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THE COMPOSITION OF THE SKIN MICROBIOTA IN CHILDREN AND ITS ROLE IN THE PATHOGENESIS OF ACNE

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Abstract
Acne is a common dermatological disease characterized by chronic inflammation of the skin and manifesting mainly in adolescence. The defeat of aesthetically significant areas inevitably reduces the quality of life of patients. This article discusses modern methods of studying the skin microbiome, describes the species composition of microorganisms in newborns and the dynamics of its changes as they grow older. Special attention is paid to the role of Cutibacterium acnes in the pathogenesis of acne as the dominant taxon in the microbiota of areas with a high density of sebaceous glands.

Keywords: Children, skin, pathogenesis acne, microbiota.

Introduction

Acne is a chronic inflammatory disease that affects the hair follicles and sebaceous glands. The pathology is widespread mainly among adolescents and young people, but in recent years the frequency of registration of the disease in adults has been increasing [1, 2]. Many patients develop persistent scarring (post-acne). Severe facial skin lesions often induce the development of depressive states and other psychological disorders. The microbiota of the skin acts as an important etiopathogenetic factor in the development of acne. Bacteria are the most numerous and well-studied representatives of the skin microbiome. Of the more than 40 genera of bacteria that colonize human skin, representatives of four types are of key importance: Actinomycetota (in particular, the suborders Corynebacterineae, Propionibacterineae), Bacillota (Staphylococcaceae), Pseudomonadota and Bacteroidota [3, 4]. The taxonomic ratio of microorganisms varies depending on the patient's age, anatomical zone, and microenvironment. In seborrheic areas (forehead, occipital region, back, nose wings), cutibacteria adapted to anaerobic conditions predominate. In wet areas of the skin (armpits, inguinal folds, popliteal fossa), Staphylococcus and corynebacteria dominate, while in dry areas gram—negative bacteria. At the same time, fungi of the genus Malassezia spp. are found everywhere in all anatomical zones. Skin microorganisms differ not only qualitatively, but also quantitatively [5, 9]. The total colonization density in an adult varies from 3.7×10^4 to 1.2×10^6 CFU/cm^2. This indicator is significantly higher in wet areas: the number of aerobic bacteria reaches 10^6 CFU/cm^2 (compared to 102 on dry skin), and anaerobic bacteria - up to 10^6 CFU/cm^2. The viral component of the microbiome is mainly represented by the Circoviridae, Polyomaviridae, and Papillomaviridae families.

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Methods of studying the microbiota of the skin. Various approaches to biomaterial expression, sequencing platforms, and bioinformatics algorithms are used to evaluate the quantitative and qualitative characteristics of the skin microbiome. Currently, there is no generally accepted "gold standard" in this field: the variability of methodological approaches at different stages of the study may lead to discrepancies in the results of the analysis for the same subject. In pediatric practice, the most common method of biomaterial collection is surface scraping (swab method), which allows to verify the composition of the microbiota of the epidermis and the upper part of the hair follicle. The qualitative identification of microorganisms has been significantly improved due to the introduction of high-performance molecular genetic technologies. These include sequencing of variable regions of the 16S ribosomal RNA (16S rRNA) gene to profile bacterial communities, sequencing of internal transcribed spacers (ITS1 or ITS2) to identify mycobiota, as well as shot-by-shot metagenomic (genome-wide) sequencing covering bacterial, viral, and fungal components. Despite the high resolution, sequencing results can also show interindividual and intraindividual variability. Genome-wide sequencing provides the most complete characterization of the taxonomic diversity and functional potential of the microbiome, but its widespread clinical use is limited by high cost. Amplicon sequencing of the 16S rRNA gene remains the most economically available and widespread method. At the same time, the accuracy of the taxonomic classification when using it is directly determined by the completeness of the reference databases and the specifics of the bioinformatics pipelines used. For an objective interpretation of the microbiome structure and a comparative analysis of microbial consortia, the assessment of biotic diversity indicators is of key importance.: -diversity (intra-group diversity and equalization of species) and -diversity (intergroup differences in the structure of communities).

Formation of the skin microbiome in the neonatal period. The processes of antenatal formation of human microbial communities remain the subject of active discussions. It is assumed that the primary presence of microorganisms in utero induces the maturation of the fetal immune system, preparing it for postnatal contact with the environment. Unlike the detailed intestinal microbiome of newborns, the patterns of formation of skin microbiocenosis in infants have not been sufficiently studied, and the available data are based primarily on the results of amplicon sequencing of the 16S rRNA gene or the ITS2 region. In the first days of life, the nature of colonization of the skin of newborns is determined by the method of delivery. At birth through the natural birth canal, the composition of bacterial and mycotic flora is relatively homogeneous and is mainly represented by maternal vaginal associates (in particular, the genus Lactobacillus and Candida albicans). On the contrary, cesarean section surgery disrupts the physiological sequence of microbial colonization: the skin of newborns is contaminated with typical environmental and skin pollutants of medical personnel (representatives of the genera Staphylococcus, Streptococcus). Invasive delivery is also associated with delayed formation of the intestinal microbiota, which is often aggravated by concomitant perinatal antibiotic therapy. The recorded increase in the colonization density of the intestine by bacteria of the genera Staphylococcus and Clostridium correlates with an increased risk of subsequent development of atopic dermatitis, bronchial asthma and obesity in childhood. Targeted translocation of the mother's vaginal secretions onto the skin of a newborn extracted by cesarean section is considered as a promising method of partial restoration of the physiological microbiome. An

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additional factor determining the architecture of the skin microbiome is the gestational age of the child at the time of birth. In full-term infants, a higher index of species diversity is verified compared to premature newborns (gestation period < 37 weeks). In the group of full-term infants, there was a significantly higher relative representation of resident skin and intestinal taxa, including Staphylococcus spp., Streptococcus spp., Corynebacterium spp., Escherichia spp. and Enterococcus spp. This variability is due to the anatomical and functional immaturity of the epidermal barrier in premature infants, which creates conditions for colonization by atypical microorganisms, as well as the high frequency of antibacterial drugs and the effects of hospital microecology in intensive care units. In modern dermatology, the concept of the "gut–skin axis" has been formulated, postulating a bidirectional interaction between these biotopes through the signaling pathways of the microbiota, their metabolites, immune mediators and nutritional factors. Dysbiotic disorders within this axis are involved in the pathogenesis of a number of dermatoses, including acne. Extrapolation of this concept to the pediatric population indicates the need for combined monitoring and correction of intestinal and dermal microbiocenoses in the management of pediatric patients.

Age-related dynamics of the formation of the skin microbiome. The skin microbiome of a healthy adult is a relatively stable ecosystem. The study of the age–related succession of microbial communities is necessary to verify the mechanisms of pathogenetic interaction in the "macroorganism-microbiota" system. The architecture of the microbiome is individual for each subject. It is determined by both endogenous skin characteristics (hydration level, lipid secretion, pH, temperature) and exogenous factors, including climatic conditions and the use of perfumes and cosmetics. The neonatal period is characterized by a relatively homogeneous distribution of microorganisms over the body surface; topographic differentiation of various anatomical zones manifests itself during the first weeks of postnatal life. During the first year of life, the qualitative composition of the microbiota remains stable, while the quantitative indicators of colonization density are steadily increasing. In subsequent periods of childhood, there is a progressive decrease in the relative representation of the genera Staphylococcus and Streptococcus against the background of a transient increase in the number of Corynebacteria and Cutibacteria. This trend persists in children aged 4 to 12 years, whose bacterial and mycological diversity indicators significantly exceed similar markers in adults. The formation of a definitive (adult) profile of the skin microbiota is completed during puberty. This process is closely associated with hormonal restructuring of the body and stimulation of the activity of sebaceous and apocrine glands. Hyperproduction of sebum creates selective conditions for the active proliferation of the lipophilic anaerobe Cutibacterium acnes. An additional regulatory factor is the maturation of local immunity, the adaptive mechanisms of which ensure long-term stability and locus specificity of the microbiome in adulthood.

The role of cutibacterium acnes in the pathogenesis of acne. Cutibacterium acnes is a dominant dermal commensal belonging to gram-positive anaerobes. This taxon accounts for about 85-90% of the total population of microorganisms colonizing the pilosebation complex. Under physiological conditions, C. acnes supports the homeostasis of the skin microbiome through the production of short-chain fatty acids and the stimulation of the synthesis of antimicrobial peptides (AMP). A direct correlation between the total population of C. acnes and the manifestation or severity of acne has not

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yet been established. Nevertheless, it has been convincingly proven that this microorganism acts as a key trigger of the pathogenesis of the disease, and the determining factor is not its quantitative presence, but strain specificity. High-resolution molecular genetic profiling made it possible to differentiate individual phylotypes and strains designated as ribotypes (RT) within the C. acnes species. Thus, the RT6 ribotype prevails in the microbiota pool of healthy skin, whereas in acne, a significant increase in the representation of RT4 and RT5 is verified. Phylotypes of C. acne-associated acnes (in particular, IA-2, IB-1, IC) induce the expression of pro-inflammatory cytokines by the macroorganism, including interleukin-17 (IL-17) and IFN-γ. On the contrary, phylotypes isolated from intact skin (II-RT6, III) stimulate the synthesis of anti-inflammatory interleukin-10 (IL-10). Subpopulations of type 17 T helper cells (Th17) activated by strains II-RT6 and III exhibit pronounced antibacterial activity, which is completely absent when induced by strains IA-2, IB-1 and IC. According to some data, acne patients are characterized by a higher heterogeneity of C phylotypes. acnes compared to healthy individuals. Topical (benzoyl peroxide, clindamycin) and systemic (isotretinoin, minocycline) drugs used in acne therapy significantly reduce the overall bacterial load, but paradoxically lead to an increase in the index of diversity of the residual microbiome of the skin. In particular, against the background of a five-month course of systemic isotretinoin, there is a transient increase in the proportion of C. acnes ribotypes with bactericidal activity. The mechanism of action of isotretinoin is indirect: suppression of sebaceous production deprives the lipophilic microflora of a nutritive substrate, which is combined with increased production of endogenous AMPS. Nevertheless, the exact pathogenetic mechanisms of the effect of targeted therapy on the skin microbiome require further study. Prolonged and non-selective use of systemic or topical antibacterial agents can induce persistent dysbiosis and lead to the development of gram-negative folliculitis caused by opportunistic flora. In this regard, the introduction of selective therapeutic approaches aimed solely at the elimination of acne-associated strains of C. acnes seems justified.

Therapeutic potential of topical microbiota modulation. The resident microbiota of the skin is able to regulate the epigenetic processes of the macroorganism by suppressing the expression of viral genes and activating the transcriptional potential of syngeneic commensals. Through the secretion of a wide range of bioactive molecules, the microbiome modulates the morphogenesis of skin appendages, the processes of carcinogenesis and chronogenesis, the functional activity of sensory nerve fibers, as well as the mechanisms of innate immunity. According to the epimmune concept, the epidermal barrier plays a fundamental role in maintaining local immune homeostasis and protecting the body from exogenous triggers. The development of dermatoses such as acne, rosacea, and atopic dermatitis is etiopathogenetically associated with a violation of the structural and functional integrity of the skin barrier, and therefore its targeted restoration leads to a lasting clinical improvement.

Topical use of probiotic strains such as Lactobacillus bulgaricus, L. acidophilus and L. plantarum increases the effectiveness of complex acne therapy by suppressing skin colonization by C. acnes. In particular, in a clinical study by N.Muizzuddin et al. against the background of L. plantarum applications in patients with mild acne, a decrease in the severity of erythema, regression of inflammatory elements and restoration of the epidermal barrier were noted [6]. Applying strain L to the skin. paracasei CNCM I-2116 helps to reduce the local concentration of soluble proinflammatory

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mediators, in particular the neuropeptide substance P. Topical use of Streptococcus salivarius K12 induces inhibition of the expression of transcription factor NF-B in keratinocytes. In addition, applications of Vitreoscilla filiformis lysate extract stimulate the production of anti-inflammatory interleukin-10 (IL-10) by dendritic cells.

In vitro studies have demonstrated the ability of S. salivarius and Enterococcus faecalis to directly inhibit the growth of C. aspes and stop the inflammatory response through the secretion of antimicrobial peptides such as bacteriocin-like inhibitory substance (BLIS). So, K. Nakamura et al. When testing a topical agent based on an unprecedented strain of E. faecalis SL-5, a pronounced antimicrobial effect and a clinically significant decrease in the number of papulo-pustular elements were recorded [7]. Antagonistic activity against C. aspes exhibits another resident skin commensal, Staphylococcus epidermidis, whose inhibitory potential is realized through the fermentation of glycerol. J.'s experiments Oh et al. confirmed in vitro the antibacterial effect of bacteriocin produced by Lactococcus sp. HY 499 against a wide range of pathogens, including S. epidermidis, Staphylococcus aureus, Streptococcus pyogenes and C. acnes. An important additional property of probiotic components is their ability to minimize the severity of adverse events (xerosis, irritation) induced by aggressive basic acne therapy [8].

Systemic (oral) administration of probiotics is also able to modulate the condition of the skin through a number of pathogenetic mechanisms, the key of which is the suppression of systemic inflammation. In particular, oral administration of probiotic strains realizes its therapeutic potential through the gut–brain–skin regulatory axis. Modification of the intestinal microbiocenosis optimizes the absorption of nutrients and essential micronutrients, which directly potentiates the barrier function of the epidermis. Thus, oral administration of Lactobacillus reuteri significantly reduces the severity of peripheral follicular inflammation in the dermis. In addition to acne therapy, systemic probiotics demonstrate clinical efficacy in the complex treatment of atopic dermatitis, as well as in stimulating reparative processes in burns and scar deformities. Not only live probiotic cultures have a positive effect on the course of acne, but also individual functional nutraceuticals that affect the metabolic profile of the macroorganism. In particular, in a clinical study, a 38.6% decrease in the number of inflammatory rashes was recorded compared with the placebo group after daily intake of fermented milk fortified with 200 mg of lactoferrin for 12 weeks. This clinical effect was accompanied by a selective decrease in the level of surface triacylglycerols in sebum in people with acne. The intestinal microbiota is actively involved in the processes of parietal digestion, absorption, and hepatic metabolism, synthesizing a number of biologically active metabolites inaccessible to endogenous anabolism in hepatocytes. In addition, the native flora is able to modulate the severity of adverse events of concomitant drug therapy, determining the enzymatic activity in the intestinal lumen.

Conclusion

The architecture of the skin microbiome in the pediatric population remains insufficiently studied to date. Nevertheless, it is obvious that the structure of microbial communities in healthy children has fundamental topographic and quantitative differences from similar indicators in adults. With the physiological development of the macroorganism and the passage of age periods, the skin microbiocenosis undergoes significant taxonomic succession. Dynamic monitoring of these changes is necessary to optimize existing and develop new therapeutic strategies for managing patients with

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dermatoses. Both the qualitative composition of the microbiota and its functional activity (including induction of synthesis of endogenous antimicrobial peptides, production of biologically active metabolites and lipids of sebum) directly determine the choice of therapeutic tactics. The use of topical and systemic probiotics is a promising and pathogenetically sound direction in dermatology. Given that a significant part of the data was obtained with high efficiency in in vitro experiments, a comprehensive study of the regulatory potential of the skin microbiome in large-scale clinical trials is an urgent and priority task for future research.

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