

Intrinsic Atopic Dermatitis is Associated with a Beta-2 Adrenergic Receptor Polymorphism

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Sir,

Atopic dermatitis (AD) is a common, chronic relapsing inflammatory skin disease with an unclear pathophysiology. Recently, many authors proposed that AD is divided into two subgroups according to the laboratory findings (1, 2). The term "intrinsic" type of AD (IAD) has been proposed as a counterpart to the term "extrinsic" type of AD (EAD). Non-allergic AD, non-atopic eczema, or non-atopic AD equals IAD, which is found among 15–45% of all patients with AD. EAD is the IgE-associated dermatitis and is frequently associated with allergic bronchial asthma or allergic rhino-conjunctivitis. Clinically, patients with IAD have similar skin lesions and distribution patterns as EAD, but have normal serum IgE levels. Hence, EAD appears to be clearly associated with allergic factors.

EAD is associated with polymorphisms of interleukin-4/IL-13 receptor gene (3), underlining the dichotomic nature of AD. AD eruptions can be triggered by stress (4), and the immune system is known to be controlled by neuroendocrine factors such as catecholamines (5). We wondered if AD, and especially IAD, could be associated with gene polymorphisms of β_2 -adrenergic receptors. We have studied three polymorphisms (Arg16Gly, Gln27Glu and Val34Met), which are known to have effects on the functioning of the β_2 -adrenergic receptors (6) in atopic and healthy subjects.

MATERIALS AND METHODS

This study was approved by the local ethics committee of Brest. Participants gave written informed consent before participating, as did a parent or guardian in assessments of subjects under 18 years of age. A total of 95 healthy volunteers (without AD, rhinitis or asthma) and 82 atopic patients (according to the UK criteria (7)) were included in the study. IAD was defined by total serum IgE levels <150 kU/l. EAD was defined by total serum IgE levels >150 kU/l.

DNA was extracted with the GFX Genomic Blood DNA purification kit (Amersham). After amplification (B2AF: AGCG-

CCTTCTTGCTGGCACCCA; B2AR: AGTAGTTGGTGAC-CGTCTGCA), DNA was sequenced and electrophoresed on ABI Prism 310. Sequencing data were analysed with "sequencing analysis" (Applied Biosystem).

Statistical analysis was performed with Epi-Info software (version 6.04). First, the distribution of the different genotypes between IAD, EAD and controls groups was compared using a χ^2 test or Fisher exact test in case of small size sample. The strength of the association between the markers and the disease (stratified in IAD and EAD) was assessed by an odds ratio (OR) with 95% confidence interval.

RESULTS

Subjects carrying at least one Glu 27 allele (Glu/Gln or Glu/Glu) had a 7-fold higher risk of developing IAD than did subjects with Gln/Gln genotype (OR=7.05, $p=0.0028$) (Table I). No difference was observed in this distribution between patients with EAD and healthy subjects ($\chi^2=2.39$, $p=0.303$). No Arg16Gly or Val34Met polymorphism was found.

DISCUSSION

This study provides the first indication of a genetic relationship between IAD and a modified adrenergic response. Whereas single nucleotide polymorphisms (SNPs) of the IL-4/IL-13 receptors are more frequent in patients with EAD (3), SNPs of β_2 receptors appear more frequent in patients with IAD. These data reinforce the idea of a dichotomic nature of AD. Hence, patients with EAD are logically more sensitive to allergic factors, whereas patients with IAD could be more sensitive to stress or neurogenic factors. Maybe we can hypothesize the adrenergic response could be modulated to deteriorate patients with IAD. There is a theoretical possibility of using β_2 agonists for the treatment of IAD. These ideas need to be confirmed by clinical studies.

How the presence of this polymorphism in cells of patients with IAD works is not easy to explain. Adrenergic

Table I. Polymorphism at nucleotide 27 in patients with intrinsic atopic dermatitis (IAD) and extrinsic atopic dermatitis (EAD) and healthy subjects

| Poly 27 | IAD patients | EAD patients | Healthy subjects | OR (95% CI) | OR (95% CI) |
|--------------------|--------------|--------------|------------------|----------------------|-------------------|
| | n (%) | n (%) | | IAD–healthy subjects | IAD–EAD |
| Glu/Glu or Glu/Gln | 8 (66.7) | 22 (31.4) | 21 (22.1)* | 7.05 (1.69-31.41) | 4.36 (1.03-19.63) |
| Gln/Gln | 4 (33.3) | 48 (68.6) | 74 (77.9) | 1.00 | 1.00 |
| Total | 12 (100.0) | 70 (100.0) | 95 (100.0) | | |

* $p = 0.00028$ compared with patients with "intrinsic" atopic dermatitis.

receptor agonists, as well as catecholamines themselves, are known to attenuate the proliferative response of human lymphocytes or other cells after activation by catecholamines (6). This long-term agonist-promoted downregulation is due to a decrease in the number of receptors by their internalization and is absent, when Glu is at position 27, thereby inhibiting the effects of catecholamines (8). β 2-receptors are expressed on cells involved in AD, such as Langerhans' cells, keratinocytes and lymphocytes. Hence, in subjects with this polymorphism, catecholamines probably activate keratinocytes or immune cells involved in AD without feedback. Stress, which is known for triggering AD eruptions, exerts an adjuvant effect on dendritic cells, resulting in increased primary and memory antigen-specific T-cell immune responses and inhibits skin barrier recovery. These effects are mediated by β 2 agonists (9, 10) and are important in AD pathophysiology. The presence of Gln27Glu polymorphism could enhance sensitivity to stress in patients with IAD.

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