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REVIEW ARTICLE

Non-Melanoma Skin Cancer: news from microbiota research

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ABSTRACT

Recently, research has been deeply focusing on the role of the microbiota in numerous diseases, either affecting the skin or other organs. What it is well established is that its dysregulation promotes several cutaneous disorders (i.e. psoriasis and atopic dermatitis). To date, little is known about its composition, mediators and role in the genesis, progression and response to therapy of Non-Melanoma Skin Cancer (NMSC). Starting from a bibliographic study, we classified the selected articles into four sections: i) normal skin microbiota; ii) *in vitro* study models; iii) microbiota and NMSC and iv) probiotics, antibiotics and NMSC. What has emerged is how skin microflora changes, mainly represented by increases of *Staphylococcus aureus, Streptococcus pyogenes* and *Pseudomonas aeruginosa* strains, modifications in the mutual quantity of β-Human papillomavirus genotypes, of Epstein Barr Virus and Malassezia or candidiasis, may contribute to the induction of a state of chronic self-maintaining inflammation, leading to cancer. In this context, the role of *S. aureus* and that of specific antimicrobial peptides look to be prominent. Moreover, although antibiotics may contribute to carcinogenesis, due to their ability to influence the microbiota balance, specific probiotics, such as *Lacticaseibacillus rhamnosus* GG, *Lactobacillus johnsonii* NCC 533 and Bifidobacteria spp., may be protective.

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Introduction

In the last years, numerous studies highlighting the relationship between microbiota and melanoma have been published (Yan et al. 2018; Gong et al. 2019; Smibert et al. 2019). Indeed, the crucial role of immune checkpoint inhibitors in improving the prognosis of melanoma patients is confirmed, and the hypothesis that the antitumor response to the anti-CTLA-4 and PD-1 monoclonal antibodies is dependent on the intestinal microbiota is supported by a lot of evidence (Vétizou et al. 2015; Dong et al. 2018; Gopalakrishnan et al. 2018; Humphries and Daud 2018; Matson et al. 2018; Chaput et al. 2019; Li et al. 2019). On the contrary, the relationship between the cutaneous microbiota and NMSC is poorly known, despite the high frequency of this neoplasm and the clear role of the immune system in its pathogenesis, evident from its increased occurrence and aggressiveness among immunosuppressed patients (Howard et al. 2018; Zavattaro et al. 2019).

In this paper, starting from a careful revision of the scientific literature, we tried to highlight the possible role of the microbiota in the pathogenesis of skin tumours of keratinocyte origin and its potential prognostic and therapeutic implications.

Methods

A bibliographic research analysis was performed in the archives of PubMedCentral®, looking for international original peer-reviewed articles published in the English language in the time frame ranging from January 2000 to February 2020. The following terms were searched as inclusion criteria, single and/or combined, to look for the most pertinent abstracts: "microbiota", "microbiome", "bacteriota", "bacteria", "dysbiosis", "antibiotics", "probiotics", "study models", "skin immunity", "skin microenvironment", "Non-Melanoma Skin Cancer (NMSC)", "Basal Cell Carcinoma (BCC)", Squamous Cell Carcinoma (SCC)", "skin cancer risk

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factors", "*Staphylococcus aureus*", "*Staphylococcus epidermidis*" , "virota", "virome", "virus", "beta Human Papillomavirus (β-HPV)", "Epstein- Barr virus (EBV)", "fungiota", "mycobiota", "fungi", "mycetes", "Candida *spp*".

Both original and review articles (human, animal, and cell studies) and their bibliographies were analysed. Studies in languages other than English, meeting abstracts and posters were excluded. We found a total of about five hundred and thirty papers. After deep reading and revision, we reported the one hundred and sixty-six relevant and pertinent to the pre-established admissibility criteria and classified them into four categories including *i)* normal skin microbiota; *ii) in vitro* study models; *iii)* microbiota and NMSC; *iv)* probiotics, antibiotics and NMSC.

The human skin microbiota

The skin is the largest interface and interactive organ of the human body. Its squamous pluristratified epithelial surface, composed of an external flat area and an inner part comprising about 5 million appendages, such as hair follicles and sweat ducts (Gallo 2017), makes it fully accessible to a plethora of microorganisms.

Thanks to the Human Microbiome Project (HMP), their complexity and variety started to be characterised since about 13 years by the National Institute of Health (NIH) (Sanford and Gallo 2013). Worldwide research studies have thus evidenced that one hundred trillion microbes, possessing 1,000 times more genes than humans and comprising bacteria, viruses, phages and fungi essential to the host immunity's welfare, reside in different body niches including the skin (Weinstock 2012). Among them, on the skin resides a core of resilient commensals together with transient microbes, both non-pathogenic in normal conditions, that perform key functions and that may change, as a consequence of chronic UV exposure as well in the course of numerous diseases, including NMSC (Figure 1) (Dréno et al. 2016; Fyhrquist et al. 2016; Abdallah et al. 2017; Strickley et al. 2019).

In particular, cutaneous bacterial microorganisms inhibit pathogens invasion through amphipathic constitutive or upregulated antimicrobial peptides (AMPs), such as the cathelicidin LL-37 and human β-defensins (i.e. hBD-1, −2 and −3 and the antimicrobial RNase 7 protein), which stimulate keratinocyte-derived innate and adaptive immune mediators, by acting on their training and maintenance, in both the epidermal and dermal compartments (Wanke et al. 2011; Chen et al. 2018). The crosstalk among primary human keratinocytes, immune cells and microorganisms, regulated by AMPs, cytokines and chemokines, is essential for skin integrity (Grice and Segre 2011).

To contribute to skin microbiota preservation, epithelial surface desquamation, which cyclically occurs during the renewal process, as well as acid pH, inhibits

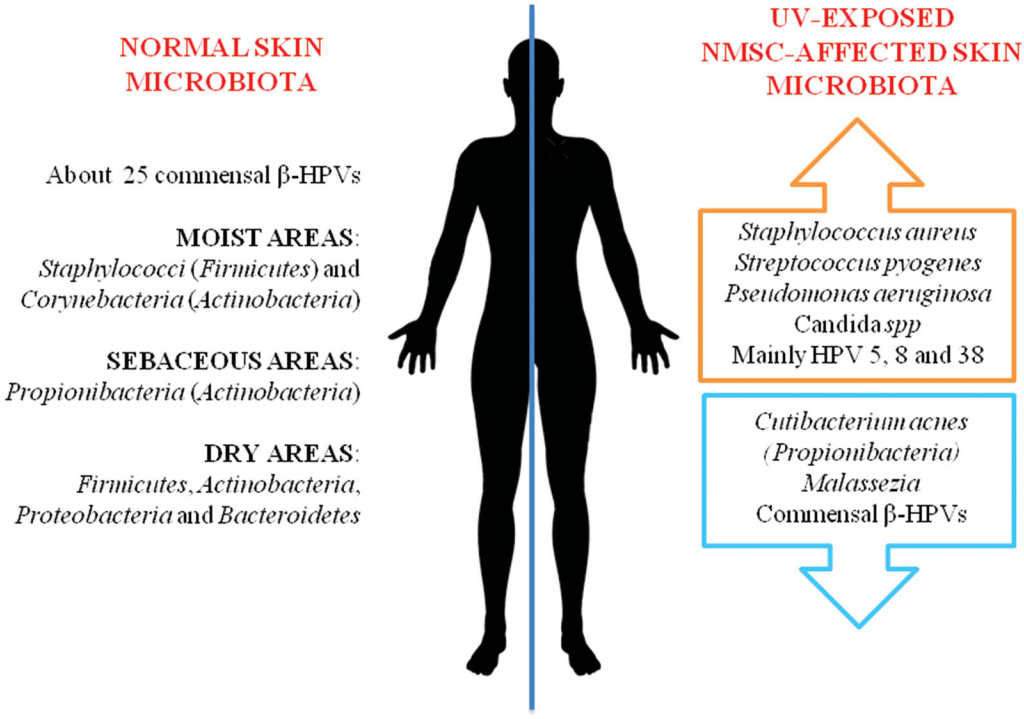

Figure 1. Non-pathogenic and altered microbiota in normal and UV-exposed NMSC-affected skin.

the growth of pathogens competing for nutrients (Candi et al. 2005; Borkowski and Gallo 2011; Coates et al. 2018). Accordingly, different factors (i.e. skincare products, smoking) could be responsible for microbiota variations (Gallo and Nakatsuji 2011; Bouslimani et al. 2019; Thompson et al. 2020).

Healthy microbiota alterations have been linked with several different diseases, including allergy, obesity, inflammatory bowel disease (IBD), diabetes mellitus, metabolic syndrome, and brain disorder; moreover, while the skin microbiota's influence on acne vulgaris, rosacea, atopic dermatitis (AD) and psoriasis (Gallo and Nakatsuji 2011; Salava and Lauerma 2014; Chang et al. 2018; Langan et al. 2018; Sun et al. 2019) has been demonstrated, only a few studies have been published on NMSC (Squarzanti et al. 2019).

In addition, while the role of gut microbiota in various diseases has been deeply investigated, studies focussed on the cutaneous counterpart are less numerous (Zeeuwen et al. 2013; Weyrich et al. 2015; Musthaq et al. 2018; Dréno 2019).

Indeed, research conducted worldwide has evidenced how skin and gut microbiota are very different: the skin is rich in *Actinobacteria*, while the gut is mostly dominated by *Firmicutes* and *Bacteroidetes* (Grice and Segre 2011). Conversely, they both possess a high intra-individual variability over time (Costello et al. 2009; Wu et al. 2020). On the other hand, in recent years, the existence of a connection between skin and gut has been investigated and a close relationship between the "gut-skin" and the "gut-brain" axes has been supposed, thus leading to the term "gut-brain-skin axis". Indeed, despite some dermatological diseases are frequently associated with gut bacterial overgrowth (also named "dysbiosis"), the gut can exert different effects on the autonomic nervous system as well as through neuro-endocrine pathway, contributing in the pathogenesis of different skin dermatoses (Arck et al. 2010). Among the other dermatoses, acne represents a paradigmatic disease that has been fully studied and universally accepted to be aggravated by gut microbiota's change due to psychological stressors (O'Neill et al. 2016; Lee et al. 2019).

Despite the use of advanced technologies and similarly to the gut microbiota, it is difficult to define the "healthy skin microbiota", since it depends on the individual eubiotic microbial community's ability to resist against pathogens colonisation (Costello et al. 2009).

What it is known, is that commensal Staphylococcal species regulate skin inflammation, via lipoteichoic acid production, through a Toll-like receptor 3-dependent pathway (Lai et al. 2009) thus activating the skin innate immunity response (Dréno et al. 2016).

As an example, to maintain skin health, *S. epidermidis* generally produces phenol-soluble modulins (Cogen et al. 2010), but when a dysbiosis occurs, due to UV over-exposure, genetic predisposition, diet errors, skincare products, drugs or indiscriminate antibiotic use, this bacterium, as many others, is lost and the infection risk is enhanced (Gallo and Nakatsuji 2011; Cundell 2018). Staphylococcal species are also reported in different cutaneous diseases: indeed, AD is linked to abundant *S. aureus* colonisation on both lesional and non-lesional skin in adults, while in 12 months AD affected infants this colonisation is absent (Kennedy et al. 2017). Moreover, chronic wounds are associated with continuous inflammation due to bacterial invasion, mainly by *S. aureus*, *S. pyogenes*, *Enterococcus* spp. or *Pseudomonas aeruginosa (P. aeruginosa)* (Grice and Segre 2011). As above described, *S. aureus*, common skin commensal, is localised in parts of the body with a high degree of humidity, preferring the groyne, the skin folds, the popliteal fossa and the nose (Grice and Segre 2011). It usually doesn't cause infections in immunocompetent people unless it contacts injured skin after surgery or traumas (Todd 2005) that can favour its colonisation.

Based on 16S ribosomal RNA gene sequencing, four main phyla (Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes) and three most common genera (*Corynebacteria*, *Propionibacteria,* and *Staphylococci*) have been described as major skin commensals (Grice et al. 2009). In fact, in moist areas (navel, axilla, groyne, sole, antecubital and popliteal fossa) *Staphylococcus* and *Corynebacterium* species, belonging to the *Firmicutes* and *Actinobacteria* phyla respectively, are dominant; regarding the sebaceous areas (forehead, alar crease, retro-auricular crease, back), *Propionibacteria* species of the *Actinobacteria* phylum have been isolated, probably due to their ability to grow in anaerobic and lipid-rich environments; finally, dry areas, such as forearm, hand, and buttocks, show the major diversity with all the four phyla well represented (Sanford and Gallo 2013).

The study published by Grice et al. demonstrated that *Proteobacteria* are the most abundant in all collected skin samples, starting from the swabs and the scrapes till the punch biopsies (Grice et al. 2008).

Moreover, as depicted by Nakatsuji et al. bacteria are detected not only on the skin surface but also within tissues, such as the dermal and adipose ones previously considered as sterile, where they directly interact with different cell types (Nakatsuji et al. 2013). For example,

in the deeper layers of the skin, the bacteria contacts with dendritic cells promote *i)* the production of IL-1, IL-17, and IFN-γ by T-cells, which migrate into the epidermis, *ii)* the activation of natural killer (NK) cells, and *iii)* the keratinocytes-mediated AMPs secretion (Egert et al. 2017). Furthermore, microbiota colonisation is also conditioned by the different oxygen tension between the epithelial surface and the deeper layers (Grice et al. 2008; Zeeuwen et al. 2012; Nakatsuji et al. 2013).

Although bacteria are the most represented organisms in the skin microbiota, fungi are also present. The fungal microbiota, named Mycobiota, is mainly represented by *Malassezia* species in healthy skin, albeit *Candida*, *Aspergillus*, *Cryptococcus, Rhodotorula* and *Epicoccum* species have also been reported (Byrd et al. 2018; Sohn 2018). The fungi's distribution over the body is determined by the characteristics either of the microorganisms or of the skin (body site, age, gender). Indeed, since *Malassezia* species lack the fatty acid synthase gene, they need the host's long-chain fatty acids to grow; consequently, they are mainly found in lipid-rich cutaneous sites (i.e. face, scalp) (Findley and Grice 2014; Limon et al. 2017). *Malassezia* is believed to play a role not only in the pathogenesis of pityriasis versicolour but also in inflammatory skin diseases, such as seborrhoeic dermatitis, atopic dermatitis and psoriasis, in which an exaggerated immune response to this yeast type is detected (Jo et al. 2017). Recently, Li et al. have characterised the Protease 1 produced by *Malassezia globosa*, one of the most frequently encountered species in the cutis, and demonstrated that this enzyme is able to hydrolyse the *S. aureus'* protein A, thus leading to counteract the bacterial biofilm formation and immune evasion, and preserving skin health (Li et al. 2018). *Candida albicans* is part of the healthy skin mycobiota, but cutaneous pH level conditions its growth: hence, any rise in pH, as can readily occur in moist areas, leads to promote its overgrowth. More specifically, the consequent exaggerated development of *C. albicans*, together with *S. aureus*, plays a pivotal role in the pathogenesis of the diaper dermatitis (Rippke et al. 2018).

Human papillomaviruses (HPV) are mainly known for their capability to cause several tumour types in humans. What has emerged from a metagenomics study conducted on 103 healthy individuals is that its prevalence is 68.9% and it is mainly distributed on the skin (61.3%), followed by other ecosystems, such as the vagina, mouth, and gut (Ma et al. 2014). Moreover, this shotgun sequencing analysis evidenced how the healthy cutaneous HPV community is more complex compared to previous evidence measured by the most used commercial kits which selectively target only some cervical high- and low-risk genotypes. The importance of these non-oncogenic viral genotypes is absolute since they could stimulate or inhibit an HPV infection by using interference or immune cross-mechanisms and thus represent a guide for the design of new clinical, epidemiological *ex vivo* and *in vitro* studies.

Summarising, the skin protects the human body from the highly colonised external environment, thanks to a complex cutaneous microbiota composed by bacteria, viruses and fungi that, despite contributing to people well-being, can be also involved in many benign and malignant skin disorders.

Therefore, the study of the microbial skin composition is deepening the knowledge of the microbial species that are present during life and their function, by distinguishing between resident and transient and what conditions make them able to express their beneficial or pathogenic potential.

In vitro study models

Different approaches, such as culturomic, quantitative real-time PCR (qRT-PCR), next-generation sequencing (NGS), mass spectrometry (Maldi-Tof), immunohistochemistry (IHC), Proximity Ligation Assay (PLA) and *in situ* hybridisation (ISH) analysis, are useful to obtain new information to understand how the human skin is colonised and what is its relationship with the hosted microorganisms. Swabs, scrapings, tape stripping, hair follicles, and skin biopsies are commonly used as biological samples to assess the cutaneous microbiota's diversity (Grice et al. 2008; Nakatsuji et al. 2013; Egert et al. 2017).

Most of the research on the relationship between dysbiosis and NMSC is indeed based on the results obtained by the comparative microbiome analysis of biopsies derived from healthy and diseased individuals. Through new powerful experimental methods, such as the NGS, scientists are scanning our microbial ecosystem, revealing an amazing diversity within the body compartments. Even if these association studies are of great relevance, however, they cannot distinguish whether microbiota changes are causes or effects of tumour development. Conversely, the use of experimental models, with the tuning of the involved factors, can allow identification of cause-effect relationships with the highest accuracy. Animal- and advanced 3 D preclinical- models employed in this field will be here presented.

Animals

Microbiota's influence in skin carcinogenesis processes

One of the main approaches to study the influence of the microbiota in skin carcinogenesis consists of inducing cancer in mice in the presence or absence of the microorganism(s) of interest, or its/their derived product(s). Skin carcinogenesis can be achieved with physical (i.e. UV damage or chronic skin trauma), chemical (i.e. 7,12-dimethylbenz(a)anthracene, DMBA/12-O-tetradecanoylphorbol-13-acetate, TPA protocol), or biological (i.e. HPV infection) agents, or through genetically engineered mouse models, as excellently already reviewed elsewhere (Huang and Balmain 2014; Nguyen et al. 2015). Thus, scientists aiming to study the microbiota-skin carcinogenesis axis used one of these well-known protocols, while they were exploring the role of a given microorganism, or product. For instance, Weill and collaborators demonstrated the protective role of lipoteichoic acids (LTA), a cell wall component of the *Lactobacilli*, in UV-irradiated female Crl: SKH-1-hrBR hairless mice (Weill et al. 2013). They observed in LTA-oral-treated mice, not only a significant delay in tumour appearance, but also a reversion of the UV-induced immune suppression, showing higher levels of interferon-γ,helper and cytotoxic T-cells in inguinal lymph nodes. The immunomodulating properties of LTA are evident since they also increase IgA + cell number in the small intestine, as well as activate dendritic cells in the mesenteric lymph nodes.

Hoste and collaborators investigated the role of flagellin, the main constituent of the bacterial flagella, in the initial step of two different skin cancer models. By using a model of wound-induced skin tumour in transgenic mice expressing activated MAPK kinase 1 (MEK1), they found that, besides wound size and inflammatory infiltrate, the tumour incidence correlated with flagellin presence, in a Toll-like receptor (TLR)-5 (the bacterial flagellin receptor)-dependent manner. Similar results were obtained with the DMBA/TPA carcinogenesis model, where the knock-down of TLR-5 mice elicited a substantial tumour development delay (Hoste et al. 2015).

Some carcinogenic protocols can also combine other agents, such as the two-stages UV carcinogenesis model, where SKH-1 hairless mice were treated for 1 week with DMBA, followed by UV-B irradiation. During UV exposure, mice were colonised by a topical application of two *S. epidermidis'* strains, one producing 6-*N*-hydroxyaminopurine (6-HAP), an inhibitor of the DNA polymerase, and the other not, as control. Interestingly, they found that the control mice had the expected higher skin tumour incidence, while the others had a significantly decreased number of tumours (Nakatsuji et al. 2018). Furthermore, when applied topically in UVB-exposed mice, *S. epidermidis* down-regulated pro-inflammatory cytokines through the production of butyric acid (Keshari et al. 2019).

Mice models have been also established to clarify the mechanisms at the basis of skin tumour development upon the combined action of β-HPVs and UV exposure (Dell'Oste et al. 2008; Rollison et al. 2019; Tommasino 2019). Tommasino and co-workers developed a transgenic mouse model expressing HPV38 oncoproteins under the control of the CK14 promoter to evaluate the potential role of β-HPVs in UV-induced NMSC (Viarisio et al. 2011). What they observed is that transgenic mice developed NMSCs after UV exposition, differently from the wild type ones, whose skin remained healthy (Viarisio et al. 2017). Therefore, the authors hypothesised that β-HPV 38 infection maintains cellular proliferation in UV-stressed cells, through E6 and E7 oncoproteins, in the early stage of skin carcinogenesis, thus acting as a UV co-factor (Viarisio et al. 2018; Tommasino 2019). Moreover, β-HPVs, similarly to the mucosal ones, modulate the inflammatory process and affect the efficiency of host immune surveillance, helping the infection persistence (Dell'Oste et al. 2008; Zhou et al. 2019).

Concerning the effect of the Mycobiota, it has been demonstrated that the injection of *C. albicans* in hairless mice induces a delayed-type hypersensitivity similarly as UV-exposure in humans (Kim et al. 2003); furthermore, BALB/c yeast injected mice have been used to investigate the effect of sunscreen to prevent the UV-induced immunosuppression, and thus skin carcinogenesis (Chen et al. 2016).

Regarding *Malassezia*, Perrins et al. evaluated the presence of the yeast in immunosuppressed neoplastic cats in which they reported a widespread fungal proliferation in those affected by pancreatic adenocarcinoma (Perrins et al. 2007). A possible involvement of *Malassezia spp.* in skin carcinogenesis has not been proven yet, although some authors have pointed out on the overlap between BCC development and *Malassezia* location in dogs and cats. The possible role of *Malassezia* has been hypothesised to be related to its production of the Aryl-hydrocarbon receptor (AhR) ligands. Such substances act on fundamental processes, such as skin immune tolerance induction, UV carcinogenesis modulation, increased vitamin D degradation, metalloproteinase-1 activation, cell proliferation and senescence inhibition. Importantly, AhR ligands interfere with the Hedgehog pathway, that currently

represents the main target of BCC therapies (Gaitanis et al. 2011).

The studies here described, in which animal models have been used, highlight numerous important functions and the role of microbial structural components and products in this context.

Skin tumours resistant- and gnotobiotic- animal models

Another interesting approach consists in the use of skin cancer highly resistant mice, such as atopic dermatitis EPI-/- AD models, which are deficient of the barrier proteins *envoplakin, periplakin and involucrin* (Cipolat et al. 2014). These mice have a defective epidermal barrier, exhibit a reduction in epidermal $\gamma\delta TCR^{+}$ $CD3^{+}$ cells (dendritic epidermal T cells, DETCs) and infiltration of $CD4^{+}$ T cells into the dermis. Interestingly, they are highly resistant to develop benign tumours when treated with DMBA/TPA, the two-stage protocol to induce at first papilloma and then SCC (Cipolat et al. 2014). Comparing the wild-type with the knock-out mice, the authors found that EPI-/- ones showed the same response to DMBA, but a more inflammatory reaction after TPA. They proposed that this intense immune and inflammatory response could help to prevent tumour formation. Given the strong connection between microbiota, inflammation and cancer, scientists further investigated whether the skin microbiota differs between EPI-/- and wild-type mice (Natsuga et al. 2016). Despite their failure to demonstrate the presence of different phyla, they did find three-fold more abundant and deeper penetrated bacteria in EPI-/- mice's skin. However, the bacterial load reduction did not reduce the atopic features of EPI-/- mice or alleviate the T-cell populations abnormalities. The authors then concluded that the increase in skin microbiota richness could likely contribute directly to the observed cancer resistance in this model (Natsuga et al. 2016).

However, the use of skin tumours resistant animal models in in this context mainly remains an unexplored area. To support this lack of information, scientists could take advantage of well-known animals which possess a different tumour development sensitivity, such as the TPA-sensitive (i.e. SENCAR, CD-1) and the TPA-resistant (i.e. C57BL/6J, BALB/c) mice (Hennings et al. 1993); their microbiota profile could be explored, eventually gaining new insights underlying their different susceptibility.

Another model is represented by gnotobiotic animals: germ-free (GF) animals, such as pigs or zebrafishes, that could be colonised with one or more specific microorganisms to assess their role in host physiology (Martín et al. 2016; Melancon et al. 2017; Hara et al. 2018) and better focus the reciprocal cause-effect relationship.

Originally obtained via Cesarean-section, GF animals are now obtained mostly by embryo transfer into GF surrogate females and maintained in an isolator, where it is possible to control air, food, and water, which must be GF too. To study the influence of microbiota in carcinogenesis, the tumour is then induced with one or more selected bacterial strains (Bhatt et al. 2017). Several studies exploring carcinogenesis, especially colorectal (CRC), have been made with this mouse model (Bultman 2014; Bhatt et al. 2017); however, to the best of our knowledge, there are no scientific studies on skin keratinocytes carcinogenesis yet.

Animals for deepening the human microbiota-cancer connections: some limitations

The use of mice in biomedical research is a longstanding practice, due to the extensive similarities in anatomy, physiology and genetics with humans (Abel et al. 2009; Barré-Sinoussi and Montagutelli 2015). Moreover, low costs, high reproduction rates and a short life span make them especially appealing. Since the mouse genome is relatively easy to manipulate, the establishment of genetically modified mice models greatly facilitates functional studies, further enhancing the interest. However, besides the ethical considerations, several pitfalls are present when biomedical research results are translated to humans, and the studies on the microbiota-cancer axis are no exceptions. For instance, skin and gut microbiota of mice and humans present some similarities, but also several differences (Grice et al. 2008; Nguyen et al. 2015). To fill this gap, the researchers succeeded in transplanting the human microbiota in the gnotobiotic mouse model (Goodman et al. 2011; Hugenholtz and de Vos 2018). Scientists further improved this model by establishing standardised microbiota in isobiotic mice, with a stable defined microbiota that can be easily shared by scientists (Macpherson and McCoy 2015).

Unfortunately, such studies limitation is that the crosstalk between microbiota and the host is host-specific; thus, the observations in mouse models cannot be translated in humans (Nguyen et al. 2015).

However, despite these limitations, the advantages they give are still numerous and far surpass other models (Nguyen et al. 2015). Being aware of this, the results and conclusions should be made with caution and complemented with new more representative preclinical models.

3D Reconstructed skin, microbiota and skin carcinogenesis

An interesting alternative can be represented by the three-dimensional (3 D) skin equivalent. Indeed, it consists of a fully differentiated and stratified epidermis plated onto a collagen or fibrin matrix containing fibroblasts, that can realistically represent the structural characteristics of human skin (Catalano et al. 2013; Randall et al. 2018). The 3 D methodology has been already validated, especially for HPV-related studies by several authors (Azzimonti et al. 2009; Borgogna et al. 2012; Squarzanti et al. 2018). They offer several advantages (Rademacher et al. 2018): *i)* the host specificity is preserved since keratinocytes and fibroblasts are of human origin; *ii)* microbes can be applied onto the epithelial surface to study their interaction with an intact barrier, or they can be added into the culture medium to simulate barrier penetration; *iii)* immune cells can be integrated into this model; *iv)* patients' derived cells can be used. However, functional studies that use 3 D models to assess the impact of the microbiota on skin diseases are still rare (Niehues et al. 2018; Rademacher et al. 2018). In fact, most of the publications in this area used 3 D *in vitro* skin models investigating the interactions between single microbial species and their host (Rademacher et al. 2018); thus, there is a strong need to implement 3 D models with human isolated and more complete microbial communities, in order to closely reproduce at best the *in vivo* context. Due to the robust knowledge of skin carcinogenesis, 3 D co-culture skin equivalents will allow exploring also this specific area.

Human skin microbiota and NMSC

NMSC is the most common human malignancy, with an incidence that gradually increases over time (Lomas et al. 2012). Based on its histopathological characteristics, NMSCs can be classified as BCC or SCC, with a BCC:SCC ratio of 4:1 in immunocompetent patients. BCCs rarely metastasise, but they can cause significant morbidity, as it occurs in sun-exposed areas. On the other hand, the risk of metastasis from SCC is relevant, with a 5-year recurrence rate of 8% for high-risk (HR) lesions and a poor long-term prognosis for metastatic patients (Barton et al. 2017). Actinic keratosis (AK) represents another kind of NMSC frequent among people with fair skin and previous strong sun-exposure. Although the potential capability of AK to transform into SCC is universally accepted, the pivotal factor leading to its progression has not yet completely understood. Bowen's disease is a further NMSC type as it consists of an *in-situ* SCC. In any case, NMSCs constitute a significant economic burden for the Health Service (Duarte et al. 2018).

The risk factor most closely related to the onset of NMSC is represented by UV chronic exposure, which explains the increased incidence of these neoplasms in elderly people (Surdu et al. 2013). Accordingly, some changes in microbiota composition (also in the gut) after UVB exposure have been recently demonstrated (Bosman et al. 2019; Yuan et al. 2020). However, a fundamental role is also played by immunologic surveillance, as demonstrated by the higher risk of NMSC and poor prognosis in chronically immunosuppressed patients, such as solid organ transplant recipients (Howard et al. 2018; Zavattaro et al. 2019) or those affected by rheumatic diseases (Diernaes et al. 2019). The ability of the immune system to counteract skin carcinogenesis has been recently elucidated by Strickley et al. They demonstrated that immunity against some commensal HPVs protects from UV-induced skin cancer in mice, and they supposed that a similar process could occur in humans (Strickley et al. 2019). Nevertheless, the role of the cutaneous microbiota both in the direct skin carcinogenesis and in the modulation of the immune system still needs to be clarified (Figure 2). Human microbiota alterations have been recently linked to different cancer types (such as colorectal, pancreatic, head and neck, and lung), several benign and malignant skin disorders (Chen et al. 2017), with more than 15% of all caused by infections (Martel et al. 2012). Similarly, a recent study by Mrázek et al. has reported significant differences in microbiota composition among healthy skin and melanoma in a pig model (Mrázek et al. 2019).

Furthermore, a worsening role in cancer has been suggested for antibiotics. Indeed, they may influence the microbiota composition and may promote a state of chronic inflammation, leading to an altered immune response against cancer. In fact, bacterial dysbiosis induced by repeated antibiotic courses has been correlated to cancer development, mainly in gastro-intestinal and lung neoplasms (Boursi et al. 2015), since they decrease the efficacy of immune checkpoint inhibitors in patients with advanced cancers (Rossi et al. 2019).

Concerning NMSC, a study conducted by Kullander et al. on lesional skin of patients affected by AK, seborrhoeic keratosis (SK) and SCC and on normal skin biopsies of control subjects, allowed to highlight how *S. aureus* can be strongly associated both to AK and SCC (Kullander et al. 2009). Specifically, through a PCR analysis in which the *S. aureus nuc* gene was amplified, it was found that the presence of this bacterium is strongly associated with SCC (29.3% positive samples)

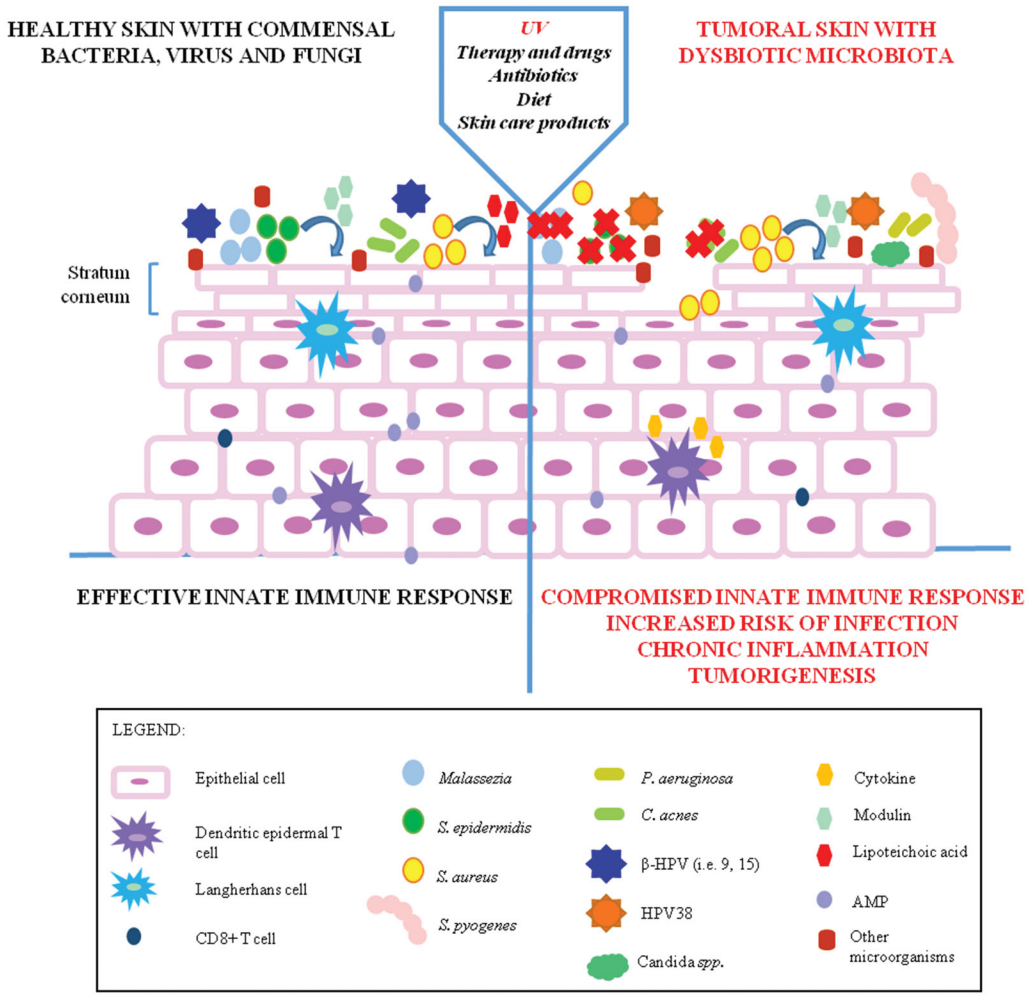

Figure 2. Skin microbiota changes during the pathogenesis of NMSC.

with a probability ratio (odds ratio, OR) SCC/healthy skin of 6.23 (5.7% of positive samples). The study also showed an association of *S. aureus* with AK (12.3%), but not with SK (1.4% positivity).

The same analysis, performed on skin swabs from tumour and healthy skin, gave similar results (OR SCC/healthy skin: 2.67). The limitation of this experimental design was that it doesn't identify whether this association implies a direct influence of *S. aureus* on the carcinogenic process or not (Balkwill and Mantovani 2001). A possible mechanism that explains this open question is given by the ability of this bacterium to induce a state of chronic inflammation (Balkwill and Mantovani 2001) that is mediated by cytokines release (Aggarwal et al. 2006). *S. aureus*, through the virulence peptide called modulin (Nakagawa et al. 2017), induces the release of IL-1α and IL-36α by keratinocytes and the signalling pathway mediated by these cytokines is required for the release of IL-17 by $\gamma\delta$ T cells. This pro-inflammatory cytokine, together with IL-22 and TNF alpha, in turn regulates the cutaneous colonisation of *S. aureus* by triggering a self-maintenance inflammation mechanism. All these molecules have a key role in triggering the tumour progression since they induce both the proliferation and metastatic migration of skin cancer cells.

Based on the evidence that AKs can progress or regress over time (Chen et al. 2013), a longitudinal and transversal survey carried out on a cohort of AK and SCC lesions of immunocompetent subjects prone to the development of NMSC and non-photodamaged controls (Non-Lesional Controls, NLC), was conducted in 2019 by Wood et al. (Wood et al. 2018). The study was carried out on skin swabs taken once a month, for 5 months, from the forearms of subjects who didn't receive antibiotics in the previous 3 months and with at least 3-5 AK lesions and a previous SCC history. Patients' clinical history allowed to establish 5 months as a enough time span for the progression to SCC of some AK lesions. Sequencing of the V3 variable region of the 16S rRNA gene showed that *Propionibacterium* and *Malassezia* are relatively more abundant in healthy

perilesional skin regions and confirmed that *Staphylococcus* is the most represented genus both in AK and in SCC, with a predominance of the *S. aureus* species (Figure 1). Specifically, 11 Operational Taxonomic Units (OTUs) of *S. aureus* were identified in the enrolled subjects; 6 of these were significantly associated with SCCs, with OTUs 50 and 216 present in all the study patients, suggesting their specific involvement in progression from AK to SCC (Wood et al. 2018). This datum has been recently confirmed by the taxonomic analysis made via a 16S rRNA gene-based microbial profiling and sequencing by Madhusudhan et al. (Madhusudhan et al. 2020). They reported *S. aureus* overabundance in SCC and AK compared with BCC samples. Accordingly, since *Malassezia* was decreased in SCCs, it has been supposed that this yeast could be potentially protective against *S. aureus* over-colonisation (Kullander et al. 2009; Madhusudhan et al. 2020).

Moreover, as far as back as Wanke et al. showed how keratinocytes mediated AMPs production is differentially regulated by these commensal and aggressive *Staphylococci*, which synergistically and respectively switch on or not the NF-kB pathway (Wanke et al. 2011). While hBD-1 is normally present in skin, others AMPs, such as hBD-2, hBD-3 and RNase7 are modulated by microorganisms. The most studied AMPs are precisely those induced by *S. aureus*; in fact it stimulates the overexpression of hBD2 by keratinocytes in a site- and age-dependent way (Madhusudhan et al. 2020). This cationic protein, working together with hBD3, cethelicidins, lysozyme and the Esp serine protease, provides a prompt and almost complete clearance from *S. aureus*.

Besides *S. aureus*, other bacteria, such as *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*, induce hBD2 (Dinulos et al. 2003).

As also depicted by Niyonsaba et al. AMPs in turn stimulate keratinocytes to produce proinflammatory cyto- and chemo-kines, that therefore participate in the remarkable trigger of their proliferation and migration, mediated by EGFR, STAT-1 and −3, events that underlie the tumorigenesis process (Niyonsaba et al. 2007).

This was confirmed by Madhusudhan et al. in co-culture studies (Madhusudhan et al. 2020); in fact *S. aureus* overgrowth in SCC has been significantly associated with an high increase of hBD-2 and tumour cell proliferation. These events suggest that *S. aureus* might promote tumour cell growth by modulating the specific expression of this AMP, thus emphasising their intercorrelation.

Overall these studies and those of Brandwein et al. clearly underline how the insights on the role of cutaneous AMPs against specific microbial species are opening the possibility to understand how host-microbiota dynamics within the skin compartments are orchestrated and how an altered AMP milieu correlates with selective skin dysbiosis (Brandwein et al. 2017).

If, as emerged, strains of *S. aureus* contribute to the genesis of the cutaneous carcinogenic process also through the promotion of a chronic inflammatory state, they could serve as markers of risk for the development of SCC; therefore, lesions with persistent infection could be ideal candidates for monitoring and interventional treatments. It could also be assumed that the high incidence of SCC observed in immunosuppressed patients could be related to the inability of the immune system to control specific SCC microbial triggers (Figure 2).

Another cutaneous disease characterised by chronic inflammation is Hidradenitis Suppurativa (HS), a recurrent and chronic disease involving the apocrine glands of the axillary, perineal, perianal and genital regions. It is characterised by a frequent relapse of swollen and painful abscess lesions leading to scarring and fistulae formation. HS has been linked to a 4.6-fold increased risk of NMSC development, mainly represented by SCC, which usually arise many years after the disease onset (Kohorst et al. 2015). Once again, the presence of bacteria such as *S. aureus, S. pyogenes, and P. aeruginosa* that are responsible for a chronic inflammatory state and suppurative recurrences, has been argued to be causative for SCC development (Samaras et al. 2010).

Hence, in summary, once the microbiota's balance has been disturbed, it promotes chronic inflammation through Th17 activation and T-reg stimulation, thus promoting carcinogenesis. Therefore, a direct crosstalk between the skin-microbiota and the immune system does exist (Iannitti and Palmieri 2010; Yu et al. 2015).

Iida et al. demonstrated that the microbiota can also influence the tumour microenvironment. Their experimental model evaluated the response of mice, either germ-free or antibiotic-treated, transplanted with tumour lines (melanoma, colon carcinoma, and lymphoma) and subsequently submitted to immunotherapy and chemotherapy. The result was consistent with a better outcome of therapy in the presence of a healthy host-microbiota balance, with a decrease in the activation of pro-inflammatory genes and cytokines, as well in Reactive Oxygen Species (ROS). Based on such results, the authors concluded that an intact commensal microbiota is required for optimal response to cancer therapy (Iida et al. 2013). Accordingly, Sivan et al. have investigated the efficacy of anti-PD-L1

treatment in melanoma mice model, and they found that the animals fed with *Bifidobacterium* spp. showed a better response, thus showing an improved capability to control tumour through the immune system (Sivan et al. 2015). Similarly, it has been demonstrated that oral supplementation with *Akkermansia muciniphila* in humans was able to ameliorate the outcome in patients treated with anti-PD-1 immunotherapy for melanoma, renal carcinoma, and lung cancer (Routy et al. 2018).

Also, the effect of other potential carcinogenic factors (i.e. UV radiation) may surely contribute to further facilitate the onset of cancer (Yu et al. 2015).

Among viruses, both HPV and Epstein-Barr (EBV) interfere into epithelial cancer progression and metastatization processes (Chen et al. 2016; Cyprian et al. 2018).

Regarding HPV infection, an *in situ* RNA and DNA hybridisation analysis evidenced a significant reduction of the viral activity and load of 25 commensal β-HPVs in cancer biopsies of NMSC affected patients respect to the adjacent healthy skin of the same subjects, suggesting a very high immune selection against HPV-infected tumoral keratinocytes. In fact, following the protection by the T cell immunity, commensal β-HPVs can protect immunocompetent hosts from skin cancer development. Conversely, when the immunity is lost or compromised together with HPV oncogenicity itself, the skin cancer risk increases by100-fold in immunocompromised patients (Strickley et al. 2019).

Moreover, the recent article of Tommasino strongly states that β-HPVs, mainly HPV38 genotype in transplanted patients, maintain the proliferative status of UV-damaged keratinocytes, thus enhancing the great attitude of these immunodeficient people towards tumorigenesis (Tommasino 2019). This supports once more the role of UV rays as NMSC drivers with beta-HPVs as partners in favouring the UV-induced DNA mutations accumulation.

EBV is a DNA virus belonging to the Human Herpes Virus (HSV) family, mainly known for its relationship with Burkitt's lymphoma and post-transplantation lymphoproliferative diseases (PTLD). Concerning epithelial neoplasms, it has been associated with gastric cancer and the quite rare nasopharyngeal carcinoma (NPC), which is frequently observed among subjects from Southern China, Indonesia and North Africa. In fact, EBV downregulates, through the latent membrane oncoprotein-1 (LMP-1) and E-cadherin expression, the activation of signalling pathways such as those of PI3K/Akt and MAPK, while upregulates PD-L1 in NPC-derived cells via the STAT3, AP-1 and NF-KB signalling (Fang et al. 2014; Cyprian et al. 2018; Outh-Gauer et al. 2018). Moreover, 44 mature EBV miRNAs have been identified as related to epithelial-mesenchymal transition (EMT) and cancer progression (Skalsky and Cullen 2015).

Data concerning possible involvement of the mycobiota in NMSC development in humans are currently lacking. On the other hand, the increased risk of cutaneous infection by opportunistic fungi, as well as yeast overgrowth in the course of immunosuppression is well known. Indeed, chemotherapy agents are responsible for epithelia damage, either in the gut or in the skin, and this could allow the penetration of fungi and yeasts (Teoh and Pavelka 2016). Similarly, radiotherapy depicts an important risk factor for skin infections, and, among fungi, the most encountered pathogens are represented by *Candida* species (Altoparlak et al. 2011; Moqbil and Kurnatowski 2012).

In the nation-wide population-based study by Chung et al. the presence of *Candida* infection resulted associated to a higher risk of cancer, mainly haematologic malignancies, of the head and neck, pancreas, skin and thyroid. Although the Authors underlined the role of the yeast in promoting cancer as a consequence of their proinflammatory impact in the tumour microenvironment, they also speculated that patients suffering from candidiasis are supposed to seek for a dermatological visit more frequently and, consequently, skin cancer should be easily diagnosed (Chung et al. 2017).

Moreover, the response of *Malassezia* spp. to Photodynamic Therapy (PDT) has been reported in patients affected by NMSCs. PDT induced a decrease in *Malassezia* in the peritumoral skin, in accordance with the therapeutic use of PDT in certain fungal skin infections (Calzavara-Pinton et al. 2012; Gilaberte et al. 2015).

How to influence the microbiota?

As stressed, the skin and gut microbiota play a very important role in conditioning the susceptibility and the development of numerous diseases, either cutaneous or affecting other organs. Since healthy microbiota may have a protective effect on numerous pathological conditions, the following questions arise: "How to preserve our microbiota?" and, in the case of dysbiosis and/or microbiota alterations," How to restore it?" Once again, the answer is represented by microorganisms, and, in detail, mainly by bacteria.

Since many years, specific bacterial strains have been used to counteract different diseases, ranging from diarrhoea to some cancer types. Indeed, the Bacillus Calmette-Guérin vaccine (BCG), represented by a specific *Mycobacterium bovis* strain, has been administered

for a long time against superficial bladder cancer (Schellhammer et al. 1986). The rationale for its use was its capability to modulate inflammation and maintain a correct immune system function (Von Hertzen et al. 2011; Sherwani et al. 2018). The cell wall skeleton of BCG, in fact, induces the CD4+ T cell subset and stimulates the differentiation from the naïve to memory phenotype, giving promising clinical effects in the adjuvant immunotherapy for cancer (Nishida et al. 2019). BCG, administered alone or in combination with dacarbazine and/or autologous tumour cell vaccine, improves the survival of metastatic melanoma affected patients (Lotem et al. 2002; Triozzi et al. 2011; Sloot et al. 2016; MMAIT-IV Clinical Trial Group 2017).

In more recent years, the terms "prebiotics" and "probiotics" have been coined to indicate exogenous substances able to interfere positively with the human microbiota, and namely keep it healthy and/or restore it. In detail, "prebiotics" include a class of non-digestible food ingredients that can selectively stimulate the growth and/or activity of beneficial microorganisms, such as bacteria and fungi. On the contrary, "probiotics" are live bacteria and yeasts that exert health benefits to the host, mainly by restoring the gut microbiota (Krutmann 2012). The most common beneficial probiotic strains belong to the *Lactobacilli* and *Bifidobacteria* genera.

Both pre- and pro-biotics selectively stimulate the growth of microorganisms in the large bowel, thus leading to different beneficial effects. Their simultaneous use is referred as "synbiotics" (Musthaq et al. 2018).

The administration of oral probiotics has demonstrated to be safe and beneficial against numerous conditions. Indeed, they are currently used in the management of digestive symptoms and diseases (i.e. diarrhoea, inflammatory bowel disease), but also in atopic dermatitis, acne, psoriasis, bacterial vaginosis, genital candidiasis, reduction of serum cholesterol level and so on (Russell et al. 2011; Kumar et al. 2014).

The main mechanisms through which probiotics exert their benefits onto the skin reside in their immunomodulatory capabilities (Wieërs et al. 2019). When administered orally, they exert their action at the gut level, thus leading to influence immune responses in other tissues (i.e. the skin). Furthermore, they can also act as antioxidants and, when applied topically, they can provide a protective barrier towards exogenous factors and compete with other cutaneous microorganisms in order to restore the healthy resident microbiota (Rahmati Roudsari et al. 2015; Maguire and Maguire 2017; Knackstedt et al. 2020).

The role of probiotics in NMSC

To date, despite many papers have supported the use of probiotics in several inflammatory cutaneous diseases (Szántó et al. 2019; Yu et al. 2020), only a few have investigated their possible application in skin cancer, either for chemoprevention or therapy purposes.

Some of these have evaluated the possibility of the oral administration of *Lactobacillus* strains in order to evaluate their photoprotective effect. As mentioned, Weill et al. have studied the effect of LTA from *L. rhamnosus* GG in hairless mice that were UV-irradiated daily for 20 consecutive days. A tumour development delay, mediated by a transitory increase in cytotoxic and helper T-cells in the draining lymph nodes, was observed (Weill et al. 2013). More recently, LTA from the same strain was discovered to be able to overcome the immunosuppressive effect of UVB and impair SCC growth once the irradiation is suspended (Friedrich et al. 2019). The UV effect on bacteria has also been previously studied by Wang et al. that measured the porphyrin level produced by *P. acnes* after inoculation in mice's ears. They observed that bacteria are responsive to UVB and γ-rays with a reduction in porphyrin production, and a consequent variable effect on protein oxidation-deoxidation, depending on the radiation type. Since porphyrin concentration in irradiated *P. acnes* may decrease before the skin damage is detected, the authors concluded that it could act as a biomarker and as a clue for radiation risk (Wang et al. 2012).

As previously mentioned, Nakatsuji et al. administered a specific *S. epidermidis* strain, either topically or intravenously in mice, and showed its antiproliferative effect mediated by 6-HAP. This molecule was produced by a common commensal strain of *S. epidermidis* able to suppress the tumour growth *in vivo* by more than 60% when given intravenously. Furthermore, UV-irradiated SKH-1 hairless mice topically treated failed to produce squamous tumours (Nakatsuji et al. 2018).

In a further randomised, double-blind placebo-controlled clinical trial on probiotics, *Lactobacillus johnsonii* NCC 533 (Lal) was administered to healthy human volunteers before UV-exposure and, subsequently, the inflammatory cells were evaluated through skin biopsy analysis. In treated patients, CD36+ monocytic cells disappeared (their differentiation in Langerhans cell precursors is supposed) and recovery of basal CD1a + cell staining was also detected. Such results highlighted a protective effect of Lal against immunosuppression due to UVB-irradiation (Peguet-Navarro et al. 2008; Guéniche et al. 2009). In a similar way, the oral administration of *L. johnsonnii* plus carotenoids prior to sun-

exposure in healthy women, showed to prevent the UV-induced Langerhans cells decrease and help to restore the immune system homeostasis. Furthermore, the Minimal Erythema Dose (MED) was increased by 19% in patients receiving oral probiotics (Bouilly-Gauthier et al. 2010).

Finally, in the study by Lee et al. the administration of the Maesil fruit extracts fermented with probiotics (*Saccharomyces cerevisiae* from Korea Collection for Type Cultures (KCTC) 7928, *Bacillus subtilis* from KCTC 1666, and *Lactobacillus acidophilus* from KCTC 3155) in different concentrations (1% and 2%) resulted to be associated with papilloma's reduction in skin carcinogenesis-induced mice. This reduction was statistically significant and more represented in mice fed with 2% probiotics fermented Maesil. The authors concluded that this mix might have an important role in skin carcinogenesis control (Lee et al. 2013). Nevertheless, in our opinion, the effect of probiotics in such experimental setting should be carefully discussed.

Accordingly, since the probiotics' market is not harmoniously regulated among countries and since the differences in their efficacy and safety mainly depend on the diversity of the microorganisms sold, their off-trial use in patients with cancer has been discouraged (McQuade et al. 2019). Furthermore, in Europe at least, cosmetics by regulation can't include more than 1000 live germs per gram, thus impeding the use of loved probiotics in this category as well. Therefore, the topical application should be carefully evaluated in order to establish their therapeutic role against skin cancer and hopefully favour their employment in this context (Lee et al. 2019).

Conclusion

Overall this review highlights some important key points on skin microbiota community research: cutaneous commensal microorganisms adapt and use host's epithelial surface nutrients, produce antimicrobial peptides, orchestrate the innate and adaptive epithelial immune system to inhibit pathogens colonisation, and maintain a healthy epithelial status possibly also when exogenous and endogenous perturbations occur. Moreover, thanks to NGS and *in vitro* study models, it will be likely possible to identify specific OTUs that could be ascribed as NMSC progression signatures and as instruments for better a management of this skin malignancy.

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