



Sweat allergy: Extrinsic or intrinsic?



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ABSTRACT

Sweat is an exacerbation factor in atopic dermatitis (AD) in all age groups. A body core temperature elevation with sweating triggers cholinergic urticaria (CholU). We recently reported that AD symptoms are improved by tannic acid-containing spray, which suppresses the basophil histamine release induced by semi-purified sweat antigen *in vitro*, and by showering, which removes antigens in sweat from the skin surface. Sweat contains small amount of proteins including proteases, protease inhibitors, and antimicrobial peptides. We finally identified MGL_1304 secreted by *Malassezia (M.) globosa* as a major histamine – releasing antigen in human sweat. MGL_1304 is a 17-kDa protein in sweat that elicits almost the highest histamine – release activity from basophils of patients with AD and CholU among antigens derived from *Malassezia* species. Moreover, serum levels of anti-MGL_1304 IgE were significantly higher in patients with AD and CholU than in normal controls. The recombinant protein produced by *Pichia pastoris* possessed comparable allergenicity to native MGL_1304. We found a monoclonal IgE antibody against MGL_1304 which did not elicit histamine release from sensitized mast cells. Desensitization therapy using autologous sweat, or MGL_1304 purified from culture of *M. globosa* or its cognates might be beneficial for patients with intractable CholU due to sweat allergy.

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1. Introduction

Atopic dermatitis (AD) is a chronic relapsing eczematous skin disease characterized by pruritus and inflammation, accompanied

Abbreviations: AD, atopic dermatitis; CholU, cholinergic urticaria.

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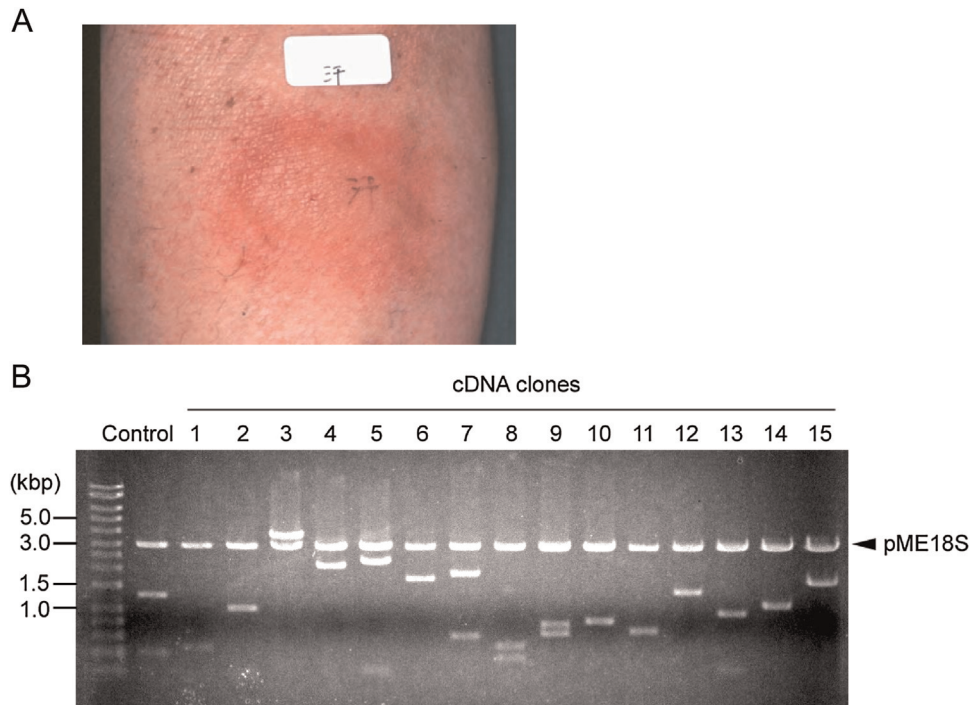


Fig. 1. (A) Positive reaction to an intradermal skin test using autologous sweat in a patient with atopic dermatitis (from clinical data of Hiroshima University). (B) A skin cDNA library constructed and used for the expression cloning of intrinsic sweat antigens. A cDNA library was generated using the pME18S mammalian expression vector and human skin mRNA, and possessed 7.9×10^6 CFUs with a mean insert size of 1.6 kbps.

by cutaneous physiological dysfunction (dry and barrier-disrupted skin) [1]. Sweat is considered as one of the major exacerbation factors in AD across all age groups [2], and might account for the characteristic distribution of eczematous lesions in sweat-susceptible areas (such as the cubital and popliteal fossa). On the other hand, sweat contains natural moisturizing factors and maintains the physiologic hydration state of the stratum corneum [3]. Cholinergic urticaria (CholU) is a subtype of chronic inducible urticaria with symptoms evoked by sweating due to an elevated body core temperature [4,5]. Although the pathogenesis of CholU has not been fully clarified, approximately half of the patients with CholU have atopic diathesis [6].

2. Background of sweat allergy

Sweat allergy, hypersensitivity to one's own sweat, was first described in the English literature by Adachi et al. in 1989. They demonstrated hypersensitivity to sweat in patients with AD [7] and subsequently CholU [8] by performing intradermal skin tests with autologous sweat. Fig. 1A shows a representative positive reaction of an intradermal skin test with autologous sweat. In 2002, we reported that patients with AD exhibit hypersensitivity to crude and semi-purified sweat based on intradermal skin tests and basophil histamine – release tests (HRTs) [9]. We further purified human sweat from healthy volunteers by histamine-releasing activity on basophils obtained from patients with AD;

our findings demonstrated that histamine release induced by the semi-purified sweat antigen is dependent on specific IgE in the sera of patients with AD [10]. These observations provided evidence that sweat allergy is a type I hypersensitivity to crude sweat or the ingredients in sweat. The positive rates of sweat allergy in AD and CholU ranged from 77% to 96% and 66% to 100%, respectively (Table 1). The antigen lost its histamine – releasing activity following treatment with proteinase K or trypsin [10], suggesting that it is a protein. Sera of patients with positive HRTs against semi-purified sweat antigen also possess histamine release neutralization activity due to either IgE and/or IgG antibodies against the sweat antigen [11]. The specific substance that induces histamine release from basophils of patients with AD and CholU, however, had not been identified even though it has been more than two decades since the first report by Adachi et al. [7].

3. Contents of eccrine sweat

Human eccrine sweat consists of water, sodium, potassium, bicarbonate, chloride, lactate, urea, ammonia, small quantities of various amino acids, and proteins [12]. The proteins in eccrine sweat include proteases (e.g. kallikreins), protease inhibitors (e.g. cystatins), and anti-microbial peptides (e.g. dermoccidin). In addition to substances that induce an immediate hypersensitivity reaction, human sweat also contains proinflammatory cytokines

Table 1
Positive rates of sweat allergy in patients with atopic dermatitis and cholinergic urticaria.

| Authors [ref.] | Atopic Dermatitis | Cholinergic Urticaria | Healthy Controls |
|----------------|-------------------|-----------------------|------------------|
| Adachi K [7] | 96% (43/45) | – | 18% (4/22) |
| Adachi J [8] | – | 100% (20/20) | 0% (0/20) |
| Hide M [9] | 85% (56/66) | – | 11% (3/27) |
| Tanaka A [10] | 77% (47/61) | – | 9% (4/46) |
| Takahagi S [6] | – | 66% (23/35) | 0% (0/14) |

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