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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 vulnerability 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 *Malassezia* 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)
<i>M. globosa</i>	93.8**	44.4	100	86.7	100	100
<i>M. restricta</i>	87.5	61.1	97.2	83.3	100	100
<i>M. furfur</i>	40.6	11.1	33.3	26.7	16.1	12.5
<i>M. sympodialis</i>	40.6	50.0	58.3	36.7	65.2	62.5
<i>M. slooffiae</i>	6.3	0	30.6	16.7	17.9	6.3
<i>M. obtuse</i>	0	0	27.8	10	14.3	12.5
<i>M. pachydermatis</i>	0	0	-	-	-	-
<i>M. yamatoensis</i>	-	-	13.9	6.7	21.4	15.6
<i>M. japonicum</i>	-	-	33.3	10	10.7	12.5
<i>M. dermatis</i>	-	-	30.6	30	37.5	34.4

\* Number of cases. \*\* Percentage of the number of patients. AD, atopic dermatitis; 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, because *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 Th1 type T cells specific to *C. albicans* antigen. It is well known that Th1 clones secrete IL-2 and IFN- $\gamma$  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.

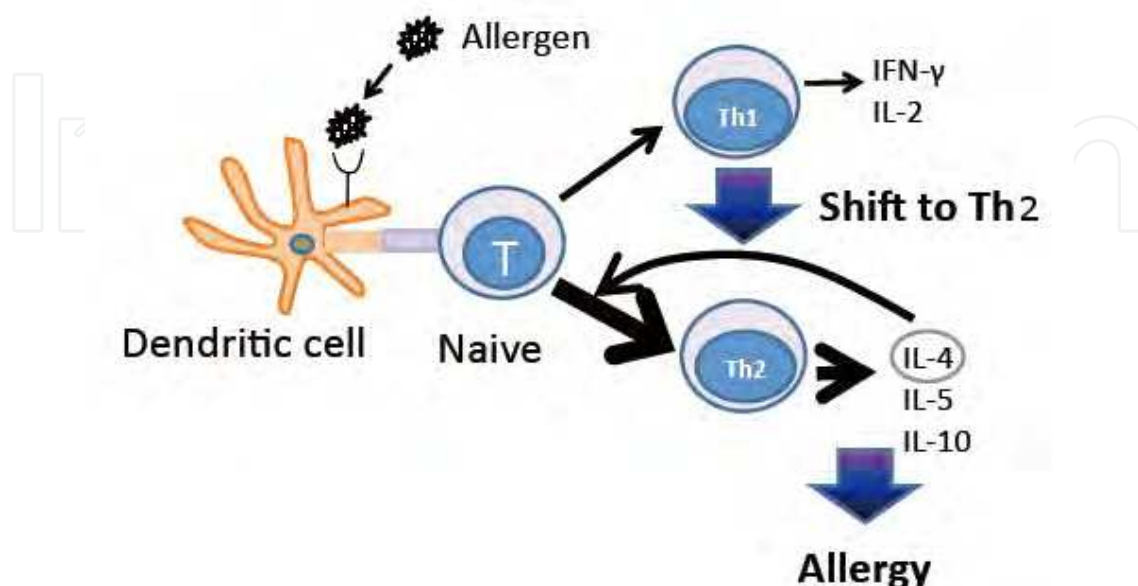


Fig. 1. Shift of Th1-type immunity to Th2-type immunity in allergic diseases including atopic dermatitis (AD). In healthy individuals, dendritic cells present fungal antigen to naive T cells which in turn differentiate to Th1 type cells, resulting in the cellular immune response. In AD patients, Th1-type 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 chronic 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 Reijssen 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 established 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.

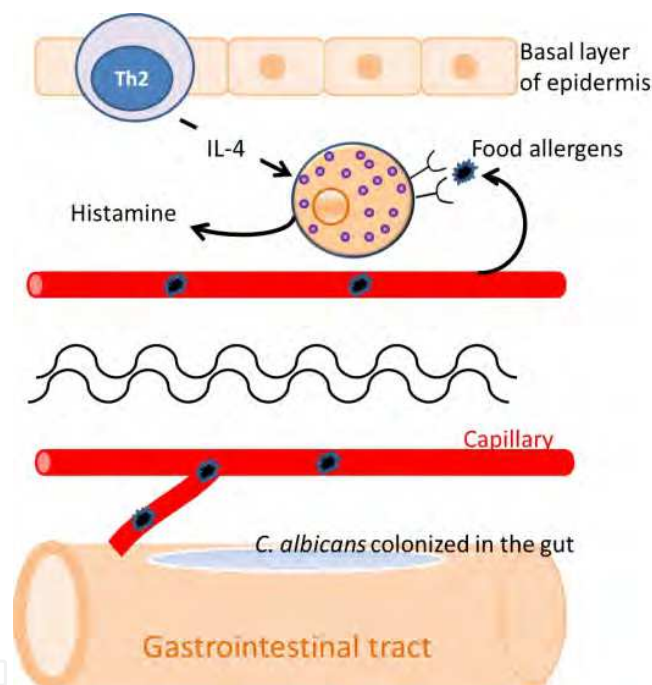


Fig. 2. *Candida albicans* gut colonization as an aggravating factor in atopic dermatitis. Excessive colonization by *C. albicans* in the gastrointestinal tract induces hyperpermeability of the gastrointestinal mucosal barrier, resulting in enhanced transport of intact and degraded antigens across the 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/W<sup>v</sup> mice but did in congenic littermate control +/+ mice. Reconstitution of mast cells in W/W<sup>v</sup> 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.

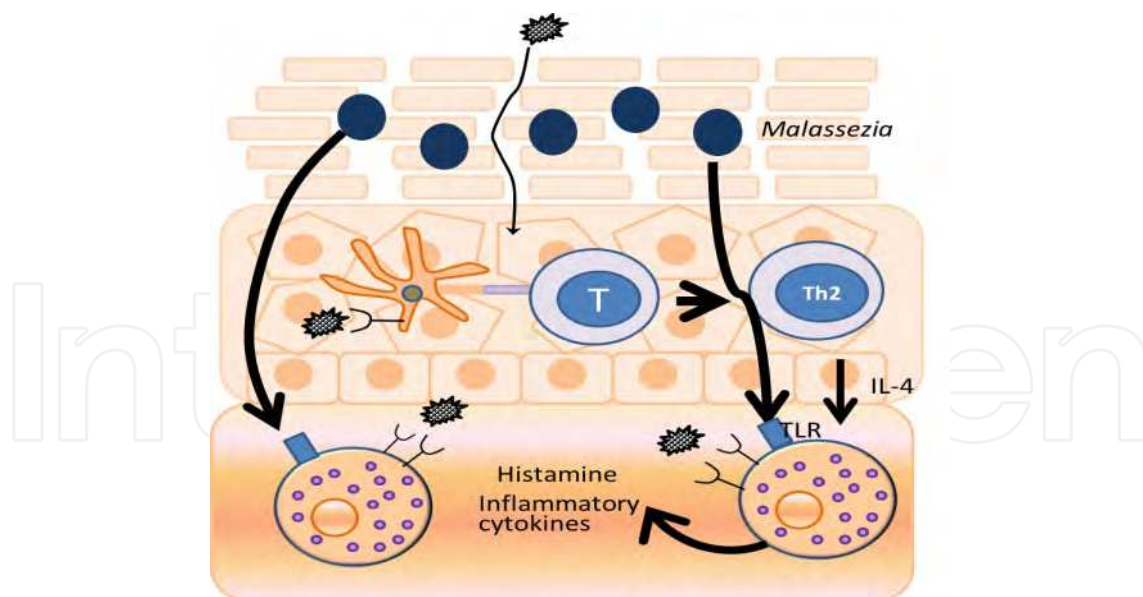


Fig. 3. Skin barrier dysfunction in combination with skin indigenous *Malassezia* as an exacerbating factor in atopic dermatitis (AD). Due to the ruptured skin barrier in AD, it is likely that *Malassezia* and/or its products come into contact with mast cells which have a wide variety of cell surface 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.

## 6. References

- Abeck, D. & Mempel, M. (1998). *Staphylococcus aureus* colonization in atopic dermatitis and its therapeutic implications. *British Journal of Dermatology*, Vol.139, Supplement 53, (December 1998), pp.13-16. ISSN 0007-0963
- Aizawa, T., Kano, R., Nakamura, Y., Watanabe, S. & Hasegawa, A. (2001). The genetic diversity of clinical isolates of *Malassezia pachydermatis* from dogs and cats. *Medical Mycology*. Vol.39, No.4, (August 2001), pp.329-334, ISSN 1369-3786
- Arzumanyan, G., Magarshak, O. & Semenov, B. (2000). Yeast fungi in patients with allergic diseases: species variety and sensitivity to antifungal drugs. *Bulletin of Experimental Biology and Medicine*, Vol.129, No.6, (June 2000) pp.601-604, ISSN 0007-4888
- Bäck, O., Scheynius, A. & Johansson, G. (1995). Ketoconazole in atopic dermatitis: therapeutic response is correlated with decrease in serum IgE. *Archives of dermatological research*, Vol.287, No.5, (May 1995) pp.448-451, ISSN 0340-3696
- Baker, S. (2006). The role of microorganisms in atopic dermatitis. *Clinical and Experimental Immunology*, Vol.144, No.1, (April 2006), pp.1-9, (ISSN 0009-9104)
- Bayrou, O., Pecquet, C., Flahault, A., Artigou, C., Abuaf, N. & Leynadier, F. (2005). Head and neck atopic dermatitis and *Malassezia-furfur*-specific IgE antibodies. *Dermatology* Vol.211, No.2, (August 2005), pp.107-113, ISSN 1018-8665
- Boguniewicz, M., Schmid-Grendelmeier, P. & Leung, Y. Atopic dermatitis. *The Journal of Allergy and Clinical Immunology*, Vol.118, No.1, (July 2006), pp.40-43, ISSN 0091-6749

- Bond, R., Curtis, F., Ferguson, A., Mason, S. & Rest, J. (2000). An idiopathic facial dermatitis of Persian cats. *Veterinary Dermatologist*, Vol.11, No.1, (March 2000), pp.35-41, ISSN 0959-4493
- Boom, H., Liano, D. & Abbas, K. (1998). Heterogeneity of helper/inducer T lymphocytes. II. Effects of interleukin 4- and interleukin 2-producing T cell clones on resting B lymphocytes. *The Journal of Experimental Medicine*, Vol.167, No.4, (April 1998), pp.1350-1363, ISSN 0022-1007
- Brehler, S., & Luger, T. (2001). Atopic dermatitis: the role of *Pityrosporum ovale*. *Journal of the European Academy of Dermatology and Venereology*, Vol.15, No.1, (January 2001), pp.5-6, ISSN 0926-9959
- Broberg, A., Faergemann, J., Johansson, S., Johansson, S. & Strannegard, I. (1992). *Pityrosporum ovale* and atopic dermatitis in children and young adults. *Acta Dermato-Venereologica*, Vol.72, No.3, (March 1992), pp.187-192, ISSN 0001-5555
- Broberg, A. & Faergemann, J. (1995). Topical antimycotic treatment of atopic dermatitis in the head/neck area. A double-blind randomized study. *Acta Dermato-Venereologica*, Vol.75, No.1, (January 1995), pp.46-49, ISSN 0001-5555
- Brown, J. & McLean, H. (2009). Eczema genetics: current state of knowledge and future goals. *The Journal of Investigative Dermatology*, Vol.129, No.3, (March 2009), pp.543-552, ISSN 0022-202X
- Bunikowski, R., Mielke, M., Skarabis, H., Herz, U., Bergmann, L., Wahn, U. & Renz, H. (1999). Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology*, Vol.103, No.1, (January 1999), pp.119-124, ISSN 0091-6749
- Buslau, M., Menzel, I. & Holzmann, H. (1990). Fungal flora of human feces in psoriasis and atopic dermatitis. *Mycoses*, Vol.33, No.2, (February 1990), pp.90-94, ISSN: 1439-0507
- Chamlin, L., Kao, J., Frieden, J., Sheu, Y., Fowler, J., Fluhr, W., Williams, L. & Elias, M. (2002). Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *Journal of the American Academy of Dermatology*, Vol.47, No.2, (August 2002), pp.198-208, ISSN 0190-9622
- Chen, A., Halliwell, E., Pemberton, D. & Hill, B. (2002). Identification of major allergens of *Malassezia pachydermatis* in dogs with atopic dermatitis and *Malassezia* overgrowth. *Veterinary Dermatology*, Vol.13, No.3, (June 2002), pp.141-150, ISSN 0959-4493
- Cork, J., Danby, G., Vasilopoulos, Y., Hadgraft, J., Lane, E., Moustafa, M., Guy, H., Macgowan, L., Tazi-Ahnini, R. & Ward, J. (2009). Epidermal barrier dysfunction in atopic dermatitis. *The Journal of Investigative Dermatology*, Vol.129, No.8, (August 2009), 1892-1908, ISSN 0022-202X
- Cork, J., Robinson, A., Vasilopoulos, Y., Ferguson, A., Moustafa, M., MacGowan, A., Duff, W., Ward, J. & Tazi-Ahnini R. (2006). New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *The Journal of*

- Allergy and Clinical Immunology*, Vol.118, No.1, (July 2006), pp.3-21, ISSN 0091-6749
- Darabi, K., Hostetler, G., Bechtel, A. & Zirwas, M. (2009). The role of *Malassezia* in atopic dermatitis affecting the head and neck of adults. *Journal of the American Academy of Dermatology*, Vol.60, No.1, (January 2009), pp.125-136, ISSN 0190-9622
- Eberlein-Konig, B., Schafer, T., Huss-Marp, J., Darsow, U., Mohrenschrager, M., Herbert, O., Abeck, D., Kramer, U., Behrendt, H. & Ring, J. (2000). Skin surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children. *Acta Dermato-Venereologica*, Vol.80, No.3, (May 2000), pp.188-191, ISSN 0001-5555
- Eigenmann, A., Sicherer, H., Borkowski, A., Cohen, A. & Sampson, A. (1998). Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*, Vol.101, No.3, (March 1998), p.E8, ISSN 0031-4005
- Elias, M. (2005). Stratum corneum defensive functions: an integrated view. *The Journal of Investigative Dermatology*, Vol.125, No.2, (August 2005), pp.183-200, ISSN 0022-202X
- Elias, M. & Choi, H. (2005). Interactions among stratum corneum defensive functions. *Experimental Dermatology*, Vol.14, No.10, (October 2005), pp.719-726, ISSN 0906-6705
- Elias, M. (2007). The skin barrier as an innate immune element. *Seminars in Immunopathology*, Vol.29, No.1, (April 2007), pp.3-14, ISSN 1863-2297
- Elias, M., Hatano, Y. & Williams, L. (2008). Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *The Journal of Allergy and Clinical Immunology*, Vol.121, No.6, (June 2006), pp.1337-1343, ISSN 0091-6749
- Faergemann, J. (1999). *Pityrosporum* species as a cause of allergy and infection. *Allergy*, Vol.54, No.5, (May 1999), pp.413-419, ISSN 1398-9995
- Faergemann, J. (2002). Atopic dermatitis and fungi. *Clinical Microbiology Reviews*, Vol.15, No.4, (October 2002), pp.545-563, ISSN 0893-8512
- Farhadi, A., Banan, A., Fields, J. & Keshavarzian A. (2003). Intestinal barrier: an interface between health and disease. *Journal of Gastroenterology and Hepatology*, Vol.18, No.5, (May 2003), pp.479-497, ISSN 0815-9319
- Fiorentino, F., Bond, W. & Mosmann, R. (1989). Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *The Journal of Experimental Medicine*, Vol.170, No.6, (December 1989), pp.2081-2095, ISSN 0022-1007
- Galli, J., Nakae, S. & Tsai, M. (2005). Mast cells in the development of adaptive immune responses. *Nature Immunology*, Vol.6, No.2, (February 2005), pp.135-142, ISSN 1529-2908
- Gupta, K., Batra, R., Bluhm, R., Boekhout, T. & Dawson, L, Jr. (2004). Skin diseases associated with *Malassezia* species. *Journal of the American Academy of Dermatology*, Vol.51, No.5, (November 2004), pp.785-98, ISSN 0190-9622
- Gupta, K., Kohli, Y., Summerbell, C., & Faergemann, J. (2001). Quantitative culture of *Malassezia* species from different body sites of individuals with or without

- dermatoses. *Medical mycology*, Vol.39, No.3, (Jun 2001), pp.243-251, ISSN 1369-3786
- Henz, M., Maurer, M., Lippert, U., Worm, M. & Babina, M. (2001). Mast cells as initiators of immunity and host defense. *Experimental Dermatology*, Vol.10, No.1, (February 2001), pp.1-10, ISSN 0906-6705
- Herz, U., Bunikowski, R., Mielke, M. & Renz, H. (1999). Contribution of bacterial superantigens to atopical dermatitis. *International Archives of Allergy and Immunology*, Vol.118, No.2-4, (February-April 1999), pp.240-241, ISSN 1018-2438
- Hirai, A., Kano, R., Makimura, K., Duarte, R., Hamdan, S., Lachance, A., Yamaguchi, H. & Hasegawa, A. (2004). *Malassezia nana* sp. nov., a novel lipid-dependent yeast species isolated from animals. *International Journal of Systematic and Evolutionary Microbiology*. Vol.54, No.2, (March 2004), pp.623-627, ISSN 1466-5026
- Huang, X., Johansson, G., Zargari, A. & Nordvall, L. (1995). Allergen cross-reactivity between *Pityrosporum orbiculare* and *Candida albicans*. *Allergy*, Vol.50, No.8, (August 1995), pp.648-656, ISSN 1398-9995
- Hudson, J. (2006). Skin barrier function and allergic risk. *Nature Genetics*, Vol.38, No.4, (April 2006), pp.399-400, ISSN, 1061-4036
- Jackson, G., Lessof, H., Baker, W., Ferrett, J. & MacDonald, M. (1981). Intestinal permeability in patients with eczema and food allergy. *Lancet*, Vol.317, No.8233, (June 1981), pp.1285-1286, ISSN 0140-6736
- Jazic, E., Coyner, S., Loeffler, G. & Lewis, P. (2006). An evaluation of the clinical, cytological, infectious and histopathological features of feline acne. *Veterinary Dermatology*, Vol.17, No.2, (April 2006), pp.134-140, ISSN 0959-4493
- Jensen-Jarolim, E., Poulsen, K., With, H., Kieffer, M., Ottevanger, V., Stahl Skov, P. (1992). Atopic dermatitis of the face, scalp and neck: type I reaction to the yeast *Pityrosporum ovale*? *The Journal of Allergy and Clinical Immunology*, Vol.89, No.1, (January 1992), pp.44-50, ISSN 0091-6749
- Jin, J.H., Ngoc, T.M., Bae K, Kim, Y.S., & Kim, H.P. (2011). Inhibition of experimental atopic dermatitis by rhubarb (rhizomes of *Rheum tanguticum*) and 5-lipoxygenase inhibition of its major constituent, emodin. *Phytotherapy Research*, Vol.25, No.5, (May 2011), pp.755-759, ISSN 0951-418X
- Kaga, M., Sugita, T., Nishikawa, A., Wada, Y., Hiruma, M. & Ikeda, S. (2009). Molecular analysis of the cutaneous *Malassezia microbiota* from the skin of patients with atopic dermatitis of different severities. *Mycoses*. Article first published online: 11 December 2009, ISSN: 1439-0507
- Kanda, N., Tani, K., Enomoto, U., Nakai, K. & Watanabe, S. (2002). The skin fungus-induced Th1- and Th2-related cytokine, chemokine and prostaglandin E2 production in peripheral blood mononuclear cells from patients with atopic dermatitis and psoriasis vulgaris. *Clinical and Experimental Allergy*, Vol.32, No.8, (August 2002), pp.1243-1250, ISSN 0954-7894
- Kato, H., Sugita, T., Ishibashi, Y. & Nishikawa, A. (2006). Detection and quantification of specific IgE antibodies against eight *Malassezia* species in sera of patients with atopic dermatitis by using an enzyme-linked immunosorbent assay. *Microbiology and Immunology*, Vol.50, No.11, (November 2006), pp.851-856, ISSN 1348-0421

- Katsarou, A. & Armenaka, M. (2011). Atopic dermatitis in older patients: particular points. *Journal of the European Academy of Dermatology and Venereology*, Vol.25, No.1, (January 2011), pp.12-18, ISSN 0926-9959
- Killar, L., MacDonald, G., West, J., Woods, A. & Bottomly, K. (1987). Cloned, Ia-restricted T cells that do not produce interleukin 4(IL 4)/B cell stimulatory factor 1(BSF-1) fail to help antigen-specific B cells. *The Journal of Immunology*, Vol.138, No.6, (March 1987), pp.1674-1679, ISSN 0022-1767
- Kitamura, K., Suga, C., Onuma, S., Kawaguchi, T., Yamazaki, F., Suguro, H. & Ikezawa, Z. (1997). Efficacy of oral amphotericin B for refractory atopic dermatitis with specific IgE to *Candida albicans* and food allergens in sera. *Allergology International*, Vol.46, No.2, (June 1997), pp.125-133, ISSN 1323-8930
- Klein, A., Clark, A. & Nicol, H. (1999). Acute infection with *Trichophyton rubrum* associated with flares of atopic dermatitis. *Cutis*, Vol.63, No.3, (March 1999), pp.171-172, ISSN 0011-4162
- Lacour M, Zunder T, Huber R, Sander A, Daschner F, Frank U. (2002). The pathogenetic significance of intestinal *Candida* colonization--a systematic review from an interdisciplinary and environmental medical point of view. *International Journal of Hygiene and Environmental Health*, Vol.205, No.4, (May 2002), pp.257-268, ISSN 1438-4639
- Lever, R., MacDonald, C., Waugh, P. & Aitchison, T. (1998). Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatric Allergy and Immunology*, Vol.9, No.1, (February 1998), pp.13-19, ISSN 0905-6157
- Linder, M., Johansson, C., Scheynius, A. & Wahlgren, C. (2000). Positive atopy patch test reactions to *Pityrosporum orbiculare* in atopic dermatitis patients. *Clinical and Experimental Allergy*, Vol.30, No.1, (January 2000), pp.122-131, ISSN 0954-7894
- Lintu, P., Savolainen, J. & Kalimo, K. (1997). IgE antibodies to protein and mannan antigens of *Pityrosporum ovale* in atopic dermatitis patients. *Clinical and Experimental Allergy*, Vol.27, No.1, (January 1997), pp.87-95, ISSN 0954-7894
- Mayser, P., Kupfer, J., Nemetz, D., Schäfer, U., Nilles, M., Hort, W. & Gieler, U. (2006). Treatment of head and neck dermatitis with ciclopiroxolamine cream--results of a double-blind, placebo-controlled study. *Skin Pharmacology and Physiology*, Vol.19, No.3, (June 2006), pp.153-158, ISSN 1660-5527
- Majamaa, H. & Isolauri, E. (1996). Evaluation of the gut mucosal barrier: evidence for increased antigen transfer in children with atopic eczema. *The Journal of allergy and clinical immunology*, Vol.97, No.4, (April 1996), pp.985-990, ISSN 0091-6749
- Marshall, S. (2004). Mast-cell responses to pathogens. *Nature Reviews Immunology*, Vol.4, No.10, (October 2004), pp.787-799, ISSN 1474-1733
- McFadden, P., Noble, C. & Camp, R. (1993). Superantigenic exotoxin secreting potential of staphylococci isolated from atopic eczematous skin. *British Journal of Dermatology*, Vol.128, No.6, (January 1993), pp.631-632, ISSN 0007-0963
- Morita, E., Hide, M., Yoneya, Y., Kannbe, M., Tanaka, A. & Yamamoto S. (1999). An assessment of the role of *Candida albicans* antigen in atopic dermatitis. *The Journal of dermatology*, Vol.26, No.5, (May 1999), pp.282-287, ISSN 0385-2407

- Morris, O., Clayton, J., Drobatz, J. & Felsburg, J. (2002). Response to *Malassezia pachydermatis* by peripheral blood mononuclear cells from clinically normal and atopic dogs. *American Journal of Veterinary Research*, Vol.63, No.3, (March 2002), pp.358-362, ISSN 0002-9645
- Mosmann, R., Cherwinski, H., Bond, W., Giedlin, A. & Coffman, L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *The Journal of Immunology*, Vol.136, No.7, (April 1987), pp.2348-2357, ISSN 0022-1767
- Mukai, H., Kaneko, S., Saito, N., Nagase, A., Arai, S. & Hiramatsu M. (1997). Clinical significance of *Malassezia furfur* specific IgE antibody in atopic dermatitis. *Alerugi*, Vo.46, No.1, (January 1997), pp.26-33, ISSN 0021-4884
- Nakabayashi, A., Sei, Y. & Guillot, J. (2000). Identification of *Malassezia* species isolated from patients with seborrheic dermatitis, atopic dermatitis, pityriasis versicolor and normal subjects. *Medical Mycology*, Vol.38, No.5, (May 2000), pp.337-341, ISSN:1369-3786
- National Center for Biotechnology Information,  
<http://www.ncbi.nlm.nih.gov/taxonomy>, May, 2011.
- Niebuhr, M., Gathmann, M., Scharonow, H., Mamerow, D., Mommert, S., Balaji, H. & Werfel, T. (2011). Staphylococcal alpha-toxin is a strong inducer of interleukin-17 in humans. *Infection and Immunity*, Vol.79, No.4, (April 2011), pp.1615-1622, ISSN 1098-5522
- Nikkels, F. & Pierard, E. (2003). Framing the future of antifungals in atopic dermatitis. *Dermatology*, Vol.206, No.4, (June 2003), pp.398-400, ISSN 1018-8665
- Nikkels, F. & Pierard, E. (2003). Framing the future of antifungals in atopic dermatitis. *Dermatology*, Vol.206, No.4, (May 2003), pp.398-400, ISSN 1018-8665
- Ogawa, H. & Yoshiike, T. (1993) A speculative view of atopic dermatitis: barrier dysfunction in pathogenesis. *Journal of Dermatological Science*, Vol.5, No.3, (June 1993), pp.197-204, ISSN 0923-1811
- Ong, Y. & Leung, Y. (2010). The infectious aspects of atopic dermatitis. *Immunology and Allergy Clinics of North America*, Vol.30, No.3, (August 2010), pp.309-321, 0889-8561
- Ordeix, L., Galeotti, F., Scarpella, F., Dedola, C., Bardagi, M., Romano, E. & Fondati, A. (2007). *Malassezia* spp. overgrowth in allergic cats. *Veterinary Dermatology*, Vol.18, No.5, (October 2007), pp.316-323, ISSN 0959-4493
- O'Regan, M., Sandilands, A., McLean, H. & Irvine, D. (2009). Filaggrin in atopic dermatitis. *The Journal of Allergy and Clinical Immunology*, Vol.124, No.3, Supplement 2, (September 2009), pp.R2-6, ISSN 0091-6749
- Orita, K., Hiramoto, K., Inoue, R., Sato, E.F., Kobayashi, H., Ishii, M., & Inoue, M. (2010). Strong exercise stress exacerbates dermatitis in atopic model mice, NC/Nga mice, while proper exercise reduces it. *Experimental Dermatology*, Vol.19, No.12, (December 2010), pp.1067- 1072, ISSN 0906-6705
- Palmer, N., Irvine, D., Terron-Kwiatkowski, A., Zhao, Y., Liao, H., Lee, P., Goudie, R., Sandilands, A., Campbell, E., Smith, J., O'Regan, M., Watson, M., Cecil, E., Bale, J., Compton, G., DiGiovanna, J., Fleckman, P., Lewis-Jones, S., Arseculeratne, G.,

- Sergeant, A., Munro, S., El Houate, B., McElreavey, K., Halkjaer, B., Bisgaard, H., Mukhopadhyay, S. & McLean, H. (2006). Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genetics*, Vol.38, No.4, (April 2006), pp.441-446, ISSN 1061-4036
- Peng, M., Jenneck, C., Bussmann, C., Bogdanow, M., Hart, J., Leung, Y., Bieber, T., Eis-Hübinger, M. & Novak, N. (2007). Risk factors of atopic dermatitis patients for eczema herpeticum. *Journal of Investigative Dermatology*, Vol.127, No.5, (May 2007), pp.1261-1263. ISSN: 0022-202X
- Pike, G., Heddle, J., Boulton, P., Turner, W. & Atherton, J. (1986). Increased intestinal permeability in atopic eczema. *The Journal of Investigative Dermatology*, 1986;Vol.86, No.2, (February 1986), pp.101-104, ISSN 0022-202X
- Proksch, E., Folster-Holst, R. & Jensen, M. (2006). Skin barrier function, epidermal proliferation and differentiation in eczema. *Journal of Dermatological Science*, 2006;Vol.43, No.3, (September 2006), pp.159-169, ISSN 0923-1811
- Qiao, H., Andrade, V., Lisboa, A., Morgan, K. & Beaven, A. F. epsilonR1 and toll-like receptors mediate synergistic signals to markedly augment production of inflammatory cytokines in murine mast cells. *Blood* 2006;Vol.107, No.2, (January 2006), pp.610-618, ISSN 0006-4971
- Rokugo, M., Tagami, H., Usuba, Y. & Tomota, Y. (1990). Contact sensitivity to *Pityrosporum ovale* in patients with atopic dermatitis. *Archives of Dermatology*, Vol.126, No.5, (May 1990), pp.627-632, ISSN 0003-987X
- Romani, L., Cenci, E., Menacci, A., Bistoni, F. & Puccetti, P. (1995). T helper cell dichotomy to *Candida albicans*: implications for pathology, therapy, and vaccine design. *Immunologic Research*, Vol.14, No.2, (June 1995), pp.148-162, ISSN 0257-277X
- Sandström, H., Tengvall, M., Johansson, C., Bartosik, J., Bäck, O., Särnhult, T., Wahlgren, F., Scheynius, A. & Faergemann, J. (2005). The prevalence of *Malassezia* yeasts in patients with atopic dermatitis, seborrheic dermatitis and healthy controls. *Acta Dermato-Venereologica*, Vol.85, No.1, (January 2005), pp.17-23, ISSN 0001-5555
- Savolainen, J., Lammintausta, K., Kalimo, K. & Viander, M. (1993). *Candida albicans* and atopic dermatitis. *Clinical and Experimental Allergy*, Vol.23, No.4, (April 1993), pp.332-339, ISSN 0954-7894
- Savolainen, J., Lintu, P., Kosonen, J., Kortekangas-Savolainen, O., Viander, M., Pene, J., Kalimo, K., Terho, E. & Bousquet, J. (2001). *Pityrosporum* and *Candida* specific and non-specific humoral, cellular and cytokine responses in atopic dermatitis patients. *Clinical and Experimental Allergy*, Vol.31, No.1, (January 2001), pp.125-134, ISSN 0954-7894
- Scalabrin, M., Bavbek, S., Perzanowski, S., Wilson, B., Platts-Mills, A. & Wheatley, M. (1999). Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and nonasthmatic control subjects. *The Journal of Allergy and Clinical Immunology*, Vol.104, No.6, (December 1999), pp.1273-1279, ISSN 0091-6749
- Schmidt, M., Zargari, A., Holt, P., Lindbom, L., Hellman, U., Whitley, P., van der Ploeg, I., Härfast, B. & Scheynius, A. (1997). The complete cDNA sequence and expression



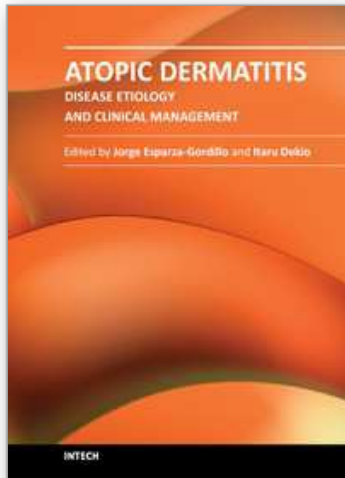
- of the first major allergenic protein of *Malassezia furfur*, Mal f 1. *European Journal of Biochemistry*, Vol.246, No.1, (May 1997), pp.181-185, ISSN 0014-2956
- Seidenari, S. & Giusti, G. (1995). Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Dermato-Venereologica*, Vol.75, No.6, (November 1995), pp.429-433, ISSN 0001-5555
- Selander, C., Engblom, C., Nilsson, G., Scheynius, A. & Andersson, L. TLR2/MyD88-dependent and -independent activation of mast cell IgE responses by the skin commensal yeast *Malassezia sympodialis*. *The Journal of Immunology*, Vol.182, No.7, (April 2009), pp.4208-4216, ISSN 0022-1767
- Setoguchi, C., Tsuji, F., Katsuta, O., Okamoto, M. & Aono, H. (2010). Combined effects of bucillamine and etanercept on a rat type II collagen-induced arthritis model. *Modern Rheumatology*, Vol.20, No.4, (August 2010), pp.381-388, ISSN 1439-7595
- Sierra, P., Guillot, J., Jacob, H., Bussieras, S. & Chermette, R. (2000). Fungal flora on cutaneous and mucosal surfaces of cats infected with feline immunodeficiency virus or feline leukemia virus. *American Journal of Veterinary Research*, Vol.61, No.2, (February 2000), pp.158-161, ISSN 0002-9645
- Sonoyama, K., Miki, A., Sugita, R., Goto, H., Nakata, M. & Yamaguchi, N. (2011). Gut colonization by *Candida albicans* aggravates inflammation in the gut and extra-gut tissues in mice. *Medical Mycology*, Vol.49, No.3, (April 2011), pp.237-247, ISSN 1369-3786
- Stout, D. & Bottomly, K. (1989). Antigen-specific activation of effector macrophages by IFN-gamma producing (TH1) T cell clones. Failure of IL-4-producing (TH2) T cell clones to activate effector function in macrophages. *The Journal of Immunology*, Vol.142, No.3, (February 1989), pp.760-765, ISSN 0022-1767
- Sugarman, L., Fluhr, W., Fowler, J., Bruckner, T., Diepgen, L. & Williams, L. (2003). The objective severity assessment of atopic dermatitis score: an objective measure using permeability barrier function and stratum corneum hydration with computer-assisted estimates for extent of disease. *Archives of Dermatology*, Vol.139, No.11, (November 2003), pp.1417-1422, ISSN 0003-987X
- Sugita, T., Suto, H., Unno, T., Tsuboi, R., Ogawa, H., Shinoda, T. & Nishikawa, A. (2001). Molecular analysis of *Malassezia* microflora on the skin of atopic dermatitis patients and healthy subjects. *Journal of Clinical Microbiology*, Vol.39, No.10, (October 2001), pp.3486-3490, ISSN 0095-1137
- Sugita, T., Tajima, M., Amaya, M., Tsuboi, R. & Nishikawa, A. (2004). Genotype analysis of *Malassezia restricta* as the major cutaneous flora in patients with atopic dermatitis and healthy subjects. *Microbiology and Immunology*, Vol.48, No.10, (October 2004), 755-759, ISSN 1348-0421
- Sugita, T., Tajima, M., Tsuboku, H., Tsuboi, R. & Nishikawa, A. (2006). Quantitative analysis of cutaneous *Malassezia* in atopic dermatitis patients using real-time PCR. *Microbiology and Immunology*, Vol.50, No.7, (July 2006), pp.549-552, ISSN 1348-0421
- Svejgaard, E., Larsen, Ø., Deleuran, M., Ternowitz, T., Roed-Petersen, J. & Nilsson, J. (2004). Treatment of head and neck dermatitis comparing itraconazole 200 mg

- and 400 mg daily for 1 week with placebo. *Journal of the European Academy of Dermatology and Venereology*, Vol.18, No.4, (July 2004), pp.445-449, ISSN 0926-9959
- Tajima, M., Sugita, T., Nishikawa, A. & Tsuboi, R. (2008). Molecular analysis of *Malassezia* microflora in seborrheic dermatitis patients: comparison with other diseases and healthy subjects. *The Journal of Investigative Dermatology*, Vol.128, No.2, (February 2008), pp.345-351, ISSN 0022-202X
- Takagi, T., Naito, Y., Inoue, M., Akagiri, S., Mizushima, K., Handa, O., Kokura, S., Ichikawa, H. & Yoshikawa, T. (2009). Inhalation of carbon monoxide ameliorates collagen-induced arthritis in mice and regulates the articular expression of IL-1beta and MCP-1. *Inflammation*, Vol.32, No.2, (April 2009), pp.83-88, ISSN 0360-3997
- Tanaka, M., Aiba, S., Matsumura, N., Aoyama, H., Tabata, N., Sekita, Y. & Tagami, H. (1994). IgE-mediated hypersensitivity and contact sensitivity to multiple environmental allergens in atopic dermatitis. *Archives of Dermatology*, Vol.130, No.11, (November 1994), pp.1393-1401, ISSN 0365-6020
- Tupker, A., Pinnagoda, J., Coenraads, J. & Nater, P. (1990). Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. *The British Journal of Dermatology*, Vol.123, No.2, (August 1990), pp.199-205, ISSN 0007-0963
- Turner, H. & Kinet, P. (1999). Signalling through the high-affinity IgE receptor Fc epsilonRI. *Nature*, 1999;Vol.402, No.6760, Supplement :B24-30, ISSN: 0028-0836
- van Reijssen, C., Felius, A., Wauters, A., Bruijnzeel-Koomen, A. & Koppelman, J. (1998). T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *The Journal of Allergy and Clinical Immunology*, Vol.101, No.2, Part1, (February 1998), 207-209, ISSN 0091-6749
- Watanabe, M., Tagami, H., Horii, I., Takahashi, M. & Kligman, M. (1991). Functional analyses of the superficial stratum corneum in atopic xerosis. *Archives of Dermatology*, 1991;Vol.127, No.11, (November 1991), pp.1689-1692, ISSN 0003-987X
- Williams, C. (2000). Epidemiology of atopic dermatitis. *Clinical and Experimental Dermatology*, Vol.25, No.7, (October 2000), pp. 522-529. ISSN 0307-6938
- Williams, C., & Wüthrich, B. (2000). The natural history of atopic dermatitis, In *Atopic dermatitis*, H.C. Williams (Ed.), 41-59, Cambridge University Press, ISBN 0-521-57075-1, Cambridge, United Kingdom.
- Wollenberg, A., Wetzel, S., Burgdorf, H. & Haas, J. (2003). Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *Journal of Allergy and Clinical Immunology*, Vol.112, No.4, (October 2003), pp.667-674, ISSN 0091-6749
- Yamaguchi, N., Sugita, R., Miki, A., Takemura, N., Kawabata, J., Watanabe, J. & Sonoyama, K. (2006). Gastrointestinal *Candida* colonisation promotes sensitisation against food antigens by affecting the mucosal barrier in mice. *Gut*, Vol.55, No.7, (July 2006), pp.954-960, ISSN 0017-5749
- Yeung, M., Balma-Mena, A., Shear, N., Simor, A., Pope, E., Walsh, S. & McGavin, J. (2011). Identification of major clonal complexes and toxin producing strains among *Staphylococcus aureus* associated with atopic dermatitis. *Microbes and Infection*, Vol.13, No.2, (February 2011), pp.189-197, ISSN 1286-4579

Yim, M., Kim, Y., Ko, H., Lee, W., Choe, B. & Ahn, J. (2010). Molecular analysis of *Malassezia* microflora on the skin of the patients with atopic dermatitis. *Annals of Dermatology*, Vol.22, No.1, (February 2010), pp.41-47, ISSN 1013-9087

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## **Atopic Dermatitis - Disease Etiology and Clinical Management**

Edited by Dr. Jorge Esparza-Gordillo

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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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