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A SHORT REVIEW ABOUT CUTANEOUS MICROBIOME

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Abstract

Since 2000, when Nobel prize winner, Joshua Lederberg defined the term "cutaneous microbiome" much attention has been drawn to clarifying the role of microorganisms in maintaining homeostasis. This article aims to outline the several implications of the cutaneous microbiome related to dermatology practice.

The skin microbiome represents the community of commensal, symbiotic, and pathogenic microorganisms that colonizes the skin. Prior research on healthy volunteers indicate the presence of four major bacterial species: Actinobacteria, Firmicutes, Proteobacteria and Bacterioides.

Previous studies have proved that the skin microbiome influences the innate and the adaptive immune responses. This theory may be the key in establishing the etiopathogenesis of chronic inflammatory diseases, such as atopic dermatitis, psoriasis, acne vulgaris and rosacea. The diversity of microorganisms harbored on the healthy skin surface is different from one body area to another, according to pH, temperature, age, hygiene. Any imbalance in the physiological features will have consequences on the commensal flora. A decrease of the commensal microorganisms will lead to higher levels of pathogens, exposing the skin barrier, leading to infection and chronic inflammation as seen in atopic dermatitis.

New studies are focusing on how treatments affect the cutaneous microbiome. Different kinds of topical treatments can interfere with the normal flora, which can cause soreness and slow healing. In psoriasis, it has been suggested that the microbial diversity is limited by the production of antimicrobial peptides, which is relieved by therapy.

Future research in this field can highlight new therapies in dermatology, provide answers concerning etiopathogeneses and better understanding of cutaneous inflammatory diseases.

Keywords: cutaneous microbiome, review, dermatology, chronic inflammatory diseases

1. INTRODUCTION

The role of cutaneous microbiome became a subject of research after the term was defined by Joshua Lederberg. It seems that the organisms that harbor our skin protect us against pathogens, interfere with the immune response, generating new hypothesis on the etiopathogenesis of chronic inflammatory diseases such as atopic dermatitis, psoriasis, acne vulgaris and rosacea. Many studies focused on presenting the types of bacteria, viruses and fungi that are found on the surface of the normal as well as lesional skin.

The skin microbiome represents the community of commensal, symbiotic, and pathogenic microorganisms that colonize the human skin. It is a complex ecosystem in which bacteria, archaea, fungi and viruses are essential to skin physiology and immunity.

Diversity of the skin microbiome

Commensal microorganisms are usually found on the surface of the skin and are considered to be harmless. Transient microorganisms arise due to environmental instabilities and may persist hours or days [1,2]. Currently there are about 200 microorganisms known as pathogenic [3].

Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes represent the majority of phyla [4]. The predominant genus are *Propionibacterium* (32%), *Streptococcus* (17%), *Staphylococcus* (8%), *Corynebacterium* (4%) and *Lactobacillus* (3%).

There is also a great diversity of fungi, the main genuses are *Malassezia*, *Penicillium* and *Aspergillus* [5].

Skin physiology plays a vital role on the development of bacteria.

The anatomical and structural differences influence the types of microorganisms that are found on the skin, hair follicles, sebaceous glands and sweat glands. The eccrine sweat glands have roles in thermoregulation, maintaining an acid pH, and the secretion of antimicrobial peptides (cathelicidins and B-defensins). The microbial colonization is regulated by the density of eccrine sweat glands [6,7].

Propionibacterium acnes survive in anoxic environment rich in lipids, such as areas with sebaceous glands connected to the hair follicle [8]. *Staphylococcus* species and *Corynebacterium* are found most commonly in moist areas, whereas dryness generates the greatest microbial diversity [9].

The skin microbiome varies from one individual to another depending on age, hygiene, use of antibiotics, temperature.

Research techniques

Initially, the optical microscope was used to highlight the first organisms. In 1980, some bacteria were cultured in the laboratory. However, 20% to 60% of the human-associated microbiome, depending on the body site, is uncultivable [10]. Therefore, the germs that could not be grown were explored using the DNA-sequencing techniques. In 2007, the National Institute of Health launched the Human Microbiome Project, using metagenomics to describe the cutaneous microbes depending on body sites. At the end of the project, in 2012, the consensus was that different communities of microbes are dependent upon the humidity, pH, quantity of sebum and exposure to the external environment [11]

Maintaining the skin barrier

The skin is an effective barrier between the environment and the body, shielding against physical, biological and chemical stress. The epidermis, a dynamic tissue, in which cells are constantly renewing, consists of four layers according to the progressive keratinization: stratum corneum, stratum granulosum, stratum spinosum, and stratum basal. Two of the main elements forming the barrier are the stratum corneum and the epidermal tight junctions [19]. It protects continuously against potentially pathogenic organisms by secreting antimicrobial peptides. The production of these peptides can be controlled by the bacteria existing in the cutaneous microbiome. *S. epidermidis* and *Propionibacterium* can recruit neutrophils which can interfere with such pathogens as *S. aureus* by inhibiting its adherence [12].

Inflammation and skin microbiome

Interferon-γ and interleukin-17 are proinflammatory cytokines. They play multiple roles in chronic inflammatory disorders. Previous studies suggest that the germ-free mice show decreased levels of interferon-γ and interleukin-17A, but express increased regulatory T (Treg) cells compared with the specific pathogen-free mice. Inoculating *Staphylococcus* to the germ-free mice can restore the production of IL-17A by T lymphocytes in the skin. In addition, in the filaggrin deficient mice, an increased expression of IL-17A was observed, dermal eosinophils and neutrophils were observed [13,14].

Skin Immunity and Microbiome

The innate immune system is considered the first line in the defense against pathogens. It is considered a sentinel in detecting invasions by microorganisms. The release of antimicrobial peptides,

chemokines and cytokines, the keratinocytes, Langerhans cells, mast cells and macrophages offers an early warning system [15].

The adaptive immune system represented by the humoral response, provides a broad response to pathogens. Recent studies have demonstrated that *S epidermidis* activates specific immune cell populations. For example, *S. epidermidis* induces the activation of the *S. epidermidis*-specific IL-17CD8 T cells which is shown to protect against infections. The keratinocytes will produce AMPs. This phenomenon is called heterologous protection [16]. These cells are involved in wound healing as well.

The research community has extensively explored the reason why streptococcal pharyngitis exacerbates guttate psoriasis. Studies have suggested that the M proteins, found on Group A, C, and G β-haemolytic streptococci may act as keratin determinants, activating T-cells [17,18].

Roles of cutaneous microbiome in atopic dermatitis

Atopic dermatitis is a chronic inflammatory disease, arising as the result of multiple factors: genetic susceptibility induces a damaged skin barrier and irregularities of the immune responses [19]. In the acute stage, atopic dermatitis is associated with increased production of T-helper 2 cytokines interleukin 4 and interleukin 13, which stimulate the production of Immunoglobin E [19]. A percent of 90% of patients with atopic dermatitis are colonized with *S. aureus* [5]. *S. aureus* superantigens play an important role in activation and multiplication of lymphocytes T helper 2 cells [20]. Decreasing chronic inflammation by suppressing the roles of T helper 2 cells is obtained by interleukin 10. *S. epidermidis* can secrete different proteoglycans which upregulate interleukin 10 secretion by antigen presenting cells [21].

Does treatment affect the cutaneous microbiome?

In psoriasis, studies have shown that before treatment with ustekinumab, the differences in cutaneous flora between lesional and non lesional skin were minor. During ustekinumab treatment, the heterogeneity increased more in lesional than in nonlesional skin. It has been suggested that ustekinumab inhibits the expression of antimicrobial peptides, excluding the factor that prevents flora variations [22].

In the case of atopic dermatitis, studies have suggested a decrease in the normal flora, which can correlate with acute stages of the disease. A study has emphasized that after anti-inflammatory and emollients treatments normal genus like *Streptococcus*, *Propionibacterium* and *Corynebacterium* increased in the skin [23-30]. We should be aware of the cutaneous side effects of topical steroids even on skin normal microbioma [31-33]. Summarizing this data, it becomes evident that the normal skin barrier implies a normal cutaneous microbiome.

Furthermore, applying ointments containing *Vitreoscilla filiformis*, a non-photosynthetic bacterium, aided restoring the skin flora [34].

CONCLUSIONS

The cutaneous microbiome can offer key answers in many fields of interest. Understanding how microorganisms contribute to homeostasis, and how an imbalance in the normal flora could lead to treatment failure or exacerbations of the disease, could imply a major outbreak in the clinical management of dermatological diseases.

Future research can highlight new therapies in dermatology, provide answers concerning etiopathogeneses and a better understanding of the cutaneous inflammatory diseases.

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