Microbiota, probiotics and common skin cancer: Association and therapeutic application

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Abstract

Numerous commensal microorganisms live on human skin and play an important role in human health. Any type of abnormality in the skin microbiome can result in skin damage and various diseases. Skin disorders such as atopic dermatitis and psoriasis are common skin complications caused by an imbalance of skin microorganisms. Probiotics are live microorganisms that, when consumed in sufficient quantities, can benefit human health. Using probiotics to treat various skin complications has gained popularity in recent years. Probiotics have proven to be a promising agent for improving skin health and condition, with the potential to reduce skin pathogens and boost skin immunity through antimicrobial agent production and nutrient competition. The rising incidence of skin cancer, particularly melanoma, over the last four decades emphasizes this point. The link between skin microbiota imbalance and skin cancer, particularly Non-Melanoma Skin Cancer (NMSC) and melanoma, is becoming clearer. As a result, based on the proven ability of probiotics to improve skin health, the use of microorganisms such as probiotics as a supplement in conjunction with immunotherapy has gained popularity. The purpose of this review is to discuss the relationship between microbiota imbalance and skin cancer, as well as the use of probiotics in cancer treatment.

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Introduction

Probiotics are non-pathogenic microorganisms that have several beneficial properties for human health.[1] Probiotic microorganisms, particularly lactic acid bacteria such as *Lactobacillus*, *Pediococcus*, and *Bifidobacterium* species, are among the most common probiotics. Probiotics have a variety of modes of action, including anti-pathogenic activity, anti-obesity effects, and immunomodulatory properties.[2]

Probiotics must be consumed on a regular basis in order to be physiologically effective in the human body.[3] Daily consumption of 108-109 Colony Forming Units (CFU)/g probiotic bacteria is thought to be necessary for bacteria to survive upper ingestion and perform the function.[4]

In the absence of living microorganisms, probiotic byproducts can have a similar effect on cellular mechanisms.[5] Postbiotics are probiotic products that can inhibit pathogenic agents such as bacteriocins, organic acids, diacetyl and acetaldehydes.[6,7]

Probiotics' ability to modulate the immune system is one of their primary physiological functions; in fact, probiotics have the ability to regulate immune system activity against diseases by interacting with various lymphocytes such as Th1, Th2, and B cells.[8] Many bacteria, including *Lactobacilli* and *Bifidobacteria*, have antibacterial properties by regulating the immune system. Probiotics such as *Lactobacilli* have been shown to reduce allergic reactions by increasing IL-10 and TGF-β production, as well as T cell response against pathogenic agents.[9]

The antiproliferative activity of various probiotics is strongly related to the host immune system. Probiotics can increase macrophage and NK cell mobilization,[10] as well as promote IgG and IgA production,[11] and stimulate apoptosis and inhibit tumor cell growth through phagocytosis.[12] Skin cancers, such as Non-Melanoma Skin Cancer (NMSC) and melanoma, are linked to microbiota imbalance.[13] Some studies, for example, have found a link between *Staphylococcus aureus* and squamous cell carcinoma.[14] It has been demonstrated that the abundance of *S. aureus* in

Squamous Skin Cancer (SSC) is significantly greater than in normal skin cells.[15,16] *Cutibacterium* spp. is a member of the skin's commensal microbiota. According to research, the frequency of bacteria in SCC has decreased.[17] Fungi and other skin microorganisms can also cause skin cancer. *Malassezia* sp. abundance is reduced in SCCs. Because the fungi have the ability to prevent *S. aureus* biofilm formation, they can act as anti-*S. aureus* agents in SCC.[18]

Melanoma is another serious skin cancer; malignant melanoma is the deadliest type of skin cancer, accounting for 75% of all skin cancer deaths.[19] A recent study of melanoma microbiota revealed that *Corynebacterium* spp. is strongly linked to stage III/IV malignant melanoma.[20]

The use of probiotics and microbiota in the treatment of skin cancer is becoming more popular.[13] Several studies have shown that *Staphylococcus epidermidis* has antiproliferative properties against SCC and melanoma.[21,22] The use of combined probiotic and immunotherapy, particularly in the treatment of melanoma, is being researched, and several ongoing clinical trials are evaluating the efficacy and safety of probiotics in melanoma immunotherapy.[23] The purpose of this review article is to examine the relationship between common skin cancers and microbiota, as well as the use of probiotics and microbiota in skin cancer treatment.

Skin microbiota and non-melanoma skin cancer

Several studies have linked *Staphylococcus aureus* to squamous cell carcinoma. The frequency of *S. aureus* in SCC has been shown to be significantly higher than in normal tissue. *S. aureus* colonization was higher in SCC samples (29.3%) than in normal skin cells (5.7%). The *S. aureus* nuc gene was linked to Actinic Keratosis (AK), interepidermal tumors with the potential to progress to squamous cell carcinoma, and SCC.[24] *S. aureus* overabundance in AK may be linked to AK progression to SCC. There was a higher correlation between *S. aureus* colonization and AK (12.3%) than with seborrhoeic keratosis (1.4%).[16] *S. aureus* may promote SCCs through immune modulation of skin immune systems and induction of chronic inflammation. Modulin is a peptide produced by *S. aureus* that has the ability to activate IL-1a and IL-36a as well as indirectly regulate T cell IL-17 release. The interaction of IL-17 with IL-22 and TNF-α influences *S. aureus* colonization.[25] The inflammatory factors mentioned above are linked to cancer progression by inducing cancer cell proliferation and metastasis.

S. aureus was identified as the most common bacteria in SCC and AK samples. A RNA seq study by 16S rRNA showed an overpopulation of *S. aureus* in AK and SCC samples.[14] Another 16S rRNA sequencing study revealed that *Propionibacterium* spp. is a common microorganism in healthy skin, in contrast to the abnormal regions of SCC and AK, where *Staphylococcus aureus* was the dominant genus.[17]

S. aureus can also promote tumor cell proliferation by modulating beta-defensin 2 expression.[14] It has been proposed that tumorigenic cells can disrupt the life cycle of lipophilic bacteria, reducing their abundance and promoting *S. aureus* growth.[17] The production of Lipoteichoic Acid (LTA) by commensal staphylococcal species via the Toll-like receptor 3-dependent pathway is specifically linked to skin immune regulation. LTA is a cell wall component of *lactobacilli*, which has been shown to inhibit tumor growth and induce immune induction by increasing the level of helper and cytotoxic T-cells. One of these commensal bacteria has the potential to protect against skin cancer.[26,27] *Staphylococcus epidermidis* may protect the skin from the growth of *Staphylococcus aureus*. *S. epidermidis* can inhibit *S. aureus* biofilm formation via an icaR-dependent pathway, as well as produce Phenol-Soluble Modulins (PSM)γ and PSM δ as antibacterial agents against *S. aureus* and group A *Streptococcus*.[28,29]

Malassezia spp. abundance decreases in SCCs compared to *Staphylococcus aureus*; studies suggested that the yeast are a protective agent against *S. aureus* overpopulation in SCCs, but other studies suggested that this yeast itself could have a carcinogenic effect due to its ability to produce Aryl-hydrocarbon receptor (AhR) ligands. Furthermore, a link between BCC development and *Malassezia* spp. location in dogs and cats has been reported.[18,26] Another significant study found a low prevalence of *Cutibacterium* species, gram-positive anaerobic bacilli that are common in skin, as a result of AK and SCC.[17]

A rise in β-Human Papillomavirus (β-HPV) prevalence is also linked to AK and SCC. Several studies have been conducted to investigate the mechanism of tumor progression via the interaction of β-HPV and UV. It has been demonstrated that NMSCs developed in genetically engineered mice expressing β-HPV 38 oncoproteins differed from wild type mice. With E6 and E7 viral proteins, β-HPV 38 appears to be capable of maintaining cellular proliferation in UV-stressed cells. The virus can also modulate inflammatory responses and interfere with host immune responses, resulting in skin tumorigenesis.[30,31]

Microbiota and melanoma

Malignant melanoma is the deadliest type of skin cancer, accounting for 75% of all skin cancer deaths. The relationship between melanoma and microbiota has recently been studied, with several studies indicating a link.[19]

According to a recent study on melanoma patients, the genus *Corynebacterium* is strongly linked to stage III/IV malignant melanoma.[20] Patients who tested positive for *Corynebacterium* spp. had a higher number of IL-17 positive cells. By upregulating IL-6, IL-17 acts as a melanoma progression regulator.[32] *Corynebacterium parvum* administration in combination with chemotherapy in patients with metastatic malignant melanoma yielded no significant results when compared to chemotherapy alone.[33] Overall, it is safe to assume that *Corynebacterium* sp. is strongly linked to malignant melanoma.

According to Mekadim and colleagues, the most common bacterial agents that cause melanoma are *Fusobacterium necrophorum*, *Staphylococcus shyicus*, and *Trueperella pyogenes*. They discovered that Fusobacteria promotes the progression of melanoma tumors. Fusobacteria are linked to cancers of the mouth, colon, and pancreas. It has been demonstrated that the bacteria can promote tumor proliferation and progression.[34] Fusobacteria can inhibit NK cell activity by interacting with the immune cell inhibitory receptor TIGIT and the Fusobacterial protein Fap2.[35] *Trueperella pyogenes* is a pathogen that can infect humans, as well as pigs and other animals. The bacteria were found to be among the most abundant microbiota isolated from Melanoma-Bearing Libechov Minipig (MeLiM) piglets with melanoma.[34]

Probiotics and non-melanoma skin cancer

Several studies have found that probiotics can help with skin cancer. Probiotics have the ability to neutralize pathogenic agents

through a variety of mechanisms. Probiotics can increase mucin and bacteriocin production and secretion;[36,37] they can also increase ceramide production without harming host cells. *Lactobacillus reuteri* and *Lactobacillus rhamnosus* were found to be effective against *S. aureus* and increased the number of normal primary human epidermal keratinocytes (NHEK) from 8.8% to 53.1% and 42.7%, respectively.[38] LGG lysates were also found to protect human keratinocytes from *S. aureus* infection.[39]

In hairless mice, Nakatsuji and colleagues discovered that *S. epidermidis* can inhibit cancer cell progression by more than 60%. Squamous cancers did not develop in hairless mice exposed to UV rays.[21]

Treatment with *Saccharomyces cerevisiae*, *Bacillus subtilis*, and *Lactobacillus acidophilus* was found to be an effective method of lowering HPV in skin tumorigenic mice.[40]

Lactobacillus salivarius REN is another probiotic that has been shown to have anti-tumorigenic activity in human tongue squamous cell carcinoma. A high dose of *L. salivarius* REN has been shown to induce antiproliferative activity. The probiotic could prevent the formation of 4-nitroquioline-1-oxide (4NQO) in cancer cells and showed anti-carcinogenic activity.[41] Kaur and colleagues discovered that AJ2 probiotics inhibited the growth of oral cancer cell lines in humanized BLT (hu-BLT) mice, as well as the modulation of proinflammatory and anti-inflammatory cytokines in NK cells. AJ2 is a probiotic compound made up of eight different gram positive bacteria (*Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Lactobacillus acidophilus*).[10]

Acetobacter syzygii was found to secrete cytotoxic metabolites against the KB cancerous cell line. This study found that *A. syzygii* has an apoptotic effect similar to cisplatin. Another finding from the study was that *Lactobacillus acidophilus* has prophylactic effects.[42]

One idea for using probiotics against skin cancer is to use Lipoteichoic Acid (LTA) as a protective agent. Treatment of UV-stressed skin tumors with LTA produced by *Lactobacillus rhamnosus* GG (LGG) increased immune system activity.[43] Another study discovered that LTA can prevent UV-induced skin tumor growth.[44]

In mice, *S. epidermidis* was found to produce 6-Nhydroxyaminopurin (6-HAP), which had an antiproliferative effect on tumor cells.[45] A recent metagenomics study discovered a *S. epidermidis* (MO34 strain) on human skin that is similar to a 6-HAP-releasing strain in mice.[21] Despite the fact that *S. epidermidis* inhibits skin tumor growth, a recent study revealed intriguing findings about the relationship between *S. epidermidis* and cancer initiation in transplant recipients. There is a significant relationship between *S. aureus* abundance and skin cancer in immunocompetent individuals, but this study found almost no incidence of *S. aureus* in skin lesions of immunocompromised patients, with *S. epidermidis* being the most common species. *S. epidermidis* found in immunocompromised SCCs lacked the 6-HAP protective agent biosynthesis gene in this study.[45]

Probiotics and melanoma

Several studies have been conducted to investigate the effect of probiotics on melanoma. The majority of the research is centered on the effect of probiotics on melanoma immunotherapy. Sivan *et al.* investigated the beneficial effect of Bifidobacteria in a melanoma mouse model, demonstrating that Bifidobacteria administration combined with immunotherapy successfully suppresses tumor growth in mice. The gut microbiota can actively participate in melanoma immunotherapy with anti-PD-L1 checkpoint inhibitors, according to this article. *Bifidobacterial* species such as *Bifidobacterium breve*, *Bifidobacterium longum*, and *Bifidobacterium adolescentis* are linked to T cell antitumor activity.[46,47]

Administering *L. reuteri* FLRE5K1 could reduce melanoma incidence by 30%, and the probiotic could also decrease the survival rate of tumorigenic cells.[48]

Blocking CTLA-4, which leads to the activation of effector cells such as (CD4 + and CD8+), as well as anti-CTLA-4 antibody therapy, can be beneficial in the treatment of cancer, particularly melanoma.[49] Probiotics and gut microbiota have been proposed as immunotherapy modulators in this regard. Several clinical trials are currently underway to investigate the role of probiotics in melanoma immunotherapy. A melanoma clinical trial (NCT03817125) is evaluating the safety and efficacy of probiotics and anti-PD-1 combination therapy. This clinical trial's probiotic is a specific bacteria (SER-401).[23] In another clinical trial, melanoma patients were recruited alongside patients with other cancers such as bladder cancer and non-small cell lung cancer to investigate the efficacy of anti-PD-1 and proprietary bacterial strain (MRx0518) combination therapy.[23]

A study found that after 4 weeks of treatment, mice treated with fecal material isolated from the responsive group had a significant reduction in tumor volume when compared to the control group.[22,23] A clinical trial (NCT03341143) on patients with resistant melanoma (resistant to Pembrolizumab) is looking into the efficacy of Fecal Transplants (FMT) in improving Immune Checkpoint Inhibitors (ICIs) activity.[23] Another ongoing clinical trial (NCT03819296) is evaluating the efficacy of FMT in the treatment of melanoma patients. The effectiveness of fecal transplant on gastrointestinal complication caused by drug in melanoma patients is being investigated in this clinical trial.[23] A recent study conducted by Chen and colleagues on the inhibitory effect of probiotic supplementation on melanoma cell metastasis to lung found that consuming VSL#3 probiotics reduced melanoma cancer cell lung metastasis. The supplement changed the gut microbiota of mice and increased the frequency of Lachnospiraceae, *Streptococcus* sp., and *Lachnoclostridium* sp. The authors reported that probiotic treatment increased propionate and butyrate levels, which resulted in increased chemokine (C-C motif) ligand 20 (CCL20) expression in lung endothelial cells and recruitment of Th17 to the lungs via the CCL20/chemokine receptor 6 axis. Th17 cell recruitment reduced the number of tumor foci in the lungs and inhibited melanoma cell lung metastasis in mice.[50]

Lactobacillus johnsonii is an intriguing microbiota that can stimulate an immune response against melanoma and other cancers. Bacterial inosine production boosts T-cell antitumor activity and promotes TH1 differentiation via the inosine-A2AR-cAMP-PKA cellular pathway; it is worth noting that inosine is an ICI modulator.[51] *Limosilactobacillus fermentum* JNU532 antioxidant and antimelagenic activity was demonstrated *in vitro* by Meng and Oh. On B16F10 cells, they found that the probiotic had the highest antioxidant activity. They also discovered that probiotic cell-free supernatant (CFS) inhibited melanogenesis. They discovered that probiotic CFS-mediated inhibition of TYR, TRP-1, TRP-2, and MITF is linked to the probiotic's antimelanogenic activity.[52-58]

Conclusions

A growing body of evidence suggests that altered microbiota play a role in the development of skin complications, particularly skin cancer. The decrease in skin commensal microbiota and the increase in pathogenic agents that are beneficial to cancer cells are well documented. According to the research, certain microorganisms are capable of reducing pathogenic microorganisms and acting as anti-tumor agents. Despite documented evidence that some microbiota species and probiotics have antiproliferative activity, the findings of these studies should be interpreted with caution.

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