppressed an age-associated increase in expression of senescence markers p16 and p53 in the colon of aged rats while also enhancing age-suppressed expression of SIRT1.[99] In another study, oral administration of *Lactobacillus brevis* OW38 suppressed the expression of senescence markers p16, p53, and SAMHD1 in the colon and the hippocampus of aged mice, inhibited inflamm-aging and restored spontaneous alternation as well as the expression of brain-derived neurotrophic factor and doublecortin in aged mice.[86] In a recent work, we sought to directly address whether probiotic bacteria can prevent the progression of cellular senescence using a stress-induced premature model of murine preadipocytes. It was observed that supplementation of secretory metabolites of probiotic *Lactobacillus fermentum* sufficiently rescued cells from stress-induced senescence as evident by a decrease in $p16^{Ink4a}$/p53/$p21^{WAF1}$ expression, markers of SASP, NF-κB activation and ROS-induced DNA damage.[100] These effects of probiotic bacteria were correlated with the inhibition of PI3K/Akt/mTOR pathway, which is rapidly emerging as a central regulator of senescence[101] and longevity,[102] thereby indicating that probiotic bacteria may suppress senescence by inhibiting aberrant mTOR activation and maintaining oxidative homeostasis. Together, these observations suggest that probiotic bacteria can influence the progression and severity of cell senescence which may have a major impact on tissue homeostasis and also provide mechanisms governing the known health-promoting effects of probiotics during aging (Figure 2). However, more detailed studies, especially targeting the identification of probiotic bacteria that may mitigate the development of SASP, selectively induce apoptosis in senescent cells or inhibit mTOR signaling during cellular senescence and aging are required to fully ascertain and establish the anti-senescence attributes of probiotics.

Secretory metabolites of probiotics that influence aging

Probiotics mediate their health beneficial effects by different mechanisms including altering the microbiota composition, maintaining epithelial barrier function and modulating mucosal and systemic immune responses. Probiotic bacteria also secrete various small bioactive metabolites in the gut which interact with epithelial cells and are absorbed into circulation by passive and active mechanisms thereby allowing their cellular modulatory effects at sites distant to the gut.[103,104] During the last few years, several studies have reported the effects of probiotic secretory factors on immunomodulation,[105] cell cycle regulation,[106] resisting infections,[107] and antioxidant activity.[108] In fact, identification and characterization of these metabolites have been implicated for the development of a new generation of functional foods, without involving live probiotic bacteria, which may have clinical relevance.[109] Probiotic secretory factors are diverse in nature and often include short-chain fatty acids (SCFAs), peptides, lactic acid, vitamins, polyamines, and polyphosphates.[110] A cause-and-effect relationship regarding aging and health has been documented with these molecules, especially with SCFAs and polyamines. It has been shown that levels of SCFAs decline with age[111] which may contribute to perturbations in the gut mucus barrier,[112] neural microglia maturation, and function,[113] as well as host cells insulin sensitivity and energy expenditure,[114] that can be implicated in the pathogenesis of aging and associated inflammatory disorders. SCFAs are produced by bacterial fermentation in the gut and supplementation of these molecules has shown evidence of improvement in inflammation, neural health, and aging.[115,116] Similarly, polyamines are small molecules that are abundantly produced by commensal bacteria and play a critical role in various cell processes.[117] The

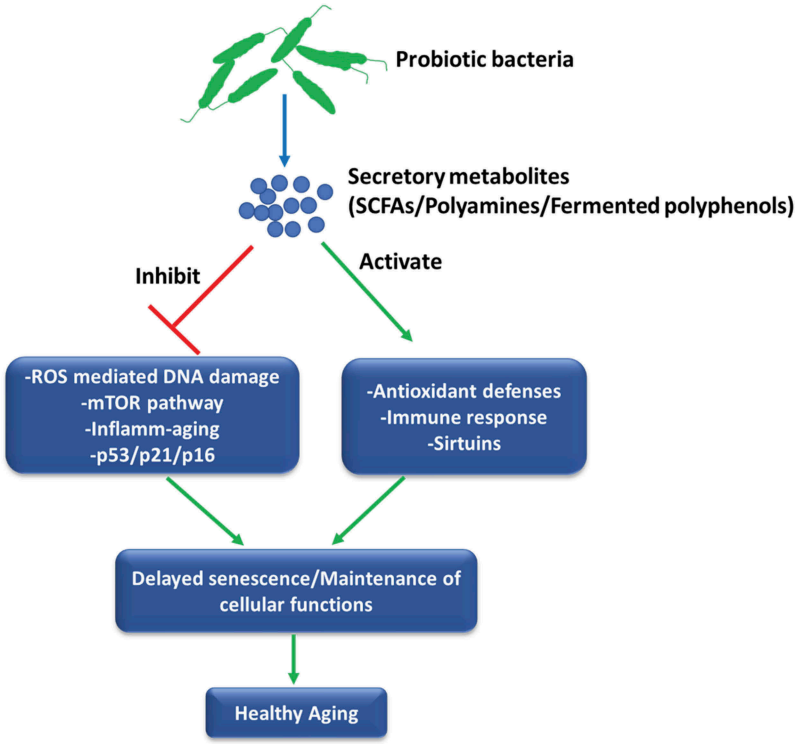

Figure 2. Probiotics can influence the process of senescence. The secretory metabolites of probiotic bacteria such as polyamines, SCFAs or probiotic-fermented polyphenols could affect different aspects of cell senescence including cell cycle regulators, oxi-inflammatory stress, mTOR pathway and immune activation that may delay the initiation of senescence program leading to the augmentation of healthy aging.

levels of polyamines also gradually decline in various organs with age[118] and supplementation of polyamines producing probiotic bacteria[74] or direct exogenous supply of polyamines[119] has shown life-span enhancing effects.[120,121] However, despite their apparent health-promoting effects during aging, to the best of our knowledge, no studies thus far have been reported that assess the anti-senescence, anti-SASP or senolytic attributes of these probiotic metabolites and therefore represent a niche area in the domain of probiotics and aging research.

Probiotics and polyphenols: prospects of novel anti-senescence combination(s)?

Nutritional interactions in vivo, and particularly in the gut, are complex and multifaceted. Probiotics and plant-polyphenols are perhaps the most vital natural sources of bioactive components present in our daily diet. As such, strategies aimed at developing potent nutritional interventions for the modulation of human health would invariably require gauging both probiotics and plant polyphenols as potential candidates. However, the mutual compatibility of probiotic bacteria and polyphenols has not always been considered favorable. While a general assumption is that polyphenols are anti-bacterial in nature; evidence is accumulating that pathogenic bacteria are actually more sensitive to polyphenols as compared to probiotics, and that polyphenols may act as prebiotic compounds.[122-124] Also, it has been shown that probiotic bacteria can metabolize polyphenols into novel bioactive compounds that may significantly enhance the biological effects of parent polyphenols.[125,126] Further, there is evidence to consider that probiotic-fermented traditional polyphenol-rich beverages are more potent in antioxidant and anti-inflammatory activities enabling their health-promoting effects on various disorders such as obesity[127] and liver damage.[128] Considering this, recently it has been advocated that amalgamation of plant polyphenols with probiotic bacteria could act as a second generation of synbiotics which would be more beneficial to human health, particularly in the mitigation of aging and associated disorders.[129,130] The known-limited bioavailability of several bioactive polyphenols (e.g. curcumin or catechins), that hampers their biological

relevance, could actually be useful in this strategy as it would allow greater interactions between probiotic bacteria and polyphenols in the gut. Since several polyphenols have already been identified as anti-senescence and anti-SASP agents, at least in vitro,[29] it is plausible that carefully identified combinations of polyphenols with probiotic bacteria[130] could offer potent and extensive effects on regulating several facets of cell senescence, aging, and associated pathologies.

Conclusions

Advances in our understanding of the role of cellular senescence has provided a causative and modifiable factor that can simultaneously affect several aspects of aging, including the known predisposition to various diseases. There is enough evidence to consider that probiotic bacteria can suppress several deleterious aspects of aging. The anti-inflammaging, antioxidant and anti-immunosenescence effects of probiotics suggest their potential as modulators of SASP and cell senescence, especially oxidative stress-induced senescence. Till now, a vast majority of studies focussing on anti-aging and longevity modulatory potential of probiotics have only targeted oxi-inflammatory and nutrient modulatory capacities of probiotic bacteria. However, given our expanding understanding of the molecular etiology of the aging process; it is imperative to identify and assess probiotic bacteria or their secretory metabolites with potential anti-senescence, anti-SASP, senolytic or specific immune-enhancing attributes that may be correlated with their observed health beneficial effects during aging. Together, it represents an exciting area of research as the diversity and abundance of probiotic bacteria, coupled with their known functional efficacy in modulating the regulatory systems of human body, highlights enormous opportunities in developing probiotic-based therapies for the modulation of cellular senescence and aging.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

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