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Letter to the Editor

Stratum corneum interleukin-33 expressions correlate with the degree of lichenification and pruritus in atopic dermatitis lesions

Dear Editor, interleukin-33 (IL-33) is a member of the IL-1 family of cytokines and promotes Th2 immune responses. IL-33 binds to ST2 and the IL-1 receptor accessory on various cells, including basophils, mast cells, keratinocytes, Th2 cells, and type-2 innate lymphoid cells (ILC2) [1]. IL-33 is released from epithelial cells by trigger factors, such as mechanical trauma, bacteria, and exogenous proteases, and activates Th2 cells, mast cells, dendritic cells, and ILC2, which produce IL-5, leading to eosinophil infiltration [1].

The expression of IL-33 and its receptors are upregulated in the lesional skin of patients with AD [2]. In addition, IL-33-induced ILC2 production is increased in the lesional skin of AD patients [3]. IL-33 downregulates filaggrin expression in keratinocytes from patients with AD and in normal human epidermal keratinocytes; therefore, IL-33 is considered to be related to epidermal barrier dysfunction and inflammation in AD [4]. These findings demonstrated that IL33 plays a role in AD. However, the relationships between IL-33 expression in the affected skin and the severity of AD or eruption type remain unclear. In this study, we utilized the tape-stripping technique to examine whether the stratum corneum IL-33 (scIL-33) expression level is correlated with the severity of AD and eruption type (erythema; edema/papule; oozing/crusting; excoriation; lichenification; xerosis) in AD patients.

Thirty patients (17 males and 13 females; median age: 42 years, range: 21–62) who had been diagnosed with AD and 29 healthy controls (11 males and 18 females; median age: 34 years, range: 22–44) were included in this study. The clinical severity of AD was evaluated as mild (n = 9), moderate (n = 11), severe (n = 7), or very severe (n = 3) according to the criteria established by the Japanese Dermatological Association [5]. Patients were treated with systemic antihistamine (n = 17) and steroids (n = 1), topical steroids (n = 28) and calcineurin inhibitors (n = 12). The severity of the eruptions on the lesion was assessed on a 5-point scale (0: none, 1: very mild, 2: mild, 3: moderate, and 4: severe) by scoring the symptoms, erythema; edema/papule; oozing/crusting; excoriation; lichenification; xerosis; and the total intensity that are added together. The pruritus numerical rating scale (NRS) score on the lesion was also evaluated. The tape-stripping method, and measurements of scIL-33 expression level were performed as described previously (see Supplementary Methods for details) [6].

We evaluated IL-33 expression in the stratum corneum of the trunk skin using immunostaining (Supplementary Fig. 1 and 2). The samples of affected sites on the trunk were obtained from representative area, and the samples of unaffected sites were obtained when patients had no lesions on the trunk. The mean fluorescence intensity of the trunk was 56.95 ± 3.85 (n = 24) in the stratum corneum tissue obtained from the affected skin of the AD patients, 38.20 ± 5.72 (n = 6) in the unaffected skin of the AD patients, and 25.12 ± 1.89 (n = 29) in the healthy individuals. The scIL-33 expression level was significantly higher in the affected areas of the AD patients than in the unaffected areas of the AD patients and the skin of the healthy subjects (Fig. 1a). These findings indicate enhanced expression of IL-33 in the stratum corneum of active AD versus both inactive disease and healthy controls. Further experiments are needed to determine whether IL-33 is driving AD pathogenesis or is simply a biomarker of the active disease state.

The correlations between the scIL-33 expression level and skin lesion severity scores or pruritus NRS score were assessed in the areas of affected and non-affected skin subjected to tape-stripping in the AD patients. The scIL-33 expression level of the trunk was significantly correlated with the lichenification score, but was not significantly correlated with the erythema score, oozing/crusting score, edema/papule score, excoriation score, xerosis score, or the total intensity scores (Fig. 1b). The pruritus NRS score was also significantly correlated with the scIL-33 expression level of the trunk. The patients with more severe lesions had more lichenified or itch lesions (Supplementary Fig. 3). However, the scIL-33 expression level of the trunk might be related to the lichenification or itch degree rather than the total intensity scores, because the scIL-33 expression level of the trunk was not statistically correlated with the total intensity scores. The relationships between the scIL-33 expression level and laboratory markers were examined. The scIL-33 expression level was not significantly correlated with serum total IgE levels ($r = 0.007$, $p = 0.976$), peripheral blood eosinophil count ($r = -0.077$, $p = 0.743$), serum LDH levels ($r = 0.270$, $p = 0.252$), or serum TARC levels ($r = 0.028$, $p = 0.905$). The data show expression of IL33, but not how it is involved in the pathogenesis or fibrosis that is characteristic of AD.

Our findings indicate that the scIL-33 expression level was correlated with the lichenification score, but not with acute-phase parameters. The chronic phase of AD is clinically characterized by lichenification, whereas it is histologically characterized by epidermal hyperplasia and dermal fibrosis involving the infiltration of eosinophils and macrophages [7]. Recent studies have shown that the subcutaneous administration of IL-33 induces cutaneous fibrosis and inflammation, and IL-33 might be involved in skin fibrosis through the ST2 receptor signaling pathway [8,9]. In this study, the cytokine expression data obtained for the stratum corneum tissue samples would reflect the cytokine expression levels of epidermal keratinocytes [6];

Abbreviations: AD, atopic dermatitis; IL, interleukin; NRS, numerical rating scale; sc, stratum corneum; TSLP, thymic stromal lymphopoietin; ILC2, type-2 innate lymphoid cells; TARC, thymus and activation-regulated chemokine

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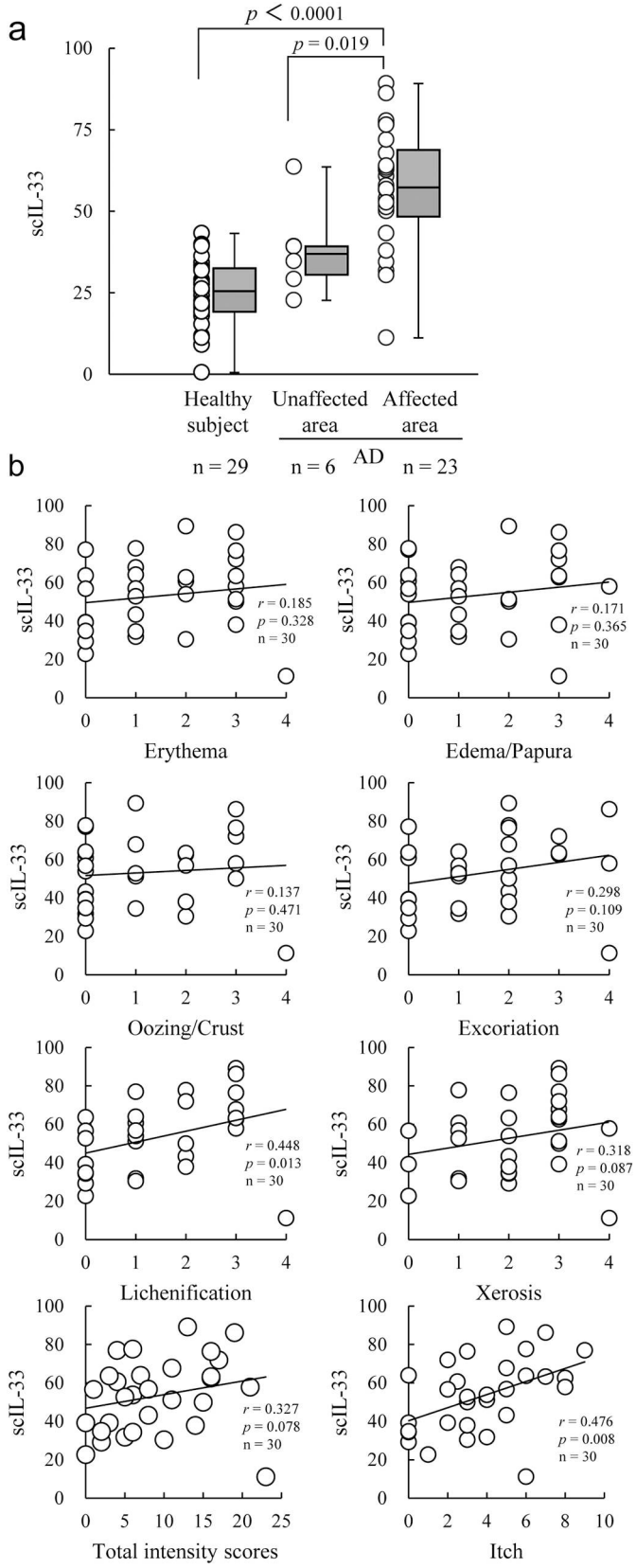

Fig. 1. (a) The stratum corneum (sc) interleukin (IL)-33 expression levels of the trunk in atopic dermatitis (AD) patients and healthy individuals. In the AD patients, samples were taken from affected and non-affected areas of the trunk. Box plots presenting median, interquartile range, maximum and minimum, and individual dots of the scIL-33 expression levels were shown. Tukey-Kramer test was used. (b) Correlation between the scIL-33 expression level and the skin symptom severity score of the affected and non-affected trunk skin. Skin samples were obtained from AD patients via the tape-stripping method. Spearman's rank correlation test was used.

therefore, epidermal hyperplasia might cause increased scIL-33 expression, and the IL-33 secreted by keratinocytes might cause further cutaneous fibrosis in lichenified skin. These findings imply that IL-33 could be involved in tissue remodeling in chronic AD lesions.

The scIL-33 expression level was also significantly correlated with the itching score. Liu B et al. have shown that functional IL-33/ST2 signaling occurs in peripheral cutaneous sensory neurons and that the administration of neutralizing antibodies against IL-33 or ST2 decreased scratching and skin inflammation in allergic contact dermatitis. In addition, in the murine model of allergic contact dermatitis, the injection of IL-33 into the skin exacerbated itching via an ST2-based mechanism that was independent of histamine [10]. These findings suggest that cytokines, such as IL-33, derived from damaged skin by scratching due to itching might be involved in pruritic inflammation in AD.

In conclusion, using the tape-stripping method we demonstrated that scIL-33 expression was elevated in AD lesions and significantly associated with the scores of lichenification and itching. IL-33 might be involved in the development of chronic lesions such as lichenification and itching in AD lesions.

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Conflicts of interest

H.M., Y.M., and E.Y. are employees of Tokiwa Pharmaceutical Co., Ltd. NOV Academic Research. None of the other authors have any conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2019.02.006.

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