Journal of Dermatological Science xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Dermatological Science

journal homepage: www.elsevier.com/jds

Letter to the Editor

Interleukin-37 is elevated in subjects with atopic dermatitis

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder caused by multiple factors [1]. In terms of immunological abnormalities, type 2 helper T (Th2) cells play a major role in the early establishment of AD and type 1 helper T (Th1) cells sequentially exacerbate the disease during the chronic phase [2]. In addition to this acquired immunity, innate immunity is engaged in the pathogenesis of AD [3]. We have previously reported that skin colonization with *Staphylococcus aureus* contributes to the production of epidermal interleukin (IL)-18 and that corneum IL-18 concentration is associated with AD severity [4]. IL-18 is a member of the IL-1 family, which now contains 11 members, of which most are proinflammatory in the innate immune system [5]. Of them, IL-37, the most recently identified IL-1 member, which was originally defined as IL-1 family member 7, is a fundamental inhibitor of innate immunity [6]. TGF-β, several toll-like receptor (TLR) ligands and proinflammatory cytokines such as IL-18, IFN-γ, IL-1β and TNF induce IL-37 production from peripheral blood mononuclear cells (PBMCs). IL-37 has five splice variants, namely IL-37a–IL-37e. IL-37b, the largest isoform, is thought to form a functional complex with Smad3 in the nucleus and suppresses both TLR-induced proinflammatory cytokine production and dendritic cell (DC) activation. However, the expression and role of IL-37 in AD remain unknown. In the present study, the expression of IL-37 in subjects with AD was investigated.

After obtaining informed consent and approval by the local ethics committee, peripheral blood was taken from 55 Japanese subjects with AD (32 men and 23 women; mean age 32.0 years, range 6–71 years) and 20 healthy controls (HC; 9 men and 11 women; mean age 32.1 years, range 24–53 years). Subjects with AD diagnosed by a dermatologist according to the criteria of Hanifin and Rajka, were evaluated for the general severity of their AD using the SCORing AD (SCORAD) index and divided into two groups according to SCORAD score (<40, mild AD; >40, severe AD) [7]. Serum IL-37 level was measured with a commercially available enzyme-linked immunosorbent assay (ELISA) kit which can specifically detect IL-37b (AdipoGen AG, Liestal, Switzerland). Serum IL-37 was significantly high in subjects with AD compared with HC ($P < 0.01$) and correlated with SCORAD, although there was no significant difference between AD groups (Fig. 1a). Remarkably, several subjects with severe AD showed low level of serum IL-37, suggesting the existence of diverse phenotypes of AD with IL-37 production (Fig. 1b). The mean ± SEM of serum IL-37 levels was as follows: HC: 8.9 ± 3.5 pg/mL; mild AD: 59.3 ± 12.4 pg/mL; and severe AD: 72.9 ± 10.4 pg/mL.

To investigate the local expression of IL-37, skin biopsy specimens were analyzed by immunohistochemical staining with mouse monoclonal antibody raised against a full length recombinant IL-37 (Abnova, Walnut, CA). IL-37 is widely detected in most tissues [8], and in the present study, IL-37 protein was found in the nuclei of keratinocytes in the epidermis and in some stromal cells in the dermis with AD, but not in infiltrated lymphocytes (Fig. 2c–e). Consistent with the sera results, IL-37 was highly expressed in AD (Fig. 2c), but poorly in HC (Fig. 2b). To seek the source of IL-37 in AD, keratinocyte cell line HEK, dermal fibroblast and PBMCs were cultured and stimulated with LPS. IL-37 protein was not detectable in each cell supernatants by ELISA. However, IL-37 mRNA was detectable not only in PBMCs as reported previously, but also in keratinocyte and dermal fibroblast cell lines (data not shown). Concerning the source and role of serum IL-37, and the signaling pathway and kinetics of IL-37 expression in AD, further investigations are required, but these findings serve as a clue.

A recent study demonstrated the role of IL-37 in a mouse model of colitis [9]. In this model, human IL-37 transgenic mice upregulate IL-37 expression during inflammation despite a

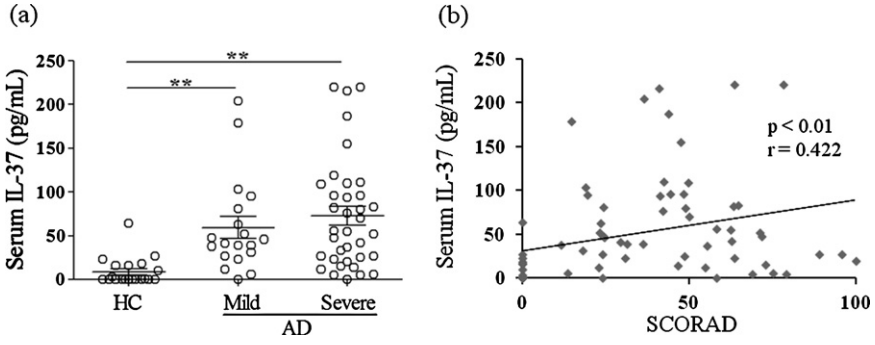

Fig. 1. Increased serum IL-37 levels in subjects with AD. (a) Serum IL-37 levels of healthy controls (HC), mild AD (SCORAD < 40) and severe AD (SCORAD > 40) were measured by ELISA. (b) Serum IL-37 showed significant differences in SCORAD. $^{**}P < 0.01$ between the indicated groups by the Mann–Whitney test.

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http://dx.doi.org/10.1016/j.jdermsci.2012.11.001

Please cite this article in press as: Fujita H, et al. Interleukin-37 is elevated in subjects with atopic dermatitis. J Dermatol Sci (2012), http://dx.doi.org/10.1016/j.jdermsci.2012.11.001

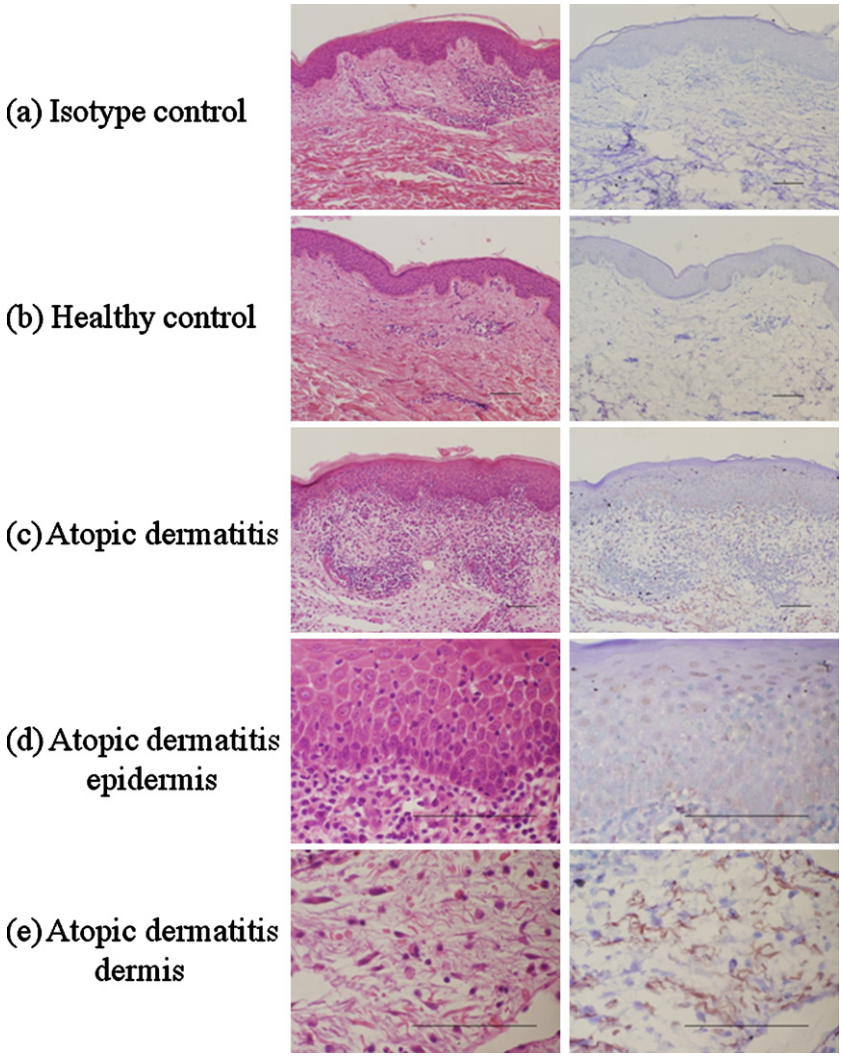

Fig. 2. Increased skin IL-37 levels in subjects with AD. The expression of IL-37 in skin was investigated by immunohistochemical staining. Isotype control showed no positive staining (a). IL-37 is highly expressed in AD skin (c) and is localized to nuclei of keratinocytes (d) and some stromal cells (e), but not abundant in HC skin (b). Data are representative of at least 3 independent staining procedures. All scale bars represent 0.1 mm.

constitutively active promoter indicating posttranscriptional regulation of mRNA expression. IL-37 is not present in the colon during the resting state, and expression is observed only upon disruption of the epithelial barrier. Moreover, IL-37 seems to reduce inflammation via decreased leukocyte recruitment into the colonic lamina propria and via IL-1β and TNF-α production by colonic explant tissue. In humans, IL-37 is highly expressed in synovial tissue of active rheumatoid arthritis, suggesting that IL-37 mediates a negative feedback mechanism to suppress excessive inflammation [6]. In addition, IL-37 is detectable in not only PBMCs [8], but also keratinocyte and dermal fibroblast cell lines. These findings support the present results which show the elevation of IL-37 level in subjects with AD. Namely, IL-37 is induced systemically and locally through disruption of the skin barrier and several subsequent stimuli such as TLR receptor ligands including *S. aureus* followed by production of proinflammatory cytokines including IL-18. Thus, IL-37 seeks to suppress atopic inflammation and is elevated in both serum and skin in AD subjects. In conclusion, IL-37 may play a role in the pathogenesis of AD by modulating innate immune reactions.

Funding

This work was partially supported by a grant in-aid for scientific research from the Ministry of Education, Science, Sports, and Culture of Japan.

Acknowledgements

None declared.

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7 June 2012

Please cite this article in press as: Fujita H, et al. Interleukin-37 is elevated in subjects with atopic dermatitis. J Dermatol Sci (2012), http://dx.doi.org/10.1016/j.jdermsci.2012.11.001