

Much Atopy about the Skin: Genome-Wide Molecular Analysis of Atopic Eczema

Hirohisa Saito

Department of Allergy and Immunology, National Research Institute for Child Health and Development,
Tokyo, Japan

Key Words

Atopic eczema · Chemokines · Microarray ·
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Abstract

Background: Atopic eczema (AE) is a chronic inflammatory skin disorder with an increasing prevalence in industrialized countries. **Methods:** Genox Research Incorporation was founded in 1996 to identify new genes involved in allergic diseases in collaboration with the National Children's Hospital in Tokyo. In the AE project, they have discovered several hundred new genes and partial DNA sequences by mainly using microarrays. Here, I review the results obtained using transcriptome analysis, performed by Genox and other investigators. **Results:** Transcriptome analysis using skin lesion, CD4⁺ T cells, monocytes and eosinophils derived from AE patients identified some differentially expressed genes which became biologically relevant in the following studies. Missing linkages between these genes have been found due to the recent development of genomics. **Conclusion:** Many AE-related genes found in the genome-wide studies still remain to be determined regarding their functions and to be systemically organized. After the comprehensive characterization of these genes by further studies, we will identify the precise molecular mechanisms involved in AE and other diseases.

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Introduction

Atopic eczema (AE) is a chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers [1, 2]. The diagnosis of AE is based on the following constellation of clinical findings: pruritus, facial and extensor eczema in infants and children, flexural eczema in adults and chronicity of the dermatitis [3]. AE usually presents during early infancy and childhood, but it can persist or start in adulthood [4]. The lifetime prevalence of AE is 10–20% in children and 1–3% in adults. Its prevalence has increased two- to threefold during the past three decades in industrialized countries. Various investigators reported that AE has a complex etiology, with an activation of multiple immunologic and inflammatory pathways [1, 2, 5]. The clinical phenotype that characterizes AE is the product of complex interactions among susceptibility genes, the host's environment, defects in skin barrier function and systemic and local immunologic responses. An understanding of the relative role of these factors in the pathogenesis of AE has been made possible by a variety of approaches, including the analysis of cellular and cytokine gene expression in AE skin lesions in humans as well as various AE model mice.

By a complete reading of the genome sequence, we will be able to determine the role of genomic DNA sequence variation among individuals, such as single nucleotide polymorphism, in the pathogenesis of diseases. The com-

prehension of the genome will also accelerate an understanding of the transcriptome, evaluating all the transcripts present in a cell [6]. Messages induced by a new therapy, such as unexpected adverse effects, will not be missed by using such a comprehensive assay. Allergic diseases will be investigated by understanding the total functional elements comprising the immune system, not just a single molecule present in an immunocyte working in our immune system [7]. The current review will summarize the progress in our understanding of the molecular biology of AE, especially by focusing on the recent transcriptome analyses.

Differentially Expressed Genes in T Cells

The key role of immune effector T cells in AE is supported by the observation that individuals with primary T cell immunodeficiency disorders frequently have elevated serum IgE levels and eczematous skin lesions following successful bone marrow transplantation. Furthermore, in animal models of AE, the eczematous rash does not occur in the absence of T cells.

In AE, memory T cells expressing the skin-homing receptor, a cutaneous lymphocyte-associated antigen (CLA) [8], produce increased levels of Th2 cytokines. These include interleukin (IL)-4 and IL-13, which are known to induce isotype switching to IgE synthesis, as well as IL-5, which plays an important role in eosinophil development and survival. These CLA⁺ T cells produce abnormally low levels of interferon (IFN) γ , a Th1 cytokine known to inhibit Th2 cell function [1, 2, 9]. Genox Research Incorporation (Genox) was founded in 1996 to identify new genes involved in allergic diseases in collaboration with the National Children's Hospital (renamed in 2002 to National Center for Child Health and Development) in Tokyo. In the AE project, they first examined differentially expressed genes present in phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells derived from severe AE patients. They also used quantitative methods such as real-time PCR to determine the expression levels of differentially expressed genes. At first, these investigators found markedly decreased PHA-induced IFN γ production in AE patients with hyper IgE (>10,000 IU/ml) who were insensitive to topical glucocorticoid therapy compared with those who were sensitive to the same treatment and with normal controls [10]. Using an oligonucleotide microarray (GeneChip, Affymetrix), IFN γ was found in the 4 most differentially expressed genes among 5,600 genes

[11]. Since upregulation of transcriptional levels in crude cells is often simply caused by an increase in cell number of a certain cell type, they purified CD4⁺ T cells from AE patients and examined differentially expressed genes. A number of genes, including CC chemokine receptor (CCR)4, an IL-2-inducible T cell-specific tyrosine kinase, a heterodimer receptor for laminin, very late antigen 6 consisting of integrin β_1 and integrin α_6 molecules and a T cell-specific global gene regulator, as well as special AT-rich sequence-binding protein 1 were shown to be highly expressed in patients with moderate and/or severe AE in comparison with controls or patients with mild AE. Because the products of these upregulated genes influence chemotaxis, adhesion, migration and Th2 polarization, the investigators suggested that circulating T cells may function differently in severer AE [12]. In the same series of the experiment, they have found a strong correlation between a transcription factor, a suppressor of cytokine signaling (SOCS)3 expression and the clinical severity of AE, as well as serum IgE levels [13]. SOCS3 is a negative signal transducer specific for IL-12 as well as a signal transducer and activator of transcription 4 signaling, and thereby downregulates IFN γ production and Th1 immunity. SOCS3 was later found to be upregulated in an AE-like skin lesion in an AE model NC/Nga mouse [14]. IFN γ and IL-12 production by peripheral blood mononuclear cells increased significantly after successful treatment with topical glucocorticoids, while the production of IL-1, IL-4 and IL-13 was not significantly changed [15]. Therefore, according to the findings obtained by Genox's genomic analysis, downregulation of Th1 cytokines, but not upregulation of Th2 cytokines, seems to be an important marker for evaluating AE disease activity. However, in contrast to the above observation, Wohlfahrt et al. [16] used nylon membrane-based cDNA arrays to find several genes for IL-4, IL-5 and IL-13, macrophage-derived chemokine (MDC) CC chemokine ligand (CCL)22 and monocyte chemotactic protein (MCP)-4 (CCL13) markedly upregulated in freshly isolated and restimulated CD4⁺ T cells from patients with allergic asthma or AE compared with healthy subjects. They also found that fractalkine (CX3CL1), I-309 (CCL1) and IL-8 were expressed at a higher level in AE patients compared with other subjects. It would be interesting to determine the absolute expression levels of these genes among the same AE population by using more quantitative methods.

Differentially Expressed Genes in Monocytes and Eosinophils

The role of IL-4 and IL-13 in the pathogenesis of skin inflammation was recently addressed by treating NC/Nga mice with an IL-4/IL-13 receptor inhibitor, kept under conventional conditions. Surprisingly, treated mice displayed an increased eczema severity and IgE levels, suggesting a downmodulatory role for IL-4 and IL-13 in the skin inflammatory immune response [for a review, see ref. 17]. This raised the possibility that IL-4 and IL-13 may regulate the production of proinflammatory cytokines by monocytes/macrophages in AE etiology, as well as in autoimmune diseases [18]. Thus, the Genox group examined the transcriptome information in peripheral blood monocytes derived from AE patients. They found that genes for the Toll-like receptors (TLR)2, TLR4 and TLR6, a signal transducer for TLR stimulation called 'ATP-binding cassette transporter' (TAP2), CD36 and the γ -chain of the high-affinity IgE receptor Fc ϵ receptor I (Fc ϵ RI γ) were markedly upregulated in monocytes derived from AE patients [19].

CD36 has been recently found to be a selective and nonredundant sensor of microbial diacylglycerides that signal via the TLR2/6 heterodimer [20]. TLR2 is essentially involved in the protection against *Staphylococcus aureus* [21], which often colonizes on the AE skin. Unlike other TLRs, TLR2 stimulation does not induce the expression of IFN α / β [22]. IFN α / β stimulates the production of IFN γ via the signal transducer and activator of transcription 4 in human T cells but not in mouse T cells [23]. A bacterial lipoprotein abundant in *S. aureus* can modulate allergen-specific Th2 effector cells in an allergic response in vivo for a prolonged period via stimulation of the TLR2 signaling pathway [24]. Taken together, monocytes derived from AE patients can induce strong inflammation by producing more proinflammatory cytokines including TNF α , granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-18 [25] in response to *S. aureus* via upregulation of the TLR2 signaling pathway. Furthermore, antigen-presenting cells derived from these TLR2-upregulated monocytes are considered to be more sensitive to allergen challenge.

Interestingly, only TLR2 among all TLRs is upregulated in response to glucocorticoid treatment in respiratory epithelial cells. Homma et al. [26] claimed that the TLR2 upregulation results in the production of β -defensin, and thus works for protection from bacteria. It should be determined whether TLR2 is upregulated in AE skin and whether the upregulated TLR2 accelerates allergen

sensitization. Regarding the upregulation of the Fc ϵ RI γ chain in AE monocytes, it is known that AE skin, compared with nonatopic skin, contains an increased number of IgE-bearing dendritic cells, which are sometimes derived from peripheral blood monocytes, expressing Fc ϵ RI. The increased expression of Fc ϵ RI on dendritic cells in atopic skin is due to the enhanced expression of the Fc ϵ RI γ chain and is preserved by increased IgE levels [27].

Next, the Genox investigators determined the transcriptome expression in eosinophils derived from AE patients. Several genes, such as those for cytokine receptors, e.g., GM-CSF receptor (GM-CSFR) α - and β -chain and IL-3 receptor (IL-3R) α -chain, CD44 and platelet-activating factor receptor were expressed at significantly higher levels in AE patients than in healthy volunteers [28]. It is known that eosinophils in inflammatory tissues are activated and express more GM-CSFR and IL-3R than peripheral blood eosinophils [29].

Differentially Expressed Genes in Skin Lesion

Upregulation of transcriptional levels in a crude tissue is often caused by an increase in recruitment of a certain inflammatory cell type. Indeed, Genox faced the difficulty in determining whether the upregulated genes in the skin are truly upregulated in the skin-dwelling cells or artifactually upregulated by the contamination of inflammatory cells. Nomura et al. [30] have succeeded in solving this problem in their microarray study on AE skin specimens by comparing the tissues derived from AE and psoriasis. They identified several genes for chemoattractant cytokines and chemokines, which play a central role in defining the nature of the inflammatory infiltrate in AE, to be differentially expressed. For example, cutaneous T cell-attracting chemokine (CCL27) is highly upregulated in AE and preferentially attracts CLA $^{+}$ T cells into the skin. Compared with psoriasis, several CC chemokines such as I-309 (CCL1), RANTES (CCL5), MCP-4 (CCL13) and eotaxin (CCL11) are increased in AE skin lesions and likely contribute to the chemotaxis of CCR3-expressing eosinophils, macrophages and Th2 lymphocytes in AE skin. Selective recruitment of CCR4-expressing Th2 cells into AE skin may also be mediated by MDC (CCL22) and thymus and activation-regulated cytokine (CCL17), which are increased in AE. It would be concluded that skin-dwelling cells in AE patients preferentially produce several CC chemokines such as I-309 (CCL1), MCP-4 (CCL13) and MDC (CCL22). However, as reported by other investigators [16], purified CD4 $^{+}$ cells from AE pa-

tients preferentially express CC chemokines. Therefore, in a future study, it should be determined whether T cells or tissue-dwelling cells can predominantly produce these CC chemokines after obtaining highly purified cells from AE patients.

Persistent skin inflammation in chronic lesions may be due to elevated IL-5 and GM-CSF expression in the skin leading to enhanced survival of eosinophils, monocyte/macrophages and dendritic cells. In addition, extracellular matrix molecules deposited in chronic skin lesions have been found to enhance the survival of memory T cells [31]. When compared with normal skin or uninvolved skin of AE patients, acute skin lesions have a significantly greater number of IL-4, IL-5 and IL-13 mRNA-expressing cells, but few IFN γ or IL-12 mRNA-expressing cells. Chronic AE skin lesions have significantly fewer IL-4 and IL-13 mRNA-expressing cells, but a greater number of IL-5, GM-CSF, IL-12 and IFN γ mRNA-expressing cells than acute AE skin lesions. However, compared with psoriasis, AE skin produces more Th2 cell-attracting CC chemokines, even in the chronic skin lesion [31].

Epidermal keratinocytes from AE patients produce a unique profile of chemokines and cytokines following mechanical stimulation, e.g. scratching, or exposure to pro-inflammatory cytokines such as TNF α . Keratinocytes in AE are also reported to be deficient in their ability to synthesize antimicrobial peptides needed for innate immune responses against microbes, and thus, this allows the colonization of *S. aureus* on the skin [32]. The same authors reported that IL-13 is a key role cytokine downregulating the production of antimicrobial peptides by keratinocytes [33]. Interestingly, another group has recently identified that staphylococcal enterotoxin-B stimulated T cells to produce IL-13 [34].

Apoptosis-Related Genes

AE is usually thought to be an allergen-driven disease with prominent roles played by antigen-presenting cells and effector Th2 cells. But keratinocytes provide an important window to the environment and are also thought to contribute to the development of AE. Here, I introduce several genomic findings regarding the interaction between keratinocytes and T cells. Keratinocytes produce inflammatory mediators that promote or maintain allergic inflammation, exert apoptosis that is induced by activated T cells [35] and respond to staphylococcal toxins and various pathogen-associated molecular patterns bear-

ing microbial agents [for a review, see ref. 1, 2]. Clearly, these findings have highlighted a more active role of the epithelium than was previously recognized. Indeed, therapeutic effects of topical glucocorticoid or FK506 are considered to be mediated by two different mechanisms, i.e. inducing apoptosis of T cells and eosinophils and blocking apoptosis of keratinocytes [36]. Genomic studies performed by Genox identified several known genes such as bcl-2 and bcl-xL [28] as well as newly found genes [37, 38] regulating apoptosis of T cells and eosinophils differentially regulated in AE patients.

Genetic Analysis of AE-Susceptible Genes

Many attempts have been made to identify the genes susceptible to the onset of AE. Since AE is an atopic disorder, candidate genes involving IgE and Th2 cytokines have been extensively examined. There has been particular focus on chromosome 5q31–33, as it contains a clustered family of Th2 cytokine genes, i.e. IL-3, IL-4, IL-5, IL-13 and GM-CSF [39]. Case-control comparisons have suggested a genotypic association between the IL-4 gene promoter region and AE, as patients with AE tend to have an increased IL-4 gene promoter activity. Similarly, this is the case with IL-13 coding region variants, a gain-of-function polymorphism in the α -subunit of the IL-4 receptor. These genes are also found among the candidate genes for ‘atopy’ asthma, since most of these studies included patients with elevated IgE levels. Genes unrelated to IgE or Th2 cytokines should also be involved in the pathogenesis of AE. NC/Nga mice undoubtedly represent the best characterized mouse model of AE currently available. Subcutaneous injection of TGF- β_1 , a regulatory cytokine, into these mice led to significant clinical improvement of skin lesions. Additionally, another regulatory cytokine, the IL-10R α gene, was found among a candidate locus of these mice by reciprocally crossing and subsequently backcrossing NC/Nga with BALB/c mice [for a review, see ref. 17]. Indeed, patients with IPEX syndrome lacking the FOXP3 gene responsible for regulatory T cells exert systemic skin eczema and hyper IgE as well [40].

Human genome screens have been performed and identified susceptibility loci for AE on chromosome 3q21 [41], which have not been linked to asthma candidate genes. This region encodes the costimulatory molecules CD80 and CD86 and may therefore modulate T cell responses. Another human genome screen reported a linkage of AE to loci on chromosomes 1q21, 17q25 and 20p. Interestingly, these same regions are known to contain

Table 1. Differentially expressed genes in the AE patients obtained by transcriptome analyses

Transcripts ^a	CD4+ T cells	Monocytes	Eosinophils	Skin
IL-4, IL-13	↑ or →	→	→	↑ (cell number)
IL-12	→	↓	→	↑ (chronic AE)
IFN γ	↓ (severe AE)	→	→	↑ (chronic AE)
IL-3R	→	→	↑	→
GM-CSFR	→	→	↑	→
CCL1 ^b	↑	→	→	↑
CCL5	→	→	→	↑
CCL11	→	→	→	↑
CCL13	↑	→	→	↑
CCL17	→	→	→	↑
CCL22	↑	→	→	↑
CCL27	→	→	→	↑
CCR4	↑	→	→	↑ (cell number)
TLR2, TLR6	→	↑	→	→
TLR4	→	↑	→	→
CD36	→	↑	→	→
TAP2	→	↑	→	→
SOCS3	↑	→	→	↑
VLA6	↑	→	→	→
ITK	↑	→	→	→
SATB1	↑ (moderate AE)	→	→	→

VLA = Very late antigen; ITK = inducible T cell-specific tyrosine kinase; SATB1 = special AT-rich sequence-binding protein 1.

^a Transcripts differentially expressed in skin lesion [30], peripheral blood monocytes [19], CD4+ T cells [10–13, 16] and eosinophils [28] derived from AE patients are summarized in this figure.

^bCC chemokines: CCL1 = I-309; CCL5 = RANTES; CCL11 = eotaxin; CCL13 = MCP-4; CCL17 = TARC = thymus and activation-regulated cytokine; CCL22 = MDC; CCL27 = CTACK = cutaneous T cell-attracting chemokine.

psoriasis susceptibility genes, which suggests common candidate genes involved in the control of skin inflammation. Although AE and psoriasis are distinct skin diseases, both conditions involve dry, scaly skin and disrupted epidermal differentiation.

AE is characterized by dry skin and even involves non-lesional skin and increased transepidermal water loss. This impairment of the skin barrier function in AE leads to increased antigen absorption contributing to the cutaneous hyperreactivity characteristic of AE. In particular, ceramides serve as the major water-retaining molecules in the extracellular space of the cornified envelope, and the barrier function of these complex structures is provided by a matrix of structural proteins that are bound to ceramides [42, 43].

A Glu420Lys polymorphism variant in the SPINK5 gene, which encodes serine proteinase inhibitors, has shown a significant association with AE in two independent cohorts [44]. This gene is expressed in the outermost layers of the skin and has been implicated in Netherton

disease, an autosomal recessive disorder characterized by ichthyosis and atopy. Recently, SPINK5^{–/–} mice faithfully replicating key features of the Netherton syndrome were established. In these mice, abnormal desmosome cleavage is seen in the skin through degradation of desmoglein 1 due to stratum corneum tryptic enzyme and stratum corneum chymotryptic enzyme-like hyperactivity. This leads to defective stratum corneum adhesion and a resultant loss of the skin barrier function [45]. Although the human SPINK5 gene is located on chromosome 5q31–33, its function is primarily unrelated to IgE production and is involved in an AE-unique function, the skin barrier dysfunction.

Conclusion

AE-related genes identified by transcriptome analysis using clinical samples are summarized in table 1 and figure 1. Genome-wide transcriptome analysis is often per-

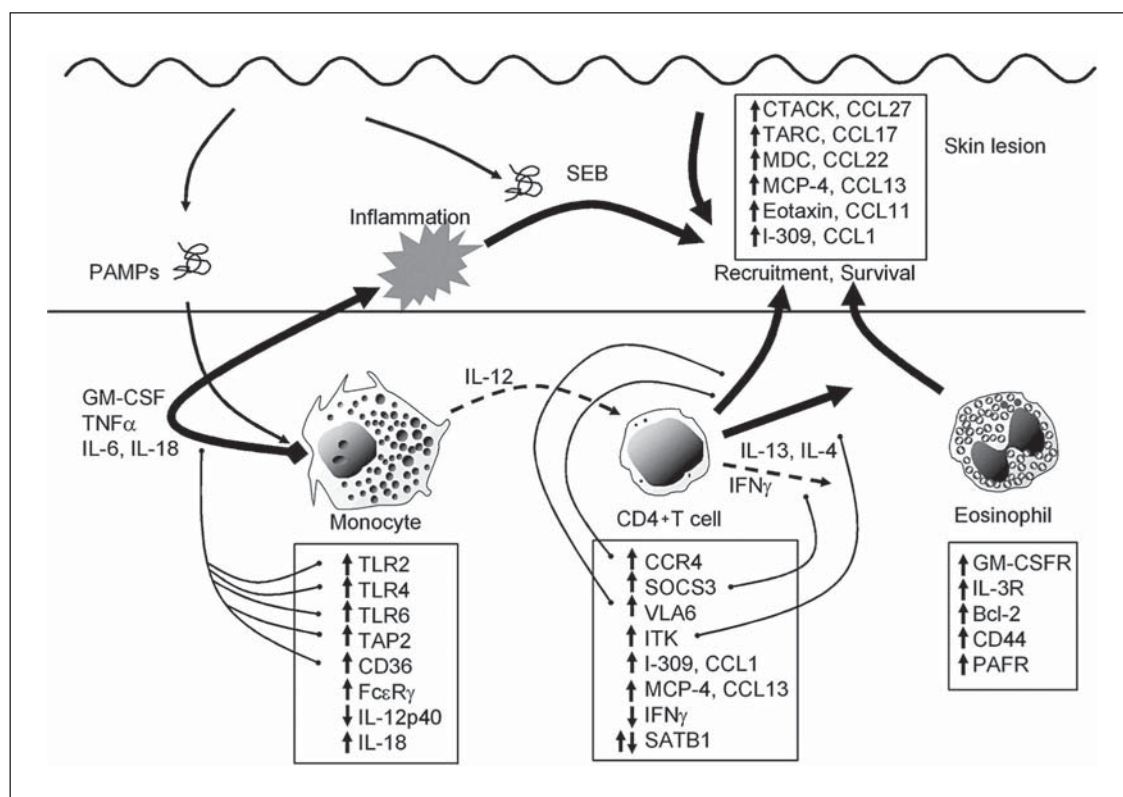


Fig. 1. Differentially expressed molecules in AE patients. Representative molecules which are differentially expressed in AE patients found in the transcriptome research are shown in the boxes. Transcripts differentially expressed in skin lesion [30], peripheral blood monocytes [19], CD4+ T cells [10–13, 16] and eosinophils [28] derived from AE patients are summarized. PAMPs = Pathogen-associated molecular patterns; SEB = staphylococcal enterotoxin-B; PAFR = platelet-activating factor receptor; explanations of other abbreviations are provided in table 1.

formed independent of hypothesis. Therefore, until a few years ago, such newly found genes sometimes seemed irrelevant to clinical aspects or even to biological significance. Some missing linkages between these genes have now been found and the biological importance of these genes is increasing due to the recent development of genomics. However, many AE-related genes found in these genome-wide studies still remain to be determined re-

garding their functions and to be systemically organized. As summarized in figure 1, immunological aspects of AE have been extensively investigated so far. Now, it appears necessary to focus on the role of skin lesion in AE patients as well as the interaction between skin and inflammatory cells. After comprehensive characterization of these genes by further studies, we will identify the precise molecular mechanisms involved in AE and other diseases.

References

- 1 Leung DY, Bieber T: Atopic dermatitis. *Lancet* 2003;361:151–160.
- 2 Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA: New insights into atopic dermatitis. *J Clin Invest* 2004;113:651–657.
- 3 Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. *Acta Derm Venerol* 1980; 92:44–47.
- 4 Spergel JM, Paller AS: Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112:S118–S127.
- 5 Novak N, Bieber T, Leung DYM: Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol* 2003;112:S128–S139.
- 6 Saito H: Translation of the human genome into clinical allergy. *Allergol Int* 2003;52:65–70.
- 7 Saito H: Translation of the human genome into clinical allergy. Part 2. *Allergol Int* 2004;53: 87–92.

- 8 Santamaria Babi LF, Picker LJ, Perez Soler MT, et al: Circulating allergen-reactive T cells from patients with atopic dermatitis and allergic contact dermatitis express the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen. *J Exp Med* 1995;181:1935–1940.
- 9 Akdis M, Akdis CA, Weigl L, et al: Skin-homing, CLA⁺ memory T cells are activated in atopic dermatitis and regulate IgE by an IL-13-dominated cytokine pattern: IgG4 counter-regulation by CLA-memory T cells. *J Immunol* 1997;159:4611–4619.
- 10 Katsunuma T, Kawahara H, Yuki K, et al: Impaired interferon- γ production in a subset population of severe atopic dermatitis. *Int Arch Allergy Immunol* 2004;134:240–247.
- 11 Heishi M, Kagaya S, Katsunuma T, et al: High-density oligonucleotide array analysis of mRNA transcripts in peripheral blood cells of severe atopic dermatitis patients. *Int Arch Allergy Immunol* 2002;129:57–66.
- 12 Matsumoto Y, Oshida T, Obayashi I, et al: Identification of highly expressed genes in peripheral blood T cells from patients with atopic dermatitis. *Int Arch Allergy Immunol* 2002;129:327–340.
- 13 Seki Y, Inoue H, Nagata N, et al: Suppressor of cytokine signaling (SOCS)-3 regulates onset and maintenance of T(H)2-mediated allergic responses. *Nat Med* 2003;9:1047–1054.
- 14 Horiuchi Y, Bae SJ, Katayama I, Mori Y, Yamanishi K: Effects of ultraviolet-inactivated herpes simplex virus type 1 on atopic dermatitis-like lesions in NC/Nga mice: role of the suppressor of cytokine signaling in the skin. *Allergol Int* 2004;53:331–340.
- 15 Kaneko S, Furutani K, Koro O, et al: Transient shift toward T helper 1 cytokine production by peripheral blood mononuclear cells following successful treatment of patients with atopic dermatitis. *Allergol Int* 2003;52:21–29.
- 16 Wohlfahrt JG, Kunzmann S, Menz G, et al: T cell phenotype in allergic asthma and atopic dermatitis. *Int Arch Allergy Immunol* 2003;131:272–282.
- 17 Gutermuth J, Ollert M, Ring J, et al: Mouse models of atopic eczema critically evaluated. *Int Arch Allergy Immunol* 2004;135:262–276.
- 18 Bessis N, Boissier MC, Ferrara P, et al: Attenuation of collagen-induced arthritis in mice by treatment with vector cells engineered to secrete interleukin-13. *Eur J Immunol* 1996;26:2399–2403.
- 19 Nagata N, Oshida T, Yoshida NL, et al: Analysis of highly expressed genes in monocytes from atopic dermatitis patients. *Int Arch Allergy Immunol* 2003;132:156–167.
- 20 Hoebe K, Georgel P, Rutschmann S, et al: CD36 is a sensor of diacylglycerides. *Nature* 2005;433:523–527.
- 21 Yoshimura A, Lien E, Ingalls RR, et al: Cutting edge: recognition of Gram-positive bacterial cell wall components by the innate immune system occurs via Toll-like receptor 2. *J Immunol* 1999;163:1–5.
- 22 Toshchakov V, Jones BW, Perera PY, et al: TLR4, but not TLR2, mediates IFN- β -induced STAT1 α / β -dependent gene expression in macrophages. *Nat Immunol* 2002;3:392–398.
- 23 Rogge L, D'Ambrosio D, Biffi M, et al: The role of STAT4 in species-specific regulation of Th cell development by type I IFNs. *J Immunol* 1998;161:6567–6574.
- 24 Revets H, Pynaert G, Grooten J, et al: Lipoprotein I, a TLR2/4 ligand modulates Th2-driven allergic immune responses. *J Immunol* 2005;174:1097–1103.
- 25 Ohnishi H, Kato Z, Watanabe M, et al: Interleukin-18 is associated with the severity of atopic dermatitis. *Allergol Int* 2003;52:123–130.
- 26 Homma T, Kato A, Hashimoto N, et al: Corticosteroid and cytokines synergistically enhance toll-like receptor 2 expression in respiratory epithelial cells. *Am J Respir Cell Mol Biol* 2004;31:463–469.
- 27 Novak N, Tepel C, Koch S, et al: Evidence for a differential expression of the Fc ϵ RI γ chain in dendritic cells of atopic and nonatopic donors. *J Clin Invest* 2003;111:1047–1056.
- 28 Ogawa K, Hashida R, Miyagawa M, et al: Analysis of gene expression in peripheral blood eosinophils from patients with atopic dermatitis and in vitro cytokine-stimulated blood eosinophils. *Clin Exp Immunol* 2003;131:436–445.
- 29 Gregory B, Kirchem A, Phipps S, et al: Differential regulation of human eosinophil IL-3, IL-5, and GM-CSF receptor α -chain expression by cytokines: IL-3, IL-5, and GM-CSF down-regulate IL-5 receptor α expression with loss of IL-5 responsiveness, but up-regulate IL-3 receptor α expression. *J Immunol* 2003;170:5359–5366.
- 30 Nomura I, Gao B, Boguniewicz M, et al: Distinct patterns of gene expression in the skin lesions of atopic dermatitis and psoriasis: a gene microarray analysis. *J Allergy Clin Immunol* 2003;112:1195–1202.
- 31 Akdis M, Trautmann A, Klunker S, et al: T helper (Th) 2 predominance in atopic diseases is due to preferential apoptosis of circulating memory/effector Th1 cells. *FASEB J* 2003;17:1026–1035.
- 32 Ong PY, Ohtake T, Brandt C, et al: Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002;347:1151–1160.
- 33 Nomura I, Goleva E, Howell MD, et al: Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003;171:3262–3269.
- 34 Lehmann HS, Heaton T, Mallon D, et al: Staphylococcal enterotoxin-B-mediated stimulation of interleukin-13 production as a potential aetiological factor in eczema in infants. *Int Arch Allergy Immunol* 2004;135:306–312.
- 35 Trautmann A, Akdis M, Kleemann D, et al: T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest* 2000;106:25–35.
- 36 Trautmann A, Akdis M, Schmid-Grendelmeier P, et al: Targeting keratinocyte apoptosis in the treatment of atopic dermatitis and allergic contact dermatitis. *J Allergy Clin Immunol* 2001;108:839–846.
- 37 Imai Y, Nakada A, Hashida R, et al: Cloning and characterization of the highly expressed ETEA gene from blood cells of atopic dermatitis patients. *Biochem Biophys Res Commun* 2002;297:1282–1290.
- 38 Ogawa K, Itoh M, Miyagawa M, et al: Expression of a human SOCS protein, HSOCp-1, in peripheral blood eosinophils from patients with atopic dermatitis. *Int Arch Allergy Immunol* 2004;134:S2–S6.
- 39 Liu X, Beatty TH, Deindl P, et al: Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 2003;112:382–388.
- 40 Gambineri E, Torgerson TR, Ochs HD: Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. *Curr Opin Rheumatol* 2003;15:430–435.
- 41 Cookson WO, Moffatt MF: The genetics of atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2002;2:383–387.
- 42 Sator PG, Schmidt JB, Honigsman H: Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. *J Am Acad Dermatol* 2003;48:352–358.
- 43 Melnik B, Hollmann J, Plewig G: Decreased stratum corneum ceramides in atopic individuals – A pathobiochemical factor in xerosis? *Br J Dermatol* 1988;119:547–549.
- 44 Kato A, Fukai K, Oiso N, et al: Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol* 2003;148:665–669.
- 45 Descargues P, Deraison C, Bonnart C, et al: SPINK5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. *Nat Genet* 2005;37:56–65.