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RESEARCH ARTICLE

Human Cutaneous Microbiome and Skin Carcinogenesis: An Immunological Conundrum

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Abstract

The advancements of new methods for understanding the microbial world provide an opportunity to re-evaluate the views of biological anthropology and disease epidemiology. Recent developments in microbial research offer a wider comprehension of the pathogenesis of skin malignancy. Current research supports the idea that the skin microbiota is indeed, an unexplored risk factor and a potential biomarker of skin cancer. Skin is an organ with a dynamic ecosystem that harbours trillions of commensal microbes. The composition of the human skin microbiome is determined by genetics, environmental factors, and the local microenvironment. While the microbiome plays a critical role in the development of the host's innate and adaptive immune system, the immune system in turn orchestrates the maintenance of host-microbe symbiosis. Thus, while skin and its microbiota have evolved to remain in homeostasis, frequent perturbations are facilitated by environmental stress, diet, gene mutations, and the microbiome itself often resulting in microbial dysbiosis and increased susceptibility to diseases. With more than 1.5 million new cases estimated in 2020, skin cancers are the most commonly diagnosed group of cancers worldwide and apart from the genotoxic stress of UVR, other risk factors including immune suppression, and chronic inflammation, suggest the skin microbiome to be an additional, unexplored risk factor and potential disease biomarker. It warrants a comprehensive understanding of the relation between skin microbiome and skin cancer which may provide insight into novel skin cancer therapy utilizing microbiota.

Keywords: Skin microbes, Commensals, Pathogen, Inflammation, Skin cancer.

1. Introduction

The human skin is a dynamic organ that not only provides first-line protection from the extrinsic environment but also houses a legion of diverse microorganisms viz. bacteria, fungi, viruses, archaea and eukaryotes which collectively concoct the skin microbiome.[1-3] As a component of the human holobiont system, a myriad of skin microbiota thrive on the skin epidermis along with its appendage structures making skin the largest epithelial surface for microbial interactions.[4] The rough texture of skin, and the desiccated, nutrient-poor, acidic environment impede the commensals to colonize. Still, a plethora of microorganisms dispersed over the human skin and the skin microbiome engages in a persistent healthy interaction with the skin immune system in order to survive.[5-7] The cutaneous microbiota exhibits striking variation in its composition according to distinct skin niches influenced by different exogenous and endogenous factors. The microbial community in the skin is liable to vacillate depending on age and sex, ethnicity, genetic makeup, body site, socioeconomic status, diet, pregnancy status of the host along with geography and environmental exposure.[8-11] The

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cutaneous microbiome instigates the development and differentiation of epidermal cells and the maintenance of skin integrity.[12] In fact, the host is conferred with a myriad of benefits from the skin microbiome, including developing and educating the immune system, protecting against pathogen invasion, breaking down metabolites, maintaining healthy skin barrier, and ensuring skin homeostasis from thermoregulation to wound repair.[13-15]

The immune system in the skin has evolved concurrently with the commensal microorganisms to acquiesce with their maintenance and exterminate the potential pathogens. Both epithelial cells and commensal microbiota partake in various protective biomechanisms of innate and adaptive immunity to function optimally.[13] However, perturbations in microbiome-immune system interactions can result in dysregulated response against evading pathogens causing microbial dysbiosis. Dysbiosis frequently causes pathogens and commensals to proliferate uncontrollably, negatively impacting skin health and leading to skin problems and sometimes systemic diseases. Dysbiosis also hinders the microbial symbiotic relationships with commensals, which imbalances cutaneous homeostasis. Aberrant skin immune environments and inflammatory skin diseases jointly render dysbiosis, which manifests as an increase in harmful microbes and a reduction in beneficial ones. This dysbiosis expedites an exacerbated inflammatory response, which leads to the development of chronic illness.[16]

Skin cancers are the most common group of cancers diagnosed worldwide, with more than 1.5 million new cases estimated in 2020.[17] Nonmelanoma skin cancer (NMSC), that includes basal cell carcinoma and squamous cell carcinoma (SCC), is the most common cancer worldwide with a highly aggravated healthcare burden.[18] Cancer that sprouts from melanocytes in the skin Melanoma, the most lethal type of skin cancer with an estimated 325,000 new cases and 57,000 deaths worldwide.[17,19] In the populations having light constitutive skin pigmentation, UVR exposure acts as a precarious risk factor for NMSC as well as melanoma enabling DNA damage, emancipating reactive oxygen species (ROS), and inflammatory cytokines that cause immunosuppression and consequent tumourigenesis.[20,21] Furthermore, the cumbersome financial burden of treatment for skin cancer triggers early prognosis, detection of new biomarkers, and risk factors along with clinical interventions. Analysis of the skin microbiome and its association with cancer progression can unfold a new avenue in skin cancer research, given the new focus on microbial composition and its connection to human disease. Since microbial dysbiosis is tethered to disease pathogenesis through immune evasion and chronic inflammation, it is possible for the skin microbiome to contribute in inflammation-mediated carcinogenesis pathways. However, the connection between skin cancer and the cutaneous microbiome is still obscure. There is still a dearth of studies to comprehend the role of an individual's unique microbiota composition in the development of skin cancer.

In this context, this review aims to discern the immunomodulatory effect of human cutaneous microbial flora associated with the pathogenesis of skin cancer and the putative molecular mechanisms orchestrating the interactions in the skin immune cells.

2. Material and Methods

We performed a literature search reviewing pertinent articles and documents available on online databases viz. Google Scholar, ResearchGate, Pubmed and Scilit. An extensive exploration of prior literature was performed, using the following headings and keywords, linked to the words human cutaneous microbiome and skin carcinogenesis: skin microbiome, immunity, immune system, skin inflammation, non-melanoma skin cancer, squamous cell cancer, melanoma to yield the necessary data.

3. Discussion

3.1 The Microbial-Immune Crosstalk

Skin, being a pivotal ecosystem is tenanted by trillions of microorganisms which maintain a homeostatic host-microbe interaction. However, perturbation in skin homeostasis through immune evasion can induce genotoxicity and chronic inflammation that can mediate clonal proliferation of tumour cells and cancer progression. Therefore, the skin microbiome especially the pathobionts is crucial in developing pro-cancer microenvironments. The innate and adaptive immune system constitute the intricate skin immune system and until the adaptive immune system is activated, the innate immune system predominantly protects the body against microbial infections.[22] Antimicrobial peptides (AMPs), produced by keratinocytes in epidermal tissues have a significant role as immunomodulators and act as first line of defence against pathogen invasion along

with cytokines, chemokines and antimicrobial lipids. The continuous microbial stimulation of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) accelerates the production and abundance of AMPs like cathelicidin LL-37 and human β-defensin (hBD).[23] The distinct chemical properties of PAMPs or DAMPs are recognised by pattern recognition receptors (PRRs), which subsequently trigger the proper immunological response that quickly eradicates and incapacitates a wide variety of pathogens (Fig 1). According to the pathogen's distinctive pattern, the intracellular expression site and the signalling mechanism, different types of PRR are recognised. These are primarily split into cytoplasmic receptors and toll-like receptors (TLRs). TLRs are expressed by keratinocytes, melanocytes and antigen-presenting cells (APCs). Continuous signalling of TLRs is required to preserve cell integrity, heal tissue, and recover from injury resulting in the outcome of innate immune response and also priming antigen-specific adaptive immune responses, thus maintaining immunological homeostasis.[24] However, unbridled activation of TLR actuates the inflammatory processes that might ultimately promote carcinogenesis.[25] TLR4 is one of the TLRs that is recognised to be crucial in both skin inflammation and cancer. The expression of genes linked to inflammation, cellular apoptosis, survival, and differentiation is influenced by the activation of transcription factors such as NF-κB, AP-1 and IRF-3, which can be induced by the activation of TLR4 and subsequent internal signalling pathways.[26] Upregulated TLR4 expression has been observed in MM, SCC and MCC.[27,28,29] TLR4 agonist G100 and TLR7 Agonist Imiquimod have been reported to be effective in enabling tumour regression.[25,30] In addition to modulating innate immune responses, the cutaneous microbiome also stimulates the adaptive immune system of skin, with subsequent implications. Different skin commensals have been shown to induce elevated levels of cytokine interleukin-1α (IL-Iα) which further activates the homing of T-cells that facilitate host defence and skin inflammation.[31,32] Th17 cells, a third kind of T-helper (Th) cells, and the inflammatory cytokine interleukin-23 (IL-23), have recently been shown to have a crucial role in cutaneous carcinogenesis.[33] However, the T-reg cells have been demonstrated to inhibit the Th17/IL-23 axis-induced inflammation.[34] Continuous exposure to microbes improves this regulatory mechanism, which decreases inflammation that promotes cancer.

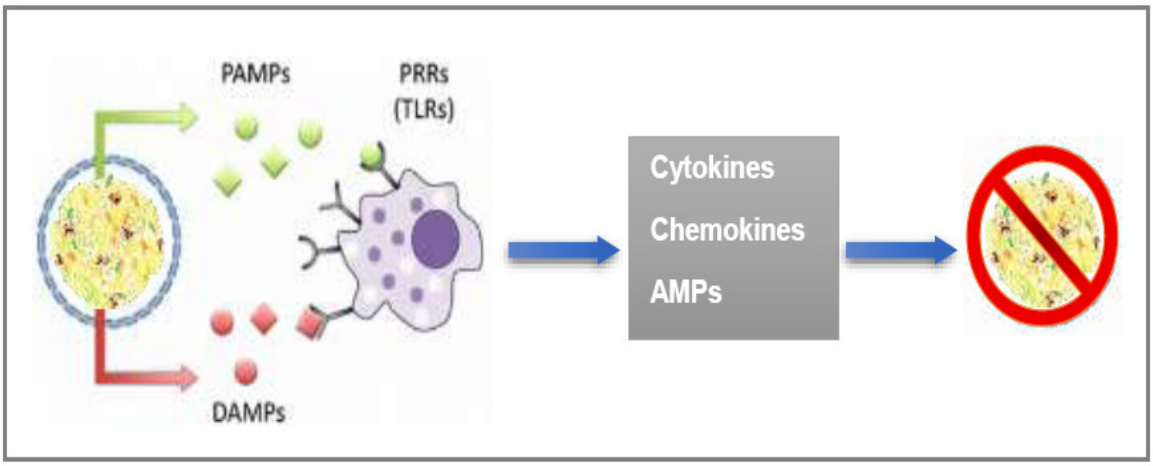

Figure 1. *The activation of keratinocyte PRRs by PAMPs and DAMPs immediately initiates the innate immune response, resulting in the secretion of antimicrobial peptides (AMPs), cytokines and chemokines and directly killing the pathogens.*

3.2 The Cutaneous Microbiota and Skin Cancer

Melanoma, squamous cell carcinoma, and basal cell carcinoma are the three primary types that constitute skin cancer. The most prevalent kind of skin cancer is basal cell carcinoma, which often manifests as a tiny, glossy nodule or a pink patch of skin. Although less frequent than basal cell carcinoma, squamous cell carcinoma can be more baleful. It frequently resembles a wart-like growth or a red, scaly area. The most serious form of skin cancer, melanoma, resembling a dark, atypical mole is the most detrimental of all.[35] There are numerous shreds of evidence that suggest potential association between skin cancer and human skin microbes (Table 1). Current research indicates how vital the skin microbiome is in inflammation modulation and speculates a relationship between commensal microbial species on the eventual skin malignancy. A possible mechanism of Skin microbial activity and the resultant carcinogenesis is described in Figure 2.

3.2.1 Malignant Melanoma

Melanoma one of the most fatal skin cancers is tumour produced by the malignant conversion of melanocytes in the epidermis and is responsible for the highest mortality among cutaneous malignancies.[36] There is a disparity with regard to melanoma incidence globally, with Australia having the highest incidence followed by New Zealand, Western Europe, Northern America, and Central Asia being the least affected region.[17,19] As a heterogeneous disease, malignant melanoma exhibits different subtypes based on the somatic mutation pattern and histopathology of the tissues it proliferates from. Although the gut microbiome has been ratified as a probable novel modulator in the pathogenesis of melanoma, the potentiality of skin microbiome in carcinogenesis is yet to be explored. Among the various microbiota, *Staphylococcus epidermidis* is purported to have a protective effect against melanoma. Specific strain of *S. epidermidis* has been demonstrated to inhibit the growth of tumour cell lines.[37] Moreover, particular strains of *S. epidermidis* produce 6-N-hydroxyaminopurin which interferes with and hinders DNA replication in tumour cells.[38] Under the influence of genotoxic UV-B irradiation, it mediates cutaneous immune response through modulation of cytokines such as CCL3, CCR2, CXCL2, IL-18rap, IL-1β, IL-6 [32] and confers protection against immune suppression caused by UV-B, as it is examined in preclinical models.[37] On the other hand, *S. epidermidis* and its antigen lipoteichoic acid can promote the survival of melanocytes with UV-B-induced DNA damage by triggering upregulation of TRAF1, CASP14, CASP5 and TP73. Nonetheless, *Propionibacterium acnes* can inhibit the survival of UV-B-stressed melanocytes through apoptotic pathways, coproporphyrin secretion and upregulation of TNFα.[39] Persistent with previous reports of the association between *Fusobacterium* and various cancers including oral, pancreatic and colorectal,[40,41,42] it is augmented in melanoma skin samples than in controls along with an abundance of *Trueperella*.[43] Among *Fusobacterium*, *F. nucleatum* is associated with cancer progression as it fetters cytotoxicity of NK cells through the crosstalk of Fusobacterial protein Fap2, T cell coinhibitory receptor T cell immunoglobulin and ITIM domain (ITIG) and resulting in the initiation of tumour proliferation.[44] Other microbial species such as *Corynebacterium* is found to have association with advanced melanoma. *Corynebacterium*-positive acral melanoma patients evince a heightened number of interleukin (IL)-17 than *Corynebacterium*-negative patients.[45] IL-17 can modulate tumourigenesis and the progression of melanoma through upregulation in the IL-6-Stat3 pathway.[46] In accordance with this, an ameliorated infiltration of γδ TCR positive IL-17A-producing T cells on the dermal skin was observed after the administration of *Corynebacterium accolens* suspension in an in vivo study.[47] When considered collectively, these results imply that *Corynebacterium* species may influence the pathogenesis of malignant melanoma development via an IL-17-dependent mechanism. *Cutibacterium acnes* is reckoned to reduce tumour size in a preclinical study by producing pro-inflammatory Th1 type cytokines like IL-12, TNF-α and IFN-γ.[48] Cutaneous HPVs can be qualified as a cofactor in melanoma development, as several epidemiological studies have hypothesized a connection between melanoma and HPVs. An elevated risk of melanoma has been linked to an HPV infection, according to a population-based cohort study.[49] Furthermore, utilising PCR-ELISA, high-risk mucosal HPVs have been discovered in 27% of melanoma samples (skin biopsy) and HPV 16 and HPV 33 were among the high-risk HPVs that were most frequently detected.[50] According to research on uveal melanoma, activating the p53 and Rb pathways can reduce the formation of tumours and stop the cell cycle by downregulating HPV 18 E6/E7.[51] In terms of beta HPVs, HPV22 is more abundant in melanoma than in the control skin of the same individual.[52] However, the direct correlation between the clinical and pathological features of melanoma and HPV prevalence is still vague. An investigation on the Merkel Cell Polyomavirus (MCPyV) revealed no connection between the virus and melanoma.[53] However, among 60 melanoma samples, a study detected four MCPyV-positive cutaneous melanomas and an insignificant correlation between MCPyV infection and melanoma burden.[54] Further research is necessary because the pathogenic connection between MCPyV and melanoma is yet to be unfurled. The pathogenic retroviral genes can be stored in cells by human endogenous retroviruses (HERVs). Activation of the ERV sequence with the concomitant melanocyte transformation causes melanoma cells to evade immune surveillance. After UVB irradiation, melanoma cell lines exhibit proliferated expression of the retroviral envelope protein and activation of the retroviral pol gene, which suggests the pathogenesis of melanoma caused by UVR.[55]

3.2.2 Non-Melanoma Skin Cancer (NMSC)

NMSC consists of Basal cell carcinoma (BCC), Squamous cell carcinoma (SCC), and Merkel cell carcinoma (MCC) which encompass almost 99% of NMSC.[56] Both in terms of clinical presentation and biological progression, these neoplasms exhibit a prodigious diversity. While the hedgehog pathway is frequently seen to be dysregulated in BCC, the mutational and neoantigen burden in SCC and MCC is substantially enhanced.[57] The prevalence of NMSC has conspicuously aggravated, heightened by 33% and reached up to 7.7. million new cases of NMSC diagnosed globally in the last decade.[58] Despite the low mortality rate of NMSC, it begets 5,400 fatalities each month globally, the majority of which are accredited to SCC.[59] *S. epidermidis* may also have a preventive effect on the growth of non-melanoma skin tumours as has been demonstrated hitherto in regard to malignant melanoma. The existence of this coagulase-negative staphylococcal species colonised on the human skin prevents the augmentation of *Staphylococcus aureus*.[37] Through an icaR-dependent pathway and the Rsp gene, an AraC-type transcriptional regulator that prevents attachment and biofilm development in *S. aureus*, cell-free conditioned media from *S. epidermidis* can suppress biofilm formation in *S. aureus*.[60] Additionally, the phenol-soluble modulins PSMδ and PSMγ (δ-toxin) the peptide toxins produced by *S. epidermidis* have been delineated to exert antimicrobial resistance against cutaneous pathogens such as *S. aureus* and group *S. pyogenes*.[61] Furthermore, it has been demonstrated that the *S. epidermidis* secretome can stimulate T-reg activity and reduce skin inflammation whereas the *S. aureus* secretome maintains a direct inhibitory effect on T-reg cells.[62] *S. aureus* is assessed to be linked to SCC after examining tumour tissues and swab samples, respectively. Compared to healthy skin biopsies (5.7%), SCC samples had a higher *S. aureus* colonisation rate of 29.3%. Moreover, swab samples from SCC had a greater prevalence of *S. aureus* (31.7%) than swab samples from healthy skin (15.0%).[63] The nuc gene which encodes thermonuclease is deployed as a specific target to identify *S. aureus* by polymerase chain reaction and it reveals a rising proliferation of *S. aureus* DNA closely linked to the development of Actinic Keratosis (AK) and SCC. Since AK is a skin lesion that precedes invasive cancer, the increased colonization of *S. aureus* denotes its liaison to the carcinogenic pathways that enable AK to metastasize into SCC.[63] *S. aureus* is found to be the most prevalent bacterial species in the lesioned skin of AKs and SCCs, which is consistent with the results of the previous research.[64] Using samples from skin biopsies, a recent study using 16S rRNA gene-based microbial community profiling discovered that *S. aureus* is abounding in AK and SCCs along with concurrent aggrandized expression of human β defensin-2 (hBD-2) in SCCs. The expression of hBD-2 was upregulated when inoculated with *S. aureus* in a co-culture study utilising Hecate cell, SCC cell lines derived from cutaneous SCCs, and *S. aureus* which subsequently led to the upheaval of tumour cell proliferation. Additionally, when SCC cells were directly challenged with hBD-2, the number of tumour cells proliferated more which suggests that SCC proliferation may be triggered by the expression of hBD-2, regulated by the overgrowth of *S. aureus*.[65] When the skin barrier remains unscathed *S. aureus* seems not to infect an immunosuppressed individual[66] but an overabundance of *S. aureus* is observed under particular conditions, including atopic dermatitis where the skin integrity is already perturbed.[67,68] *S. aureus* secretes various virulence factors including the protein phenol soluble modulin α (PSMα), causing barrier disruption and inflammation through proteolysis.[69] These findings indicate barrier dysfunction in SCC promotes *S. aureus* to colonize effectively. Although multitudinous research has detected a nimiety of *S. aureus* in SCCs, the causal link between *S. aureus* and SCCs is yet to be established. Study suggests the augmented growth of *S. aureus* causes the depletion of skin commensal *C. acnes* in SCC.[18] An Australian cohort study revealed that AK and SCC skin has lower levels of *Cutibacterium* than healthy skin since lipophilic bacteria *C. acnes* typically inhabit sebaceous regions of the skin. It has been hypothesised that the dry and scaly surface of AKs, caused by the decreased availability of sebum, may be the source of the lower abundance of *Cutibacterium* in AK and SCC. As *C. acnes* secretes AMPs which prohibit pathogen invasion, a reduction in *C. acnes* may be linked to the microbial dysbiosis in the skin of AKs and SCCs. The study further suggests that altered metabolism in tumour cells could both promote the growth of *S. aureus* and hinder the growth of lipophilic commensals such as *Cutibacterium*.[64] Several studies have emerged exhibiting a plausible association between SCC and human papillomavirus (HPV). A meta-analysis also discovered that those with cutaneous SCC had a higher risk of contracting HPV than people with skin that appeared normal. In addition, immunodeficient

individuals are conferred with a higher prevalence of HPV than immunocompetent patients.[70] In patients with NMSC, there is a higher probability of HPV infection than in controls, according to a recent population-based study from Taiwan.[49] About 200 subclasses encompass the HPV family which can harm the skin and mucosal epithelium.[71] About 50 different beta HPV varieties have been discovered so far, with the majority of these being linked to cutaneous SCC.[72] The development of cutaneous SCC may be significantly influenced by a synergistic interaction between UVR and certain strains of cutaneous beta HPV. Patients with epidermodysplasia verruciformis, the precursor of SCC, have had beta HPV strains including HPV5 and HPV8 isolated from their skin.[73] A recent large-scale HPV survey employing a shotgun sequencing method among a cohort of 103 healthy human volunteers, mapped HPV infections at different body regions, showing some site specificity and co-occurrence or exclusion. The study reveals the non-random organisation of HPV which connotes competitive or cooperative interactions between microorganisms.[74] Diverse in vivo studies corroborate that cutaneous beta HPV can function as cocarcinogens to trigger cellular damage in UVR exposure. The expression of Beta HPV type E6/E7 oncogenes is upregulated in concurrence with UV irradiation resulting in an increased rate of mutations in p53 and Notch genes that transcribe into cancer progression.[75-78] Some non-oncogenic HPV strains may lower the risk of cancer by eradicating oncogenic viral infections through viral interference or cross-immunity.[74] The T cell immunity induced by commensal HPV can prevent carcinogenesis in immunosuppressed individuals as loss of T cell immunity is tethered with an elevated risk of skin cancer in them.[79] The diverse role of HPV in cancer progression warrants further elaborative research to recognize the association pathways. The pathogenesis of Merkel cell carcinoma (MCC) is influenced by a newly discovered Merkel cell polyomavirus (MCPyV). High tumour load of MCC is also related to MCPyV presence.[54] MCPyV was found in 15% of DNA samples from immunocompetent SCC patients, according to research on SCC.[80] Despite the prevalence of MCPyV in SCC, more research is necessary to clarify any potential connections between MCPyV and SCC. In comparison to non-leisonal healthy skin, AK and SCC exhibit a diminution of *Malassezia* colonisation.[64,65] Colonisation of lipophilic commensal *Malassezia* in SCCs may have decreased due to disruption of the skin barrier and a reduction in sebum availability. According to recent reports, *Malassezia* inhibits the growth of *S. aureus* biofilms by secreting certain proteases.[81] It can be inferred from the data obtained from recent researches that *Malassezia* serves as a barrier to *S. aureus* colonisation in SCC.

3.2.3 Cutaneous T Cell Lymphoma

The most prevalent variety of primary cutaneous lymphoma is cutaneous T cell lymphoma (CTCL). It is an extranodal non-Hodgkin's lymphoma distinguished by an accumulation of malignant T cells restricted to the skin with mycosis fungoides (MF) and Sezary syndrome (SS) being the most common forms. The clinical course of advanced stages of MF and/or SS, which is traditionally referred to as a leukemic type of CTCL associated with erythroderma, is comparatively belligerent. Chronic exposure to antigenic stimuli, such as skin microbiota, can cause CTCL in genetically susceptible patients.[82,83] Various studies have found an association between *S. aureus* and CTCL. A study revealed that 63% and 54% of patients had skin and nasal colonisation of *S. aureus*, respectively and topical treatment with nasal mupirocin twice daily for consecutive days and oral antibiotics for 4 weeks decimated the pathogen colonisation and clinically improved 58% of CTCL patients.[84] Following intravenous and oral antibiotics therapy, skin lesions in eight individuals with treatment-resistant CTCL achieved clinical improvement. After therapy, malignant T cells were reduced in lesional skin biopsy tissues, and mRNA expression patterns were altered. Following antibiotic treatment, a definite reduction of IL-2 signalling and STAT3 activation was observed in CTCL.[85] Previous studies have shown a connection between CTCL and the HLA-DR5 and DQB1*03 class II alleles, alluding to the potential involvement of the *S. aureus* superantigen.[86,87] Similarly, the activation of STAT3 and IL-17 in primary malignant T lymphocytes was reported to be induced by Staphylococcal enterotoxin A (SEA), present in the CTCL lesioned skin which substantiates the persistent research that found patients ensconced by *S. aureus* are carriers of enterotoxin genes.[88,89] Apart from *S. aureus* spoilages like β-hemolytic *Streptococci*, *Enterococci*, *Enterobacteriaceae* and Pseudomonads were preponderant in CTCL lesions.[90,91] Possible causation between CTCL and *Chlamydophila pneumoniae* and *Borrelia burgdorferi* has also been discovered.[92] A recent study using metagenomic sequencing from skin swabs demonstrated an amplification of the pathogen *Corynebacterium* spp. and a curtailed *Cutibacterium* spp., signifying a microbial shift.[93] Another study

using both 16s and WGS revealed a differential abundance of bacterium species with *Staphylococcus argenteus* being more prolific among them in CTCL lesions than in control skin.[94] *S. argenteus* is revealed to enhance the level of α-hemolysin exotoxin by 4-6 folds compared to *S. aureus*.[95] Further elucidation is required to decipher the potential pathogenic role of *S. argenteus* in CTCL. Human T cell lymphotropic virus (HTLV), Epstein-Barr virus, and human herpesvirus 8 have all been implicated in the aetiology of CTCL.[96-98] The link between CTCL and viral risk factors, however, has not been specifically identified by studies.[99] Research conducted hitherto has produced contradictory results about the viral and fungal aetiologies of CTCL.[93] The precise functions of the microbiota and antibiotic treatments in CTCL require further investigation.

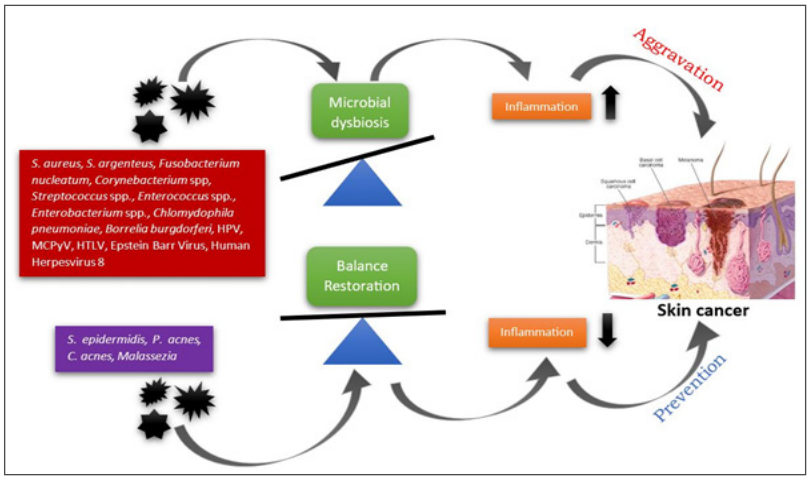

Figure 2. *Different hazardous skin microbes contribute to microbial dysbiosis which upregulates inflammatory response and promotes skin cancer. On the contrary, diverse skin commensals restore the balance which downregulates inflammatory response and consequent prevention of skin cancer.*

Table 1. *Types of skin cancer and associated different skin microbiota*

Type of Cancer	Associated Skin Microbes
Malignant Melanoma	*Staphylococcus epidermidis*[37-39]
	Propionibacterium acnes[39]
	Fusobacterium nucleatum[43,47]
	Cutibacterium acnes[48]
	Corynebacterium spp[45.47]
	Human Papilloma Virus (HPV)[49,50,52]
	Human Endogenous Retrovirus (HERVs)[55]
Squamous Cell Carcinoma	*Staphylococcus epidermidis*[37]
	Staphylococcus aureus[37,63-65]
	Cutibacterium spp[64]
	Human Papilloma Virus (HPV)[49,70,72,75-77]
	Merkel Cell Polyomavirus (MCPyV)[80]
	Malassezia spp.[64,65]
Merkel Cell Carcinoma	Merkel Cell Polyomavirus (MCPyV)[54]
Cutaneous T Cell Lymphoma (CTCL)	*Staphylococcus aureus*[84,86,87,89]
	Staphylococcus argenteus[94]
	Corynebacterium spp[93]
	Cutibacterium spp[93]
	Chlamydophila pneumoniae[92]
	Borrelia burgdorferi[92]
	Streptococcus spp[90,91]
	Enterococcus spp[90]
	Enterobacteriaceae spp[90]
	Pseudomonas spp[90,91]
	Human T cell lymphotropic virus[96]
	Epstein-Barr virus[97]
	Human herpesvirus 8[98]

4. Conclusion

In summary, recent developments in microbial research provide us with an understanding of the association of skin microbiota with skin carcinogenesis though the research is still in its infancy and the discrepancies in the results create an abstruse knowledge regarding this connection. Further studies utilising advanced sequencing technology will ensure a deep apprehension of the complex human microbiome and its relationship with the host. The majority of the research on microbiota and cancer has focused mostly on the gut microbiome and similarly, research on skin microbiome may escalate procuring knowledge regarding skin cancer. There are still various unsolved facets of the tangled connection between human microbiome and skin cancer. UV-R can induce the abundance of both commensals and pathogens on the skin and modulate the immune system which can be detrimental and tumourigenic.[100] Analysing the microbiome to evaluate the environment of skin cancer, would elucidate new avenues in cancer research. Further research on the skin microbiome and skin cancer may imply the development of microbiome-based therapies to combat or treat skin cancer. Treatment using probiotics or prebiotics can be developed to promote the growth of beneficial commensals on the skin microbiome or utilize the neoplastic potential of microbial molecules to modulate immune responses and reduce skin cancer risk. Understanding the interactions between the skin microbiome and skin cancer facilitate effective methods to early prognose and detect skin cancer as well as to manufacture avant-garde techniques for its prevention and treatment. Research on the intricate interactions between the cutaneous microbes, the immune system and skin cancer may eventually deliver novel perspectives on microbial treatments and its therapeutic potential.

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Conflict of Interest

The authors declare no conflict of interest in preparing this article.

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