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Commentary

Non-Melanoma Skin Cancer and the Cutaneous Microbiota Network

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ABSTRACT

Commentary on the emerging role of the human microbiota in epithelial carcinogenesis

Keywords: Microbiota; Non-Melanoma Skin Cancer (NMSC); Ultraviolet (UV) rays; Vitamin D; Human Papillomavirus (HPV)

COMMENTARY

Non-melanoma skin cancer (NMSC) is the most common tumor in Caucasians; its incidence, certainly underestimated, increases annually by about 10%, with 2-3 million new diagnoses/year worldwide. Therefore, since NMSC constitutes an important public health problem, the factors involved in its development and progression are constantly under research, in order to look for new prevention and treatment strategies. Ultraviolet (UV) ray overexposure, beta Human Papillomavirus (HPV) infection, genetic predisposition, vitamin D deficiency and immunosuppression are the most recognized [1].

In recent years, the host's microbiota is gaining an increasingly prominent role. What it is now well clear is that its dysregulation can also promote, among the others, diverse immune and cutaneous disorders [2,3]. Only now, however, the first steps are moving towards knowledge of its involvement in the genesis and progression of NMSC [4].

The findings of the *in vivo*, *ex vivo* and *in vitro* studies are fundamental, but they are difficult to integrate for a practical and profitable employment.

How can we use the information we are acquiring? And therefore, above all, how can we preserve the skin microbiota balance? How not to go around and hit the target instead?

We are aware that all the microbial species of the human niches are interconnected, but many pieces of the puzzle still lack. What we know is that within each healthy skin area there is a plethora of communities composed by commensals, symbionts and pathogens, well balanced and in a correct numerical proportion. In such a context, microbial quorum sensing orchestrates their reciprocal interaction and that one with human eukaryotic cells.

Skin microbiota balance preserving is a life's task; its loss could happen at some point. In fact, when one or more external/internal stimuli arrive, a "coup d'état", or rather a "low blow to health", occurs. In such conditions, many microbial representatives are lost. In fact, pathogens, thanks to their ability to better resist these events by virtue of their protective virulence factors, begin to prevail in number to the detriment of commensals and symbionts. This determines the loss of the network and the modification of the local environmental conditions, since some final microbial effectors do not receive the correct information. This is the true transposition of what also happens in the human communities. It is not a philosophical thought, even if it comes very close.

In normal skin, cutaneous microbiota is mainly constituted by 19 bacterial phyla; among them, Actinobacteria, Corynebacteria and Propionibacteria are the most represented [5]. Although skin-related viruses cannot be easily cultured in vitro and only some consensus sequences allow their detection by molecular methods, numerous evidences suggest that skin and hair follicles also host α-, β- and γ-HPVs [6].

Perturbations due to genetic predisposition, organ transplant, aging and the misuse of topical and systemic corticosteroids determine a general reduction of the microbial diversity/quantity and of the host's immune defenses. To aggravate this picture, over-exposure to UV sun rays can destroy bacteria and double stranded DNA viruses; hair removal habit contributes to empty hair bulbs, which are reservoirs of a lot of commensals (HPV and Propionibacteria in primis); moreover, the misuse of aggressive surfactants based on cationic polymers and cutaneous anionic surfactants may behave like real weapons of destruction. Despite the capability of skin

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creams in restoring hydrolipidic film, they often contain alcohol and/or preservatives that negatively select good commensals and favor more aggressive microorganisms.

In several disbiotic patterns, *Staphylococcus aureus* and *Streptococcus pyogenes* (phylum Firmicutes), *Pseudomonas aeruginosa* (phylum Proteobacteria) and the β-HPV-5, -8, -38 genotypes often become dominant. The activated pathogenic mold form of Candida spp may also increase, promoted by cortisone treatments, sugar-based diets and immunodepression.

Moreover, during skin carcinogenesis an impairment of sebum production occurs, thus reducing both *Propionibacterium acnes* and *Malassezia globosa* colonization [7,8].

Based on the current knowledge, pathogens therefore contribute to the proliferation and metastatic migration of skin cancer cells only in the presence of an uncontrolled chronic inflammatory response [9], in turn mediated by bacteria moving deeper in the damaged epithelial barrier. Indeed, it appears that *S. aureus* does not infect the skin of immunocompetent individuals until it is damaged; the ulcerative nature of the SCC and the modified metabolism of neoplastic cells favor colonization by this pathogen [9].

We can imagine our skin is like a culture medium. If it is rich of nutrients, there will be a future for all, while, if poor, only the less metabolically demanding, in most cases the most virulent ones, will survive.

Bacteria can be the enemy, but also the cure, since the ones considered as "good" and "bad" coexist in times of peace. It's just a question of balance to be maintained. On one hand, while the presence of bacteria responsible for inflammation and DNA damage increase has been implicated in squamous cell carcinoma (SCC) development [10-13], on the other side this phenomenon seems to be countered by the probiotic *Lactobacillus johnsonii* in UV-stimulated human skin [14] and by the lipoteichoic acid from *Lacticaseibacillus rhamnosus* GG, at least in chronically photo-exposed mice models [15]. The same action has also been suggested for *Bifidobacterium longum* [16].

At the end what can we say? The resident microorganisms possess all the characteristics to exert beneficial and rescue functions, protecting us from pathogenic species colonization and processing skin proteins, free fatty acids, and sebum. Microbiota can and will save the world, if the world does not make a clean sweep before.

CONFLICTS OF FINANCIAL INTEREST

The authors declare no conflicts of interest.

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