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SKIN MICROBIOTA AND ITS INFLUENCE UPON THE DEVELOPMENT OF ATOPIC DERMATITIS

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Abstract. Human skin is the largest organ that performs many functions. Skin condition significantly affects the quality of human life. Modern allergology and dermatology have made significant progress in diagnosing and treating skin diseases. Skin is a habitat for various populations of microorganisms: viruses, bacteria, fungi. Changes in the microbial composition of the skin affect its functional component. Skin microbiota can change under the influence of various factors: gender, age, used care products. Skin diseases can occur due to the influence of exogenous factors (physical, mechanical, chemical, biological and infectious). Cosmetics have the most adverse effect on skin microbiota in the modern world. Cosmetics affect the structure of the microorganisms themselves on the surface of the dermis. In addition to exogenous factors, endogenous factors that can change the condition of the skin also participate in changing the microbiological composition of the skin: blood diseases, immunodeficiency states, stress, genetic factors and intercurrent diseases. In modern studies, more and more attention is paid to the study of the role of human skin microbiota in the development of a number of dermatoses: atopic dermatitis. In atopic dermatitis, the number of *S.aureus* and *S.epidermidis* increases. Patients with AD have weakened skin immunity due to the activity of *S.aureus*. The review also presents modern data on the composition of healthy skin microbiota, and demonstrates the mechanisms of its influence on the course of various diseases. The role of microbiota imbalance in the development of chronic skin diseases, including atopic dermatitis, is analyzed.

Keywords: microbiota, skin, atopic dermatitis



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МИКРОБИОТА КОЖНЫХ ПОКРОВОВ ЧЕЛОВЕКА И ЕЕ ВЛИЯНИЕ НА ТЕЧЕНИЕ АТОПИЧЕСКОГО ДЕРМАТИТА

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Резюме. Кожа человека представляет собой самый обширный орган, который выполняет множество функций. Состояние кожи существенно влияет на качество жизни человека. Современная аллергология и дерматология достигли значимого развития в диагностике и лечении заболеваний кожи. Кожа является средой обитания для разнообразных популяций микроорганизмов: вирусов, бактерий, грибов. Изменение микробного состава кожи влияет на ее функциональную составляющую. Микробиота кожи может изменяться при воздействии различных факторов: пол, возраст, применяемые средства ухода. Болезни кожи могут возникать вследствие воздействия экзогенных факторов (физических, механических, химических, биологических и инфекционных). Самое неблагоприятное воздействие в современном мире на микробиоту кожи оказывают косметические препараты. Косметические средства влияют на структуру самих микроорганизмов на поверхности дермы. Кроме экзогенных факторов, в изменении микробиологического состава кожи участвуют и эндогенные факторы, способные изменить состояние кожного покрова: болезни крови, иммунодефицитные состояния, стрессы, генетические факторы и интеркуррентные заболевания. В современных исследованиях все больше внимания уделяется изучению роли микробиоты кожи человека в развитии дерматозов, например атопического дерматита. При атопическом дерматите повышается количество *S. aureus* и *S. epidermidis*. Больные с атопическим дерматитом имеют ослабленный кожный иммунитет, обусловленный жизнедеятельностью *S. aureus*. В обзоре также представлены современные данные о составе здоровой микробиоты кожи, продемонстрированы механизмы его влияния на течение различных заболеваний. Проанализирована роль нарушения состава микробиоты в развитии хронических заболеваний кожи, включая атопический дерматит.

Ключевые слова: микробиота, кожа, атопический дерматит

INTRODUCTION

The skin is the largest organ in the human body and the most vulnerable part of our body. The condition of the skin significantly affects a person's quality of life, in particular their success in their professional activities. Thanks to technological advances and accumulated experience, modern dermatology and allergology have made significant progress in the treatment and diagnosis of various pathological skin diseases [1, 2].

Microbiome is a collection of various groups of microorganisms that colonize human skin. The skin has important protective and immune functions. Changes in the microbial composition and structure also change the functional component, so it is important to know the structure of the skin in normal and pathological conditions for early diagnosis, prevention of various diseases, and rational and personalized, individually tailored treatment [3, 4].

Various factors affect the skin microbiota, such as age, gender, climatic characteristics, profession, and the cosmetics and hygiene products used [5, 6].

In our review, we set out to systematize knowledge about the microbiome composition of human skin and its variability under the influence of external and internal environmental factors, in the presence of a concomitant disease, atopic dermatitis, as well as the mutual influence of changes in the skin microbiome and the development of atopic dermatitis.

THE MICROBIOME OF HUMAN SKIN AND ITS INFLUENCE ON THE COURSE OF ATOPIC DERMATITIS

Human skin is the largest and most complex organ, which performs a variety of functions. The skin barrier is crucial for survival, preventing moisture loss and the penetration of infectious or toxic substances. The skin is a system closely linked to the internal environment of the body and the external environment. It is a complex habitat for diverse populations of microbiota [7, 8]. Considering the normal condition of the skin, ideal for the existence of non-pathogenic or conditionally pathogenic microflora, it is necessary to note several physical and chemical indicators such as pH, moisture, frequent trauma, temperature, and the amount of fat inclusions. Normally, the skin has an acidic reaction, and the stability of this indicator is very important, since a shift in pH toward alkalinity creates favorable conditions for the reproduction of pathogenic microorganisms. Moisture plays an important role in the species diversity of the microbiome. A significant increase in moisture will contribute to the colonization of the fungal component of pathogenic microflora. When humidity decreases, cracks appear on the skin and, as a result, the protective function of the skin decreases.

At the same time, the microflora (conditionally pathogenic) does not radically change its composition, but can infect the area of "cracked" skin. The temperature of the skin is a prerequisite for maintaining the normal composition of the microflora. Both an increase and a decrease in temperature will affect the number of non-pathogenic representatives. Changes in the lipid index are important when considering human skin during adolescence. This index is of great importance in the formation of adolescent acne [9, 10].

The composition of the skin microbiome is diverse and includes bacteria, viruses, fungi, and parasites. To date, the composition of the bacterial skin microbiome has been studied most extensively. Bacterial cells significantly outnumber human cells: it is estimated that, on average, a human body weighing 70 kg contains 3.8×10^{13} bacterial cells [11]. The skin is the second organ (after the gastrointestinal tract) in terms of the number of microorganisms. The density of the skin microbiome is 1 million bacteria per 1 cm² of skin [11, 12].

To date, 19 taxonomic phyla of microorganisms have been identified on the skin. Among them, the predominant microorganisms are *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Micrococcus* spp., *Sarcina* spp., *Propionibacterium* spp., representatives of *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Corynebacterium*. Transient microorganisms that temporarily persist on the skin surface include *Peptococcus* spp., *Bacillus subtilis*, *Escherichia coli*, *Enterobacter* spp., *Acinetobacter* spp., *Lactobacillus* spp., and *Candida albicans*. Conditionally pathogenic microorganisms that are constantly present on the skin surface include *Staphylococcus aureus* and *Staphylococcus saprophyticus*. The fungal component is most often represented by the genera *Malassezia* and *Candida*. Viruses may be transiently present on the skin. All these representatives exist in symbiosis with each other, forming a single ecosystem that has a commensal relationship with its host, the human [13, 14].

Different areas of the skin have their own set of microorganisms. Lipophilic microorganisms, such as *Propionibacterium* and *Staphylococcus aureus*, are more prevalent in areas of the skin where sebaceous gland production is increased. These areas include the nasal wings, chin, forehead, and skin on the back of the head. In addition to bacteria, the sebaceous glands contain large numbers of *Malassezia fungi*, lipophilic yeasts, and *Demodex mites*. Areas of the dermis with high moisture content are dominated by *Corynebacterium*, which is responsible for the strong odor in the armpits. *Staphylococci* use urea from the secretions of the hollows as a source of nitrogen. The areas of the skin with the highest moisture content are the feet, navel area, armpits, groin folds, and popliteal fossae. On dry skin



areas, such as the buttocks and forearms, *Bacteroidetes* and *Proteobacteria* are found. A distinctive feature of the scalp is the predominance of *Malassezia fungi* in the microflora [15–17].

One of the complex issues is the change in normal microflora depending on age. Microbiota colonizes the skin from the first days of life. At the same time, the type of delivery has the greatest impact on the formation of skin microbiota. In the case of vaginal delivery, the microflora of the fetus's skin will be similar to the mother's vaginal microflora. In this case, *Lactobacillus*, *Sneathia*, *Corynebacterium*, and *Propionibacterium* will predominate on the baby's skin. In the case of a cesarean section, the microbiota of the newborn will be identical to the microbiota of the mother's abdominal skin, with a predominance of *Corynebacterium* and *Staphylococcus*. There may be differences in the composition of the skin microbiota between a child who has completed a full intrauterine cycle and a newborn who has been gestated for less than 37 weeks. The skin of premature babies has a greater number of bacteria such as *Staphylococcus*, *Corynebacterium*, and *Flavobacterium* [18, 19].

During puberty, the composition of the skin microflora changes [20]. At this age, *Bacteroidetes* and *Cutibacterium* are most commonly found on the skin. The number of pathogenic *Propionibacterium acnes* on the skin increases, which is observed in the development of acne. In addition, sebum production increases during adolescence, leading to an increase in the number of lipophilic bacteria, such as *Propionibacterium* and *Staphylococcus aureus* [21–23].

Healthy adult skin can include all of the above representatives. Statistically, *Actinobacteria* predominates on healthy adult skin — 40%, *Firmicutes* — 36.6%, *Proteobacteria* — 20%, and to a lesser extent *Bacteroidetes* [24]. Young people have more diverse skin microflora than older people. This parameter can also be influenced by a person's place of residence, as the composition and properties of the air differ between rural and urban areas. Older people living in rural areas most often have *Proteobacteria* on their skin [25]. In young people living in cities, *Enterobacteriaceae* predominates, and on dry areas of the skin, *Cutibacterium* predominates. In families living in the same house, the microorganisms on the skin are similar. The skin of pets has the same bacterial communities as their owners [26, 27].

Until recently, it was believed that bacteria lived only on the surface of the skin and in natural depressions such as hair follicles. However, recent studies have shown that bacteria can also be found in deeper layers, including the dermis and subcutaneous fat layer, which were previously considered completely sterile [28, 29].

Fungi are another important group of microorganisms that inhabit the skin. The totality of skin fungi forms the mycobiome. Studies show that the predominant skin fungi are *Malassezia* species, lipophilic yeasts that mainly inhabit the sebaceous areas of the skin. Just like bacteria, fungi have topographical differences. For example, there are a relatively large number of fungi of the genera *Aspergillus*, *Cryptococcus*, and *Candida* on the feet, but they are considered part of the normal microbiome of this location. However, in general, the number of fungi on human skin is minimal [30]. At the same time, fungal microorganisms are more often involved in dermatological diseases than others [27]. Problems that currently exist in the study of the mycobiome include the relatively low abundance of fungi, as well as the limited number of publicly available reference methods for studying fungal diversity compared to those for bacteria.

Skin viruses are another area of active research. Viruses currently identified on the skin include bacteriophages, human papillomaviruses, and Merkel cell polyomavirus [31–33]. Unlike bacteria and fungi, the distribution of viruses is specific to a particular individual rather than to an anatomical niche [30]. Research on human skin viruses is also difficult because viral genomes are small compared to bacterial, fungal, and parasitic genomes, and the sequences that make up viral genomes can be overwhelmed by all the other larger ones found in human skin samples [34].

A huge number of factors that can alter the structure, physical and chemical properties, and function of the skin influence changes in the normal microflora and the development of pathogenic microflora. Skin diseases can arise as a result of exposure to exogenous factors (physical, mechanical, chemical, biological, and infectious) [10, 35]. In today's world, cosmetic products have the most adverse exogenous effect on the skin microbiota. Cosmetics affect not only the condition of the skin microbiota, but also the structure of the microorganisms themselves, which are localized on the surface of the dermis. The chemical ingredients of cosmetic products remain on the skin surface for a long time, regardless of daily showering. The abundant application of cosmetic products changes skin hydration, which indicates a decrease in the number of normal skin microorganisms: *Cutibacterium*, *Staphylococcus*, *Corynebacterium*. There is a significant increase in the number of *Ralstonia*, which is capable of altering the chemical ingredients of the cosmetic product and suppressing their effect [36, 37].

Household cleaning products, such as dishwashing detergents, soap, and body gels, can also damage the skin's microbiota. They contain anionic surfactants that aggressively affect the skin's surface [25, 38, 39].

In addition to exogenous factors, endogenous factors that can affect the condition of the skin, such as blood diseases, immunodeficiency states, stress, genetic factors, and intercurrent diseases, also contribute to changes in the microbiological composition of the skin [40, 41].

The condition of the human gastrointestinal tract (GIT) is closely related to the condition of the skin. Hippocrates described skin diseases associated with the condition of the GIT, such as chronic urticaria and rosacea. According to modern data, pathological changes in the small intestine have a particularly strong influence on the development of dermatoses. Impaired intestinal absorption of substances, especially a decrease in selective absorption, as well as impaired breakdown of incoming substances, can lead to the entry of toxic substances into the body and their accumulation. In turn, toxic substances have the ability to cause an allergic reaction, one of the manifestations of which is skin rashes. The consumption of allergens themselves can also cause dermatoses [42, 43].

How does the composition of microflora and skin structure change in certain dermatoses, particularly in atopic dermatitis?

Atopic dermatitis (AD) is a multifactorial allergic inflammatory skin disease that begins in childhood, tends to progress, and significantly reduces the quality of life of patients. It is currently a very common disease, especially in countries with developed industrial production. AD should be considered a polyetiological disease based on a combination of immune response defects, microbiota disorders, and damaging environmental factors. The development of AD is influenced by environmental and genetic factors that affect the basic functions of the skin — maintaining the skin's epithelial barrier and immune response.

The diversity of microbiota on affected areas of skin in atopic dermatitis is poorer compared to unaffected areas [44]. Changes in the composition of skin microflora in AD are associated with an increase in the number of *S. aureus* (*Staphylococcus aureus*) and *S. epidermidis*. *Staphylococcus aureus* is a commensal bacterium found in 30% of the population. It colonizes the nasal mucosa and affected skin areas, creating conditions that allow pathogenic microbes and toxins to penetrate the tissue [45]. Patients with AD have weakened skin immunity, as *S. aureus* secretes staphylococcal enterotoxin B, which enhances inflammation by activating T lymphocytes and macrophages. In the acute stage of the disease, *Staphylococcus aureus* stimulates the production of thymic stromal lymphopoietin, IL-25, and IL-33, which generate an immune response. In addition, *S. aureus* disrupts the proteolytic balance in the skin by producing various extracellular proteases and increasing the production of serine proteases by keratinocytes and metallopro-

teases in dermal fibroblasts, which can further destroy the skin barrier [46]. In AD, there is a decrease in the number of *Corynebacterium* species, which indicates the presence of antimicrobial compounds on the skin surface produced by *S. aureus* and *S. epidermidis* microorganisms [47]. A similar disruption of the normal skin microbiota occurs with the use of drugs to treat acute AD. The aims of AD treatment are to restore the skin barrier and reduce the impact of triggering factors such as stress and allergic reactions [45, 48–52].

CONCLUSION

The normal microflora of human skin is diverse and includes up to 80,000 species. The basis of this diversity is made up of 19 taxonomic species, among which *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* predominate in adults. Changes in the composition of the human skin microbiota within normal limits depend on various factors, such as age, gender, place of residence, topographical location of the skin fragment under study, professional affiliation, and environmental conditions. Pathogenic changes in the composition and functions of the skin can occur due to exogenous, endogenous, and genetic factors. This can lead to chronic dermatoses such as atopic dermatitis. Analysis of the literature has shown that this disease causes specific changes in the composition of the skin microbiota. In atopic dermatitis, the number of *S. aureus* and *S. epidermidis* increases. Patients with AD have weakened skin immunity due to the activity of *S. aureus*. Modern ideas about the formation and composition of the skin microbiota can significantly change our understanding of the pathogenetic mechanisms of a number of chronic skin diseases.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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