InaJCC The Indonesian Journal of Cancer Control

Review Article

Microbial allies and enemies: How the skin microbiome influences skin cancer

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e-ISSN 2797-457X
DOI: 10.52830/inajcc.v3i3.72

Received: January 26, 2024
Accepted: August 15, 2024

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Abstract

The microbiota is a population of bacteria that inhabit the human body, whereas the microbiome is the set of genes encoded by these microorganisms. While the microbiota refers to the organisms living in various parts of the human body, microbiome is regarded as their genetic information. The microbiota can affect skin cancer risk and treatment response through influencing immune processes, production of certain metabolites and toxins, and their interactions. Cancer is defined as uncontrolled or abnormal cell proliferation. The pathogenesis of skin cancer is multifactorial which includes disruption of the skin barrier, the immune system, metabolites and toxins from microbes, and ultraviolet radiation. The microbiome is an important component of the tumor microenvironments, both in the skin and gut. Microbial dysbiosis is associated with chronic inflammation which may further mediate carcinogenesis. The polymorphic microbiome is considered one of the enabling characteristics of the hallmarks of cancer. Abnormal skin microbiota will produce cytokines and chemokines that contribute to tumor growth. Various microbiota has tumorigenesis effects such as *Staphylococcus aureus*, beta-HPV, *Corynebacterium*, and *Fusobacterium*, but there is also protective microbiota namely *Cutibacterium, Malassezia,* and *Staphylococcus epidermidis.* Studies showed that the presence of microbiome polymorphic variability between individuals has a profound impact on cancer phenotypes.

Keywords: *carcinogenesis, dysbiosis, microbiome, skin cancer*

Abstrak

Mikrobiota adalah populasi bakteri yang menghuni tubuh manusia, sedangkan mikrobiom ialah kumpulan gen yang dikodekan oleh mikroorganisme tersebut. Mikrobiota mengacu pada organisme-organisme yang hidup di berbagai bagian tubuh manusia, sedangkan mikrobiom adalah informasi genetik yang dibawa mereka. Mikrobiota dapat mempengaruhi risiko kanker kulit dan respon pengobatan dengan memengaruhi proses imun yang terjadi, produksi dari metabolit dan toksin tertentu, serta interaksi antar mereka. Kanker didefinisikan sebagai proliferasi sel yang tidak terkendali atau abnormal. Patogenesis kanker kulit bersifat multifaktorial yang meliputi gangguan pada *barrier* kulit, sistem imun, metabolit dan racun dari mikroba, serta radiasi ultraviolet. Mikrobiom adalah komponen penting dari *tumor microenvironments*, baik pada kulit maupun usus. Disbiosis mikroba berhubungan dengan peradangan kronis yang selanjutnya dapat memediasi karsinogenesis. Mikrobiom polimorfik dianggap sebagai salah satu karakteristik *the hallmarks of cancer*. Mikrobiota kulit yang abnormal akan menghasilkan sitokin dan kemokin yang berkontribusi terhadap pertumbuhan tumor. Berbagai mikrobiota memiliki efek tumorigenesis seperti *Staphylococcus aureus, beta-HPV*, *Corynebacterium, dan Fusobacterium*, namun ada juga mikrobiota yang bersifat protektif yaitu *Cutibacterium, Malassezia,* dan *Staphylococcus epidermidis.* Studi menunjukkan bahwa adanya variabilitas polimorfik mikrobiom antar individu memiliki dampak besar pada fenotipe kanker.

Kata kunci: *disbiosis, kanker kulit, karsinogenesis, mikrobiom*

Background

The human body's largest organ is the skin, which functions as a physical barrier against invading microorganisms. Millions of bacteria, fungi, and viruses, both pathogenic and commensal microbiota, inhabit the skin. When the barrier is damaged, or the equilibrium between pathogenic and commensal microbiota is altered, skin disease or systemic disease may develop.[1] Microbial dysbiosis is associated with the ability of eluding immune responses, carcinogenesis processes stimulated by inflammation, and chronic inflammation, where chronic inflammation is attributed to cancer progression.[2]

Cancer is an uncontrollable or abnormal proliferation of cells caused by genetic abnormalities or environmental factors.[2] Incidence rates of skin cancer have increased worldwide during the past decade. In the United States, skin cancer affects around 3,3 million people. Among the various types of skin cancer, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), collectively known as non-melanoma skin cancer, and malignant melanoma (MM) are the most prevalent. For instance, in 2017, the National Central General Hospital Dr. Cipto Mangunkusumo (RSCM) recorded 263 cases of skin cancer, with BCC accounting for 66.9%, followed by SCC at 27.4%, and MM at 5.7%.[3]

The pathogenesis of skin cancer is complex, with ultraviolet light, chemicals, bacteria, fungi, and viruses playing crucial roles in cancer formation.[4] The microbiota is a population of bacteria that inhabit the human body, whereas the microbiome is the set of genes they encode.[5] While the microbiota refers to the organisms living in various parts of the human body, microbiome is regarded as their genetic information. The microbiota can affect skin cancer risk and treatment response. Skin microbiota, together with damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and microbial toxins can prompt chronic inflammation and cellular damage to the skin.[2] Chronic inflammation and microbial dysbiosis are interrelated, which may mediate the carcinogenic process.[2] The microbiota, DAMPs, PAMPs, toxins, immune cells, cytokines, and chemokines contribute in immunosuppression, cellular proliferation, and inflammation, thus modifying the tumor microenvironment and promoting skin cancer.[2] Research indicates that the microbiome could be used to treat various diseases, including cancer.[4] This leads to microbiome studies to determine the development of cancer.[2]

The characteristics and role of normal microbiomes on the skin

The human body contains various types of commensal and pathogenic bacteria. Distinct organisms, including bacteria, fungi, and viruses, have different distributions on the skin. Compared to the digestive system, the weight of skin microbes is relatively low, but the amount of bacterial diversity in the skin is comparable to that of the large intestine. Intrinsic (age, nutrition, sex, immunological status, and genetic susceptibility) and extrinsic (environment and behavior) factors determine microbial diversity.[6]

Microbiota distribution depends on local skin's physiological characteristics, such as moist, dry, and sebaceous (oily) areas. The sebaceous area is dominated by lipophilic *Propionibacterium* species, whereas *Staphylococcus* and *Corynebacterium* are prevalent in moist areas such as skin folds.[1] Commensal *Streptococcus* regulates skin inflammation by producing lipoteichoic acid, which activates the skin's innate immune response. *Staphylococcus* species have been identified in different skin diseases, such as atopic dermatitis, with abundant *Staphylococcus aureus* (*S. aureus)* colonization in lesional and non-lesional skin in adults.[7]

A study found that Proteobacteria are the most prevalent bacteria in all skin swabs, scrapings, and biopsies samples.[8] Bacteria were discovered not only on the skin surface but also in previously considered sterile layers such as the dermis and adipose tissue.[9] This colonization is influenced by the varying oxygen levels between the skin surface and deeper layers. Proteobacterial interaction with dendritic cells can induce the production of IL-1, IL-17, and IFN-γ by T cells migrating to the epidermis, activate natural killer cells, and stimulate keratinocytes to secrete antimicrobial peptides (AMP). Furthermore, microbiota colonization is also affected by the difference in oxygen pressure between the skin surface and the deeper layers.[8,9]

While bacteria are the most prevalent species in the skin microbiome, fungi are also observed. On healthy skin, the fungal microbiota, also known as mycobiota comprises *Malassezia* species primarily, along with *Candida, Aspergillus, Cryptococcus, Rhodotorula,* and *Epicoccum* species. The fungal distribution throughout the body is determined by the characteristics of the microbe, the area of the body affected, age, and gender.[7] The trunk and arms are dominated by fungi of the genus *Malassezia*, while the feet are colonized

by *Malassezia spp., Aspergillus spp., Cryptococcus spp., Rhodotorula spp.,* and *Epicoccum spp*.[10] Due to the absence of fatty acid synthesis genes in the genus *Malassezia*, which mainly requires human long-chain fatty acids for growth, this species is found in areas of oily skin. *Malassezia globosa's* protease 1 can hydrolyze protein A from *S. aureus*, allowing it to prevent bacterial biofilm formation, and immune evasion strategies, and maintain healthy skin.[11]

Candida albicans is also a component of the skin's mycobiota; the skin's pH affects its growth. An increase in pH, which is common in moist environments, promotes overgrowth. *C. albicans* and *S. aureus* overgrowth play a crucial role in the etiology and pathogenesis of skin cancer.[11]

In contrast to bacteria and fungi, the anatomical location of the body does not affect the colonization of eukaryotic DNA viruses. There are no unique gene markers for distinguishing viruses; nonetheless, viral diversity can be observed by sequencing viral-like particles or through shotgun metagenomics. Eukaryotic viruses play a role in skin diseases, including oncoviruses that cause Merkel cell polyomavirus, which is a rare but aggressive skin cancer.[11]

Metagenomic studies on 103 healthy individuals revealed a significant prevalence of human papillomavirus (HPV) in the skin (61.3%), followed by other ecosystems such as the vagina, mouth, and intestines. This virus is known to cause multiple forms of tumors in humans. It is found to increase the risk of SCC of the skin. Shotgun sequencing analysis demonstrated that the HPV population of healthy skin is more complicated. In addition, it is crucial to understand the genotypes of non-oncogenic viruses, as these genotypes can either drive or inhibit HPV infection.[12]

Invasion of pathogens including HPV on the skin will trigger the main components of innate immunity such as keratinocytes to increase AMP production. AMPs such as cathelicidin LL-37 and human β-defensins (i.e., hBD-1, 2, 3, and the antimicrobial protein RNase 7) induce innate and adaptive immunity mediators to prevent pathogenic skin invasion. Therefore, the regulation of the interaction between keratinocytes, immune cells, and microbes by AMP, cytokines, and chemokines is essential for skin integrity.[7,13]

Survival of the skin microbiota is regulated by the desquamation of the stratum corneum epithelium and the skin's pH, inhibiting the growth of pathogens that compete for nutrition. Other variables, such as the use of skin care products or smoking, can further influence the variety of microbiota.

The relationship between skin microbiomes and gut microbiomes

Human commensal microbiota resides primarily in the intestine, although there is an interaction between the skin and gut microbiota.[2] The microbiome is symbiotically associated with the barrier tissue of the body that is exposed to the external environment, primarily the skin and the internal environment, particularly the gut mucosa. There is growing evidence that microbiome variation between individuals within a population can significantly affect cancer phenotype.[14] The skin microbiota is dominated by *Actinobacteria*, whereas the gut microbiota primarily consists of *Firmicute*s and *Bacteroidetes*. Both possess substantial intra-individual variation. The relationship between skin and gut microbiomes is a complex and dynamic interplay that extends beyond their local environments. This relationship, often referred to as the gut-skin axis, involves bidirectional communication between these two microbiomes and the immune system. Understanding how changes in one microbiome impact the other can provide valuable insights into maintaining skin and gut health.[7]

The modulating effect of the gut microbiome

The modulating effect of the gut microbiome on immune function plays a crucial role in maintaining overall health. For instance, certain gut bacteria can influence the development and function of immune cells, impacting the body's ability to respond to infections and regulate inflammation. The ability of the gut microbiota to express chemokines and immunomodulatory cytokines which ultimately enter the systemic circulation provides evidence of the association between colon cancer and melanoma. This can affect the development and therapeutic response of cancer in other organs.[14] For example, patients with melanoma who responded to anti-programmed cell death (PD) 1 treatment had more "good bacteria" in their intestines than those who did not respond. These data imply that the gut microbiome is essential for skin cancer immunity regulation.[2]

The mechanism by which the microbiome modulates this immune response remains unknown. However, the tumor-inducing microbiome has two known impacts. The first effect is colonic epithelial mutagenesis, caused by the production of bacterial toxins and other substances that directly damage DNA, affecting

systems that preserve genome integrity or indirectly inhibit DNA replication and repair. The second mechanism is the presence of particular bacterial species that stimulate carcinogenesis, specifically butyrate-producing bacteria, whose populations are increased in colorectal cancer patients. The complex physiological consequences of butyrate metabolite products include the production of senescent epithelial cells and fibroblasts.[14]

The role of skin microbiome in the development and progression of skin cancer

The interaction between a compromised skin barrier, ultraviolet (UV) exposure, and commensal bacteria on the skin can impact the composition of the skin microbiome. A combination of altered skin microbiota, DAMPs, PAMPs, and microbial toxins can induce persistent inflammation and cellular damage, which can result in the beginning and progression of skin cancer. Microbiota, DAMPs, PAMPs, microbial toxins, CD8+ T cells, regulatory T cells, tumor macrophages, cytokines, and chemokines are the most influential variables in the tumor microenvironment (TME) in skin cancer. By inducing immunosuppression, cell proliferation, and inflammation, it contributes to the development of skin cancer (Figure 1,2). In addition, gut microbial metabolites, cytokines, and chemokines may indirectly affect cutaneous TME via systemic circulation.[2]

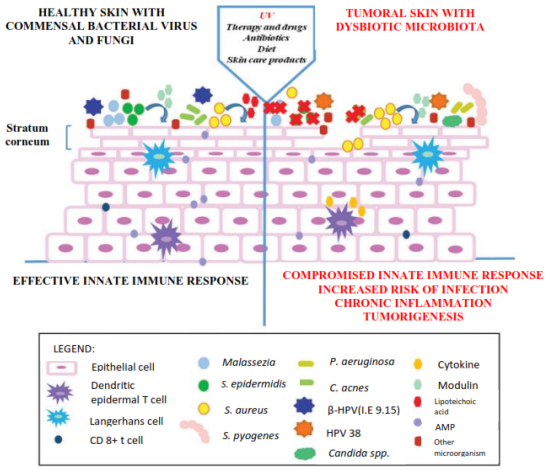

Figure 1. Changes in the microbiome in the pathogenesis of skin cancer.[7]

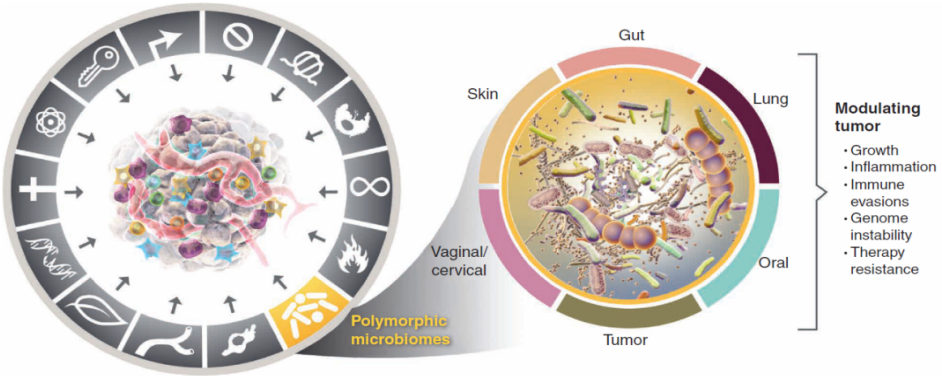

Figure 2. Polymorphic microbiomes. Left, polymorphic microbiomes in one individual can diversely influenced by either inducing or inhibiting many of the hallmark capabilities. Right, multiple tissue microbiomes are implicated in modulating tumor phenotypes and modulating the acquisition both positively and negatively of the hallmark capabilities in certain tumor types.[14]

Skin barrier disruption on skin cancer

A damaged skin barrier may result in microbial dysbiosis. Multiple studies have demonstrated that disruption of the skin barrier can lead to microbial dysbiosis, altering the skin's homeostasis and commensal microbiome.[15] This dysbiosis can be exacerbated by proteases produced by the skin microbiota, which can damage the epidermal barrier. In a mouse model of non-melanoma skin cancer, studies have shown that excessive colonization of S. aureus can promote the expression of human defensins and tumor cell proliferation.[16] Additionally, chronic inflammation of damaged or chronically diseased skin is known to potentially contribute to the development of SCC. However, further research is needed to understand the specific microbiota associated with barrier alteration in skin cancer.[17]

Skin immune system and skin cancer

The interaction between the immune system and microbiota has a role in the development of tumors. The microbiome can stimulate cancer by causing chronic inflammation, disrupting the balance between cell growth and death, and stimulating the immune system. The immune system of the skin is comprised of both the innate and adaptive immune systems. The dysbiosis of this antibacterial defense system allows the movement of cellular and microbial components across the barrier, resulting in an inflammatory innate immune response.[5] Keratinocytes, endothelial cells, fibroblasts, neutrophils, macrophages, dendritic cells, and mast cells are the primary components of innate immunity, while T and B cells are categorized as adaptive immune cells.

Keratinocytes produce various cytokines, chemokines, antimicrobial lipids, and AMP. Under the stimulation of microbial PAMPs or DAMPs, AMPs, specifically cathelicidin LL-37 and human β-defensin, are continually generated and regulated.[18] Macrophages are also significantly involved in the development of melanoma. M1 macrophages target the tumors to induce phagocytosis and immune responses aimed at inhibiting advancement and metastasis of cancer. However, cancer cells express CD47 to evade macrophages. Hydrolysate 3-(trihydroxygermyl) propanoic acid (THGP) displays the ability to enhance antitumor immunity by stimulating polarization of M1 macrophages and decrease presentation of signal-regulatory protein alpha (SIRP-α) in macrophages as well as CD47 in cancer cells.[19]

Pattern recognition receptors (PRR) produced from macrophages, dendritic cells, and epithelial cells also play an important role. PRR can distinguish the distinct molecular properties of PAMPs and DAMPs and elicit an appropriate immune response. Various PRR types correlate to the pathogen's distinctive pattern, intracellular location, expression, and signaling pathway. The majority are classified into cytoplasmic receptors and toll-like receptors (TLRs). Approximately ten TLRs have been found in humans.[18]

Toll-like receptors (TLRs) play a crucial role in the skin's immune response. They can be expressed by various cell types in the skin, including keratinocytes, melanocytes, and antigen-presenting cells. Activation of TLRs initiates the innate immune response by recognizing PAMPs or DAMPs. However, chronic TLR activation can lead to chronic inflammation, which is implicated in various skin disorders and diseases, including skin cancer. Understanding the specific TLRs involved in skin inflammation and their role in disease development is an active area of research. TLR 4 is the only type of TLR recognized to significantly impact skin inflammation and malignancy. Activation of TLR 4 and subsequent internal signaling pathways might result in the activation of transcription factors such as NFκ-B, interferon regulatory factors 3 (IRF-3), and activator proftein-1 (AP-1), which regulate the expression of genes involved in inflammation, cellular apoptosis, survival, and differentiation.[2] Increased TLR expression has been found in skin cancer. Compared to the control, the expression of TLR 4 was higher in SCC. In UV-induced animal models, topical administration of the TLR 4 inhibitor resatorvid has diminished tumor size and number. This suggests that TLR suppression is beneficial for UV-induced non-melanoma skin cancer. Overexpression of TLR 4 in both radial and vertical melanoma growth phases was related to recurrence in malignant melanoma (MM). Imiquimod, a TLR 7 agonist, is an effective treatment for various skin malignancies, including SSC, BCC, CTCL, and lentigo maligna melanoma.[2]

Adaptive immunity, especially elevated T-cell infiltration, has displayed an enhanced overall survival in patients with advanced melanoma.[20] Researchers have performed various trials to induce T-cell inflamed tumors from its condition of T-cell deficit.[20] An oncolytic virus with simultaneous expression of granulocytes-macrophage colony-stimulating factor (GM-CSF) and programmed death ligand (PDL-1) stimulates T-cell infiltration into TME.[20] In comparison to various cancers, melanoma and non-melanoma skin cancers

respond better to immunotherapy.[19] Imiquimod, an immune-modulating agent, can fight against primary and metastatic skin cancer.[19] Immune checkpoint inhibitor (ICI) therapies, including PDL-1 and cytotoxic T-lymphocyte-associated protein (CTLA-4), have also been developed and proved to be an effective on immunotherapy for both types of skin cancers.[19] These ICIs activate exhausted CD8+ T lymphocytes found in tumors.[20] Stromal cells found in TME, such as the tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), may function as targets for some immunotherapies.[19] Regardless on how immunotherapy has displayed remarkable effectivity towards skin cancer, it may not be well responded by every case, highlighting the need for further research.[19]

During immunosuppressed states, for instance, post receiving organ transplant individuals and patients suffering rheumatic diseases, the risk of skin infections by opportunistic fungus and yeast overgrowth increases.[7] Radiotherapy and chemotherapy can cause epithelium damage through the disturbance of epithelial cells regeneration, thus enabling the penetration of fungi and yeasts due to the impaired barriers.[7] Opportunistic infections should not be underestimated as they contribute to increased morbidity and mortality, diminished quality of life, and impose patients with significant healthcare costs. It is of the best interest to identify, prevent, and treat infections accordingly, especially for immunosuppressed patients, as they are at higher risks and may suffer adverse consequences. Hence, understanding how chemotherapy and radiotherapy recipients are more prone to infections can aid in improving skin cancer treatment strategies.

Microbial metabolites and toxins in skin cancer

TME in skin cancer consists of various cell types, including immunocytes, fibroblasts, vascular and lymphatic endothelial cells, pericytes, adipocytes, and numerous chemicals, released by tumor and non-tumor cells. The microbiome, including its metabolites, is an integral part of TME.[5] Metabolites produced by microorganisms can interact directly with cancer cells or promote carcinogenesis through modulating TME components, such as immune cells and stromal cells. Immune cells like the TLRs and NOD-like receptors (NLRs) are classified as PRRs to identify microbial components. For example, certain microbial metabolites that are found in different cell organelles have been shown to promote inflammation or alter the local immune environment, contributing to tumor growth and progression. By regulating the availability of metabolites, initiating DNA damage, and regulating the system, the mechanism of action of microbial metabolites might influence the development of cancer.[18] Microbial metabolites produced toxins that change DNA and cause oncogenic mutations. Several studies have associated exotoxins from *S. argenteus* and *Staphylococcus enterotoxin A* with CTCL. Currently, most research indicates that microbial metabolites and toxins are expressed by the gut microbiome; however, it is believed that the skin microbiome can also produce them.[18]

Ultraviolet radiation and the skin microbiome in skin cancer

UV rradiation is a significant carcinogen in skin cancer development. UV light promotes DNA damage and mutations, leading to the clonal proliferation of cancer cells. Additionally, UV exposure induces the production of reactive oxygen species (ROS) and inhibits the immune system, contributing to photocarcinogenesis.[21] Recent research has also highlighted the role of the skin microbiome in UV-induced skin damage. The microbiome's composition and function can be altered by UV exposure, influencing the skin's response to UV radiation and potentially affecting the development of skin cancer. The altered skin microbiome may generate changes in gene expressions that associate with immune processes. A study discovered that exposure to UVB can alter the skin and gut microbiome.[22] In the presence of a microbiome, UV exposure reduces systemic immunosuppression, according to the findings of other researchers. In addition, the degree of epidermal hyperplasia and neutrophil infiltration increased in the presence of the microbiome, whereas the infiltration of mast cells, monocytes, and macrophages increased regardless of the microbiome. There are also significant changes in genomic expression based on the skin microbiome's existence. Based on these data, it is possible to conclude that the skin microbiome can reduce UV-induced immunosuppression via modifying cytokine expression genes and skin cellular infiltration.[21] Further studies are needed to elucidate the complex interplay between UV radiation, the skin microbiome, and skin cancer.

Intratumoral microbiota and skin cancer

Intratumoral microbiota found in TME is found to be capable of entering tumor cells. Some of its peptides can be expressed by antigen-presenting cells (APCs) of the immune system and may trigger immune responses from the host. In certain malignancies, regulatory T cells are known to inhibit anti-tumor

immune responses and create immunosuppressive TME. Regulatory T cell infiltration is frequently detected in SSC, BCC, and MM skin samples, decreasing T cell activity and establishing an immunosuppressive TME for skin cancer.[2]

Depending on the species, intratumoral bacteria have positive and negative correlations with tumor growth. *Lachnoclostridium* bacteria demonstrated the strongest positive correlation with CD8+ T cell infiltration, followed by *Gelidibacter, Flammeovirga*, and *Acinetobacter*, whereas *Algibacter* and *Epilithnimonas* demonstrated a negative correlation. A positive correlation exists because these bacteria enhance the infiltration of CD8+ T lymphocytes, which increases the expression of the chemokines CXCL9, CXCL10, and CCL5. *Lachnoclostridium* was significantly related to a reduced risk of mortality, suggesting that enhanced infiltration of CD8+ T cells and an increased number of *Lachnoclostridium* may provide a favorable prognosis in melanoma patients.[20]

Mechanism of the relationship between skin microbiomes and skin cancer

Non-melanoma skin cancer

The relationship between the skin microbiome and non-melanoma skin cancer, particularly squamous cell carcinoma (SCC), involves several key mechanisms. The skin microbiome can influence the development of SCC through its effects on the immune system, the production of metabolites, and the modulation of inflammatory pathways. For example, certain bacteria in the skin microbiome can produce metabolites that promote inflammation and cell proliferation, contributing to the development of SCC. Additionally, the skin microbiome can interact with immune cells in the skin, leading to an imbalance in the immune response that favors tumor growth. Understanding these mechanisms is crucial in developing targeted therapies that can modulate the skin microbiome for SCC prevention and treatment.

Non-melanoma skin cancer is the most prevalent skin cancer worldwide, and its frequency is increasing. Non-melanoma skin cancer, including SCC and BCC, is a malignant skin tumor not associated with melanocytes.[2] BCC metastasizes less frequently than SCC but has a significant morbidity rate. Actinic keratosis is a non-melanoma skin cancer that frequently affects white individuals with extensive sun exposure.[7] Due to a lack of references, this literature review focuses solely on the microbiome of SCC.

In one study, biopsies and swabs of tumors revealed an association between *S. aureus* and SCC. *S. aureus* is found to be significantly increased in the skin microbiome of patients suffering from skin diseases. Colonization with *S. aureus* was higher in SCC biopsies (29.3%) than in healthy skin biopsies (5.7%), and the prevalence of *S. aureus* in SCC swab samples (31.7%) was higher than in healthy skin swab samples (15,0%). As actinic keratosis are precancerous lesion of SCC, an increase in *S. aureus* colonization is related to the progression of actinic keratosis to SCC.[16] A recent study on the 16S ribosomal RNA sequencing gene in skin biopsies revealed that *S. aureus* levels were high in actinic keratosis and SCC.[17] Increased *S. aureus* numbers were also associated with elevated hBD-2 expression in SCC. The SCC cells with hBD-2 directly accelerated tumor cell proliferation. A study revealed that a high number of *S. aureus* could affect the expression of hBD-2, which can promote the proliferation of SCC.[16,17]

S. aureus stimulates the secretion of IL-1a and IL-36a by keratinocytes via the peptide modulin. This cytokine-mediated signaling pathway is required for T cell IL-17 secretion. Along with IL-22 and tumor necrosis factor-alpha (TNF-α), these pro-inflammatory cytokines regulate *S. aureus* colonization of the skin by activating inflammatory pathways. All these substances significantly initiate tumor growth by promoting the proliferation and migration of skin cancer cells with metastatic disease.[7]

Microbial profiling analysis revealed that S. *aureus* was more prevalent in SCC and actinic keratosis samples than in BCC. When the skin barrier is intact, *S.aureus* can not infect immunocompromised individuals; nevertheless, some circumstances, such as burns or atopic dermatitis, might lead to *S. aureus* infection.[2]

Due to chronic inflammation, *S. aureus* strains contribute to skin carcinogenesis and function as risk markers for developing SCC. Consequently, lesions with a persistent infection should be monitored and treated. As the reason for SCC development, the existence of bacteria such as *S. aureus, S. pyogenes*, and *P. aeruginosa*, which are responsible for chronic and suppurative inflammation, is still debatable.[7]

Cutibacterium and Malassezia play significant roles in inflammation that promotes tumorigenesis. They are, respectively, the most abundant bacterium and yeast that thrive in healthy, sebaceous skin. Their dysbiosis in the skin microbiome can be a biomarker for certain

diseases. The number of *Cutibacterium* and *Malassezia* in the skin of patients with actinic keratosis and SCC was lower than that of healthy, non-lesional skin, based on an Australian cohort study. The decreased number of *Malassezia* in SCC increases the likelihood of the yeast's protective feature.[7,23,24]

Cutibacterium is a genus of skin bacteria predominantly found in lipophilic regions, specifically the sebaceous area. The decrease in the number of *Cutibacterium* in actinic keratosis and SCC can be attributed to a dry and scaly surface of actinic keratosis accompanied by a decrease in sebum, which represents a decrease in skin hydration and an increase in skin pH. In addition, since *Cutibacterium acnes* (C. acnes) can create AMP, reducing the number of *Cutibacterium* can also promote the growth of *S. aureus*.[2]

Staphylococcus epidermidis (*S. epidermidis*) can inhibit the growth of skin cancers. Commonly present on healthy human skin, *S. epidermidis* is a coagulase-negative bacteria whose presence inhibits the growth of *S. aureus*.[22] *S. epidermidis*'s secretome can inhibit skin inflammation by activating regulatory T cells. Recent research indicates that the 6-N-hydroxy-aminopurine (6-HAP) generated by *S. epidermidis* can inhibit DNA synthesis and the proliferation of tumor cells. Colonization of a 6-HAP-releasing *S. epidermidis* strain reduced UV-induced tumor growth in a mouse model compared to the colonization of a 6-HAP-free control strain.[2]

The current study indicates a relationship between SCC and HPV. Compared to healthy individuals, patients with non-melanoma skin cancer had a higher likelihood of HPV infection.[25] In addition, a meta-analysis revealed an elevated risk of HPV infection in SCC compared to normal skin. In addition, immuno-compromised patients were shown to have a higher HPV prevalence than immunocompetent patients.[26] Approximately 50 beta HPV varieties associated with SCC have been identified to date. The synergistic effect between beta strains of cutaneous HPV and UV radiation is crucial to developing SCC. Beta HPVs, including HPV 5 and HPV 8, have been isolated from the skin of patients with epidermodysplasia verruciformis, which typically progresses to SCC. Several investigations have demonstrated that beta-cutaneous HPVs function as a carcinogen to initiate cell damage in response to UV exposure but are not required to preserve SCC as HPV is not transcribed in SCC's maintenance phase.[25] The mechanism of beta HPV in skin carcinogenesis is known as the hit-and-run mechanism. However, this is still debatable and warrants additional study.[27]

Candida is the most prevalent fungal pathogen. According to a nationwide population-based epidemiological study, *Candida* infection is related to an elevated risk of numerous malignancies, including hematological, head and neck, pancreatic, skin, and thyroid. The role of yeast in cancer development is via pro-inflammatory mechanisms in the TME. However, experimental studies directly identifying the association between the fungal microbiome and skin cancer are scarce.[2] In patients with non-melanoma skin cancer, another study on the response of *Malassezia* to photodynamic therapy (PDT) revealed that PDT decreases *Malassezia* in the peritumoral skin (Figure 3).[7]

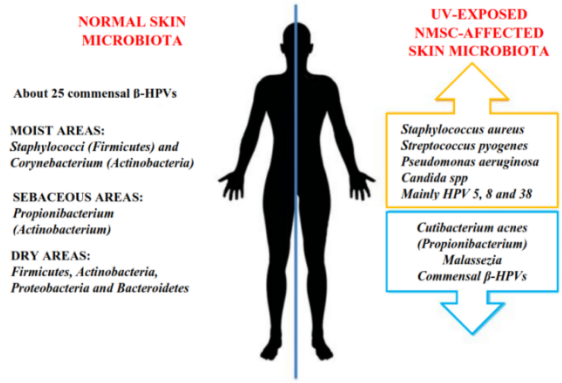

Figure 3. Non-pathogenic microbiota and their changes in normal skin and non-melanoma skin cancer due to UV exposure.[7]

Malignant Melanoma

Seventy-five percent of all skin cancer-related deaths are caused by MM, making it the most devastating type of skin cancer. It is not easily susceptible to treatment and can lead to fatal outcomes. Incidence and mortality of MM have increased substantially during the past four decades in western regions, rising to 10-50 new cases for every 100 000 people in a year (approximately 3-8% increase). Malignant melanoma is a heterogeneous illness with distinct subtypes based on anatomical distribution, somatic mutation patterns, and histological characteristics.[28] Microbiota such as bacteria and viruses can generate various immune pathways that lead to beneficial or detrimental effects on MM. Culture-based microbial study on 27 acral melanoma patients revealed that the genus *Corynebacterium* was more closely related to stage III/IV MM patients than stage I/II MM patients. Interleukin (IL)-17 levels were higher in patients with positive *Corynebacterium* than in those with negative

Corynebacterium.[29] By upregulating IL-6, signal transducers, and activating transcription 3, IL-17 can promote melanoma growth. As established in mouse model research, *Corynebacterium* species can affect the development of MM via an IL-17-dependent pathway. In another study using a mouse model, intratumor injection of *C. acnes* significantly reduced tumor size. Melanoma cell growth was suppressed by the production of Th1 cytokines, including IL-12, TNF-α, and interferon-gamma (IFN-γ), following intra-tumor injection of *C. acnes*.[30] It was also reported that *C. acnes* can suppress the survival of UVB-irradiated melanocytes by increasing apoptosis, coproporphyrin secretion, and TNF-α regulation.[31]

Studies have shown that bacteria residing on the skin vary between healthy individuals and cancer patients. The multifaceted impact of certain microbiota and metabolites of the skin microbiome on MM, combined with specific interactions and environmental influence, can lead to proliferation or inhibition of the tumor. A study found that intravenous injection of 6-HAP produced from *S. epidermidis* could decrease the proliferation of melanoma cells and strengthen *S. epidermidis*' protective effect against MM.[32] In contrast, some researchers reported that *S. epidermidis* and lipoteichoic acid from *S. epidermidis* could improve melanocyte survival by upregulating TRAF1, CASP14, CASP5, and TP73 in response to UVB irradiation. The skin microbiota plays a role in melanocytic illnesses such as melanoma and melanocytic nevi. Control samples were obtained from the same patients' normal skin on the contralateral side.[33] After getting the skin swabbed, the samples obtained were analysed through partial sequencing of the 16S ribosomal RNA gene using the 454 GS-FLX Titanium platform, followed by bioinformatic and statistical processes. 16S ribosomal RNA sequencing demonstrated a modest decrease in microbial diversity between melanoma and melanocytic nevi skin samples. A study of the skin microbiome on pig models with melanoma revealed significant differences between cancer and normal skin samples in the variety of bacterial and microbial compositions.[32] Numbers of *Fusobacterium* and *Trueperella* were higher in melanoma skin samples than in control samples.[34] Previous studies have indicated a correlation between elevated *Fusobacterium* levels and several types of cancer, including pancreatic, colorectal, and oral malignancies.[35] *Fusobacterium nucleatum* can enhance tumor proliferation by suppressing natural killer cell cytotoxic via the interaction of its Fap2 protein with T cells.[2]

Besides bacteria, viruses are also components of the microbiota implicated in the progression of MM. However, the function of viruses in cutaneous melanoma is somewhat ambiguous. Multiple epidemiological studies have demonstrated an association between HPV and melanoma. A population-based cohort analysis revealed an association between HPV infection and an elevated risk of melanoma.[25] High-risk mucosal HPV viruses were detected in 27% of MM samples from skin biopsies using PCR-ELISA. HPV 16 and HPV 33 were the most frequently detected viruses.[36] A study on ocular melanoma indicated that down-regulation of HPV 18 E6/E7 could decrease tumor growth and cell cycle progression by activating the p53 and Rb pathways. HPV 22 was discovered more frequently in melanoma than in the normal skin of the same individual as a control. However, neither MM's clinical nor histological features were related to HPV prevalence. Further research is required to identify whether cutaneous HPV is a cofactor in the development of MM.[37]

Human endogenous retroviruses (HERVs) can serve as cellular reservoirs for retroviral genes with pathogenic characteristics. ERV sequence activation is related to melanocyte transformation and melanoma cells' ability to avoid immune surveillance. UVB-induced melanoma cells exhibited increased expression of retroviral envelope protein and activation of the retroviral pol gene, suggesting that UV radiation is involved in the pathogenesis of melanoma..[38]

Conclusions

Particular bacterial species can directly stimulate the hallmark of proliferative signaling and modulate growth suppression; whereas direct effects on other hallmarks capabilities, such as avoiding cell death; inducing angio-genesis; and stimulating invasion and metastasis; remain obscure. Polymorphic variation in microbiomes constitutes a distinctive enabling characteristic for the acquisition of hallmark capabilities, albeit intersecting with and complementing those of genome instability and mutation, and tumor-promoting inflammation via immunomodulation, toxin production, as well as cell disruption.[14]

Various skin microbiomes related to skin cancer and their corresponding mechanisms could be either preventive or carcinogenic (table 1). The interaction between a damaged skin barrier, UV exposure, and skin commensal bacteria affects the composition of the skin microbiome.[2] Abnormal skin microbiota, accompanied by microbial metabolites and toxins,

can generate persistent skin inflammation and cellular damage, resulting in skin cancer development. Numerous cytokines and chemokines are the most influential factors in the TME of skin cancers.[18] Cytokines and chemokines contribute to tumor growth by promoting inflammation, immunosuppression, and cell proliferation. In addition, it is known that microbial metabolites, cytokines, and chemokines from the gut can enter the systemic circulation and indirectly influence the malignant microenvironment of the skin. Additional study is required to establish the varied roles of the microbiome in skin cancer in terms of carcinogenesis and protective effects against cancer development that may be beneficial to the prevention and treatment of skin cancer.[18]

Table 1. Various skin microbiomes associated with skin cancer and their mechanisms.

Skin microbiome	Data collection	Mechanism
Non-melanoma skin cancer[5]		
An increased number of or associated with a tumor-forming action		
Staphylococcus aureus	Humans, skin biopsies, and swabs	Causes chronic inflammation Associated with increased hBD-2 expression causing tumor cell proliferation Produced by disruption of the skin barrier
Beta type HPV	Mouse model, skin biopsy Human, skin biopsy	Acts as co-carcinogenesis, causing cellular damage under UV radiation but was not required for SCC maintenance
Reduced number or associated with antitumor activity		
Cutibacterium spp.	Human, skin swab	Metabolic changes in SCC can inhibit the growth of *Cutibacterium* and induce the growth of *Staphylococcus aureus*
Malassezia spp.	Human, skin swab	Resulting from disruption of the skin barrier and decreased sebum availability in SCC Inhibits the growth of *S. aureus* 6-HAP biofilm formation
Staphylococcus epidermidis		*S. epidermidis* derived 6 HAP suppresses DNA synthesis and provides an antiproliferative effect on tumor cells
Melanoma maligna[5]		
An increased number of or associated with a tumor-forming action		
Corynebacterium spp.	Human, skin swab	Increases dependent-IL-17
Staphylococcus epidermidis	Pig, skin scraping Human, skin biopsy	Increases melanocyte survival through upregulation of TRAF1, CASP14, CASP5, and TP73 during UVB radiation
Fusobacterium nucleatum		Inhibits NK cell cytotoxicity through interaction with Fap2
High-risk mucosal HPVs		May serve as a cofactor in MM development
Reduced number or associated with antitumor activity		
Cutibacterium acnes		Induces Th1 cytokines such as IL-12, TNF-α, and IFN-γ Promote apoptosis, increase secretion of coproporphyrins, and upregulate TNF-α
Staphylococcus epidermidis		*S. epidermidis*-derived 6-HAP inhibits melanoma cell growth

Acknowledgements

The authors thank Adhimukti T. Sampurna M.D, Agassi S Sutarjo M.D, Danang T Wahyudi M.D, Fadhli A Mughni M.D, Inge A Krisanti M.D, and Irwan S Batubara M.D for their suggestions and comments on the manuscript.

Conflict of Interests

The authors have no financial conflicts of interest.

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