



Association of *Malassezia* to Atopic Dermatitis

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Abstract

Purpose of Review Atopic dermatitis (AD) is a common chronic, inherited, relapsing, inflammatory skin condition. A multifactorial etiology has been postulated, including genetic and immunological factors, impaired skin barrier function and environmental triggers, all of them are relevant in the pathogenesis. *Malassezia* spp. is the most common fungi of the skin microbiome. Most of the studies comparing the skin colonization with *Malassezia* spp. in healthy people and AD patients did not show difference between both groups. This review aims to show the studies carried out in this regard and the reported evidence about the role of *Malassezia* spp. in the pathogenesis of AD.

Recent Findings The rate of IgE-mediated sensitization *Malassezia* spp. is very high in AD patients, mainly in adult patients and in patients with involvement in the head and neck. Different mechanisms have been postulated to explain the interaction of *Malassezia* spp. with human skin cells and immune cells and how its interaction contributes to the inflammation process in AD. Systemic and topical azole antifungals have been used with doubtful results showing beneficial effects in some AD patients.

Summary There is no clear explanation for the high frequency of *Malassezia* spp. sensitization in AD patients in relation with healthy individuals. Further research is necessary to determine the specific role of *Malassezia* in AD and the indication for the use of antifungals in this disease.

Keywords Atopic dermatitis · IgE · *Malassezia* spp. · *Malassezia globosa* · *Malassezia dermatis*

Introduction

Atopic dermatitis (AD) is a common chronic, inherited, relapsing, inflammatory skin condition; its main characteristics

are intense itching, xerosis and lichenification (Fig. 1a and b). It usually begins in infancy and early childhood. The exact incidence and prevalence of AD are difficult to establish, as many of the mild cases are not noted [1]. However, the prevalence of AD has increased three times in the last 30 years, currently affecting up to 30% of children and 10% of adults of developed countries [2•]. The pathogenesis of atopic dermatitis is not fully known. A multifactorial etiology has been postulated, including genetic and immunological factors, impaired skin barrier function, and environmental triggers, all of them are relevant in the pathogenesis [3•, 4].

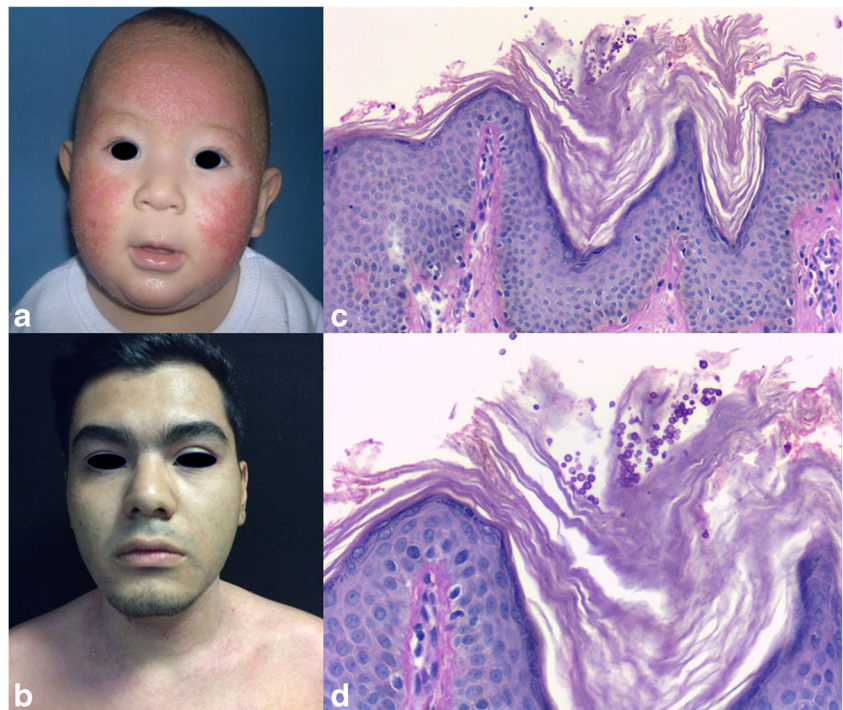
AD appears to be under the influence of strong genetic effects. It has been observed that there are genetic loci related with dermal inflammation and immunity and in the most superficial layers of the skin some of the genes are expressed [5]. Genetic research have shown the importance of mutations in the filaggrin (FLG) gene as an central feature in the pathogenesis of AD; other genes that have been associated with AD include innate/adaptive immune system genes, human leukocyte antigens (HLA), cytokines, chemokines, and drug-metabolizing genes [1, 6].

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Fig. 1 **a** Atopic dermatitis in a child. **b** Atopic dermatitis in an adolescent. **c** *Malassezia* yeasts located in cornea layer (H&E, 10×). **d** Approach of *Malassezia* yeast clusters, (H6E, 60×)



On the other hand, in AD patients, the skin immune system has abnormalities in Th1/Th2 activity to more targeted immune; they have increased levels in some cytokines such as interleukin (IL)-4, IL-10, and IL-13; these cytokines decrease production of essential components of the skin's innate immune system and the defense against pathogens such as anti-microbial peptides LL-37, human beta defensin (hBD)-2, and hBD-3 in keratinocytes. Recently, AD has been associated with specific signaling pathways such as IL-3 and IL-14 which contribute to IgE production, Th17 cells, and production of other cytokines including IL-17, IL-22, IL-18, and serine-protease inhibitor kazal-type 5 (SPINK5) [1, 7••].

Finally, impaired skin barrier function has been described in patients with AD and it is related to increased trans-epidermal water loss, lower hydration in the stratum corneum, pH increased at surface and tight junction components with less expression [4, 8].

There are many triggers of outbreaks in AD patients that include environmental aspects. The skin microbiome—the community of microorganisms colonizing the skin—is one of the environmental factors that has been related in the etiopathogenesis of AD. The colonization and growth of microorganisms on the skin of AD patients can be a consequence of the impaired skin barrier function and the altered skin immune system that may play intertwining roles [2••, 4]. The cutaneous colonization in AD patients has been described for bacteria, in particular *Staphylococcus aureus*. Recently the study of microbiome has considered that fungi may have part in the pathogenesis of AD, especially yeast organisms belonging to

Malassezia genus [3•]. We are going to review the principal aspects of *Malassezia* spp. biology on normal skin and the reported evidence about the role of *Malassezia* spp. in the pathogenesis of AD.

***Malassezia* Spp. in Normal Skin and AD Patients Skin Microbiome**

All the microorganisms colonizing the skin make up the skin microbiome. The skin is the largest organ of the human body, colonized by diverse microorganisms—including bacteria, fungi, and viruses—they can be beneficial or harmless to their host. Colonization varies depending on body site, host, and environmental factors.

The concept that the skin is like an ecosystem—composed of living biological and physical parts occupying diver's habitats—permit us to understand the fragile balance between host and microorganism. Break in the balance on either side can result in skin disorders or infections [9].

Fungi are part of the normal skin flora at all body sites accordingly with the phylogenetic profiling of the skin microbiome and comprise 1–22% of the composition of the skin microbiome. *Malassezia* spp. is almost the only fungal flora of the normal human skin and therefore the main eukaryotic member of cutaneous microbial flora [4].

Malassezia spp. is a genus of lipophilic yeasts and it is considered part of human skin flora since the mid-nineteenth century. Morphology, ultrastructure, physiology, and

Table 1 Currently Identified *Malassezia* species

<i>Malassezia</i> species	Year of description
<i>M. furfur</i>	1889
<i>M. pachydermatis</i>	1925
<i>M. sympodialis</i>	1990
<i>M. globosa</i>	1996
<i>M. obtusa</i>	1996
<i>M. restricta</i>	1996
<i>M. slooffiae</i>	1996
<i>M. dermatis</i>	2002
<i>M. japonica</i>	2003
<i>M. nana</i>	2004
<i>M. yamatoensis</i>	2004
<i>M. caprae</i>	2007
<i>M. equina</i>	2007
<i>M. cuniculi</i>	2011

Adapted from ref. [2]

molecular biology are the principal aspects considered in the current form of *Malassezia* spp. taxonomy defined in 1996.

Malassezia spp. belongs to the phylum Basidiomycota and 14 species have been described (Table 1). In humans, the most frequently isolated species are *Malassezia globosa*, *Malassezia restricta*, *Malassezia sympodialis*, *Malassezia furfur*, *Malassezia slooffiae*, *Malassezia dermatis*, *Malassezia japonica*, *Malassezia obtusa*, and *Malassezia yamatoensis*. Most reports show that in healthy human skin of almost all individuals and body sites, *M. globosa*, *M. restricta*, and *M. sympodialis* predominate. There are differences in the distribution of particular *Malassezia* spp. according to the geographical location of host. In Canada, Russia, Poland, and Sweden, *Malassezia sympodialis* is the most frequent species described whereas *Malassezia furfur* was also reported in Japan and Iran [10, 11]. The discrepancy in the isolation frequency of *Malassezia* spp. is not completely clear but may be related not only to different factors, including ethnic origin, demographic aspects, and lifestyle habits, but also methodological differences, such as the use of different sampling techniques (swabbing, scraping), culture media (modified Dixon agar, Lemming-Notman agar, Sabouraud-dextrose+olive oil agar), or the method used for species identification. The traditional identification schemes, based on morphological characteristics and biochemical activities are being complemented or replaced by DNA-based molecular techniques, allowing more reliable results [11].

Sebum-rich areas of the skin, including the trunk and the head region, eyelids are the places where *Malassezia* yeast inhabits; the highest level of colonization has been described between 20 and 45 years of age. [12]. It begins immediately after birth and it increases progressively during the neonatal stage. It has been described that *Malassezia* yeast colonization

is 5% at the first week and 30% at 2–4 weeks of life. The highest carriage of *Malassezia* spp. occurs during puberty being found in 75–98% of healthy people in this age group; this is related to the increase in the activity of sebaceous glands. The predominant species of *Malassezia* yeasts described from the first months of life are the same as previously described: *M. globosa*, *M. restricta*, and *M. sympodialis*.

Different species of *Malassezia* yeasts have been described according to the body site: In healthy scalp skin, *M. restricta* is the most common species cultured, whereas in the trunk, *M. globosa*, *M. furfur*, and *M. sympodialis* are the most frequently isolated species. No difference has been reported between women and men [11].

Most of the studies comparing the skin colonization with *Malassezia* spp. in healthy people and AD patients did not show difference between both groups [4]; however, some reports describe higher prevalence of *Malassezia* spp. in AD patients [13].

According to the studies of *Malassezia* taxonomy, *M. dermatis* has been considered as a representative species in AD together with *M. globosa* (Fig. 1b and c), *M. restricta*, and *M. sympodialis* [11, 14•].

Supporting the higher prevalence of *Malassezia* spp. in AD patients, Jain C, et al. studied Single Nucleotide Polymorphism (SNP) in IL10 and IFN γ genes of AD patients and its relation with susceptibility to *Malassezia* infection; they found significant association between specific cytokine gene polymorphism and AD, it allows to suspect genetic susceptibility to *Malassezia* infection in these patients and can be used to direct investigation for predicting the likelihood of disease manifestation from a commensal organism in genetically susceptible host [15••].

AD Patients and IgE-Mediated Sensitization to *Malassezia* Spp.

As explained previously, *Malassezia* spp. are part of the skin microbiome so it is in close relationship with the skin immune system; therefore, it is normal to find *Malassezia* spp.-specific immunoglobulin G (IgG) and IGM antibodies in healthy people [2••, 16•]. On the other hand, in normal skin, the rate of IgE-mediated sensitization to *Malassezia* spp., is very low or even absent, in contrast, most patients with AD are sensitized to this yeast: one third of children and two thirds of adults with AD using standardized commercial kits (ImmunoCAP m70 and ImmunoCAP m227) [17, 18]; some studies have reported positive skin prick tests in up to 80% of adult AD patients [2••].

There is no clear explanation for the high frequency of *Malassezia* spp. sensitization in AD patients in relation with healthy individuals but it can be related to several factors including: skin barrier defects and genetic and environmental factors [4].

Particularly in adult patients, sensitization to *Malassezia* spp. can be correlated to the severity of AD; head and neck AD have higher sensitization rates also compared to other affected sites. Therefore, particularly in this location, some authors consider that *Malassezia* spp. participates in the pathogenesis of AD [2•, 19].

Lipid content of sebum is a mandatory requirement for skin colonization with *Malassezia* spp. because *Malassezia* yeasts are lipophilic organisms. In childhood, skin produces less amount of sebum, this condition does not favor the proliferation of *Malassezia* yeast; these poor growth conditions in pediatric age explain less *Malassezia* spp.-sensitization and the lack of correlation between *Malassezia* spp.-specific IgE and AD severity in this age group compared with adults [2•]. Thus, sensitization to *Malassezia* spp. seems to occur more frequently in adult population, while in pediatric patients sensitization to food allergens and aeroallergens is more common [4, 20•].

Specific IgE response is triggered by some allergens of *Malassezia* spp. Currently, at least 14 allergens of 3 *Malassezia* spp. (*M. furfur*, *M. sympodialis*, and *M. globosa*) have been described on a molecular basis (Table 2). In the atopic skin, these allergens are found in higher concentration, for example, Mala s 12 allergen is in greater quantity at pH 6.0 characteristic of AD skin and lower at pH 5.5 of healthy skin [21]. The percentage of IgE-mediated sensitization varies from 40 to 92% to the different allergens described. It has not been clarified whether this IgE response is part of the etio-pathogenic of AD or is only a marker of disease severity [2•, 4].

Skin Immune System and *Malassezia* Spp. Relationship

It has been considered that the relationship of *Malassezia* spp. with skin cells and immune cells participates as a

Table 2 Allergens from *Malassezia* spp. in atopic dermatitis

Allergen	Source
Mala f 2	<i>Malassezia furfur</i>
Mala f 3	<i>Malassezia furfur</i>
Mala f 4	<i>Malassezia furfur</i>
Mala s 1	<i>Malassezia sympodialis</i>
Mala s 5	<i>Malassezia sympodialis</i>
Mala s 6	<i>Malassezia sympodialis</i>
Mala s 7	<i>Malassezia sympodialis</i>
Mala s 8	<i>Malassezia sympodialis</i>
Mala s 9	<i>Malassezia sympodialis</i>
Mala s 10	<i>Malassezia sympodialis</i>
Mala s 11	<i>Malassezia sympodialis</i>
Mala s 12	<i>Malassezia sympodialis</i>
Mala s 13	<i>Malassezia sympodialis</i>
MGL_1304	<i>Malassezia globosa</i>

proinflammatory factor and in this way helps to generate inflammation in AD.

The interaction between *Malassezia* spp. and skin cells and how this binomial participates to generate skin inflammation in AD has not been clearly established; different mechanisms have been proposed:

1. Patients with atopic dermatitis are characterized by defects of skin barrier; the *Malassezia* spp. allergens and the whole cells of this agent have an entry way through the disturbed epidermis. In this way the keratinocytes and the cells of the immune system (dermal dendritic cells, Langerhans cells, natural killer cells, and fibroblasts) recognize *Malassezia* spp.
2. In AD patients, the dendritic and mast cells are stimulating by nano-vesicles of *Malassezia* spp. proteins to release cytokines that contribute to skin inflammation such as necrosis factor- α (TNF- α), interleukin-6 (IL-6), IL-8, IL-10, and IL-12p70.
3. On keratinocytes and dendritic cells toll-like receptors 2 (TLR2) recognize *Malassezia* spp. stimulating them to release pro-inflammatory cytokines.
4. Dendritic and T cells by the action of *Malassezia* spp., induce the activation of B cells to produce *Malassezia* spp.-specific IgE antibodies. Probably through mast cells, these IgE antibodies can participate in skin inflammation in AD patients.
5. In skin dendritic cells, NLRP3 inflammasome activated by *Malassezia* spp. stimulate the production of proinflammatory cytokines such as IL-1 β , IL-4, IL-5, and IL-13 [2•, 4].
6. Independent to the immune mechanisms already described, *Malassezia* allergens produce inflammation directly; at least two examples have been described:
 - a. Mala s 13 is a fungal thioredoxin that is very similar to a human thioredoxin. CD4⁺T cells recognized Mala s 13 and may cross-react to the human enzyme expressed in keratinocytes inducing a T cell-mediated skin inflammation [22].
 - b. Mala s 11 is a manganese-dependent superoxide dismutase (MgSOD) that produce induction of autoreactive T cells and T cell-mediated inflammation also [23].

Antifungals in Atopic Dermatitis

Treatment of AD include skin emollients and other measures to repair the impaired skin barrier, identification and elimination of trigger factors, anti-inflammatory treatment with topical steroids or calcineurin inhibitors, antibiotics to reduce bacterial over-colonization, mainly by *Staphylococcus aureus*, among others.

It has been proposed that antifungal therapy may be useful in the treatment of AD. Systemic and topical azole antifungals have been used with doubtful results showing beneficial effects in some AD patients. To demonstrate the benefit in AD patients of antifungal therapy, more randomized, placebo-controlled studies on large patient populations, with main involvement of AD in the head and neck are needed [2••].

Conclusions

Malassezia spp. is the most common fungi of the skin microbiome. In AD patients IgE-mediated sensitization to *Malassezia* spp. has been shown to be greater, mainly in adolescence and adult patients and in patients with involvement in the head and neck. Different mechanisms have been postulated to explain the interaction of *Malassezia* spp. with skin cells and immune cells and how its interaction contributes to the inflammation process in AD. Systemic and topical azole antifungals have been used with doubtful results showing beneficial effects in some AD patients. Further research is necessary to determine the specific role of *Malassezia* in AD and the indication for the use of antifungals in this disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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