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The role of the skin microbiome in the development of alopecia areata

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Abstract

Human skin is a habitat to a variety of microbes that, along with their host genetic material, make up microbiome of the human skin. The composition of the microbiota in the gut and skin is influenced by many factors, such as life stage, nutrition, lifestyle and gender. Recently,

there is more and more discussions about the increasing role of the microbiome in the development of other diseases. According to many studies, any changes in the skin microbiota are associated with the development of several dermatoses. Better understanding of the human microbiome and its interactions with the immune system could help us understand many diseases as well as could have an impact on the development of some new therapeutic methods. In this article, the current knowledge on the skin microbiome and its influence on the development of alopecia areata will be discussed. Alopecia areata (AA) is caused by an autoimmune process that destroys the hair follicles. The exact pathogenesis is unknown, but the triggering factors include: immune disorders, environmental exposures, genetic predisposition, and possibly the microbiome.

Keywords: microbiome, alopecia, alopecia areata, skin

The skin is the outer barrier between the body and the environment. Its area is estimated at 25 m2 [1]. Regional changes in skin temperature, humidity and density of sebaceous glands create an environment in which bacteria, fungi, viruses and mites can develop.

The microbiome of the human skin is a collection of all commensal, symbiotic and pathogenic microorganisms with their genetic elements and environmental interactions. Actinobacteria (36-51%), Firmicutes (24-34%), Proteobacteria (11-16%), Bacteroidetes (6-9%) [4] are the four main types of bacteria found on the skin. In wet places, the most abundant bacteria are Staphylococcus (included in the Firmicutes group) and Corynebacterium (Actinobacteria).

The fungal species include Malassezia spp., Cryptococcus spp., Rhodotorula spp., Aspergillus spp. and Epicoccum spp. Malassezia spp. are the most common, constituting about 80% of the total fungal flora on human skin [5,6]. Demodex spp. are small mites also living in the hair [7,8]. Most of them are in the so-called hair-sebaceous units [8]. Viruses are the less studied elements of the skin microflora. Human papillomaviruses (HPV) have been reported to be ubiquitous on the skin surface, but are rare in contrast to the bacterial flora inhabiting the skin [7].

It has been established that the colonization of the microflora begins at birth. The method of delivery has a significant influence on its composition [9,10]. Then, its composition is determined by internal factors (interpersonal variability, ethnicity, gender and age), as well as external factors such as: lifestyle, hygiene, use of cosmetics, antibiotics, geographic location or climate [11, 12, 13]. The composition of the microbiota in the gut and skin is influenced by many factors, such as life stage, nutrition, lifestyle and gender.

The skin microbiome plays an essential role in maintaining skin homeostasis and a healthy environment. It also protects it from invading pathogens and participates in the modulation of immunity [7,14]

The term dysbiosis refers to the imbalance between microorganisms in certain areas of the body, which can lead to the onset or progression of diseases [15]. Several skin diseases such

as atopic and seborrheic dermatitis, acne, alopecia areata, psoriasis and acne may result from dysbiosis [15, 16].

Alopecia areata (AA)

Alopecia areata is non-scarring type of alopecia. The incidence of alopecia areata appears to increase with age, but the mean age of onset is estimated to be 25–36 years [24]. Early-onset AA (in the pediatric population) has a more severe course.

The course of hair loss can vary from well-defined circular patches to diffuse or complete hair loss, which may involve the hairy skin of the entire hair.

In the course of alopecia areata, changes may also appear in the nail plates of about 10-15% of patients [26].

The pathogenesis of AA remains unknown. It is believed that autoimmunization, mainly autoimmune changes in hair follicles, plays a large role in the etiology of disease [19, 20]. The disease is associated with an increased overall risk of other autoimmune diseases (16%), including lupus erythematosus, vitiligo, and autoimmune thyroid disease (Hashimoto's disease). Moreover, there is an association with atopic dermatitis, which coexists with AA in 39% of cases [25].

Moreover, other reasons include: genetic predisposition and environmental factors. Alopecia areata appears to have a strong genetic component. A 55% conformity factor was observed between identical twins. However, the antigens responsible for inducing autoimmune changes in these individuals remain unknown [38]. In recent studies, the skin and gut microbiome has been linked to autoimmunization in AA [21,22,23].

Changes in the microbiome may be associated with loss of homeostasis, modulation of immune responses and intense periocular inflammation in AA [27].

The symbiosis of Corynebateriaceae, Propionibacteriaceae, Staphylococcaceae and Malassezia is associated with a healthy scalp. In contrast, dysbiosis can cause pathological conditions.

The studies by Pinto and co-authors found microbiological changes in people with alopecia areata showing excessive colonization by C. acnes along with a reduced number of S. epidermidis [28]. Additionally, it has been suggested that cytomegalovirus is involved in the triggering of alopecia, but later studies have not confirmed this fact [29]. In the study by Rudnicka and co-authors, a hypothesis was put forward suggesting a relationship between the colonization of the scalp by Alternaria spp. and alopecia areata, after culturing this microorganism from epidermal scrapings in patients [30].

Active alopecia areata has been proved to be associated with the presence of perifollicular inflammatory infiltrates, mainly CD8 + T cells, but also other mononuclear cells and eosinophilia [30]. Zhao and co-authors [39] showed that in most patients with diffuse AA the onset of the disease was observed in spring and summer, which may suggest that diffuse alopecia may be caused by an increase in seasonal allergens.

Taking under consideration that melanogenesis-related antigens have been discussed as triggers of autoimmunization in AA [40,41], it is also important that several of the fungi that make up the scalp microbiome, including Alternaria species, are melanin-producing microorganisms. Therefore, it can be assumed that the exposure of people predisposed to fungal substances involved in melanin production may contribute to the development of autoimmune reactions directed against peptides involved in melanin synthesis.

Recent studies also suggest a significant influence of intestinal dysbiosis. In the last few years, several studies have shown the influence of microflora on many immune-related diseases, such as diabetes, Crohn's disease and multiple sclerosis. In the study by Polak-Witek and co-authors, a significant correlation was shown [31]. This was also confirmed by the research carried out in the following years by De Pessemier and co-authors [32]. AA-related genes can influence gut colonization by microorganisms, which in turn induce a response with increased production of gamma interferon. There are two reported cases of alopecia areata with long-term hair regrowth after fecal microflora transplants that confirm the role of the gut microbiome [33] in the pathophysiology of AA.

Alopecia areata is associated with autoimmune disorders. It is believed that modern lifestyle can alter the composition of the intestinal flora, thus, disrupting the immune system. The intestinal dysbiosis is influenced by many factors involved in hair growth, such as: biotin production by bacteria, short-chain fatty acids produced by the intestinal microbiota, and vitamin D deficiency [34]. Restoring the balance of the intestinal microflora may contribute to hair regrowth in patients with alopecia areata by increasing the absorption and synthesis of nutrients [35]. Many scientific studies suggest that the influence of the gut microbiome extends beyond the gut and thus contributes to the function and dysfunction of distant organs [42] such as the skin, explaining this by the existence of the so-called "gut-skin axis" [43].

The intestinal microbiota influences the pathophysiology of parenteral tissues, including the skin. One study indicated that metabolic changes associated with intestinal dysbiosis and dietary modifications may affect skin physiology. A study in mice has shown that intestinal dysbiosis caused by treatment with certain antibiotics, e.g. metronidazole, and in particular Lactobacillus murinus (L. murinus) overgrowth, impairs biotin biosynthesis by the intestinal microbiota and the intestinal metabolic functions, leading to alopecia. It was found that the lack of biotin in the diet of dysbiotic mice treated with antibiotics led to a systemic biotin deficiency, causing the development of alopecia [47].

Additionally, it is worth noting that an innovative treatment option for alopecia areata is currently the therapeutic manipulation of the microbiome. This manipulation can be achieved by transplanting the fecal microflora [35] or the use of microbial metabolites, such as postbiotics [36]. There is only one case of hair growth after fecal microflora transplantation. It refers to two patients suffering from alopecia areata, which may suggest a potential role of the intestinal microflora in the mechanism of disease development [44].

Despite the growing number of evidence showing that the human microbiome plays a key role in human health and in the development of various diseases, it is still unclear whether changes in it play a causative role in alopecia areata or it is a result of an inflammatory microenvironment [37]. Therefore, it is extremely important that more research is needed to fully understand how the microbiome, in combination with genetic and environmental factors, can contribute to the development of the disease. It would also enable the understanding of

the detailed interactions between the microbes that make up the microbiome and the immune system.

In addition, it is worth mentioning that antimicrobial treatment, which is directed against pathogens that cause skin diseases, is also directed at microorganisms that create a beneficial bacterial flora. Therefore, it is extremely important to maintain proper skin homeostasis. For this, special probiotics, symbiotics, as well as fecal transplant procedures are used. In the coming years, the actual therapeutic efficacy of these treatments will probably be established.

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