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Fungus as an Exacerbating Factor of Atopic Dermatitis, and Control of Fungi for the Remission of the Disease

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1. Introduction

Atopic dermatitis (AD) is a common, chronic fluctuating skin disease with prevalence in children (Williams, 2000; Williams & Wüthrich, 2000). The disease is an inflammatory skin disorder characterized by itching, and chronically relapsing course. Moreover, it also produces vulnerablity to surface infections caused by pathogenic bacteria, fungi and viruses. The most common skin infections in AD patients are caused by *Staphylococcus aureus* and herpes simplex virus (Ong & Leung, 2010). *S. aureus* is frequently detected in AD patients (Abeck & Mempel, 1998; Katsarou & Armenaka, 2011) and becomes an aggravating factor. In addition, toxins, such as staphylococcal enterotoxins and toxic shock syndrome toxin-1 (McFadden et al., 1993; Bunikowski et al., 1999), generated from *S. aureus* may act as superantigens (Herz et al., 1999; Niebuhr et al., 2011; Yeung et al., 2011). In AD patients, viral infection is most often caused by herpes simplex virus (HSV) (Wollenberg et al., 2003). Eczema herpeticum is a potentially life-threatening disseminated HSV type 1 or type 2 infection that occurs in 10% to 20% of AD patients (Peng et al., 2007). However, not only bacteria and viruses but also fungi, such as *Malassezia* species and *Candida* species, may play an important role as aggravation factors in AD patients. It has been reported that antifungal therapy is beneficial in the treatment of some AD patients (Bäck et al. 1995; Svejgaard et al. 2004; Broberg et al. 1995; Mayser et al., 2006). In addition, several candidate *Malassezia* antigens have been implicated in the pathogenesis of AD. In this chapter, the involvement of fungi in the pathogenesis of AD is discussed.

2. Fungi isolated from AD patients and treatment

The genus *Malassezia* has recently been shown to consist of fifteen species based on the database of National Center for Biotechnology Information (2011), one lipid-independent species, *M. pachydermatis* and fourteen lipid-dependent species, *M. sympodialis*, *M. furfur*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffiae*, *M. caprae*, *M. equine*, *M. dermatis*, *M. equi*, *M. japonica*, *M. nana*, *M. yamatoensis* and *M. cuniculi*. *Malassezia* species have been recognized as members of the microbiological flora of human and animal skin. *M. globosa* and *M. restricta* are frequently isolated from the skin scales of human AD (Sugita et al., 2001; Tajima et al., 2008; Kaga et al., 2009) and *M. pachydermatis* and *M. nana* are isolated from some animals (Aizawa et al., 2001; Hirai et al., 2004). Antifungal drugs, e.g. ketoconazole and itraconazole,

are used in AD patients with signs of a fungal infection (Sugita et al., 2005; Bäck et al., 1995). Antifungal therapy may remit the severity of AD by controlling these *Malassezia* yeasts.

2.1 Related pathogenic fungi

The yeasts of the genus *Malassezia* are members of the normal cutaneous flora. However, *Malassezia* colonization on the skin of AD patients shows a different pattern from that on healthy skin (Faergemann, 2002; Gupta et al., 2001; Nakabayashi et al., 2000; Sandström et al., 2005; Sugita et al., 2004, 2006) and may aggravate AD due to an allergic reaction, especially on the head and neck area in adults (Brehler & Luger, 2001; Broberg et al., 1992; Faergemann, 1999; Huang et al., 1995; Jensen-Jarolim et al., 1992; Lintu et al., 1997; Rokugo et al., 1990; Schmidt et al., 1997; Nakabayashi et al., 2000; Savolainen et al., 2001; Scalabrin et al., 1999). Scalabrin et al. (1999) measured total IgE and specific IgE to *Malassezia furfur* in 73 AD patients. In the AD patients, specific IgE to *M. furfur* was observed more frequently in adults than children. The reaction of specific IgE to *M. furfur* was 132 times higher than that in healthy subjects. This result suggests that *Malassezia* yeast is associated with IgE-mediated skin inflammation in AD.

Culture-dependent methods have been used for the detection of *Malassezia* species from AD patients (Nakabayashi et al., 2000; Sandström et al., 2005). However, in recent years, many researchers have attempted the detection of *Malassezia* species from AD patients by means of a molecular-based culture-independent method that is not affected by the isolation medium, sampling method, or incubation period. Table 1 summarizes the three major studies applying molecular based PCR assay to detect *Malassezia* species from AD patients and healthy subjects, indicating that the number of detected *Malassetia* species was similar to AD patients and healthy subjects (Sugita et al., 2001; Tajima et al., 2008; Kaga et al., 2009).

Species	Sugita et al.		Tajima et al.		Kaga et al.	
	AD (32)*	HS (18)	AD (36)	HS (30)	AD (56)	HS(32)
M. globosa	93.8**	44.4	100	86.7	100	100
M. restricta	87.5	61.1	97.2	83.3	100	100
M. furfur	40.6	11.1	33.3	26.7	16.1	12.5
M. sympodialis	40.6	50.0	58.3	36.7	65.2	62.5
M. slooffiae	6.3	0	30.6	16.7	17.9	6.3
M. obtuse	0	0	27.8	10	14.3	12.5
M. pachydermatis	0	0	-	-	-	-
M. yamatoensis	-	-	13.9	6.7	21.4	15.6
M. japonicum	-	-	33.3	10	10.7	12.5
M. dermatis	-	-	30.6	30	37.5	34.4

* Number of cases. ** Percentage of the number of patients. AD, atopic detmatitis; HS, healthy subjects. -, not detected.

Table 1. Comparison of published research on *Malassezia* colonization in AD patients and healthy subjects.

In both AD patients and healthy subjects, the predominant species were *M. globosa* and *M. restricta*. However, the study by Kaga et al. (2009), who applied real-time PCR to determine the number of rDNA copies of *M. globosa* and *M. restricta*, revealed that *Malassezia* colonization in severe AD patients was approximately two to five times higher than that in

other AD patients (mild and moderate) and healthy subjects. Since the species-specific DNA of *M. globosa* and *M. restricta* were frequently and massively detected, the two *Malassezia* species may be related to the severity of AD.
Besides the *Malassezia* species, *Candida* species and dermatophytes are also involved in the pathogenesis of AD, and especially *C. albicans* may play a role in the alimentary canal of AD patients, becuase *Candida* species have been cultured more frequently from the gastrointestinal tract in AD patients than healthy subjects (Arzumanyan et al., 2000; Savolainen et al., 2003). Moreover, the possible involvement of dermatophytes, especially *Trichophyton rubrum*, in the inflammation in AD patients was reported (Klein et al., 1999).

2.2 Control of fungi in AD patients

Ketoconazole and itraconazole, azole antimycotics, have been the most frequently studied therapeutic agents for AD. The antimycotics showed strong antifungal activities against *Malassezia* species isolated from AD patients *in vitro* (Sugita et al. 2005). In clinical studies, ketoconazole and itraconazole have shown a significant therapeutic effect on AD patients. Bäck et al. (1995) assessed the efficacy of oral ketoconazole treatment on 20 AD patients using a positive radioallergosorbent test. The AD patients were treated with ketoconazole 200 mg daily for 2 months and 200 mg twice a week for another 3 months. Of the 20 patients, 18 completed the ketoconazole treatment regimen for 5 months and most patients showed a good to moderate response for ketoconazole 200 mg daily during the 2 months but no further improvement after the administration of ketoconazole 200 mg twice a week for another 3 months. Svejgaard et al. (2004) evaluated the efficacy of oral itraconazole in the treatment of AD patients with head and neck dermatitis in a randomized, double-blind, placebo-controlled study. The AD patients were treated daily with itraconazole 200 mg, 400 mg or placebo for 7 days. The treatment with 200 mg and 400 mg of itraconazole exerted a remarkable therapeutic effect on AD patients. Therefore, the systemic antimycotic administration is expected to be highly effective in treating AD patients.
Meanwhile, the application of topical antimycotics could decrease *Malassezia* colonization and the severity of eczematous lesions in AD patients. For instance, as reported by Broberg et al. (1995), the treatment of AD patients who had head and neck dermatitis with twice-daily miconazole-hydrocortisone cream and twice weekly ketoconazole shampoo for 4 weeks resulted in decreased *Malassezia* colonization although clinical scores were not greatly improved. In addition, they confirmed the effect of ciclopiroxolamine on AD patients with moderate to severe head and neck dermatitis, which is often difficult to be treated, in a double-blind, placebo-controlled study.

3. Fungal infection in animals with AD

Fungal infection in animals with AD has been reported mainly in canines and felines. For instance, Morris et al. (2002) reported that cell-mediated and humoral reactivities to *M. pachydermatis* contribute to the pathogenesis of AD in dogs but are not directly correlated. They investigated whether the potential cell-mediated immune response of atopic dogs to the yeast *M. pachydermatis* is correlated with the type-1 hypersensitivity (humoral) response of the same population of dogs. Atopic dogs with cytologic evidence of *Malassezia* dermatitis had an increased lymphocyte blastogenic response to crude *M. pachydermatis* extract, compared with clinically normal dogs and dogs with *Malassezia* otitis. The blastogenic responses in atopic

control dogs (without *Malassezia* dermatitis or otitis) did not differ significantly from those in atopic dogs with *Malassezia* dermatitis. No significant correlation was found between the lymphocyte blastogenic response and the type-1 hypersensitivity response to *M. pachydermatis* within any of the groups, suggesting that modification of the dysregulated immune response toward *M. pachydermatis* may assist in the reduction of pathologic changes associated with an AD phenotype in dogs. In another study, Chen et al. (2002) compared IgE responses to separated proteins of *M. pachydermatis* in atopic dogs with *Malassezia* dermatitis and clinically normal dogs. The results of their study showed that the majority of atopic dogs with *Malassezia* dermatitis have a greater IgE response than normal dogs, suggesting an IgE-mediated immune response may be clinically important in the pathogenesis of the disease. In felines, *Malassezia* spp. have been more frequently isolated from healthy ear canals and skin in feline leukaemia (FeLV)- or feline immunodeficiency virus (FIV)-infected cats than in those noninfected (Sierra et al., 2000). In addition, *Malassezia* spp. overgrowth has been described in feline localized benign exfoliative skin diseases, such as chin acne and the idiopathic facial dermatitis of Persian cats (Jazic et al., 2006; Bond et al., 2000). Based on these findings, Ordeix et al. (2007) conducted a multicentre, retrospective and descriptive study to document *Malassezia* spp. overgrowth in allergic cats. Their results suggested that *Malassezia* spp. overgrowth may represent a secondary cutaneous problem in allergic cats particularly in those with greasy adherent brownish scales on their skin. The favorable response to treatment with antifungal agent alone suggests that, as in dogs, *Malassezia* spp. may be partly responsible for both pruritus and cutaneous lesions in allergic cats.

4. Mechanisms by which fungi act as an exacerbating factor for atopic dermatitis

4.1 Antigen-specific inflammation caused via activation of antigen-specific T cells

Allergy to fungi such as *Candida* spp. and *Malassezia* spp. has been implicated as an exacerbating or intractable factor in the symptoms of AD (Savolainen et al., 1993; Tanaka et al., 1994; Kitamura et al., 1997; Morita et al., 1999; Linder et al., 2000; Faergemann 2002; Kanda et al., 2002; Svejgaard et al., 2004). *Candida* spp. are indigenous fungi inhabiting the oral cavity, digestive tract and vagina. Healthy people are thought to acquire the Th1 type immunity against *Candida* spp. (Tanaka et al., 1994; Romani et al., 1995). For instance, the activation of Th1-type CD4+ cell induces phagocyte-dependent immunity, which apparently represents an important mechanism of anti-*Candida* resistance, and it was demonstrated that healthy subjects with a normal immune response show high peripheral blood lymphocyte proliferative responses as well as positive scarification patch tests to *C. albicans* antigen, suggesting the dominant presence of Thl type T cells specific to *C. albicans* antigen. It is well known that Thl clones secrete IL-2 and IFN-γ and preferentially induce delayed type hypersensitivity (Stout & Bottomly, 1989), while Th2 clones produce IL-4, IL-5 (Mosmann et al., 1986) and IL-10 (Fiorentino et al., 1989) and help to promote IgE production (Boom et al., 1988; Killar et al., 1987). In AD patients, Th1-type immunity has been shown to shift to Th2-type (Fig. 1) since the patients immediately react to skin testing using *Candida*-antigen (Tanaka et al., 1994; Kitamura et al., 1997), and *Candida*-specific IgE increases with the severity of the symptoms of AD (Tanaka et al., 1994). Specifically, AD patients displayed a significantly lower incidence of positive patch test reactions to *C. albicans* allergen than the healthy control subjects, and the patients with negative *C. albicans* patch tests tended to have

higher levels of total serum IgE including anti-*C. albicans* IgE antibody. In other words, the delayed-type hypersensitivity to *C. albicans* antigen, which is highly prevalent in atopics without dermatitis as well as non-atopics, was reduced in most of the AD patients.

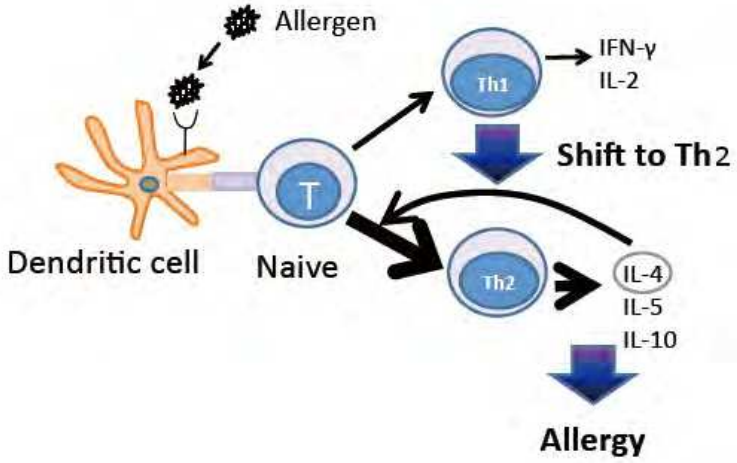

Fig. 1. Shift of Th1-type immunity to Th2-type immunity in allergic diseases including atopic dermatitis (AD). In healthy individuals, dendritic cells present fungal antigen to naive T cells which in turn differentiate to Th1 type cells, resulting in the cellular immune response. In AD patients, Th1-type immunity shifts to Th2-type immunity in which Th2 clones produce IL-4, IL-5 and IL-10 and induce IgE production.

The lipophilic fungus *M. furfur* indigenously inhabits the seborrheic region of the body, such as head, neck and upper part of the back. It was also reported that the fungus may be implicated in rosacea-like dermatitis and edematous erythema, which are chromic and intractable symptoms characteristic to the face with adult-type AD (Mukai et al., 1997), and that *Malassezia*-specific IgE level is high in the head and neck of AD patients (Bayrou et al., 2005; Darabi et al., 2009). Regarding the 11 currently recognized *Malassezia* species as an exacerbating factor in AD, *M. globosa* and *M. restricta* are found to frequently colonize the skin of AD patients. For instance, specific IgE antibodies against eight *Malassezia* species (*M. dermatitis*, *M. furfur*, *M. globosa*, *M. obtusa*, *M. pachydermatis*, *M. slooffiae*, *M. sympodialis*, and *M. restricta*) in sera from AD patients were examined using an enzyme-linked immunosorbent assay, and it was found that the specific IgE value against *M. restricta* was greater than those against the other *Malassezia* species (Kato et al., 2006).

4.2 *Candida albicans* gut colonization

It has been hypothesized that excessive colonization by *C. albicans* in the gastrointestinal tract may constitute an aggravating factor in AD, but this remains controversial (Faergemann et al., 2002; Lacour et al., 2002; Nikkels & Pierard, 2003). To date, laboratory and clinical investigations have demonstrated that IgE mediated food allergy plays a pathogenic role in a subset of AD patients (Eigenmann et al., 1998; Lever et al., 1998; van Reijsen et al., 1998). Some reports have shown increased gastrointestinal permeability in

AD patients (Jackson et al., 1981; Majamaa et al., 1996; Pike et al., 1986). Hyperpermeability of the gastrointestinal mucosal barrier results in enhanced transport of intact and degraded antigens across the gastrointestinal mucosal barrier, which could induce food protein sensitization and food allergy in susceptible individuals (Farhadi et al., 2003) (Fig. 2). Yamaguchi et al. (2006) therefore hypothesized that gastrointestinal colonization by *C albicans* may be involved in aggravation of AD by affecting the mucosal barrier in a manner that results in increased permeation of food allergens and subsequent manifestation of a food allergy. Using mice, they examined whether gastrointestinal colonization by *C. albicans* contributes to the aggravation of AD. *Candida* colonization was establised by intragastric inoculation with *C. albicans*, and then mice were intragastrically administered ovalbumin every other day for nine weeks. As a result, ovalbumin specific IgG and IgE titres were higher in BALB/c mice with *Candida* colonization than in normal mice, suggesting that gastrointestinal permeation of ovalbumin was enhanced by colonization in the mice. Histological examination showed that colonization promoted infiltration and degranulation of mast cells.

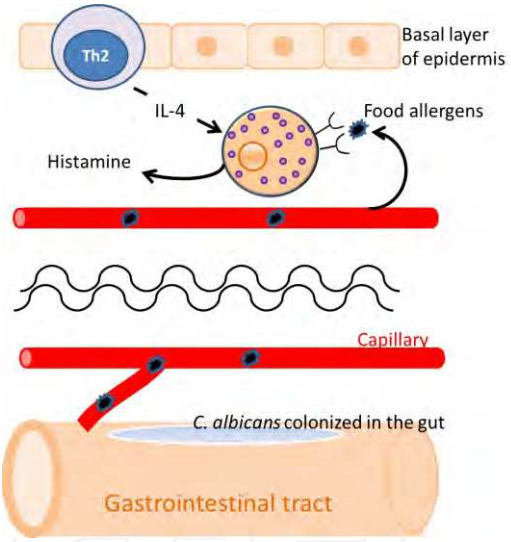

Fig. 2. *Candida albicans* gut colonization as an aggravating factor in atopic dermatitis. Excessive colonization by *C. albicans* in the gastrointestinal tract induces hyperpermeability of the gastrointestinal mucosal barrier, resulting in enhanced transport of intact and degraded antigens across the gastrointestinal mucosal barrier. This induces food protein sensitization and food allergy in susceptible individuals.

Candida colonization did not enhance ovalbumin permeation in mast cell deficient W/Wv mice but did in congenic littermate control +/+ mice. Reconstitution of mast cells in W/Wv mice by transplantation of bone marrow-derived mast cells restored the ability to increase ovalbumin permeation in response to *Candida* colonization. These results suggest that gastrointestinal *Candida* colonization promotes sensitization against food antigens, at least partly due to mast cell-mediated hyperpermeability in the gastrointestinal mucosa of mice. To confirm that gut colonization of *C. albicans* aggravates atopic dermatitis, Sonoyama et al.

(2011) examined whether *C. albicans* gut colonization aggravates immune diseases in mice. Mice were inoculated intragastrically with *C. albicans* to establish chronic and latent *C. albicans* gut colonization. Allergic diarrhea was induced by repeated intragastric administration of ovalbumin in BALB/c mice. Contact hypersensitivity was evaluated by measuring ear swelling after topical application of 2, 4-dinitrofluorobenzene in NC/Nga mice, which are often used as a mouse model of AD (Jin et al., 2011; Orita et al., 2010). Arthritis was induced by intradermal injection of bovine type-II collagen emulsified with complete Freund's adjuvant in DBA/1J mice. *C. albicans* gut colonization increased the incidence of allergic diarrhea, which was accompanied by gut hyperpermeability, as well as increased infiltration of inflammatory cells in the colon. Contact hypersensitivity was also exacerbated by *C. albicans* gut colonization, as demonstrated by increased swelling, myeloperoxidase activity, and proinflammatory cytokines in ear auricles. Furthermore, *C. albicans* gut colonization promoted limb joint inflammation in collagen-induced arthritis in an animal model of rheumatoid arthritis (Setoguchi et al., 2010; Takagi et al., 2009). These findings suggest that *C. albicans* gut colonization in mice aggravates inflammation in allergic and autoimmune diseases, and evokes the necessity of investigating the pathogenic role of *C. albicans* gut colonization in immune diseases in humans.

4.3 Skin barrier dysfunction

Skin barrier dysfunction (Ogawa et al., 1993; Cork et al., 2006 & 2009; Elias et al., 2008; Palmer et al., 2006) has emerged as a critical driving force in the initiation and exacerbation of AD with a recent major breakthrough in the genetics of AD (O'Regan et al., 2009; Hudson et al., 2006; Brown SJ, McLean, 2009). For instance, as addressed by Ogawa et al. (1993), dryness of the skin is an important component of the atopic diathesis, thereby reflecting possible skin barrier dysfunction. When the two abnormalities, dry skin/barrier dysfunction and allergy/immunological dysfunction, are considered as the major underlying defects of AD, the wide range of clinical manifestations seen in AD can be more easily comprehended. A defect of the mucocutaneous barrier readily allows penetration of multiple antigens or haptens, which enhances allergic inflammation. On the other hand, an allergic inflammation derived from the immunological abnormalities damages barrier functions. This sequence cycle could answer the question as to why AD patients show IgE production against, and contact hypersensitivity to, various antigens or haptens. A set of protective/defensive functions generated in the epidermis is likely mediated by its unique differentiation end product, the stratum corneum (Elias 2005; Elias & Choi, 2005). Basically, a markedly increased transepidermal water loss and a markedly decreased water holding capacity of the stratum corneum were reported in AD patients (Watanabe et al., 1991). In addition, since the patients showed a higher transepidermal water loss following irritant exposure, the susceptibility to irritants in AD patients seemed to be closely related with a breakdown in the barrier function of the stratum corneum (Tupker et al., 1990). More recently, it has been proposed that AD is a multifactorial, heterogenous disease that arises as a result of the interaction between both environmental and genetic factors (Cork et al., 2009). Changes in at least three groups of genes encoding structural proteins, epidermal proteases, and protease inhibitors make AD patients prone to a defective epidermal barrier, resulting in increased risk of developing AD. Loss-of-function mutations found within the FLG gene, which encodes the structural protein, filaggrin, could be the most significant genetic factor toward AD. In addition, enhanced protease activity and decreased synthesis of the lipid lamellae lead to exacerbated

breakdown of the epidermal barrier. It can be summarized that these functions include the permeability barrier, which prevents transcutaneous evaporative water loss, and an antimicrobial barrier, which simultaneously encourages colonization by nonpathogenic ''normal'' flora (Elias, 2007). According to the report by Selander et al. (2009), approximately 50% of adult AD patients have allergen-specific IgE reactivity to the skin commensal yeast *Malassezia* spp. Due to the ruptured skin barrier in AD, it is likely that *Malassezia* come into contact with mast cells, which are known to be involved in AD. Since mast cells are located in the superficial dermis close to blood vessels, they are advantageously positioned to react with allergens diffusing through a ruptured epidermis. They are, therefore, recognized as key effector cells during IgE-associated Th2-type immune responses (Galli et al., 2005), and cross-linking of the high-affinity IgE receptor (FcεRI) leads to release of potent inflammatory mediators (Turner & Kinet, 1999) such as histamine, proteases, chemotactic factors, cytokines, and metabolites of arachidonic acid (Henz et al., 2001). Mast cells have a wide variety of cell surface receptors that can interact directly with pathogens, including Toll-like receptors (TLRs), which are involved in innate immune recognition of invading microorganisms (Qiao et al., 2006). Fungal products such as zymosan can activate mast cells through TLR2 (Marshall, 2004). It has recently been reported that a synergistic activation between TLR2 and FcεRI can occur in mast cells, resulting in increased production of inflammatory cytokines (Qiao et al., 2006) (Fig. 3). Although both a defective epidermal permeability (Sugarman et al., 2003; Seidenari & Giusti, 1995; Proksch et al., 2006; Chamlin et al., 2002; Eberlein-Konig et al., 2000) and a propensity to secondary infection (Boguniewicz et al., 2006; Baker, 2006) are well-recognized features of AD, these abnormalities have been widely assumed to reflect downstream consequences of a primary immunologic abnormality.

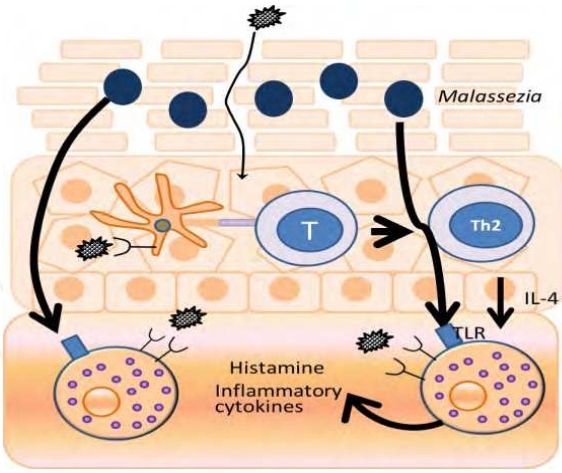

Fig. 3. Skin barrier dysfunction in combination with skin indigenous *Malassezia* as an exacerbating factor in atopic dermatitis (AD). Due to the ruptured skin barrier in AD, it is likely that *Malassezia* and/or its products come into contact with mast cells which have a wide variety of cell surface receptors that interact directly with pathogens, including Toll-like receptors (TLRs). A synergistic activation between TLR and IgE receptor (Fcε RI) can occur in mast cells, resulting in increased production of inflammatory cytokines.

5. Conclusion

Well-known representative fungi that exacerbate AD are the resident fungi in the skin, *Malassezia* spp. such as *M. furfur*, *M. globosa* and *M. restricta*, and the resident fungus in the intestinal tract, *C. albicans*. The lipophilic fungus *M. furfur* indigenously inhabits the seborrheic region of the body such as the face, cervical part, and upper part of back. It was also reported that the fungus may be implicated in rosacea-like dermatitis and edematous erythema, which are chronic and intractable symptoms characteristic to the face in adult-type AD. Regarding the underlying mechanism by which clinical manifestation of AD is affected in the presence of *M. furfur*, the following points have been proposed: 1) antigen-specific inflammation caused via activation of antigen-specific T cells, and 2) dysfunction of skin barrier. A defect of skin barrier readily allows penetration of multiple antigens or haptens, which enhances allergic inflammation, and vice versa. That is, an allergic inflammation derived from the immunological abnormalities damages barrier functions. This sequence cycle could answer the question as to why AD patients show IgE production against, and contact hypersensitivity to, various antigens or haptens. Gut colonization of *C. albicans* is also regarded as the other fungal factor exacerbating AD by promoting sensitization against food antigens, at least partly due to mast cell-mediated hyperpermeability in the gastrointestinal mucosa.

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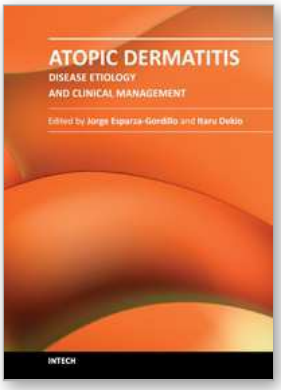

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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