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The Skin Microbiome: A New Key Player in Melanoma, From Onset to Metastatic Stage

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ABSTRACT

The skin microbiome plays a crucial role in maintaining skin health, defending the body against harmful pathogens, and interacting with melanoma. The composition of the skin microbiome can be affected by factors like age, gender, ethnicity, lifestyle, diet, and UV exposure. Certain bacteria like *Staphylococcus* and *Veillonella* are important for wound healing, while *Cutibacterium acnes* can play a role in dermatoses. UV radiation alters the skin microbiome, originates a "UV-resistome" and can lead to skin cancer initiation. Specifically, *Staphylococcus epidermidis* has shown protective effects against skin cancer, whereas *Cutibacterium acnes* can induce apoptosis in melanocytes postirradiation. The microbiome also interacts with melanoma treatment, affecting responses to immune checkpoint inhibitors. Strategies like bacteriotherapy, involving the manipulation of the gut microbiome but also the skin microbiome (with the gut–skin axis or through topical treatment) could improve treatment outcomes and show promise in melanoma therapy. Understanding the complex interplay between the skin microbiome, UV exposure, and melanoma development is crucial for developing personalized therapeutic approaches. Investigation into the skin microbiome and its potential role in melanoma progression continues to be an exciting area of research with implications for future therapeutic interventions.

1 | Introduction

The skin is the human body's largest organ, colonized by a diverse milieu of microorganisms, most of which are harmless or even beneficial to their host. Colonization is driven by the ecology of the skin surface, which is highly variable depending on topographical location, endogenous host factors, and exogenous environmental factors. The cutaneous innate and adaptive immune responses can modulate the skin microbiota, but the microbiota also functions in educating the immune system. The development of molecular methods has led to an emerging view of the resident skin bacteria as highly diverse and variable (Grice et al. 2008). This diverse array of microorganisms, living as commensals, plays a crucial role in maintaining homeostasis, helping it face numerous environmental challenges. Microbiologic dysbiosis leads to activation of innate immunity. Skin microbiota also participates in the development and modulation of innate and adaptive immunity and therefore affects skin cancer susceptibility and subsequent therapeutic outcome (Zhu et al. 2024).

Several environmental factors contribute to the pathogenesis of skin cancers such as melanoma and nonmelanoma skin cancers. To date, the current literature tends to focus more on the influence of the "gut microbiome" and skin carcinogenesis, but research on the "skin microbiome" is scarce, and very rare for interactions between skin cancer and microbiome melanoma (Sun et al. 2024). It has recently been shown that the skin microbiome

Summary

- The skin microbiome seems to be closely linked to melanoma issues. There is a growing interest in studying the skin microbiome and the whole range of issues surrounding melanoma: from exposome and UV-resistome to oncological responses to immunotherapy and bacteriotherapy.

can influence the skin's response to UV radiation through different mechanisms. First, it can strengthen the skin barrier, reducing DNA damage caused by UV radiation; some commensal bacteria produce molecules that neutralize reactive oxygen species (ROS) generated by UV exposure, limiting oxidative stress—a key driver of cancer; and finally, the microbiome can modulate local immune responses, potentially reducing chronic inflammation, a risk factor for cancer development.

In addition, the composition of the tumor microbiome varies among patients with different survival rates, which may indicate a prognostic indicator. This hypothesis is illustrated by an analysis of tumor antigen epitopes in melanoma in patients with distinct prognoses, which revealed homology between certain tumor neoantigens and microbial epitopes (Guardamagna et al. 2022).

A review of existing studies highlights the role of the "skin microbiome" throughout the history of melanoma, from the impact of UV radiation—a major factor in melanoma onset (with an attributable fraction of nearly 90% [Centre International de Recherche Sur le Cancer Lyon 2018])—to the strong interactions between the microbiome and melanoma at both primary and metastatic stages.

This study, based on the literature, offers an analysis of the different interactions between the skin microbiome and skin cancer a—kind of yin and yang—and a constant interplay, which must be known and understood in order to make them potential therapeutic targets and prognostic elements and to integrate them into the multi-omics models of tomorrow.

1.1 | Part One: Skin Microbiome in Melanoma Initiation

The skin microbiome is vital in maintaining skin health and defending the body against harmful pathogens (Savoia et al. 2023). It helps sustain the local pH balance, inhibits the growth of detrimental bacteria, and produces l antimicrobial peptides and stimulates secretion by cutaneous cells like keratinocytes. The composition of the skin microbiome can vary based on factors such as age, gender, ethnicity, and lifestyle (Chen, Zhao, et al. 2022). Environmental influences, including diet, hygiene practices, and exposure to UV radiation and pollutants, can also modify the skin microbiome (Savoia et al. 2023). As the skin acts as the primary barrier between the host and the environment, a disrupted skin barrier can lead to microbial dysbiosis (Zeeuwen et al. 2012; de Koning et al. 2011) with constant communication between the skin barrier and the commensal microbiome (Woo et al. 2022). It is essential to note that commensal bacteria remain commensal, and it is the environment that makes them pathogenic, unlike pathogenic bacteria, which are pathogenic in all circumstances. The skin's distinct microbiome is dominated by Gram-positive bacteria, notably *Staphylococcus* and *Veillonella*, which are crucial for wound healing. Commensal skin microorganisms, such as *Cutibacterium acnes*, can acquire pathogenic gene activation under the influence of the microenvironment (Simpson et al. 2022). *Propionibacteria*, the most abundant commensal skin bacteria, produce porphyrins similar to those in humans and are pro-inflammatory, relating to inflammatory skin diseases (Shu et al. 2013) as they act as skin probiotics against methicillin-resistant *Staphylococcus aureus*.

When the skin is damaged, (Woo et al. 2022) noted that altered skin microbiomes present damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and microbial toxins, which can induce chronic inflammation and cellular damage, potentially leading to skin cancer initiation and progression (Figure 1). The microbiome, DAMPs, PAMPs, microbial toxins, $CD8^+$ T cells, regulatory T cells, tumor-associated macrophages, and their corresponding cytokines and chemokines are significant factors affecting the tumor microenvironment in skin cancers, promoting tumor progression through immunosuppression, cellular proliferation, and inflammation. Antimicrobial peptides (AMPs, such as cathelicidin and human β-defensin) produced by keratinocytes (Tokumaru et al. 2005), are regulated by PAMPs or DAMPs (González-Sánchez and DeNicola 2021), indicating ongoing dialogue and adaptation between the microbiome and the immune system. One example of aggression is UV-induced damage, which presents the mechanisms mentioned above.

This adaptation of the microbiome occur when the skin is attacked by UV-B radiation, so that the concept of the UV-resistome has emerged, characterized by genetic and physiological adaptation post-exposure (Portero et al. 2019) of microbiome. While UVA penetrates deeper into the dermis than UVB (Bruls et al. 1984), it is less genotoxic (de Gruijl 2002). It is estimated that 88.5% of new melanoma cases are attributable to solar ultraviolet radiation exposure (Centre International de Recherche Sur le Cancer Lyon 2018). Ongoing research aims to determine the role of the skin microbiome in UV radiation exposure on microorganisms (Burns et al. 2019; Rai, Rai, and Kumar 2022), screening, or protection (Rai, Rai, and Kumar 2022), examining UVR's impact on the skin microbiome and homeostasis (Grice and Segre 2011). Under physiological conditions, melanocytes do not directly contact bacteria, only bacterial by-products (Wang et al. 2017). Lipo-teichoic acid (LTA) from *S. epidermidis* helps melanocytes avoid UVB-induced apoptosis by upregulating TRAF1, CASP14, CASP5, and TP73 (Wang et al. 2018) without affecting DNA damage generation (CPD formation), which is the underlying pathophysiological mechanism in melanoma development. Conversely, *C. acnes* inhibits CPD-bearing melanocytes survival and proliferation after UVB radiation by increasing apoptosis, producing coproporphyrins, and upregulating TNF-α, which eventually leads to massive melanocytes death after direct UVB exposure (Wang et al. 2018). Skin microbiome inhibits the immunosuppressive effect of UV-B irradiation on the induction of hypersensitivity to DFNB in mice, when comparing germ-free mice without microbiome and mice with

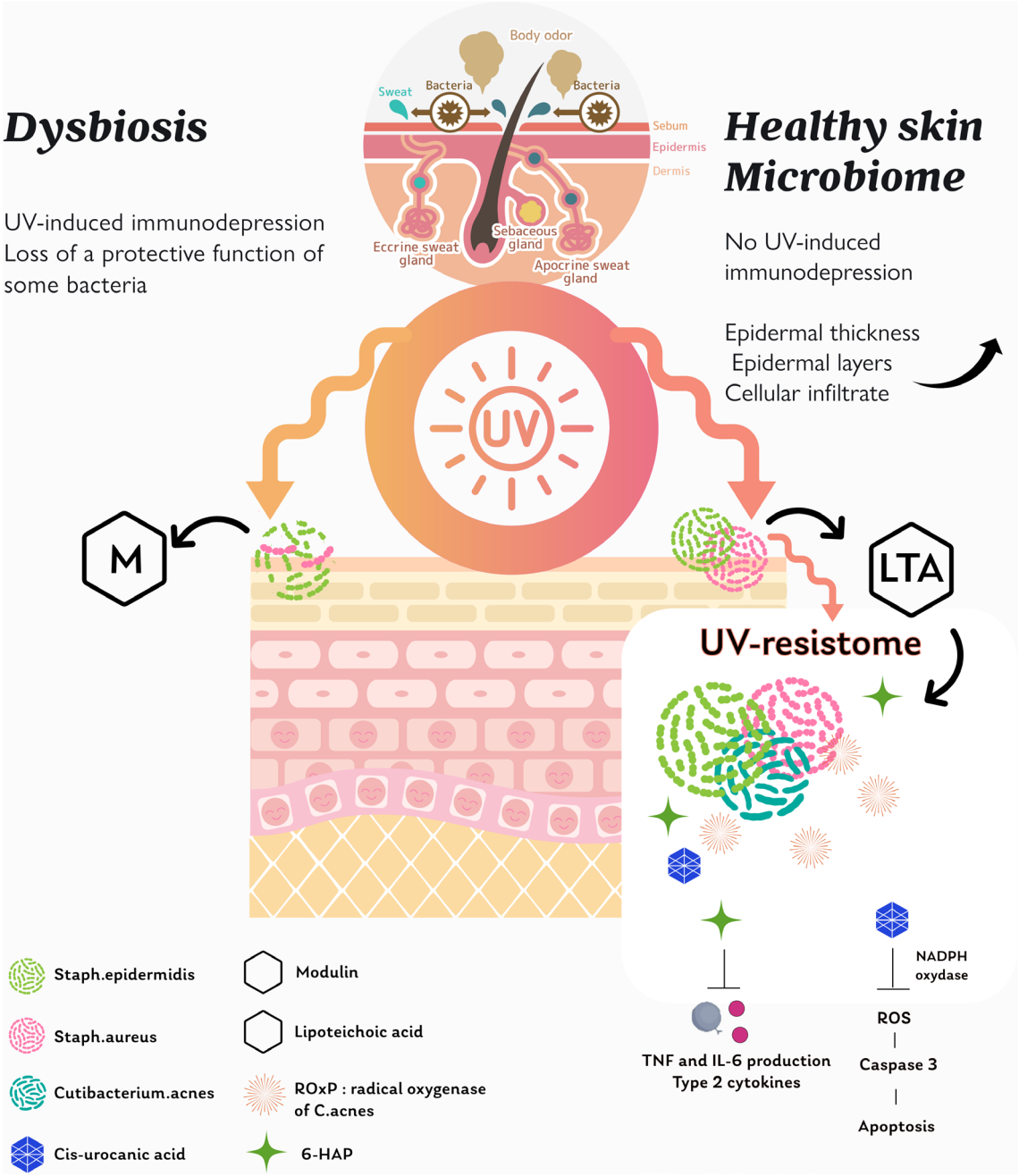

FIGURE 1 | Skin microbiome and cancer initiation, with IL, IinterleukineInterleukin; LTA, Llipoteichoic acid; M, Mmodulin; RoxP, Rradical oxygenase of P. acnes P. acnes; UV, Uultraviolet.

skin microbiome. The second ones showed a better epidermal thickness, epidermal layers and cellular infiltrate in response to UV-B radiation. It underlines that that microbiome protects from UV-induced immunosuppression (59.5% vs. 28.6%) (Patra et al. 2019). Squarzanti et al. (2020) described the microbiological profile of commensal skin flora in normal and pathological situations. In a physiological situation, the normal skin microbiota is about 25 commensal β-HPVs and differs regarding the considered area is moist, dry, or sebaceous. Representatives of the commensal flora of moist regions are mainly Staphylococci (Firmicutes) and Corynebacteria (Actinobacteria), while sebaceous areas are mostly colonized by Propionobacetria (Actinobacteria) and dry areas by Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes. The fragile microbial balance is altered by UV radiation, and the UV-induced microbiome shows an increase in *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, Candida spp., and mainly HPV5, 8, and 38. At the same time, a decrease in *Cutibacterium acnes* (Propionibacteria), Malassezia and commensal β-HPVs is noticed. A high abundance of proteins was involved in the synthesis and transfer of osmoprotectants (Pérez et al. 2017), composed of UV-resistant bacteria such as *Acinetobacter* sp. *Ver3*, *Exiguobacterium* sp. *S17*, *and Nesterenkonia* sp. *Act20*. Microorganisms have evolved mechanisms of synthesizing metabolites such as mycosporines and mycosporine-like amino acids (MAAs), melanin, and carotenoids as defense mechanisms against high solar UVB rays (Rai, Rai, and Kumar 2022; Joshi, Mohandass, and Dhale 2018; Kageyama and Waditee-Sirisattha 2019; Abiola, Whittock, and Stavros 2020).

Thus, UV causes direct changes to the skin microbiome due to antimicrobial effects and suppression of the immune system (Patra et al. 2018; Patra, Byrne, and Wolf 2016), and skin microbiome change (Grant, Kohli, and Mohammad 2024) and nutrients (Patra et al. 2020; Patra et al. 2023) are key parameters to have high photoprotection by reducing reactive oxygen species (ROS) production (Burns et al. 2019; Patra et al. 2020; Chen, Ly, et al. 2022; Souak et al. 2021; Bouilly-Gauthier et al. 2010). These considerations suggest a new concept which is skin microbiome could be a protection against skin cancer, or, conversely, a certain altered skin microbiome could favor the development of melanoma and SCC by providing a favorable environment for cancerous tumors. Metabolites from the common skin commensal *S. epidermidis* have shown protective effects against epithelial skin cancer, suggesting that some individuals' microbiomes can confer cancer protection (Nakatsuji et al. 2018), as *S. epidermidis* promotes the survival of melanocytes with UVB-induced DNA damage, whereas *Cutibacterium acnes* inhibits melanocyte survival by increasing apoptosis (Wang et al. 2018). Savoia et al. (2023) described that *Staphylococcus* species, predominantly found on the skin surface, are considered part of the normal commensal skin microbiome. While *S. epidermidis* is beneficial, *S. aureus* is pathogen, causing skin infections and could have a role in the development of epithelial skin cancer. Bacteria of our skin microbiome could protect against epithelial skin cancers by secreting different AMPs. Dysbiosis would be detrimental because of loss of a protective function of some bacteria as *S. epidermidis* inducing chronic inflammation (Laihia et al. 2010), via *S. aureus*, which creates a pro-inflammatory environment (Krueger et al. 2021). For instance, cis-urocanic acid inhibits immunosuppression induced by UV exposure and suppresses melanoma growth and 6-N-hydroxyamino purine (6-HAP) produced by *S. epidermidis* inhibits DNA polymerase activity (Hug, Dunkerson, and Hunter 1999). Some strain of *S. epidermidis* produces 6-N-hydroxyaminopurine (6-HAP), a molecule that inhibits DNA polymerase activity (Nakatsuji et al. 2018). In culture, 6-HAP selectively inhibits proliferation of tumor lines but did not inhibit primary keratinocytes, and intravenous injection of 6-HAP in mice suppresses the growth of B16F10 melanoma without evidence of systemic toxicity. Resistant cells to 6-HAP express mitochondrial amidoxime reducing components (mARC), enzymes absent in cells sensitive which blocks apoptotic effects of 6-HAP. In short, skin colonization by *S. epidermidis* strain MO34 producing 6-HAP protects from UV-induced neoplasia. 6-HAP strain are found in the metagenome from multiple healthy human subjects, suggesting that microbiome of some individuals may confer protection against skin cancer. The pathophysiological mechanisms of *S. aureus* can be explained by looking at oncodermatological studies on non-melanoma cutaneous cancers. *S. aureus* is strongly associated with both AK and SCC *S. aureus* (29.3% in SCC, OR: 6.23) (Krueger et al. 2021). *S. aureus* secretes virulence peptide called "modulin" which induces a secretion of IL-1α, IL-6, and TNFα and activates Th17 cells and T_{Reg} with release of IL-17 (Squarzanti et al. 2020; Kullander, Forslund, and Dillner 2009). *Corynebacterium* is associated with stage III, IV in melanoma patients and in a mouse model, upregulating the IL-17 cells (Mizuhashi et al. 2021). IL-17 can induce the growth of melanoma, suggesting that *Corynebacterium* might promote growth of melanoma through an IL-17-dependent pathway (Chen, Zhao, et al. 2022; Mizuhashi et al. 2021; Chen and Gao 2019). This observation was validated in mice, where topical application of *Corynebacterium accolens* led to dermal recruitment of IL-17A-producing γδ T cells (Ridaura et al. 2018). Cytokine profile IL-17 and IL-22 increases cutaneous colonization of *S. aureus* triggering a chronic inflammation, which is a key factor in the development of tumor cells, and an upregulation of the potentially oncogenic beta-defensin-2 (Madhusudhan et al. 2020) is noticed.

Surface bacterial load increases, and alpha diversity decreases in skin cancers due to an increased abundance of *Staphylococcus* species and a relative decrease of skin commensals (Krueger et al. 2022). Thus, dysbiosis of the skin microbiome could impact melanoma progression (Mekadim et al. 2022), as bacteria such as *Corynebacterium*, *S. epidermidis*, *Fusobacterium*, and *Trueperella* have protective and detrimental effects on melanoma. Mrázek et al. (2019) showed that the bacterial composition and diversity of the skin were significantly different between normal skin and melanoma-affected skin. *Fusobacterium* and *Trueperella* were abundant in melanoma samples.

There are specific features in skin microbiome and intratumoral mechanisms in primary melanoma and adjacent healthy tissue. The diversity of intratumoral bacterial DNA representation (commensal or pathogenic) varies according to cancer type, ranging from just 14.3% in melanoma to over 60% in breast, pancreatic, and bone tumors (Nejman et al. 2020). A growing body of evidence points to the presence of intratumoral pathogenic bacteria, thanks to the development of metagenomics and culturomics (Nejman et al. 2020; Kalaora et al. 2021; Fu et al. 2022; Galeano Niño et al. 2022). These microbiome alterations are particularly noticeable in oncology, where practitioners often encounter highly odorous cancer wounds. Bacterial metabolites such as dimethyl trisulfide (DMTS) and putrescine are associated with the odor of malignant fungating wounds and the degradation of periwound skin (Vardhan et al. 2019). This issue is not limited to advanced cancers but also occurs in early-stage cancers like primary melanoma. As early as 1989, the hypothesis that melanoma could be diagnosed by "sniffer" dogs was proposed (Williams and Pembroke 1989). The pathophysiological hypothesis for canine diagnosis was suggested using the experimental model of lung cancer: Dogs can detect volatile organic compounds (VOCs) and maintain their performance stability over time, even when the testing environment varies (Mazzola et al. 2020). Cambell et al. described that melanoma (Campbell et al. 2013) could be diagnosed by sniffer dogs due to metabolic changes in tissue. A recent study identified three VOCs that are preferentially expressed in primary melanoma: 4-methyl decane, dodecane, and undecane [6], confirming that changes in the skin microbiome are relevant for the management and even diagnosis of primary melanoma.

A new role of skin commensal bacteria in host defense has been discovered (Squarzanti et al. 2020) against melanoma, since there is a constant communication between the skin microbiome and gut microbiome and tumor progression (Sepich-Poore et al. 2021), as they can modulate the immune system locally. So, in the future, another way to prevent UV-induced damage will no longer require the simple application of anti-UV mineral filters with antimicrobial properties (Grant, Kohli, and Mohammad 2024), impacting the microbiome (Rowenczyk et al. 2017; Azizi-Lalabadi et al. 2019; Torbati and Javanbakht 2020) over several weeks (Chen, Zhao, et al. 2022;

Iglesia, Kononov, and Zahr 2022; Bouslimani et al. 2019), but will need to monitor the skin's bacterial flora to make it favorable to UV defense. This approach is supported by oral administration of lipoteichoic acids (LTAs) from the same strain (Friedrich et al. 2019) delaying UV-induced tumor development (Ramsey et al. 2016) and UV-induced immunosuppression (Weill et al. 2013). Supplementation with *Lactococcus and Lactobacillus rhamnosus GG* (Ciorba et al. 2012) has demonstrated immunomodulatory and antitumor properties (Savoia et al. 2023), modulating Th1 and Th2 immune cell responses (Valdéz et al. 2005). *Lactobacillus johnsonii* enables the prevention of UV-induced Langerhans cells decrease and helps restore the immune system homeostasis (Bouilly-Gauthier et al. 2010; Guéniche et al. 2010), whereas *Bifidobacterium lactis*, combined with *Lactobacillus plantarum*, inhibited the PI3K/AKT pathway involved in melanocyte proliferation (Laud et al. 2003). Topical application of *Bifidobacterium longum* lysate reduced skin inflammation mediated by substance P (Guéniche et al. 2010), and topical application of *Lactobacillus plantarum* reduced skin colonization by *P. aeruginosa*, a Gram-negative opportunistic pathogen involved in carcinogenesis (Yu et al. 2020). In another experimental model, other than in melanoma, local eradication of *S. aureus* was associated with clinical improvement (Le et al. 2020; Lindahl et al. 2019; Lindahl et al. 2022).

1.2 | Part Two: Microbiome as a New Therapeutic Approach With Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICI) have transformed the treatment of melanoma, yielding long-lasting clinical responses in many patients (Figure 2). However, not all patients experience these benefits (Topalian et al. 2012). Indeed, several resistance mechanisms have been proposed to explain the lack or loss of immunotherapy efficacy. Some of these mechanisms are intrinsic to the tumor (impacting gene expression, cell signaling, or immune recognition), while others are environmental, either immediate or distant. Several mechanisms highlighting the interaction between the microbiome and the immune system have been identified (Lam et al. 2021; Routy et al. 2018; Schaupp et al. 2020) in both the innate and adaptive immune systems. Regarding adaptive immunity, various distinct gut microbial genera and species are associated with $CD8^+$ T-cell infiltration and survival in melanoma patients (Gopalakrishnan et al. 2018) and intracellular bacteria in metastatic melanoma cells facilitate tumor recognition and clearance by tumor-infiltrating lymphocytes (Kalaora et al. 2021; Zitvogel et al. 2021). All these elements suggest a correlation between the microbiome and immunity. At a time when ICI is the gold standard for the treatment of melanoma, it is reasonable to think that the microbiome may influence the response to ICI. Pathogenic bacteria can enter primary tumors, including solid melanoma, by a variety of routes. In mice, pathogenic bacteria such as *L. reuteri* cross the colonic epithelial barrier and then colonize subcutaneous melanoma cells to locally produce I3A and enhance ICI efficacy (Bender et al. 2023). This highlights that local changes in the skin microbiome in melanoma would influence the response to systemic treatment, leading to the idea that the modification may not just be local, but more general, with constant adaptation and communication, particularly with the gut microbiome, known to have multiple effects on tumor biology, such as the transformation process, tumor progression, and the response to anticancer therapies including immunotherapy (Gopalakrishnan et al. 2018; Routy et al. 2024; Wong et al. 2017; Kostic et al. 2013; Matson et al. 2018; Viaud et al. 2013; Iida et al. 2013; Helmink et al. 2019; Rutkowski et al. 2015). Another body of evidence regarding the impact of the intratumoral microbiome on ICI response was provided by (Zhang et al. 2023) who suggest that *Eudoraea* and *Desulfonatronospira* have significantly higher abundance in the beneficial group and could enhance anti-PD-1 immunotherapy in melanoma by increasing the active immune cells (as $CD8^+$ T cells and cytolytic T cells) in the tumor microenvironment. It suggests that intratumor microbiomes should be a predictive biomarker for ICI response. If the response to ICIs can be modulated by the skin microbiome, the reverse is also possible, that is, that ICIs modify the skin microbiome. Taxa more abundant in tumors of responders included Clostridium, whereas *Gardnerella vaginalis* was more abundant in tumors of nonresponders to ICI (Nejman et al. 2020). These findings underscore the potential impact of the skin microbiome on melanoma.

There is an interaction between the development of melanoma and the gut microbiome (O'Neill et al. 2016; Salem et al. 2018). The established theory of the "gut-skin axis" illustrates the interplay between the gut, its intestinal microflora, and the skin via the immune system (Nam et al. 2020) and is particularly relevant to ICI response. It remains unclear whether melanoma itself alters the gut microbiome or if the altered microbial ecosystem is carcinogenic, but a colonization by certain pathogens can lead to ICI resistance, making certain pathogens prognostic factors. This is all the more important now that we have entered the era of precision oncology, with medicine and treatment options that are increasingly tailored to the individual patient, aiming to target the appropriate microbes to enhance ICI response (Glitza et al. 2024; Lombardi and Pinato 2024). The use of antibiotics can significantly disrupt the balance of the gut microbiome, raising concerns about their potential role in fostering resistance to immunotherapy (Patel et al. 2021). Gut dysbiosis has been observed in melanoma patients (McCulloch et al. 2022), where a reduction in alpha diversity is linked to tumor invasiveness (Vitali et al. 2022) as it decreases in advanced stages. Cross-reactivity mechanisms between these pathogens and tumor neo-antigens might heighten the production of inflammatory cytokines like IFN-γ or stimulate dendritic cells (DC) and antigen presentation (Pitt et al. 2016). The cytotoxin-associated gene A encoded by *H. pylori* activates the ERK/MAPK pathway, a shared proliferation pathway with melanoma (Laud et al. 2003), which could lead to ICI resistance (Oster et al. 2022; Tonneau et al. 2022; Che et al. 2022), decreasing DC cross-presentation. Elevated serum levels of butyrate and propionate have been linked to resistance to anti-CTLA-4 and an increase in Treg cells in melanoma patients (Uribe-Herranz et al. 2020; Coutzac et al. 2020). Some pathogens can release metabolites that directly activate T lymphocytes, affect intestinal epithelial or endothelial barriers, or target tumor cells (Wang et al. 2020; Mager et al. 2020; Zhang et al. 2022). For instance, tryptophan metabolites like indole-3-aldehyde (I3A) derived from *L. reuteri* improved ICI efficacy in a mouse model, and melanoma patients responding to ICI had higher serum I3A levels than nonresponders (Bender et al. 2023). We could classify these prognostic germs as beneficial or harmful, and details are given in Table 1.

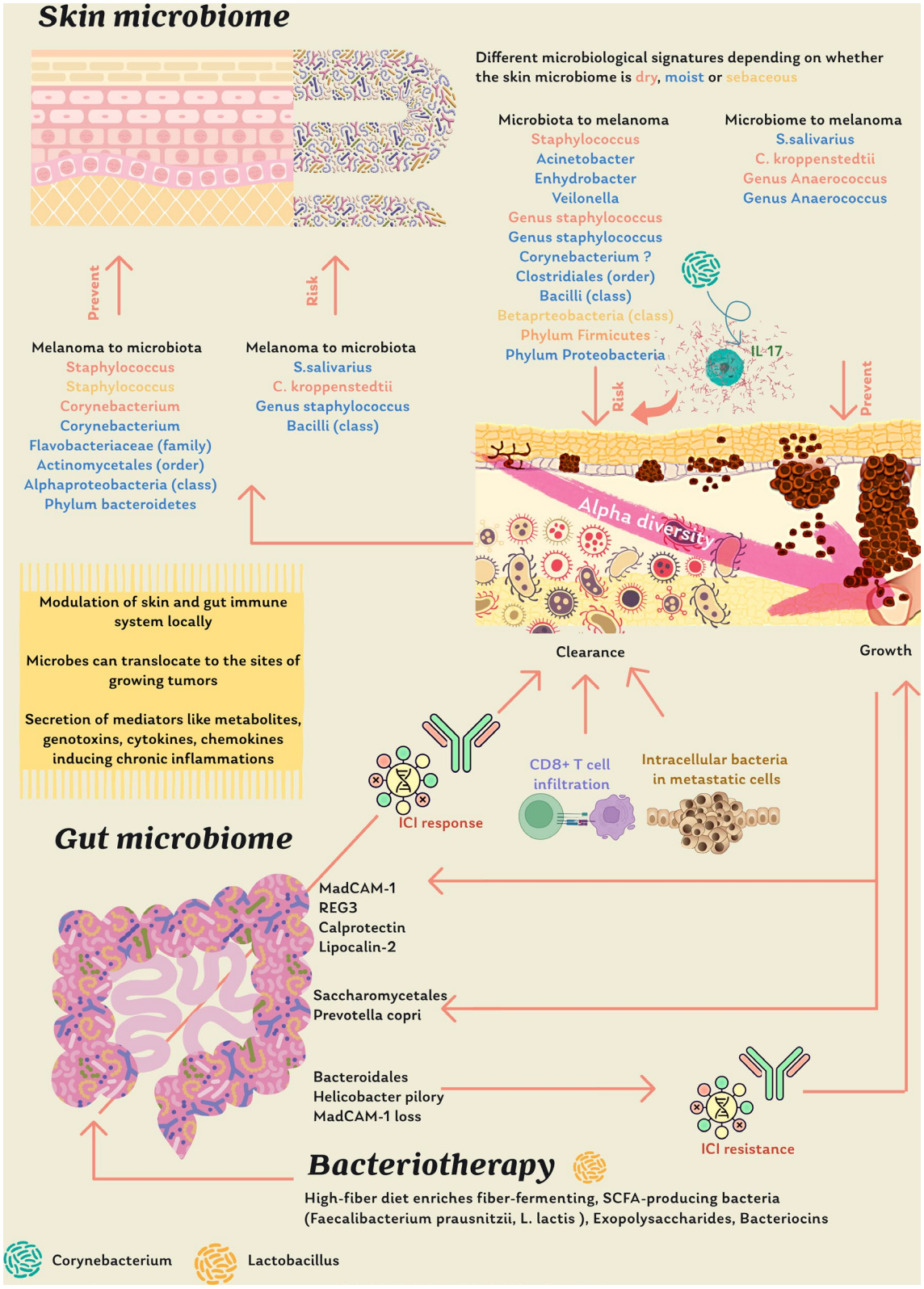

FIGURE 2 | Microbiome, ICI, and oncogenesis, with ICI, Immune checkpoint inhibitor.

Fecal samples also serve as clinical indicators of dysbiosis, showing upregulation of MAdCAM-1, REG3, calprotectin, and lipocalin-2 (Fidelle et al. 2023; Zollner et al. 2021; Jang et al. 2023), although no specific bacterial taxon or diversity consistently correlates with response across all studies (Witt et al. 2023). A transplant of the human gut microbiome into mice to yield patient-specific avatar mice (Andrews et al. 2021) showed that, in nonresponders to ICI, oral supplementation with *A. muciniphila* restores efficacy of PD-1 blockade in an interleukin-12-dependent manner, suggesting that some modification of the gut and/or tumor microbiomes may be advantageous for one modality of therapy while disadvantageous for another. Fecal

TABLE 1 | Beneficial and pathogenic germs in the carcinological response to ICI, adapted from Kumar et al. (2022).

Beneficial germs		Harmful germs	
Ruminococcus genus	*Faecalibacterium prausnitzi* Andrews et al. (2021)	*Clostridium* genus	*C. asparagiforme* *C. clostridioforme* *C. citroniae* *C. boltae* *C. lavalense* *C. hatewayi* *C. symbosium* *C. aldenense*
Lachnospiraceae family	*Dorea* genus *Coprococcus* genus *Roseburia* genus *Eubacterium* genus *Blautia obeum*	Proteobacteria phylum	*Enterobacteriales* (*E. coli*, *Shigella*, *Klebsiella*) *Biophila wadsworthia*
Actinobacteriaceae family	*Collinsella* genus *Bifidobacterium* genus	Actinobacteria phylum	*Atopobium parvulum* *Eggerthella lenta* *Actinomyces* spp
Archae	*Methanobrevibacter smithii*	*Veillonella* genus	*V. parvula*
Verruco microbiaceae family	*Akkermansia muciniphila*	*Bacteroides* genus	*B. uniformis* Wang et al. (2020) *B. distasonis*
Bacteroidales order	*Prevotella copri* McCulloch et al. (2022) *Barnesiella intestinihominis* *Alistipes senegalensis*	Streptococcaceae	*Streptococcus* spp McCulloch et al. (2022)

microbiome transplantation (FMT) modulates peripheral and intratumoral immune responses, enhancing $CD8^+$ T activation (Davar et al. 2021). In melanoma, intestinal bacteria translocation to tumors has been observed following immunotherapy (Shi et al. 2020), as a primary cutaneous melanoma tumor can trigger intestinal translocation via β-adrenergic-mediated stress ileopathy, increasing intestinal permeability (Yonekura et al. 2022).

There is an interplay between cutaneous melanoma and the gut and skin microbiome (Kumar et al. 2022), suggesting that gut microbiome drives the response to immunotherapy, making microbiome as a potential therapeutic target to prevent skin cancer and enhance ICI response (Routy et al. 2024). It introduces the concept of therapeutic approaches using bacteriotherapy (Wastyk et al. 2021). The rationale behind bacteriotherapy is to create a microbacterial environment more conducive to tumor response, fostering ecological competition where a commensal bacterium prevents pathogen colonization of the host (Shu et al. 2013). Recent observational studies in melanoma patients have shown benefit of sufficient dietary fiber intake (Spencer et al. 2021), stool SCFA (short-chain fatty acid) levels and polysaccharide A from bacteria (Nomura et al. 2020) or higher omega-3 (Simpson et al. 2022; Bolte et al. 2023) are associated to ICI response. A high-fiber diet enriches fiber-fermenting, SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, which are also associated with ICI response. In mice, dietary fiber deprivation was shown to abolish the ICI response and decrease propionate levels in stool (Glitza et al. 2024). Fermented milk (*L. lactis* and metabolites like SCFAs, exopolysaccharides, and bacteriocins) improved the immune system by upregulating innate and acquired immune responses through cytokine production (e.g., IL-4, IL-12, IL-6, IFN-g, and TNF-a by Th1 and Th2 lymphocytes) (Valdéz et al. 2005) and TLR4 activation (Hosseini et al. 2018) on macrophage and other dendritic cells, showing promising anticancer potential by release of IL-1Beta and TNF, while CpG DNA of gut bacteria induces a response from TLR9 on $CD4^+/8^+$ T cells to produce inflammatory cytokines IL-17 and interferon gamma. In the context of ICI treatment, modulating the microbiome could be used to control immune adverse events such as diarrhea (Delia et al. 2007), with probiotic formulations containing *Bifidobacterium bifidum*, *L. acidophilus*, and *Lactobacillus casei* (Wang et al. 2022).

Given the emerging role of the skin microbiome in the pathophysiology of primary melanoma, it is likely that in the near future, we will need, microbiota-centered interventions (Derosa et al. 2021). Pharmacokinetic tools aiming at monitoring drug recovery and short- or long-term stability in the recipient host intestine will be needed. It will lead to microbial therapies and biomarkers for cancer and explain microbial mechanisms in cancer in omics model of precision oncology. This approach illustrates the transition from empirical medicine to "data-driven" medicine (Merino and Florez 2018), enabling better adaptation to the challenges of treating a disease (more targeted treatments, more precise subpopulations, "individualised" medicine) by using "real-life" data to better understand future problems, with patient-centred objectives.

2 | Conclusion

The skin microbiome, less studied than its digestive counterpart, seems to be closely linked to melanoma issues. Characterizing the skin microbiome could help identify patients at greater risk of developing melanoma or have prognostic value, defining subcategories of patients more responsive to specific treatments or more prone to treatment-related adverse events. Ultimately, the microbiome accompanies melanoma throughout its history, from primary melanoma to advanced melanoma, with growing interest in bacteriotherapy as a therapeutic weapon in melanoma.

Author Contributions

Jean-Matthieu L'Orphelin: investigation, writing – original draft, writing – review and editing, conceptualization, data curation. **Anne Dompmartin:** supervision, writing – review and editing. **Brigitte Dréno:** conceptualization, supervision, methodology, writing – review and editing, writing – original draft.

Conflicts of Interest

Jean-Matthieu L'Orphelin has received speaker and consultant honoraria from BMS, Novartis, MSD, Laboratoires Gilbert, and Pierre Fabre Oncology. Anne Dompmartin has received speaker and consultant honoraria from BMS, MSD, and Novartis. Brigitte Dréno has received speaker and consultant honoraria from BMS, Novartis, and Pierre Fabre Oncology.

Data Availability Statement

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

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