were chosen for validation. Intense pruritus is another major feature of AD. The pathogenesis of cutaneous pruritus is not well understood, but it is thought to be induced by the various products from the inflammatory effector cells, including neuropeptides, histamine, leukotrienes, and proteolytic enzymes. The prolyl endopeptidase and cathepsin B might be genes responsible for producing the inflammatory agents. Finally, coxsackie virus and adenovirus receptor and delta sleep inducing peptide are genes that were found repeatedly in the SSH library and their expression levels were confirmed. Five genes showed increased expression levels in the AD samples compared to normal control samples (Figure 1). The coxsackie virus and adenovirus receptor, prolyl endopeptidase, delta sleep inducing peptide, and sphingosine-1-phosphate lyase genes showed markedly increased expression levels in the AD samples compared to the normal and psoriasis samples, but their expression levels in the psoriasis samples were lower than in the normal control samples. CTBS was the only gene that had a greater expression in the psoriasis samples than in the AD and normal samples (Figure 1).

In conclusion, this study was the first attempt to identify differentially expressed genes in lesional AD skin to help increase our understanding of AD with its complicated disease mechanism. Although the known and unknown genes found by using the SSH method may be helpful in understanding the complicated atopic pathophysiology, there is a drawback that we used only one normal sample. However, among the 5 genes that were examined at the transcription level, sphingosine-1-phosphate lyase, coxsackie virus and adenovirus receptor, prolyl endopeptidase, and delta sleep inducing peptide are genes that have not yet been studied for the other skin diseases as well as AD. Therefore, besides the known factors, these genes are thought to provide an important clue in analyzing the complex mechanism of dry skin and itching. In recent years, single-nucleotide polymorphism studies have made active progress to grasp the individual genetic causes of AD. However, most of the studies focused on the known genes. Thus, we adopted several tools to cover as many genes as possible and complement the significance of the selected genes with the SSH method. We are currently in progress on an SNP study centering on the genes included in the SSH library. We hope that the selected genes can be used for the treatment and diagnosis of this common allergic skin disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Elevated Serum CTACK/CCL27 Levels in CTCL

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TO THE EDITOR

Cutaneous T-cell-attracting chemokine (CTACK), also called CCL27, belongs to the CC chemokine family and is a ligand for CC chemokine receptor (CCR) 10. It is selectively and constitutively produced in skin by epidermal keratinocytes (Morales *et al.*, 1999) and displayed on the surface of dermal endothelial cells (Homey *et al.*, 2002). It selectively attracts cutaneous lymphocyte antigen positive, CCR10-positive memory T cells into inflammatory sites (Morales *et al.*, 1999). We and other researchers previously reported that serum levels of this chemokine reflect disease activity of atopic dermatitis (Kakinuma *et al.*, 2003a; Hijnen *et al.*, 2004; Hon *et al.*, 2004).

Abbreviations: CCR, CC chemokine receptor; CTACK, cutaneous T-cell-attracting chemokine; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; TBI, tumor burden index

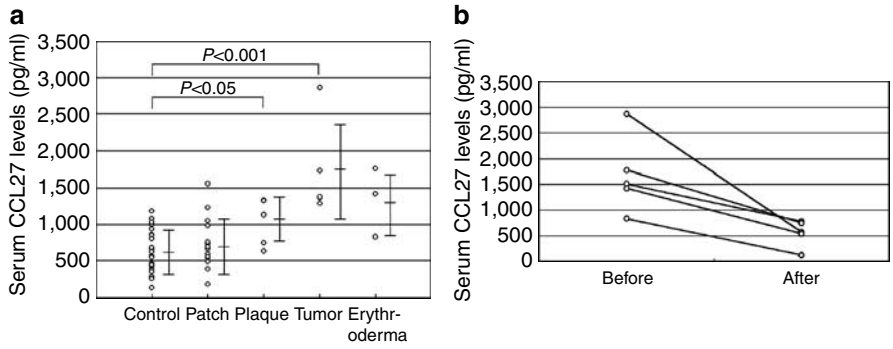

Figure 1. Serum CTACK/CCL27 levels. (**a**) Serum CTACK/CCL27 levels in patients with CTCL and in healthy controls. Patients were divided based on types of skin lesions. Data are presented as mean ± SD. (**b**) Serum CTACK/CCL27 levels before and after successful treatment of CTCL.

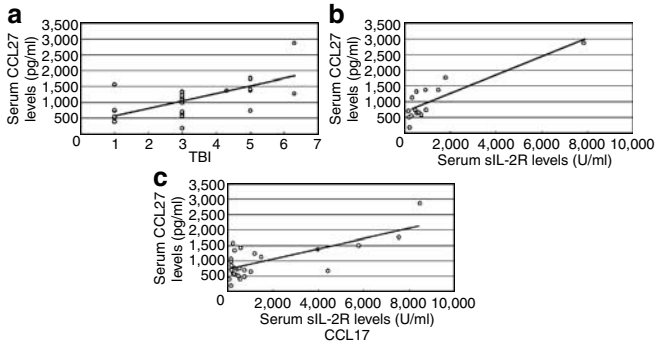

Figure 2. Correlation coefficient between serum CTACK/CCL27 levels and TBI. (**a**), serum soluble IL-2 receptor levels (**b**) or serum thymus and activation-regulated chemokine/CCL17 levels (**c**) in patients with CTCL.

Mycosis fungoides (MF) and Sezary syndrome are common types of cutaneous T-cell lymphoma (CTCL) (Willemze *et al.*, 2005). CCR4 and CCR10 are expressed on tumor cells of MF and Sezary syndrome (Ferenczi *et al.*, 2002; Notohamiprodjo *et al.*, 2005). We previously reported that serum levels of thymus and activation-regulated chemokine/CCL17, a ligand of CCR4, reflect disease activity of MF (Kakinuma *et al.*, 2003b). However, there has been no report of serum CTACK/CCL27 levels in patients with CTCL. This prompted us to investigate the relationship between CTACK/CCL27 and CTCL.

Twenty-eight patients with CTCL (25 MF cases and three Sezary syndrome cases) (mean ± SD age: 59.7 ± 14.5 years), and 25 control subjects (49.4 ± 21.0 years) were enrolled in this study. The medical ethical committee of the University of Tokyo approved all described studies and the study was conducted according to the Declaration of Helsinki Principles. Informed consent was obtained to use sera from patients and controls. All patients with CTCL were given diagnoses according to WHO-EORTC classification for cutaneous lymphomas (Willemze *et al.*, 2005). Disease extent was classified with types of skin lesions (patch, plaque, tumor, and erythroderma) and tumor burden index (TBI) (Schmid *et al.*, 1999). TBI is calculated as follows; TBI = 1 + (patches × 2) + (plaques × 2) + (tumor × 1.3), where the patches factor equals 0 if 30% or less of the skin area is involved and 1 if >30% of the skin area is involved, and where the plaque or tumor factor equals 1 if plaques or tumors are present. In two MF patients and three Sezary syndrome patients, we collected the sera before and after treatment. The 25 healthy controls had no history of allergy, psoriasis, or CTCL. All sera were stored at −20°C until use. CTACK/CCL27 immunoassay kits were from R&D systems (Minneapolis, MN). Serum levels of CTACK/CCL27 were measured as previously described (Kakinuma *et al.*, 2003a). Data obtained from the ELISA are presented as mean ± SD. Data were analyzed using Mann–Whitney's *U*-test and paired *t*-test. Correlation coefficients were determined by using the Spearman's rank correlation test. A *P*-value <0.05 was considered statistically significant.

The serum CTACK/CCL27 levels of patients with CTCL were 1036.4 ± 558.3 pg/ml, which was significantly higher than those of controls (651.6 ± 291.1 pg/ml, $P<0.01$). In CTCL with patch ($n=15$), plaque ($n=5$), tumor ($n=5$), or erythroderma ($n=3$), the serum CTACK/CCL27 levels were 719.6 ± 357.8, 1030.5 ± 322.3, 1724.6 ± 658.6, and 1333.3 ± 471.5 pg/ml, respectively (Figure 1a). The levels of patients with plaque and tumor were significantly higher than those of controls ($P<0.05$ and 0.001, respectively). The levels of patients with tumor were significantly higher than those of patients with patch or plaque ($P<0.005$ and 0.05, respectively). In five patients with CTCL (three males and two females, age ranged from 42 to 73 years), we measured serum CTACK/CCL27 levels before and after treatment. Two of them are MF with tumor, and the others are Sezary syndrome. Topical and oral corticosteroids, UV phototherapy, electron beam, oral etretinate, and/or systemic interferon gamma were used. All cases, at least temporarily, showed clearance of skin lesions. The serum CTACK/CCL27 levels significantly decreased from 1672.3 ± 746.8 to 553.9 ± 264.8 pg/ml after treatment in accordance with the improvement of skin conditions ($P<0.01$, Figure 1b).

We next compared serum CTACK/CCL27 levels with other clinical or laboratory data: age, TBI, serum lactate dehydrogenase, IgE, soluble interleukin 2 receptor, thymus and activation-regulated chemokine/CCL17 levels, and numbers of eosinophil and white blood cell in peripheral blood. The serum CTACK/CCL27 levels were significantly correlated with TBI ($r=0.64$, $P<0.005$) (Figure 2a), the serum soluble IL-2 receptor, and thymus and activation-regulated chemokine/CCL17 levels ($r=0.72$, $P<0.005$; $r=0.40$, $P<0.05$,

respectively) (Figure 2b and c). Other factors were not correlated with serum CTACK/CCL27 levels (data not shown).

In this study, we showed that serum CTACK/CCL27 levels in patients with CTCL strongly correlated with types of skin lesions, TBI, serum soluble IL-2 receptor, and thymus and activation-regulated chemokine/CCL17 levels, all of which are already reported to be good makers of disease activity (Wasik *et al.*, 1996; Schmid *et al.*, 1999; Kakinuma *et al.*, 2003b). In addition, serum CTACK/CCL27 levels in patients with CTCL decreased after treatment. This is the first report describing the relationship between CTACK/CCL27 and CTCL. CTACK/CCL27 is expressed at a small amount even in normal skin (Kakinuma *et al.*, 2003a) and that may be the reason of a large overlap of CTACK/CCL27 levels between healthy controls and an early stage of CTCL (Figure 1a). Serum CTACK/CCL27 levels in patients with tumor were higher than those in erythrodermic patients probably because three out of five patients with skin tumor had systemic involvement. In addition, erythrodermic CTCL is very rare and the number of cases may not be enough. Therefore, further study with larger number of patients would be useful to fully determine the potential usefulness of CTACK/CCL27 levels as a treatment- and diagnosis-related biomarker.

Previous reports showed that CCR10 is expressed in CTCL (Notohamiprodjo *et al.*, 2005) and that CCR10 engagement by CTACK/CCL27 allows melanoma cells to escape host immune antitumor killing mechanisms (Murakami *et al.*, 2003). The same pathway may be involved when CTCL cells escape host immunity. Our data suggest its possibility and that functional blocking of CTACK/CCL27 would be another target for treatment.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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The Receptor for *Cis*-Urocanic Acid Remains Elusive

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TO THE EDITOR

The number of human diseases in which the immunomodulatory effects of UV radiation play a role is expanding, and include not only the development of skin cancers but also autoimmune and infectious diseases. In addition, UV has long been recognized as an important therapeutic for the treatment of inflammatory skin conditions. Molecules in skin that absorb UV radiation include the DNA and membrane lipids of epidermal cells, as well as *trans*-urocanic acid (*trans*-UCA), a major molecule of the stratum corneum. On irradiation, it is converted to the more soluble *cis*-isomer. The action spectrum of UVB-induced systemic suppression of contact hypersensitivity responses in mice closely follows the absorption spectrum of UCA (De Fabo and Noonan, 1983).

Abbreviations: DOI, 2,5-dimethoxy-4-iodophenyl-2-aminopropane; 5-HT, 5-hydroxytryptamine; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; PGE_2, prostaglandin E_2; TNF-α, tumor necrosis factor-alpha; UCA, urocanic acid