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Review Article

Staphylococcus aureus as a signature species of skin microbiome in actinic keratosis and squamous cell carcinoma: A narrative review

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Abstract

Cutaneous squamous cell carcinoma (cSCC) is a common type of skin cancer and the second most common type of nonmelanoma skin cancer. Actinic keratosis (AK) is a premalignant lesion that can progress to cSCC over time. AK and cSCC are associated with microbial dysbiosis and an increased abundance of the bacterium *Staphylococcus aureus*. Although AK and cSCC are highly colonized with *S. aureus*, a bacterium of the skin microbiota, it is not yet known whether this bacterium is associated with cancer development. Here, we analyze the studies on the relationship between *S. aureus* and keratinocytic skin neoplasia, evaluating the contribution of *S. aureus* to the development and prognosis of cSCC and AK lesions. The overabundance of *S. aureus* and the compounds secreted by this bacterium can induce cancer-promoting changes in skin cells. The presence of high amounts of certain *S. aureus* strains in premalignant skin lesions may constitute a protumorigenic stimulus by inducing oxidative stress and DNA damage and downregulating DNA repair mechanisms. *S. aureus* associated with AK and cSCC can trigger keratinocytes to produce inflammatory cytokines typically upregulated in cSCC. These circumstances also suggest a potential specific involvement of *S. aureus* in the progression from AK to cSCC.

Key words: Actinic keratosis, cancer, cutaneous squamous cell carcinoma, skin microbiome, *Staphylococcus aureus*

Introduction

Cutaneous squamous cell carcinoma (cSCC) is a common type of skin cancer, the second most common type of nonmelanoma skin cancer, and the sixth most commonly diagnosed cancer worldwide.[1,2] cSCC originates from epidermal keratinocytes or adnexal structures and typically develops from actinic keratoses AKs), which are premalignant precursor lesions. However, most of AKs do not progress to cSCCs.[1,2] Progression to invasive cSCC occurs in 10% of cases, and the risk of malignant transformation of a single AK to cSCC ranges from 0 to 0.53% per year.[2] Although various pathways have been suggested for malignant transformation, it is not yet predictable which AK lesions will progress to cancer.[1,3]

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Alternatively, it has also been reported that cSCCs may develop *de novo* from photodamaged skin (PDS).[1]

The role of chronic sun or ultraviolet radiation, a primary risk factor for both AK and SCC, cannot be overlooked. Chronic sun exposure not only induces direct DNA damage in keratinocytes but may also influence the composition of the skin microbiome, promoting the dominance of pathogenic organisms such as *Staphylococcus aureus*. This interplay between environmental factors, skin microbial composition, and host responses highlights the need for a comprehensive understanding of the skin microbiome's role in cutaneous carcinogenesis. The association between *S. aureus* and these conditions underscores the importance of understanding microbial communities in skin pathology. Overall, there are common microbial signatures that can distinguish healthy skin (HS) from the conditions such as AK and cSCC.[1,3,4] The skin microbiota of cSCC and AK is characterized by a notable increase in *S. aureus*, which is associated with pro-inflammatory and potentially carcinogenic effects. In contrast, the skin commensal *Staphylococcus epidermidis* is more abundant on healthy, normal skin.[5] *Propionibacterium* and *Malassezia* are more commonly found in nonlesional, photodamaged skin than in AK and cSCC lesions, suggesting a potential protective role or a decrease in their abundance in lesional skin.[6] An increased relative abundance of Corynebacterium has been noted in patients responding to certain treatments for AK, indicating its potential role in skin health or response to therapy.[7] However, more research is needed to fully understand the implications of these microbial signatures or differences on development, diagnosis, and treatment of skin diseases. This article presents a comprehensive overview of the role of *S. aureus* in the skin microbiome's relationship with AK and cSCC.

Risk and Progression Factors for Actinic Keratosis and Squamous Cell Carcinoma

Gaining insight into the causes of this damage and the factors that elevate your risk of developing SCC can empower you to detect the disease early or potentially prevent it from arising altogether. Chronic sun exposure causes inflammation leading to disruption of skin barrier and transepidermal water loss, resulting in the dry, scaly, and red appearance of AKs.[4] This chronic exposure is the main risk factor for the development of PDS, AK, and cSCC. Progression of PDS to AK and cSCC is multifactorial, and gene mutations, immunosuppression, and chronic inflammation are the well-known factors promoting cancer development.

Genomic analyses have revealed insights into the molecular mechanisms that drive the transition from benign to malignant keratinocytes.[1,8,9] cSCC has been shown to be a malignancy with the highest tumor mutation burden, resulting from the accumulation of genetic and epigenetic changes in keratinocytes over time.[9-11] Studies have revealed that some of the mutated driver genes, including NOTCH1-3, TP53, FAT1, PIK3CA, CDKN2A, HRAS, KMT2C, KNSTRN, EGFR, CARD11, MYC, MLL2, MAP3K9, PTEN, SF3B1, VPS41, and WHSCI, promote tumorigenesis from AKs to cSCC.[9] When compared to normal skin, PDS and AK have a higher somatic mutation rate, especially observed in TP53, NOTCH1-3, CDKN2A, and KNSTRN genes.[1]

By transcriptome profiling, it was reported that differentially expressed genes between AKs and cSCCs were involved in epidermal differentiation, cell cycle regulation, cell migration, and metabolism. Specifically, mitogen-activated protein kinase pathway plays a key role in cSCC.[8] Studies have shown that the oncogenes, such as JUN, PAK, and MET, are upregulated, and tumor-suppressor genes, such as AZGP1, RORA, and PDZD2, are downregulated in cSCC.[1,8] In addition, loss of differentiation with downregulation of some genes (KRT9, KRT10, FLG, FLG2, LCE1B, and LOR) and acquisition of invasive features, such as cell migration and extracellular matrix remodeling with upregulated matrix metalloproteinases, are observed in cSCC.[8]

One of the key factors in the progression of AK or PDS to cSCC is immunosuppression. Among immunocompromised individuals, such as organ transplant recipients, the incidence of cSCC is remarkably high, reaching rates 65–250 times higher than those with intact immune systems.[12] Due to the impaired immune system of these patients, there is an increase in the development of various virus-related cancers such as human papillomavirus-associated cervical cancer and Kaposi's sarcoma, suggesting that immune suppression causes deterioration in the ability to control tumorigenic viruses.[13] As these viruses can interact with host cellular mechanisms, they may contribute to the transformation of normal cells into cancerous ones. The prolonged quest to uncover an infectious basis for cSCC stems from the understanding that similar to other virus-related cancers, there may be specific viral influences that contribute to cSCC development, particularly in immunocompromised individuals. The scientific community is investigating whether certain viruses may play a direct role in promoting cSCC, thus linking the observed increase in virus-related cancers with the need to explore infectious etiologies in cSCC specifically.

Role of the Skin Microbiome and *Staphylococcus aureus* in Actinic Keratosis and Squamous Cell Carcinoma

The skin microbiome consists of a diverse community of microorganisms that inhabit the skin surface and contribute to its health by protecting against pathogens, modulating immune responses, and maintaining skin barrier integrity. Dysbiosis, or an imbalance in this microbial community, can lead to various dermatological disorders, including inflammatory diseases and malignancies.

Based on the literature, the data on the role of microbial dysbiosis in the development of various cancers have recently been increasing. It has been firmly determined that infections are

responsible for more than 15% of malignancies worldwide.[14] Three main mechanisms have been identified to explain the causative role of infections in cancer development: (i) The inhibition of tumor-suppressor genes or insertion of oncogenes leading to cellular transformation; (ii) Immunosuppression promoting an environment conducive to carcinogenesis; and (iii) Production of cytokines and nitric oxide caused by infection-induced chronic inflammation contributing to the carcinogenesis process.[15-18] On the other hand, given the recent emphasis on the relationships between microbiota and cancer, it has begun to be investigated whether the human microbiota affects skin cancer risk and response to treatment.[19] Unfortunately, not much information is available about the impact of human microbiota, especially skin microbiota, on skin cancer. Therefore, it should be considered that there is a need to further investigate the connection between the skin microbiome and skin or skin-related malignancies.

S. aureus, a Gram-positive coccus, is commonly found as commensal bacteria on the human skin, preferring body sites characterized by elevated humidity levels, including the nasal, inguinal, gluteal crease, popliteal, antecubital fossa, and feet. The prevalence of *S. aureus* carriers in the adult population is estimated to be around 10%–40%, according to various studies.[20-22] *S. aureus* infections on the skin of immunocompetent individuals are typically associated with impaired skin barriers due to injury or damage.[23] Hence, it could be suggested that the ulcerative nature of cSCC might facilitate *S. aureus* colonization. Furthermore, it is worthnoting that, chronic wounds, burn scars, and osteomyelitis sites that eventually progress into cSCCs exhibit a notable predominance of *S. aureus* as the most frequently isolated organism.[24,25] It has been shown that *S. aureus* can induce NF-kB transcription factor and interleukin-8 (IL-8), thus causing chronic inflammation.[26] This may point to the potential role of *S. aureus* in the development of cSCC.

Relationship of *Staphylococcus aureus* with Actinic Keratosis and Squamous Cell Carcinoma

In recent years, there has been increasing evidence linking cSCCs and AKs to microbial dysbiosis, especially with the bacterium *S. aureus* [Table 1].[5-7,27-33] *Staphylococcus* is the dominant taxon on the skin of the AKs and SCCs, and the majority of this taxon is *S. aureus*. The presence of *S. aureus* on the skin can lead to an inflammatory response and toxins secreted by it can cause DNA damage, oxidative stress, and overexpression of inflammatory factors, promoting skin carcinogenesis[5,28,29,32] [Table 2 and Figure 1a].

First, the relationship between *S. aureus* and cSCC was investigated by a case–control study. Kullander *et al*. obtained both biopsies and cotton swab samples from SCC, basal cell carcinoma (BCC), seborrheic keratosis, AK lesions, and HS in 353 immunocompetent patients.[27] They investigated the presence of *S. aureus* by PCR targeting the nuc gene in the samples. The prevalence of *S. aureus* in both biopsies (29.3%) and swab samples (31.7%) was the highest in cSCC lesions, and the results also revealed a strong association between *S. aureus* and cSCC compared to the HS, with both types of samples. In addition, when HS and cSCCs of the same patient were compared to determine the susceptibility of the patient to *S. aureus*, it was found that the prevalence of *S. aureus* was higher in cSCCs. Hereby, they eliminated the likelihood of overall susceptibility to bacterial colonization. However, the study's methodology does not permit a conclusive determination whether the presence of *S. aureus* plays a role in influencing carcinogenesis or SCC inherently possesses a high susceptibility to colonization by *S. aureus*. Although the findings also revealed a likelihood of *S. aureus* might be linked to AK, no such connection was shown in BCC or seborrheic keratosis. Therefore, this study suggested that the abundant colonization of *S. aureus* occurs in the early stages of the carcinogenic process, as AK is the precursor of cSCC.[27]

To establish the potential role of *S. aureus* in AK-cSCC progression, Wood *et al*. performed a longitudinal microbiome analysis on skin swabs of 112 AK lesions and 32 cSCCs obtained from a cohort of 13 patients and compared them to nonlesional PDSs. In this study, PCR amplifications were performed from the individual swab samples using primers, which have broad specificity and targeting bacterial, archaeal, and eukaryotic small-subunit rRNA genes. The study revealed a notable difference in the relative abundances of *Malassezia* and *Propionibacterium* strains between nonlesional skin and AK/cSCC lesions, with higher levels detected on nonlesional skin. In contrast, lesional skins exhibited relatively higher levels of *S. aureus* strains compared to nonlesional areas, indicating their potential specific involvement of this bacterium in the progression from AK to cSCC.[6]

Andersson *et al*. analyzed skin microbiota and RoxP concentration (an antioxidant that is secreted by *Cutibacterium acnes*) in a study that included skin swabs of AKs and BCCs of 54 patients. In this study, AKs and BCCs were associated with microbial dysbiosis characterized by reduced *C. acnes* prevalence. In addition, the findings showed that AK-affected regions had a decreased concentration of RoxP compared to HS, which supports the role of RoxP in the protection from UV irradiation.[28]

In the study conducted by Madhusudhan *et al*., microbial compositions of 88 biopsy materials from the sun-exposed skin areas (13 BCC, 25 AK, 22 cSCC, and 28 nonlesional skin) were compared. According to the taxonomic analysis, both AKs and cSCCs exhibited increased levels of *Staphylococcus*. Furthermore, cSCCs showed a notable overabundance of the *S. aureus* species, which was significantly correlated with elevated human B-defensin 2 (hBD-2) expression, which belongs to the class of protective skin-antimicrobial peptides. In contrast, a low abundance of *S. aureus* was associated with reduced hBD-2 expression and Th17 cell-mediated pro-inflammatory immune response. Considering the potential involvement of antimicrobial peptides as tumor promoters, the

Table 1: Summary of the literature studies showing *Staphylococcus aureus* associated with actinic keratosis and cutaneous squamous cell carcinoma

Reference	Type of sample	Patient's samples (*n*)	Method	Conclusion
Kullander, 2009[27]	Human-skin biopsy, swab, *in vivo*	AK (57), SCC (82), BCC (142), SK (72), 353 HS	PCR targeting the *nuc* gene of *S. aureus*	A strong association between *S. aureus* and SCC, and a tendency for association of *S. aureus* with AK
Wood, 2018[6]	Human-skin swab, *in vivo*	AK (112), SCC (32), PDS (29)	16s rRNA, 18s rRNA sequencing	Strains of *Cutibacterium* and *Malassezia* were relatively more abundant in nonlesional PDS, whereas *S. aureus* strains were relatively more abundant in lesional skin
Andersson, 2019[28]	Human-skin swab, *in vitro*, *in vivo*	AK (18), BCC (18), HS (18)	16s rRNA sequencing, analysis of *RoxP* concentration in skin swabs, *RoxP* gene expression	Markedly decreased *Cutibacterium* and increased *Staphylococcus* in lesions compared to HS. *C. acnes* protects the keratinocytes from oxidative stress via secreted antioxidant *RoxP*
Madhusudhan, 2020[5]	Human-skin biopsy, *in vitro*, *in vivo*	BCC (13), AK (25), SCC (22), HS (28)	Histopathology, 16s rRNA sequencing, FISH, qPCR, infection assay	Overabundance of *S. aureus* in SCCs. Challenging human SCC line with *S. aureus* induces hBD-2 expression and increased tumor cell growth
Krueger, 2022[29]	Human-skin swab, *in vitro*, *in vivo*	AK (8), IEC (8), SCC (38), PDS (13)	RNA sequencing of skin cancer biopsies, whole genome sequencing of *S. aureus* strains, mass spectrometry analysis of supernatants and secretomes of *S. aureus*	Toxins secreted from *S. aureus* strains isolated from keratinocytic skin cancers mediate a pro-tumorigenic inflammatory response in the skin
Voigt 2022[31]	Human-skin swab, *in vivo*	AK (76), SCC (122), 138 HS	Whole genome shotgun sequencing	Pronounced decrease of *C. acnes*, accompanied by an abundance of *S. aureus* in AK/SCCs compared to HS
Krueger, 2022[30]	Human-skin swab, *in vivo*	AK (51), SCC (24), SCC-PL (24), PDS (73), HS (27)	qPCR, SSU rRNA gene sequencing	An increase in *Staphylococcus* species and relative decrease in skin commensals in AK/SCC compared to HS. In contrast to SCCs from immunocompetent subjects dominated by *S. aureus*, *S. epidermidis* was predominant in SCCs from transplant recipients
Krueger, 2022[32]	Human-skin swab, *in vitro*, *in vivo*	AK, IEC, SCC lesions	RNA sequencing, shotgun proteomics, ELISA, IFA, mass spectrometry analysis	Exposure of secretomes of skin cancer-associated *S. aureus* strains causes DNA damage in human keratinocytes by reducing DNA repair and inducing oxidative stress
Kehrmann, 2023[7]	Human-skin swab, *in vivo*	321 samples of AK (59)	16 s RNA sequencing, PCR	The reduction of the *S. aureus* in AKs after field-directed treatment. Treatment response-related changes have the potential as a predictive therapeutic biomarker in AK

AK: Actinic keratosis, SCC: Squamous cell carcinoma, SCC-PL: Squamous cell carcinoma-perilesional, BCC: Basal cell carcinoma, IEC: Intraepidermal carcinoma, SK: Seborrheic keratosis, PDS: Photo-damaged skin, HS: Healthy skin, hBD-2: Human beta-defensin-2, *S. aureus: Staphylococcus aureus, S. epidermidis: Staphylococcus epidermidis, C. acnes: Cutibacterium acnes*, ELISA: Enzyme-Linked ImmunoSorbent Assay, IFA: Immunofluorescence assay

Table 2: Molecules involved in the development of cutaneous squamous cell carcinoma caused by *Staphylococcus aureus*

Molecules	Effects of molecules	References
IL-6, IL-8, TNF-alfa	Overexpressed in cSCC, promoting cell proliferation, inhibiting apoptosis, and activating survival pathways	[28]
Human B-defensin 2/3	*S. aureus* overabundance increases hBD-2 expression, promoting tumor cell growth and potentially affecting tumor progression	[27]
MMP	Overexpression of MMP1, MMP3, and MMP10 in cSCC	[31]
Kallikrein serine proteases	Overexpressed in cSCC	[31]
Reactive oxygen species, particularly nitric oxide	Increased keratinocyte ROS levels and *S. aureus* secretion cause human keratinocytes to produce nitric oxide	[31]
Phenol-soluble modulin toxins	Significant correlation between secretome PSM levels and keratinocyte DNA damage	[31]

S. aureus: *Staphylococcus aureus*, cSCC: Cutaneous squamous cell carcinoma, ROS: Reactive oxygen species, TNF: Tumor necrosis factor-alpha, IL: Interleukin, MMP: Matrix metalloproteinases, PSM: Peptides spectral matches, hBD-2: Human B-defensin 2

study performed a modeling of interactions between *S. aureus* and cSCC cells through co-culture experiments. The results showed a specific induction of hBD-2 expression by *S. aureus* challenge, resulting in an increase in tumor cell proliferation. Subsequently, direct exposure of cSCC cells to hBD-2 further validated the growth-promoting action of this antimicrobial peptides [Figure 1b and c]. In conclusion, the findings suggest that microbial alterations in keratinocytic skin tumors influencing antimicrobial peptide expressions could promote tumor cell growth and potentially impact tumor progression.[5]

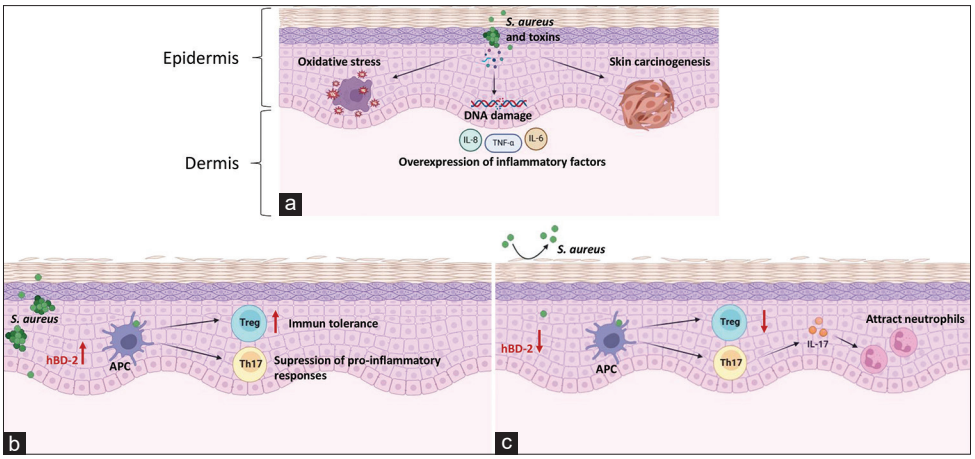

Figure 1: Schematic display of the effects of *Staphylococcus aureus* on the skin epithelium. (a) *S. aureus* can create an inflammatory reaction when it is present on the skin, and the toxins it secretes can damage DNA, increase oxidative stress, and overexpress inflammatory proteins, all of which can contribute to the development of skin cancer. Local environment colonized with (b) and without *S. aureus* (c). The overabundance of *S. aureus* is significantly correlated with elevated human B-defensin 2 expression and an immune tolerance and suppression of pro-inflammatory responses, whereas low abundance of *S. aureus* is associated with low hBD-2 expression and immune activation. IL-6: Interleukin-6, APC: Antigen-presenting cell, Treg: Regulator T cell, Th17: T helper 17 and all images were created with BioRender.com.

Krueger *et al*. revealed that secretomes originating from *S. aureus* strains isolated from PDS, AK, and cSCC can trigger a notable increase in gene expression levels of TNFα, IL-6, and IL-8 in human keratinocytes. Furthermore, in this study, certain secretomes exhibited a particularly potent capacity to induce these protumorigenic inflammatory mediators, and keratinocytes exposed to *S. aureus* secretome associated with cSCC or intraepidermal carcinoma (IEC) secrete substantially high levels of IL-6 in response. This suggests that colonization with specific *S. aureus* strains may have a more important role in creating a microenvironment that promotes skin tumorigenesis compared to others.[29] These findings were remarkable to explain the relationship between *S. aureus* and IL-6 in tumor development, as prior studies revealed that the upregulation of IL-6 in cultured human keratinocytes suppresses apoptosis and promotes angiogenesis, proliferation, and migration.[33,34]

Recently, Voigt *et al*. performed shotgun metagenomics on skin swabs of AK, cSCC, and HS to show the microbial alterations specific to AK and cSCC. Here, an increase of *S. aureus* accompanied by markedly diminished skin commensal, *C. acnes*, was found in AK/cSCC compared to HS. In addition, *C. acnes* associated with lesional skin and HS were detected differently at strain level, suggesting specific functional changes associated with its depletion in cSCC. The results of the study showed a transitional microbial dysbiosis from HS to AK to cSCC, supporting the need for further investigation of the role of skin microbiome in cancer progression.[31]

Krueger *et al*. analyzed skin microbiome in PDS, AK, IEC, and invasive cSCCs of 32 transplant patients using the skin swab samples.[30] The study reported an overabundance of *Staphylococcus* species and a relative decrease of skin commensals in lesions. When the findings of the study were compared with those of a previous study conducted on 13 immunocompetent subjects,[6] *S. epidermidis* predominated in cSCCs from immunosuppressed organ transplant recipients, in contrast to cSCCs of immunocompetent patients. The results suggest that AKs and cSCCs of immunocompetent and immunosuppressed patients have distinct microbial dysbiosis.[6,30]

Another study performed shotgun proteomics and RNA sequencing on primary human keratinocytes following exposure to secretomes derived from four *S. aureus* strains isolated from AK and cSCC. The secretomes derived from two distinct *S. aureus* strains induced overexpression of MMPs and kallikrein serine proteases in primary human keratinocytes, which is associated with skin carcinogenesis and disruption of the skin barrier integrity. In addition, the strains under investigation were found to induce the expression of reactive oxygen species (ROS) in keratinocytes. Specially, ROS and reactive nitrogen species from all secretomes displayed the ability to suppress DNA repair mechanisms. The findings were confirmed by additional experiments using a wide range of lesional *S. aureus* strains, showing that exposure to their secretomes leads to increased oxidative stress and induces DNA damage in primary human keratinocytes. A significant correlation was observed between the concentration of *S. aureus* phenol-soluble modulin toxins in the secretome and the oxidative stress level and genotoxicity in keratinocytes.[32]

However, studies investigating alterations in the skin microbiome after the treatments of AK and cSCC are much more limited. Kehrmann *et al*. analyzed lesional microbiome alterations after field-directed treatment in 321 AKs in a longitudinal prospective study. Skin swabs collected before the treatment, at the end of the field-directed treatment, and 3 months after the end of the treatment were analyzed by the

16s rRNA sequencing. In addition, a PCR assay targeting the *tuf* gene was performed to evaluate the relative abundance of *S. aureus*. After treatment, it was determined that the abundance of *S. aureus* decreased in responders compared to nonresponders, while the abundance of *Corynebacterium* increased. The findings support the potential role of skin microbiome as a predictive therapeutic biomarker in AK.[7]

Future directions

Available literature data suggest that skin microbial dysbiosis contributes to the development of AK/cSCC. Particularly, the abundance of *S. aureus* has been detected in AKs/cSCCs of immunocompetent patients. Although data on this subject are very limited, the skin dysbiosis in AK/cSCCs of organ transplant patients is distinct from that of immunocompetent patients, with an abundance of *S. epidermidis*. On the other hand, inflammation and oxidative stress caused by *S. aureus* contribute to the development of AKs and their progression to cSCCs. Moreover, the secretomes of *S. aureus* strains lead to DNA damage by inducing oxidative stress and downregulating DNA repair mechanisms in keratinocytes and overexpression of genes involved in protumorigenic inflammatory responses. Studies showing microbial dysbiosis in AK and microbial changes after AK treatments also reveal the role of the skin microbiome as a promising predictive therapeutic biomarker in AKs.

Given the recent emphasis on the association between *S. aureus* and keratinocytic skin neoplasia, further research is needed to determine whether eradicating *S. aureus* and restoring eubiosis in AK lesions might prevent the progression from AK to cSCC. In addition, it needs to be elucidated whether the eradication of *S. aureus* in cSCC lesions might contribute to the overall prognosis.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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