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IL-31 and IL-33 circulating levels in allergic contact dermatitis

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KEY WORDS

Allergic contact dermatitis; cytokines; interleukin-31; interleukin-33; pruritic skin disease; pruritus

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Summary

Enhanced IL-31 expression in skin biopsies is present in allergic contact dermatitis (ACD). IL-33 expression is induced in keratinocytes and in skin of ACD patients. This overexpression is present in both allergic and irritant conditions. The aim of this work was to test the systemic involvement of IL-31 and IL-33 in ACD. IL-31 levels were significantly higher in patients than in controls. IL-33 serum levels, on the contrary, were similar in patients and controls. This work shows a possible systemic involvement of IL-31 and the absence of a systemic involvement of IL-33 in ACD. IL-31 levels do not seem related to the allergen involved, and did not change on the strength of the allergen involved. More likely, IL-31 levels are related to the itch. IL-33, instead, is secreted from damaged or inflamed tissue and might function as an early warning system at the site of skin damage. In the future, IL-31 could be a possible therapeutic target of all pruritic skin diseases resistant to conventional therapies.

Introduction

Allergic contact dermatitis (ACD) involves epidermal cells, such as keratinocytes and Langerhans cells, fibroblasts and endothelial cells, as well as invading leukocytes, interacting amongst themselves under the control of cytokines and mediators network (1). Interleukin (IL)-31, a recently discovered cytokine, is involved in both innate and adaptive immunity in tissues in close contact with the environment, such as the skin (2).

IL-31 is produced by human mast cells, monocytes, macrophages, monocyte-derived dendritic cells, human epidermal keratinocytes and dermal fibroblasts upon various stimulations (2). Enhanced IL-31 expression in skin biopsies is present in pruritic diseases as atopic dermatitis, ACD and prurigo nodularis, and elevated serum IL-31 levels have been found in chronic urticaria and pruritic skin lesions related to epidermal growth factor receptor-tyrosine kinase inhibitors treatment (3-7).

IL-33, a cytokine of the IL-1 cytokine family has recently been attributed to the epithelial "alarmin" defense system. IL-33 is released by the epithelial cells in various tissues and organs, including keratinocytes, endothelial cells, and immune cells and, as other cytokines of IL-1 family, by necrotic structural cells, as fibroblasts and keratinocytes (8,9).

The aim of this study was to measure the circulating IL-31 and IL-33 levels in patients with ACD to test the hypothesis that these cytokines could have a systemic involvement in this pruritic skin disease.

Material and Methods

We enrolled 20 patients (15 females, 5 males), with ACD (mean age 36.84 ± 12.62 years; range 18-62 years), diagnosed by patch testing with SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) series, in accordance

with the International Contact Dermatitis Research Group guidelines. The three main allergens involved in manifestations were nickel sulphate (15 patients), potassium dichromate (11 patients) and cobalt chloride (4 patients). At the moment of blood collection all patients presented moderate-severe skin manifestations. All patients signed an informed consent to the study. Twenty-five sex- and age-matched healthy subjects were used as controls.

Serum IL-31 and IL-33 concentrations were measured by a standard sandwich ELISA kit (USCN Life Science, Houston, USA). All samples were analyzed in duplicate.

Data were expressed as median $\pm$ SEM. Differences between two unpaired groups were analyzed by Mann-Whitney test using SPSS for Windows (version 17.0). Statistical significance was set at $P < 0.05$.

Results

IL-31 levels were significantly higher in patients than in controls (8.27 ± 2.04 vs. 5.18 ± 1.46 pg/ml; $P = 0.034$) (**figure 1**). IL-33 serum levels were similar in patients and controls (2.67 ± 2.38 vs. 2.48 ± 1.29 pg/ml; $P = 0.668$) (**figure 2**). No correlation between cytokines levels and age of patients and duration of disease was found.

Discussion and conclusions

ACD is usually considered a Th1-driven disease; however, in some patients a mixed Th1/Th2 phenotype can be observed (3). Therefore, cytokines expression in ACD could be heterogeneous: in previous works elevated serum levels of IL-18 (10) and IL-22 (11) cytokines produced by different cellular subsets were found.

IL-31 is usually expressed by Th2 clones and not by Th1, Th17 or Th22. However, this expression depends on the microenvi-

ronment: indeed, it is linked to autocrine IL-4 expression, and, in presence of IL-4, Th1 clones can also express IL-31 (12).

Moreover, IL-31 seems to play an important role in pruritic skin diseases.

To our knowledge this is the first work showing a possible systemic involvement of IL-31 in ACD, one of the most common pruritic skin diseases. IL-31 levels do not seem to be related to the allergen involved, as our patients were positive to different allergens and the cytokine level did not change on the strength of the allergen involved. More likely, IL-31 levels are related to the itch.

IL-33 has been found to play a role in the pathogenesis of ACD by promoting Th2 immune responses (8,13). The expression of this cytokine is induced in human keratinocytes cell line (8) and in involved and uninvolved skin of ACD patients (9) and its blockade attenuates ACD in a murine model (8). However, the overexpression of IL-33 in ex vivo skin culture was detected in both allergic and irritant conditions (9).

We did not find significant differences in IL-33 serum levels between ACD patients and controls. This could mean that in ACD there is not a systemic involvement of this cytokine. Therefore, these data suggest that IL-33 is secreted from damaged or inflamed tissue and might function as an early warning system at the site of skin damage.

In the future, IL-31 could be a possible therapeutic target of all pruritic skin diseases resistant to conventional therapies.

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Figure 1 - IL-31 serum levels in ACD patients and controls; lines represent medians.

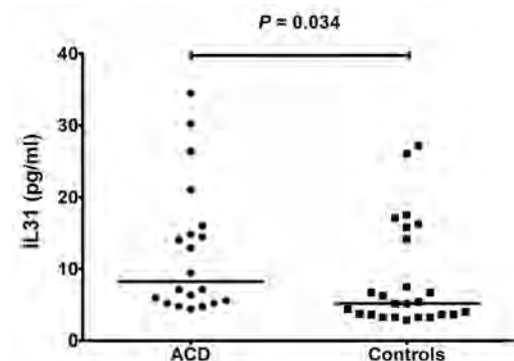
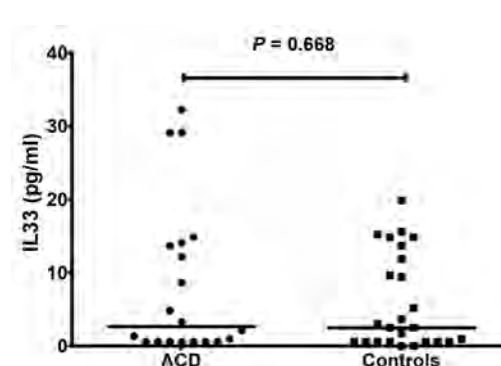


Figure 2 - IL-33 serum levels in ACD patients and controls; lines represent medians.



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