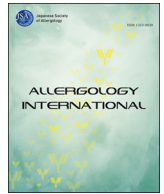




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Invited review article

Sweat allergy

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ABSTRACT

Sweat allergy is defined as a type I hypersensitivity against the contents of sweat, and is specifically observed in patients with atopic dermatitis (AD) and cholinergic urticaria (CholU). The allergic reaction is clinically revealed by positive reactions in the intradermal skin test and the basophil histamine release assay by sweat. A major histamine-releasing antigen in sweat, MGL_1304, has been identified. MGL_1304 is produced at a size of 29 kDa by *Malassezia (M.) globosa* and secreted into sweat after being processed and converted into the mature form of 17 kDa. It induces significant histamine release from basophils of patients with AD and/or CholU with MGL_1304-specific IgE, which is detected in their sera. Patients with AD also show cross-reactivity to MGL_1304-homologs in *Malassezia restricta* and *Malassezia sympodialis*, but MGL_1304 does not share cross antigenicity with human intrinsic proteins. *Malassezia* or its components may penetrate the damaged epidermis of AD lesions and interact with the skin immune system, resulting in the sensitization and reaction to the fungal antigen. As well as the improvement of impaired barrier functions by topical interventions, approaches such as anti-microbial treatment, the induction of tolerance and antibody/substance neutralizing the sweat antigen may be beneficial for the patients with intractable AD or CholU due to sweat allergy. The identification of antigens other than MGL_1304 in sweat should be the scope for future studies, which may lead to better understanding of sweat allergy and therapeutic innovations.

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Introduction

Sweat is an indispensable means to maintain the homeostasis of the skin for the thermal regulation of the body, and the retention of moisturization on the skin surface. The anti-microbial peptides in sweat also play a role in skin defense against microbes. On the other hand, sweat is considered as the triggering or exacerbating factor for atopic dermatitis (AD) and cholinergic urticaria (CholU); the skin lesions in AD are exacerbated in association with sweating, and CholU is evoked by sweating due to an elevated body core temperature. Regarding the involvement of sweat in the pathogenesis of AD and CholU, two mechanisms are possible. One is that the irritation of damaged skin by the contamination or altered pH in sweat may result in itching in AD lesions. Another possibility is the specific hypersensitivity against sweat contents, which is suggested by positive reactions in the intradermal skin test (Fig. 1) and the basophil histamine release assay by sweat. It has been postulated that endogenously produced substances in sweat cause the

observed skin reaction and histamine release. However, a major histamine-releasing antigen in sweat has been recently identified in a protein secreted by *Malassezia*, the most common fungus on the skin as part of the normal skin microbial flora, and contaminated in sweat. Moreover, there may be other intrinsic or extrinsic antigens in sweat still to be unveiled. Thus, it is controversial whether the sweat hypersensitivity is elicited exclusively by an extrinsic factor produced by the microbe and contaminated in sweat or also by an intrinsic factor secreted by the sweat gland cells. We, herein review the hypersensitivity to sweat in the context of its pathomechanism of the type I allergic reaction to sweat content.

AD and sweat

AD is a chronic, relapsing eczematous skin disease characterized by pruritus and inflammation with personal or family history of atopic diseases.¹ High levels of IgE production are observed in the sera of patients with AD, indicating that the involvement of IgE is an important factor in the pathogenesis of AD. Numerous factors such as house dust mites, foods, pollens, animals and microbes trigger the exacerbation of AD through the IgE-mediated sensitization process and the subsequent immunological responses.

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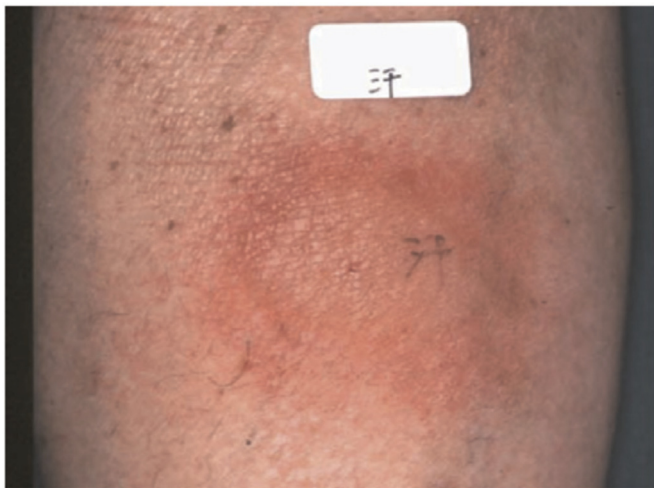


Fig. 1. A positive skin reaction in response to the intradermal injection of autologous sweat. Adapted from Hiragun M *et al.* MB Derma 2014; 220: 67–72 with permission.

Sweat is considered as one of the major exacerbation factors in AD across all age groups. Williams *et al.* reported that almost a half of children with AD viewed sweating as an aggravating factor in a large-scale study by self-completed questionnaires.² Moreover, atopic eczematous lesions, especially in children, distribute predominantly in sweat-susceptible parts of the body such as the cubital fossa, the popliteal fossa and the neck, implying the association of sweat in the formation of atopic skin lesions. In a clinical practice setting, the exacerbation of AD in school children is often observed at the time and/or seasons when sweating is frequent, whereas it is improved by continuous efforts to remove sweat by taking a shower or wiping with a wet towel. Kameyoshi *et al.* and other groups reported that skin symptoms of severe AD in school children improved by taking a shower at school during the summer season, indicating that dealing with sweat by showers at school is efficacious for the management of AD for children with severe disease.^{3–5}

The exacerbation of AD by sweat may be associated with the primary irritation evoked by the elevation of the body temperature, the altered pH of the skin surface or the contamination of dust in sweat. Nevertheless, previous literature suggested that a certain hypersensitivity to sweat is involved in the exacerbation of AD. More than 85% of patients with AD show a positive reaction upon performance of intradermal skin tests with autologous sweat (Table 1).^{6,7} The *in vitro* assay revealed that basophils from patients with AD released histamine in response to crude sweat from both healthy volunteers and patients with AD.⁷ There was no difference in the histamine release activity between sweat collected from healthy volunteers and that from patients with AD.⁷ Furthermore, sweat from healthy volunteers was semi-purified with reference to histamine releasing activity on basophils obtained from patients with AD.⁸ The semi-purified sweat antigen induced histamine release from basophils in 77% of patients with AD (Table 1), depending on the specific IgE in the sera of patients with AD.⁸ The histamine release activity in response to sweat could be transferred to basophils from healthy donors by the pre-incubation with the serum of patients with AD.⁸ Levels of the specific IgE against the semi-purified sweat antigen in sera of patients with AD were detected at a higher level than that of normal controls and were related to the severity of AD.⁹ These observations provide evidence that patients with AD have a specific IgE-mediated (type I) hypersensitivity to the contents in sweat.

Table 1

Positive rates of sweat allergy in patients with atopic dermatitis and cholinergic urticaria.

Authors	Methods	Atopic dermatitis	Cholinergic urticaria	Healthy control
Adachi K ⁶	ASwST	96% (43/45)	–	18% (4/22)
Hide M ⁷	ASwST	85% (56/66)	–	11% (3/27)
Tanaka A ⁸	HRT by purified sweat antigen	77% (47/61)	–	9% (4/46)
Adachi J ¹²	ASwST	–	100% (20/20)	0% (0/20)
Fukunaga A ¹³	ASwST	–	65% (11/17)	0% (0/10)
	HRT by autologous sweat	–	59% (10/17)	0% (0/10)
Takahagi S ¹¹	HRT by purified sweat antigen	–	66% (23/35)	0% (0/14)

ASwST, autologous sweat skin test; HRT, histamine release test.

CholU and sweat

CholU is characterized by unique clinical features; pin-sized, highly pruritic wheals with surrounding erythema induced by sweating during physical exercise, taking a bath, raising the body temperature or emotional stress.¹⁰ This disorder usually affects young adults and approximately half of the patients with CholU have atopic diathesis.¹¹ The precise underlying mechanism of the wheal response in CholU has not yet been clarified, but it has been proposed that the hypersensitivity to sweat may be involved in the pathogenesis. Indeed, more than 65% of patients with CholU showed positive immediate-type skin reactions when performing an intradermal skin test with autologous sweat (Table 1).^{12,13} A wheal and flare reaction in patients with CholU may also be produced, in the normal-appearing skin, in response to sweating induced by the intradermal injection of acetylcholine, which stimulates the muscarinic M3 receptor and induces sweating in the local site of its injection. Moreover, 66% of patients with CholU showed histamine release against the semi-purified sweat antigen,¹¹ while 75% of patients with AD did (Table 1).⁸ Levels of the specific IgE binding to the semi-purified sweat antigen in sera of patients with CholU were significantly higher than those of normal controls, as seen in AD.⁹ Furthermore, recent reports have mentioned that omalizumab, a humanized monoclonal antibody against IgE, is effective for patients with CholU, indicating that CholU may be mediated by pathogenic IgE.¹⁴

These facts suggest that IgE-mediated hypersensitivity to the constituents of sweat is also involved in the pathogenesis of CholU as in AD. Nakamizo *et al.* suggested that CholU can be categorized into at least four subtypes: (i) CholU with poral occlusion; (ii) CholU with acquired generalized hypohidrosis; (iii) CholU with possible sweat allergy; and (iv) idiopathic CholU.¹⁰

MGL_1304 secreted by *Malassezia* as a histamine release molecule in sweat

The specific substance that induces histamine release from basophils of patients with AD and CholU had not been identified, even after more than two decades since the first report of IgE binding to crude sweat components by Adachi *et al.*⁶ We semi-purified human sweat from healthy volunteers by chromatography techniques with reference to its histamine releasing activity on basophils obtained from patients with AD (Fig. 2a).⁸ The semi-purified sweat antigen was further purified with two additional reverse phase chromatography steps (Fig. 2b, c). As a result, mass spectrometric analysis of a peak fraction of UV absorption, which corresponded to the peak fraction of histamine releasing activity revealed a sequence identical to a part of the hypothetical protein secreted by *Malassezia* (M.)

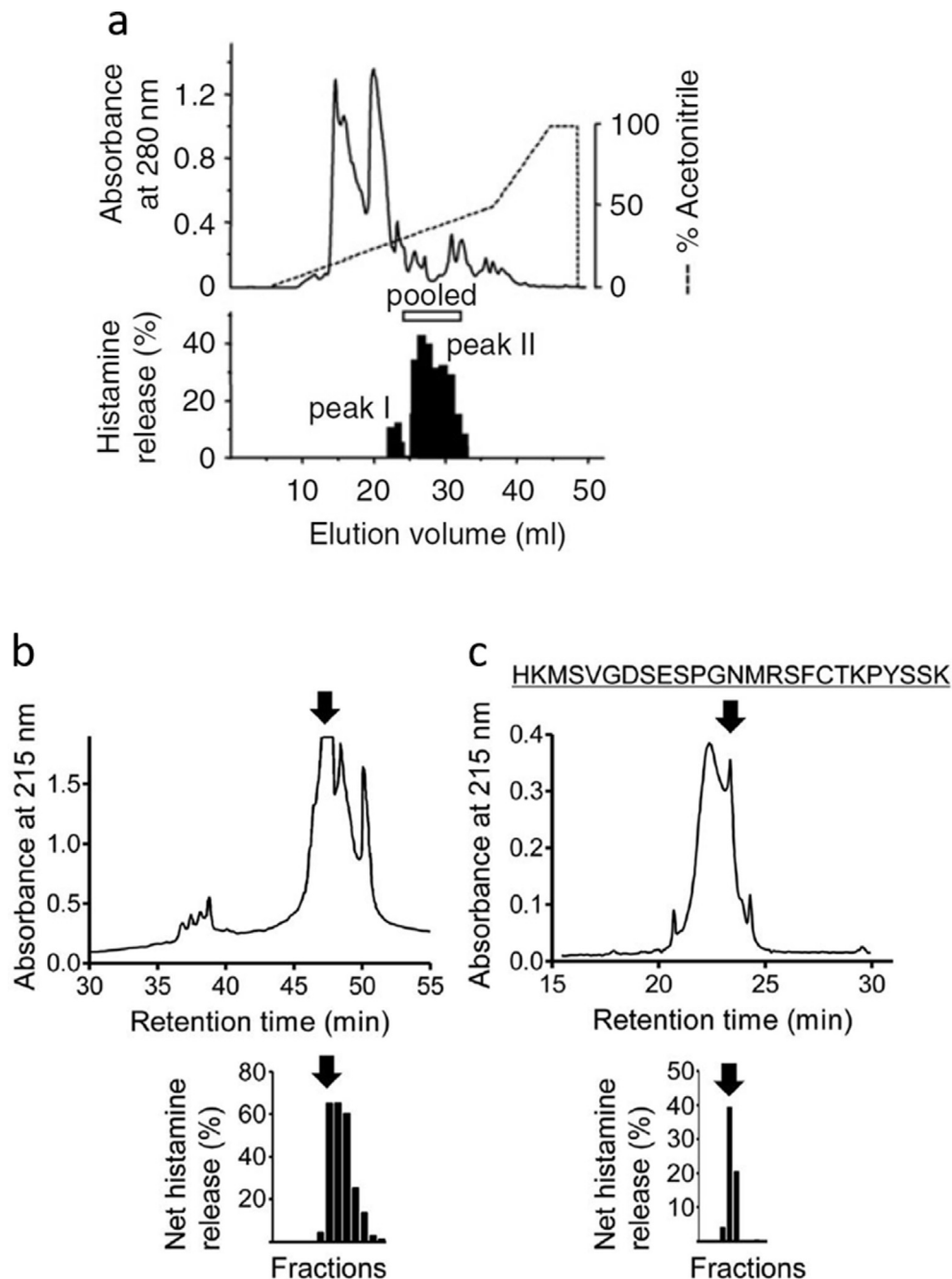


Fig. 2. Chromatographic profiles of the histamine-releasing activity and identification of MGL_1304 in sweat. (a) Sweat was purified with SOURCE 15RPC ST 4.6/100 column chromatography. The fractions with histamine-releasing activity indicated by open bar were used as “semi-purified sweat antigen (QRX)” (From ref 8 with permission). QRX was further purified with an Aqua 5 m-C18-200 Å column (b) and with a Jupiter 5 m-C18-300 Å HPLC column (c) based on histamine-releasing activity. The fraction indicated by arrows in (b) was further purified in (c). The peptide sequence identified by mass spectrometry is shown in (c), which corresponded to a partial sequence of MGL_1304. Adapted from Hiragun et al.¹⁵ with permission.

globosa, MGL_1304 (Fig. 2c).¹⁵ The recombinant MGL_1304 expressed in *Escherichia coli* evoked histamine release from basophils of patients with AD.¹⁵ It was immunologically identical to the previously reported “semi-purified sweat antigen”⁸ as analyzed in neutralization assays using immunoblotting and degranulation assays with RBL-48 cells, a rat basophilic leukemia cell line that expresses the human high affinity IgE receptor (Fig. 3a).¹⁵

MGL_1304 is produced at a size of 29 kDa in *M. globosa* and secreted into sweat after being processed by unidentified proteases and is then converted into the mature form of 17 kDa.¹⁵ The conformational structure of secreted MGL_1304 is critical for the

binding of IgE from patients with AD.¹⁵ None of the four partially overlapping peptides of MGL_1304 bound to IgE of the patients with AD.¹⁵ MGL_1304-specific IgE was detected in sera of both patients with AD and CholU.⁹ Levels of MGL_1304-specific IgE in sera of patients with AD were significantly higher than those of normal controls, along with the significant correlation with disease severities of AD.⁹

MGL_1304 was identified as a major histamine releasing antigen in sweat. However, neither lysates nor culture supernatants of *M. globosa* showed a clear IgE-binding band detected by immunoblotting with sera of patients with AD, while a 42-kDa protein

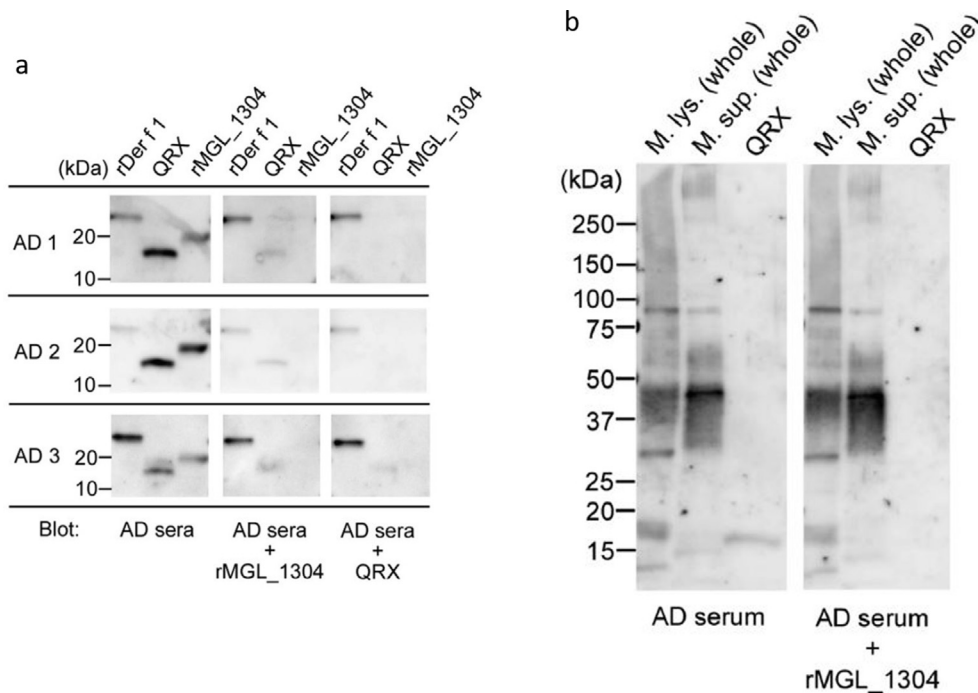


Fig. 3. rMGL_1304 captured immunoreactive IgE against the semi-purified sweat antigen (QRX) from sera of patients with AD. **(a)** Antigens (rDer f 1, QRX, and rMGL_1304) were blotted with sera of patients with AD, sera pretreated with rMGL_1304, or sera pretreated with QRX. IgE-reactivity to QRX and rMGL_1304 was absorbed by the pretreatment with rMGL_1304 or QRX, respectively. Adapted from the reference 15 with permission. **(b)** The whole lysate (M. lys. (whole)) and whole culture supernatant (M. sup. (whole)) of *M. globosa*, and QRX were blotted by serum of a patient with AD or the serum pretreated with rMGL_1304. The pretreatment with rMGL_1304 depleted the immunoreactive IgE against QRX, whereas the IgE-binding patterns to whole lysate and whole culture supernatant of *M. globosa* were not affected. Adapted from the Hiragun *et al.*¹⁵ with permission.

band was dominantly detected in accordance with a previous report of an *M. globosa* antigen (Fig. 3b).¹⁶ Moreover, the concentration of MGL_1304 in sweat was determined as 0.6–8.0 ng/ml (3.76 ± 2.64 ng/ml, mean $\pm$ SD),¹⁷ while the concentration of total protein in sweat was 186 ng/ml.⁸ These findings suggest that MGL_1304 consists of a minor amount of proteins in sweat, but has a particular allergic activity that induces histamine release in patients with AD.

Malassezia as a source of the sweat antigen

The sweat antigen, MGL_1304 is secreted by *Malassezia* which is now believed to be the most common skin inhabitants of human and animals and currently encompasses 17 species.¹⁸ *Malassezia* occupies a part of the normal cutaneous flora that is composed of numerous kinds of microbiota such as bacteria, fungi and viruses. Most of *Malassezia* have a predilection for sebaceous skin sites such as the head and neck, because they rely on exogenous fatty acid sources to satisfy their nutritive requirement due to their lack of genes for fatty acid synthesis.¹⁹ Ten of the 17 *Malassezia* species are found mainly on the human skin, but the other 7 species on animal skin.¹⁸

Malassezia comprises a large portion (53–80% depending on different sites) of the fungal flora of the healthy skin,²⁰ but also plays a pathogenic role in skin diseases such as pityriasis versicolor, *Malassezia* folliculitis, seborrheic dermatitis and atopic dermatitis. Several studies have recently investigated the precise epidemiology of *Malassezia* in healthy and diseased skin by culture-independent, molecular methods. Overall, *Malassezia restricta* and *M. globosa* are the most commonly identified species on human skin, with *Malassezia sympodialis* a distant third.¹⁸ However, considerable species diversity exists with high site specificity between body sites. For example, *M. restricta* predominates on scalp and facial areas, while *M. globosa* dose on scalp, back, and groin.²¹ The hands

and arms are characterized by mixed proportions of *M. globosa*, *M. restricta*, and *M. sympodialis*.²¹

A comparison of healthy individuals and AD patients did not reveal a difference in the frequency of skin colonization with *Malassezia*.^{19,22} However, levels of *Malassezia* colonization in patients with severe neck and head AD was approximately 2- to 5-fold of that in mild and moderate neck and head AD and healthy controls.²² Two major microbiota, *M. globosa* and *M. restricta*, accounted for more than 80% of all *Malassezia* colonization in AD patients, and their proportions differ in association with disease severity. In mild and moderate AD patients, *M. restricta* was predominant over *M. globosa*, whereas the proportions of *M. globosa* and *M. restricta* were almost identical in severe patients.²²

It has been speculated that the difference of the amount and proportion of *Malassezia* species between the AD and the healthy skin depends on the altered skin conditions in patients with AD and the microbial strains residing in lesions. In fact, the skin pH, epidermal water content and composition of anti-microbial peptides and lipids may affect the difference of fungal microbiota between patients with AD and healthy individuals.²³ Moreover, sequence analysis for polymorphism of the intergenic spacer (IGS) in *M. globosa* and *M. restricta* genome has revealed the difference between the genotypes of *Malassezia* obtained from AD patients and healthy subjects.^{24,25} It suggests that strains of *M. globosa* and *M. restricta* in patients with AD may be specifically pathogenic for the disease.

Malassezia antigens and their cross-reactivity with human counterparts

Patients with AD are predisposed to develop high levels of IgE production against numerous antigens such as house dust mites, foods, pollens, animals and microbes. In addition, *Malassezia* as part of the skin flora interacts with the skin immune system especially

in skin lesions of AD, resulting in the production of *Malassezia*-specific IgE antibodies through the dendritic cells and T cell-mediated activation of B cells.¹⁹ Indeed, *Malassezia*-specific IgE are found in 5%–27% of children and 29%–65% of adults with AD, while healthy individuals are usually not sensitized to this fungus.¹⁹ Levels of *Malassezia*-specific IgE positively correlate to the severity of AD²⁶ as the same manner with MGL_1304-specific IgE.⁹ The high frequency of *Malassezia*-sensitization in AD patients compared to healthy individuals may be attributed to a combination of dysfunctional skin barrier, genetic background, and environmental factors seen in patients with AD.¹⁹ Moreover, it is controversial if the *Malassezia*-specific IgE-mediated response plays a pathogenic role in lesions of AD or rather serves as a marker for the severity of AD.¹⁹

To date, 13 allergens from two *Malassezia* species, *M. furfur* and *M. sympodialis*, are approved and listed by the WHO/IUIS Allergen Nomenclature Sub-committee (<http://www.allergen.org>) (Table 2). Additively, two other antigens from *M. globosa* have been recently reported; MGL_1304¹⁵ and MGp42¹⁶ (Table 2). Ishibashi *et al.* found that a 42 kDa protein (MGp42) was the major allergen of *M. globosa* determined by immunoblotting for AD.¹⁶ Further, patients with AD showed hypersensitivities against MGL_1304 and cross-reactivity to its homologs in *M. restricta* (i.e. Mala s 8) and *M. sympodialis* (Mala s 8).^{15,27}

A certain population (38%) of patients with AD shows IgE reactivity to various human self-proteins.²⁸ Such autoreactivity associated to AD is described for the repertoire of at least 140 IgE-binding self-antigens.²⁹ The IgE autoreactivity was specifically found in AD, but failed to be shown in allergic rhinoconjunctivitis and other control individuals.²⁸ The pathological roles of such autoantigens in AD remain controversial, but some have cross reactivity to environmental allergens derived from pollen or fungi.³⁰ A part of the *Malassezia* antigens also share cross antigenicities with certain human proteins. For example, human manganese superoxide dismutase and thioredoxin are highly cross reactive to counterparts of *M. sympodialis*, Mala s 11 and Mala s 13, respectively.^{31,32} Regarding *M. globosa* antigens, MGp42 showed sequence similarity to members of the heat shock protein 70 (HSP70) family. However, there is no IgE cross-reactivity between MGp42 and human HSP70 in terms of IgE binding activity.¹⁶ A human counterpart for MGL_1304 has not yet been identified. Sweat antigens with histamine releasing ability were explored in a cDNA library of 120,000 clones from mRNA of human skin using a histamine releasing assay. However, it failed to detect cDNA clones

that induce histamine release from basophils of patients with AD in the same manner as cDNA of MGL_1304.³³

As for the development of such autoreactivity, it has been speculated that scratching at the site of AD lesions results in cellular damage and release of membranous and intracellular self-antigens from keratinocytes and possibly other skin cells, which allows these self-antigens to interact with the immune system and potentially to induce autoallergy.³⁰ Although the autoantibody may subsequently cross-react to *Malassezia* antigens, the sensitization to *Malassezia* antigens has the strong correlation to the severity of AD, implying that the production of *Malassezia*-specific IgE is the primary immunological reaction and the response to human counterparts is subsequently elicited. In fact, *Malassezia* or its components penetrates the epidermis through the disturbed skin barrier in AD lesions and the interaction with skin immune system may evoke the autoreactivity between fungal antigens and their human counterparts, which may sustain skin inflammation in AD.¹⁹

Sweat allergy as a type I allergic reaction to sweat

Sweat is indispensable to maintain the homeostasis in mammals with a stable body temperature. Humans have eccrine sweat glands over the body and perspire to regulate body temperature effectively along with the activation of the other thermal control mechanisms, such as expiration and heat transfer.³⁴ Sweat is also a constituent of the sebum film which covers the skin surface as a protective wall.³⁴ The film exerts a moisturizing effect on the surface of the skin and a cultivation effect of the skin's normal microflora. Human eccrine sweat is a dilute electrolyte that contains water, sodium, potassium, bicarbonate, chloride, lactate, urea, ammonia, and small quantities of various amino acids.³⁵ The proteins in eccrine sweat include proteases (e.g. kallikreins), protease inhibitors (e.g. cystatins), anti-microbial peptides (AMPs; e.g., dermcidin³⁶ and cathelicidin³⁷) and secretory IgA,³⁸ which act to defend against external pathogens. In addition to substances that induce an immediate hypersensitivity reaction, human sweat also contains proinflammatory cytokines (interleukin (IL)-1 α , IL-1 β , and IL-31) which activate keratinocytes.³⁹

Sweat allergy is defined as the IgE-mediated immediate type reaction against such sweat contents as seen in patients with AD and CholU. The allergic reaction can be examined by an *in vivo* positive reaction of the intradermal injection of sweat, the detection of reactive serum IgE against sweat contents by ELISA or western blotting, and functional histamine release from basophils against the sweat contents.^{8,9,11} These examinations support the involvement of type I allergy against MGL_1304 in both patients with AD and patients with CholU. Despite the same characteristics as type I allergic reactions, the skin lesions present in both diseases are apparently different. The skin lesions of AD show acute and chronic eczematous inflammation with epidermal change, while CholU shows short time urticarial reactions along with wheal and flare, which repeatedly emerges and disappears with the intact epidermis. Although other substances may affect the presentation of both skin lesions, there is no explanation for the difference of skin lesions between AD and CholU – one is eczematous and another is urticarial.

Sweat allergy is a highly specific phenomenon in AD and CholU. Reactivity to the semi-purified sweat antigen shows high sensitivity and specificity for patients with AD and/or CholU, whereas no histamine release is observed in basophils from healthy controls and other control individuals, such as patients with psoriasis.⁸ Moreover, serum levels of specific IgE against MGL_1304 in patients with AD were significantly higher than those of normal healthy controls.⁹ However, the titers of MGL_1304 specific IgE in the serum of patients with bronchial asthma and patients with allergic conjunctivitis do not show a significant difference to

Table 2
Allergic proteins from *Malassezia*.

Species	Allergen	Biological activity	Molecular weight
<i>Malassezia furfur</i>	Mala f 2	Peroxisomal membrane protein	21
	Mala f 3	Peroxisomal membrane protein	20
	Mala f 4	Mitochondrial malate dehydrogenase	35
<i>Malassezia sympodialis</i>	Mala s 1	Cyclophilin	
	Mala s 5		
	Mala s 6		
	Mala s 7		
	Mala s 8		
	Mala s 9	Heat shock protein 70	86
	Mala s 10		
	Mala s 11		
	Mala s 12		
	Mala s 13	Thioredoxin	13
<i>Malassezia globosa</i>	MGp42	Heat shock protein 70	42
	MGL_1304		17

normal healthy controls.⁹ Thus, the sensitization of MGL_1304 seems to be relevant to AD and CholU rather than atopic diathesis.

Hypersensitivity against sweat has been revealed as the IgE-mediated immediate type allergic reaction against a fungal secreting protein, MGL_1304. This means that the sweat-evoked allergic reaction is due to a reaction against an extrinsic substance that is mixed with human sweat, but not against genuine endogenous substances produced by sweat glands. It is certain that a main part of the histamine-release substance in sweat is due to MGL_1304, but this cannot explain all activities of antigens in sweat. Indeed, Tanaka *et al.* eluted two peaks of semi-purified sweat antigen(s) with reference to histamine release from basophils: peak I and peak II (Fig. 2a).⁸ The fractions corresponding with peak II were pooled as the fraction from which semi-purified sweat antigen and consequentially MGL_1304 was purified and identified as the histamine releasing activity (Fig. 2). The fractions composing the other peak, peak I, may include other histamine releasing antigens. Thus, sweat may contain other exogenous or even endogenous antigens with biological activities and pathological relevance to AD. In fact, Kaneko *et al.* reported the usefulness of sweat management for patients with adult AD regardless of the reactivity in a sweat allergy test by using semi-purified sweat antigen.⁴⁰ The identification of such antigens in sweat should be the scope of future studies.

Dealing with sweat allergy

Although sweating is an essential physiological phenomenon, leaving excess sweat on the skin surface contributes to the exacerbation of AD symptoms. Since antigens as well as contamination are contained in sweat on the surface of the skin, removal of antigens from the skin surface by showering or bathing is an easy and convenient way to deal with sweat allergy in patients with AD^{3–5} (as mentioned above in the Section entitled “AD and sweat”). Moreover, damaged skin barrier promotes the infiltration of sweat antigen into the dermis, resulting in contact of the antigen with Langerhans cells and subsequent sensitization of mast cells to release inflammatory mediators such as histamine. Therefore, improvement of impaired barrier functions by topical corticosteroids and emollients for AD lesions may be effective to prevent the sensitization and reaction against sweat in patients with AD.

Systemic antifungal therapy is considered useful to reduce the amount of *Malassezia* on the skin, which represents the source of the major histamine releasing antigen, MGL_1304. Indeed, the efficacy of systemic antifungal therapy for patient with AD has been reported in several randomized, placebo-controlled trials involving the short-term use of oral ketoconazole or itraconazole.^{41,42} Itraconazole and other azole antifungals over a 2-year period have also been reported to be effective for more than two-thirds of adult patients with head and neck predominant AD.⁴³ Regarding the use of long term antifungal agents, the safety and the development of resistance by medications should be an important concern. Moreover, antifungal treatments could suppress the entire growth of microbiota with a disturbance of normal flora, and may cause unexpected adverse events in patients. For example, a protease secreted by *M. globosa* was reported to be beneficial for skin health by hydrolyzing the *Staphylococcus* (*S.*) *aureus* protein A and blocked the formation of biofilm by *Staphylococcus aureus*.⁴⁴ Therefore, the removal of *M. globosa* by antifungal treatment may induce the growth and activation of *S. aureus* on the skin. Thus, the specific removal or inactivation of only pathological antigen is preferred to non-specific antifungal treatments.

The induction of tolerance against sweat antigen(s) is another strategy to overcome sweat allergy. Desensitization by purified sweat antigen or crude autologous sweat has been reported to be effective

for CholU. Tanaka *et al.* reported that a patient with CholU, who showed a positive skin reaction against autologous sweat and histamine release from his peripheral-blood leukocytes against the purified sweat antigen, was desensitized by using partially purified sweat antigen.⁴⁵ Following treatments over 21 months, both pruritus and wheals were improved, and the reactivity of peripheral blood leukocytes against sweat antigen decreased as immunotherapy proceeded.⁴⁵ In another study, six patients with severe CholU and positive intradermal skin tests by the own sweat were enrolled in a rapid desensitization protocol, which attenuated the responses for skin tests with autologous sweat and reduced symptoms.⁴⁶

Molecular targeting drugs, which inhibit specific molecules involved in the development of diseases, have been emerging for the treatment of various diseases, including allergic diseases, such as AD and urticaria. A human monoclonal IgE (ABS-IgE) was identified to bind to MGL_1304, but does not induce histamine release from basophils and mast cells.¹⁷ ABS-IgE prevents histamine release from mast cells and basophils by neutralizing MGL_1304 not only in a free form in solution, but also on FcεRI expressed on the cell surface without cell activation. This feature of ABS-IgE is beneficial for the specific prevention and treatment of sweat allergy by MGL_1304, because not only does it neutralize the causative antigen, but it also prevents the sensitization of FcεRI with pathological IgE that activates mast cells and basophils. Thus, ABS-IgE may be used for the treatment of diseases caused or aggravated by type I allergy to MGL_1304.

Another substance that neutralizes the histamine-release ability of semi-purified sweat allergen is tannic acid (TA), which is a natural polyphenolic compound and protein-denaturing agent contained in grapes and green tea. TA suppresses histamine release by semi-purified sweat antigen in a dose-dependent manner *in vitro*.⁴⁷ A TA spray applied after bathing, and an aerosol spray containing TA both improved the symptoms of patients with AD.⁴⁷ TA may degenerate antigens and/or make soluble proteins insoluble. Lower concentrations of TA inhibit the binding of recombinant MGL_1304 produced by *Pichia Pastoris* to IgE, and a higher concentration of TA transferred the antigen to an insoluble fraction.³³ More recently, Nakamura *et al.* reported the application of TA to mouse skin treated by tape stripping and reconstructed human epidermal model. They showed that levels as low as 0.5 and/or 5 mg TA prevent the penetration of fluorescent dye, the development of erythema index and IL-1α production.⁴⁸

Conclusions

MGL_1304, which is produced and secreted by *M. globosa*, was found to be a main antigen in human sweat. It induces histamine release from basophils of patients with AD and those with CholU. Damage of the skin barrier in AD may promote the penetration of MGL_1304 into the epidermis and its action on dermal mast cells bearing specific IgE. However, it has not been directly proved whether the IgE-mediated reaction is associated with clinical exacerbation of skin inflammation in the lesions of AD. Moreover, there may be other histamine releasing antigens in sweat that are involved in the pathogenesis of AD and CholU. It is currently unknown whether *M. globosa* play a mutualistic or a pathogenic role for the immune homeostasis of the host. Further studies are needed for better understanding of sweat allergy and to innovate improved therapies for allergic diseases associated with sweat, such as AD and CholU.

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Conflict of interest

The authors have no conflict of interest to declare.

References

1. Saeki H, Nakahara T, Tanaka A, Kabashima K, Sugaya M, Murota H, et al. Clinical practice guidelines for the management of atopic dermatitis 2016. *J Dermatol* 2016;**43**:1117–45.
2. Williams JR, Burr ML, Williams HC. Factors influencing atopic dermatitis—a questionnaire survey of schoolchildren's perceptions. *Br J Dermatol* 2004;**150**:1154–61.
3. Murota H, Takahashi A, Nishioka M, Matsui S, Terao M, Kitaba S, et al. Showering reduces atopic dermatitis in elementary school students. *Eur J Dermatol* 2010;**20**:410–1.
4. Mochizuki H, Muramatsu R, Tadaki H, Mizuno T, Arakawa H, Morikawa A. Effects of skin care with shower therapy on children with atopic dermatitis in elementary schools. *Pediatr Dermatol* 2009;**26**:223–5.
5. Kameyoshi Y, Tanaka T, Mochizuki M, Koro O, Mihara S, Hiragun T, et al. [Taking showers at school is beneficial for children with severe atopic dermatitis]. *Arerugi* 2008;**57**:130–7 (in Japanese).
6. Adachi K, Aoki T. IgE antibody to sweat in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1989;**144**:83–7.
7. Hide M, Tanaka T, Yamamura Y, Koro O, Yamamoto S. IgE-mediated hypersensitivity against human sweat antigen in patients with atopic dermatitis. *Acta Derm Venereol* 2002;**82**:335–40.
8. Tanaka A, Tanaka T, Suzuki H, Ishii K, Kameyoshi Y, Hide M. Semi-purification of the immunoglobulin E-sweat antigen acting on mast cells and basophils in atopic dermatitis. *Exp Dermatol* 2006;**15**:283–90.
9. Hiragun M, Hiragun T, Ishii K, Suzuki H, Tanaka A, Yanase Y, et al. Elevated serum IgE against MGL 1304 in patients with atopic dermatitis and cholinergic urticaria. *Allergol Int* 2014;**63**:83–93.
10. Nakamizo S, Egawa G, Miyachi Y, Kabashima K. Cholinergic urticaria: pathogenesis-based categorization and its treatment options. *J Eur Acad Dermatol Venereol* 2012;**26**:114–6.
11. Takahagi S, Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Shindo H, et al. Sweat antigen induces histamine release from basophils of patients with cholinergic urticaria associated with atopic diathesis. *Br J Dermatol* 2009;**160**:426–8.
12. Adachi J, Aoki T, Yamatodani A. Demonstration of sweat allergy in cholinergic urticaria. *J Dermatol Sci* 1994;**7**:142–9.
13. Fukunaga A, Bito T, Tsuru K, Ohashi A, Yu X, Ichihashi M, et al. Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes. *J Allergy Clin Immunol* 2005;**116**:397–402.
14. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. *J Allergy Clin Immunol* 2018;**141**:638–49.
15. Hiragun T, Ishii K, Hiragun M, Suzuki H, Kan T, Mihara S, et al. Fungal protein MGL 1304 in sweat is an allergen for atopic dermatitis patients. *J Allergy Clin Immunol* 2013;**132**:608–15.e4.
16. Ishibashi Y, Kato H, Asahi Y, Sugita T, Nishikawa A. Identification of the major allergen of *Malassezia globosa* relevant for atopic dermatitis. *J Dermatol Sci* 2009;**55**:185–92.
17. Ishii K, Hiragun M, Hiragun T, Kan T, Kawaguchi T, Yanase Y, et al. A human monoclonal IgE antibody that binds to MGL 1304, a major allergen in human sweat, without activation of mast cells and basophils. *Biochem Biophys Res Commun* 2015;**468**:99–104.
18. Grice EA, Dawson Jr TL. Host-microbe interactions: *Malassezia* and human skin. *Curr Opin Microbiol* 2017;**40**:81–7.
19. Glatz M, Bosshard PP, Hoetzelnecker W, Schmid-Grendelmeier P. The role of *Malassezia* spp. in atopic dermatitis. *J Clin Med* 2015;**4**:1217–28.
20. Gao Z, Perez-Perez GI, Chen Y, Blaser MJ. Quantitation of major human cutaneous bacterial and fungal populations. *J Clin Microbiol* 2010;**48**:3575–81.
21. Findley K, Oh J, Yang J, Conlan S, Deming C, Meyer JA, et al. Topographic diversity of fungal and bacterial communities in human skin. *Nature* 2013;**498**:367–70.
22. Kaga M, Sugita T, Nishikawa A, Wada Y, Hiruma M, Ikeda S. Molecular analysis of the cutaneous *Malassezia* microbiota from the skin of patients with atopic dermatitis of different severities. *Mycoses* 2011;**54**:e24–8.
23. Zhang E, Tanaka T, Tajima M, Tsuboi R, Nishikawa A, Sugita T. Characterization of the skin fungal microbiota in patients with atopic dermatitis and in healthy subjects. *Microbiol Immunol* 2011;**55**:625–32.
24. Sugita T, Kodama M, Saito M, Ito T, Kato Y, Tsuboi R, et al. Sequence diversity of the intergenic spacer region of the rRNA gene of *Malassezia globosa* colonizing the skin of patients with atopic dermatitis and healthy individuals. *J Clin Microbiol* 2003;**41**:3022–7.
25. Sugita T, Tajima M, Amaya M, Tsuboi R, Nishikawa A. Genotype analysis of *Malassezia restricta* as the major cutaneous flora in patients with atopic dermatitis and healthy subjects. *Microbiol Immunol* 2004;**48**:755–9.
26. Glatz M, Buchner M, von Bartenwerffer W, Schmid-Grendelmeier P, Worm M, Hedderich J, et al. *Malassezia* spp.-specific immunoglobulin E level is a marker for severity of atopic dermatitis in adults. *Acta Derm Venereol* 2015;**95**:191–6.
27. Kohsaka T, Hiragun T, Ishii K, Hiragun M, Kamegashira A, Hide M. Different hypersensitivities against homologous proteins of MGL 1304 in patients with atopic dermatitis. *Allergol Int* 2018;**67**:103–8.
28. Tang TS, Bieber T, Williams HC. Does "autoreactivity" play a role in atopic dermatitis? *J Allergy Clin Immunol* 2012;**129**:1209–15.e2.
29. Zeller S, Rhyner C, Meyer N, Schmid-Grendelmeier P, Akdis CA, Cramer R. Exploring the repertoire of IgE-binding self-antigens associated with atopic eczema. *J Allergy Clin Immunol* 2009;**124**:278–85. 85.e1–7.
30. Cipriani F, Ricci G, Leoni MC, Capra L, Baviera G, Longo G, et al. Autoimmunity in atopic dermatitis: biomarker or simply epiphenomenon? *J Dermatol* 2014;**41**:569–76.
31. Schmid-Grendelmeier P, Fluckiger S, Disch R, Trautmann A, Wuthrich B, Blaser K, et al. IgE-mediated and T cell-mediated autoimmunity against manganese superoxide dismutase in atopic dermatitis. *J Allergy Clin Immunol* 2005;**115**:1068–75.
32. Balaji H, Heratizadeh A, Wichmann K, Niebuhr M, Cramer R, Scheynius A, et al. *Malassezia sympodialis* thioredoxin-specific T cells are highly cross-reactive to human thioredoxin in atopic dermatitis. *J Allergy Clin Immunol* 2011;**128**:92–9.e4.
33. Hiragun T, Hiragun M, Ishii K, Kan T, Hide M. Sweat allergy: extrinsic or intrinsic? *J Dermatol Sci* 2017;**87**:3–9.
34. Murota H, Katayama I. Exacerbating factors of itch in atopic dermatitis. *Allergol Int* 2017;**66**:8–13.
35. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. *J Am Acad Dermatol* 1989;**20**:537–63.
36. Schitteck B, Hipfel R, Sauer B, Bauer J, Kalbacher H, Stevanovic S, et al. Dermicidin: a novel human antibiotic peptide secreted by sweat glands. *Nat Immunol* 2001;**2**:1133–7.
37. Murakami M, Ohtake T, Dorschner RA, Schitteck B, Garbe C, Gallo RL. Cathelicidin anti-microbial peptide expression in sweat, an innate defense system for the skin. *J Invest Dermatol* 2002;**119**:1090–5.
38. Okada T, Konishi H, Ito M, Nagura H, Asai J. Identification of secretory immunoglobulin A in human sweat and sweat glands. *J Invest Dermatol* 1988;**90**:648–51.
39. Dai X, Okazaki H, Hanakawa Y, Murakami M, Tohyama M, Shirakata Y, et al. Eccrine sweat contains IL-1alpha, IL-1beta and IL-31 and activates epidermal keratinocytes as a danger signal. *PLoS One* 2013;**8**:e67666.
40. Kaneko S, Murota H, Murata S, Katayama I, Morita E. Usefulness of sweat management for patients with adult atopic dermatitis, regardless of sweat allergy: a pilot study. *Biomed Res Int* 2017;**2017**:8746745.
41. Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo K. Systemic ketocazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. *Allergy* 2001;**56**:512–7.
42. Svejgaard E, Larsen PO, Deleuran M, Ternowitz T, Roed-Petersen J, Nilsson J. Treatment of head and neck dermatitis comparing itraconazole 200 mg and 400 mg daily for 1 week with placebo. *J Eur Acad Dermatol Venereol* 2004;**18**:445–9.
43. Kaffenberger BH, Mathis J, Zirwas MJ. A retrospective descriptive study of oral azole antifungal agents in patients with patch test-negative head and neck predominant atopic dermatitis. *J Am Acad Dermatol* 2014;**71**:480–3.
44. Li H, Goh BN, Teh WK, Jiang Z, Goh JPZ, Goh A, et al. Skin commensal *Malassezia globosa* secreted protease attenuates *Staphylococcus aureus* biofilm formation. *J Invest Dermatol* 2018;**138**:1137–45.
45. Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Hide M. [Cholinergic urticaria successfully treated by immunotherapy with partially purified sweat antigen]. *Arerugi* 2007;**56**:54–7 (in Japanese).
46. Kozaru T, Fukunaga A, Taguchi K, Ogura K, Nagano T, Oka M, et al. Rapid desensitization with autologous sweat in cholinergic urticaria. *Allergol Int* 2011;**60**:277–81.
47. Shindo H, Takahagi S, Mihara S, Tanaka T, Ishii K, Hide M, et al. [Efficacy of sweat-antigen-inactivating skin care products on itching of patients with atopic dermatitis]. *Arerugi* 2011;**60**:33–42 (in Japanese).
48. Nakamura T, Yoshida N, Yasoshima M, Kojima Y. Effect of tannic acid on skin barrier function. *Exp Dermatol* 2017. <https://doi.org/10.1111/exd.13478>.