

LETTERS TO THE EDITOR

Increased expression of CRTH2 on eosinophils in allergic skin diseases

Editor

Prostaglandin D2 (PGD2) is an arachidonic acid metabolite that is secreted from activated mast cells. The biological activities of PGD2 are mediated through the DP and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). CRTH2 is expressed on eosinophils, basophils, and a subpopulation of Th2 cells.¹ On exposure to PGD2, these cells exhibit chemotaxis.¹ Despite these findings, the role that the PGD2–CRTH2 interaction plays in human skin diseases has not been elucidated. To examine the link between CRTH2 and skin diseases characterized by blood and/or tissue eosinophilia, the surface expression of CRTH2 on eosinophils was studied.

Study participants included subjects with atopic dermatitis ($n = 23$; M: 14, F: 9; mean age: 31.9 years), acute urticaria during the onset of skin symptoms ($n = 7$; M: 3, F: 4; mean age: 30.4 years), chronic urticaria in the absence of skin symptoms ($n = 5$; M: 1, F: 4; mean age: 28.2 years), prurigo nodularis ($n = 4$; M: 1, F: 3; mean age: 56.0 years), and healthy volunteers ($n = 8$; M: 2, F: 6; mean age: 28.2 years).

Eosinophil CRTH2 expression (phycoerythrin-conjugated anti-human CRTH2 monoclonal antibody, BM16, Miltenyi Biotec GmbH) was analysed using whole-blood flow cytometry.² This study was approved by the ethics committee of Tokyo Medical and Dental University.

Blood eosinophils expressed CRTH2 (Fig. 1a). CRTH2 expression on eosinophils was significantly increased in atopic dermatitis, chronic urticaria, and prurigo nodularis patients (Fig. 1b). Importantly, in atopic dermatitis patients, there was a correlation between the CRTH2 levels and the clinical severity score (Eczema Area and Severity Index)³ by the Pearson's correlation coefficient test (correlation coefficient = 0.61; Fig. 2). However, neither serum IgE levels nor blood eosinophil counts were correlated with CRTH2 expression levels (data not shown).

While atopic dermatitis patients generally had higher surface eosinophil CRTH2 levels, eosinophils from some of the atopic dermatitis patients had low CRTH2 levels (Fig. 1). This might be

Abbreviations: CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; PGD2 prostaglandin D2.

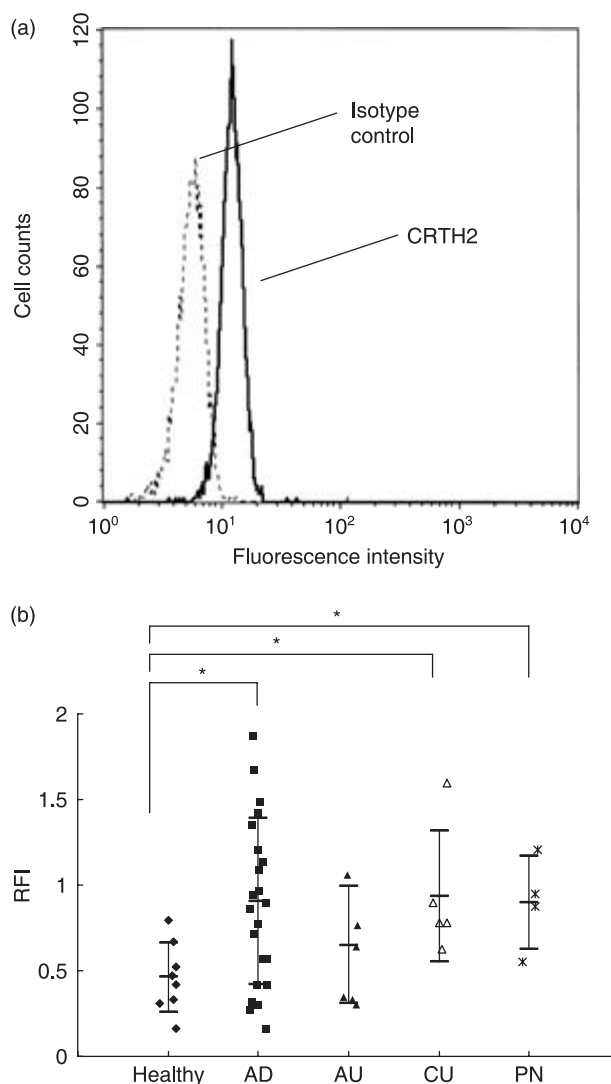


Figure 1 CRTH2 expression on eosinophils. (a) Representative data of the flow cytometric analysis for CRTH2 expression on eosinophils. (b) Eosinophils from atopic dermatitis, chronic urticaria, and prurigo nodularis patients expressed higher CRTH2 levels as expressed by relative fluorescence intensity (RFI) than those of healthy subjects.

$$RFI = \frac{\text{Mean FI (CRTH2)} - \text{Mean FI (control Ab)}}{\text{Mean FI (control Ab)}}$$

The Student's *t*-test was used to assess the statistical significance of differences between mean values of healthy subjects and patients.

* $P < 0.05$.

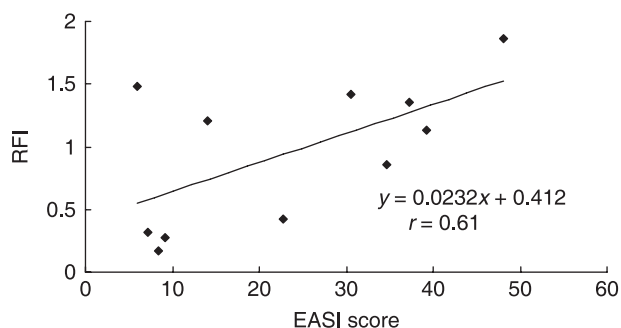


Figure 2 Correlation between eosinophil CRTH2 expression and the clinical severity (EASI) score in atopic dermatitis patients.

due to interleukin-5 (IL-5)-mediated eosinophil activation, since IL-5 reduces the surface expression of CRTH2 on eosinophils.⁴ Alternatively, the reduced level of surface CRTH2 might be due to the activation of eosinophils through PGD2-CRTH2 signals. CRTH2 agonists induce rapid internalization of CRTH2.⁵

Eosinophils obtained from acute urticaria patients, unlike those from chronic urticaria patients, expressed CRTH2 that were similar to those from healthy subjects. Eosinophil activation may not occur during the onset of acute urticaria. Alternatively, rapid eosinophil mobilization from the bone marrow into the peripheral circulation might be induced by PGD2 or its metabolite, delta 12-PGJ2,⁶ which is secreted from activated mast cells during an urticarial reaction; subsequently, surface CRTH2 could be internalized due to the agonistic effect of PGD2 or delta 12-PGJ2.

The molecular mechanisms of CRTH2 up-regulation in eosinophils are still uncertain. The increased expression of CRTH2 on eosinophils obtained from atopic dermatitis, chronic urticaria, and prurigo nodularis patients, but not acute urticaria

patients, suggests that events that occur during chronic or persistent allergic conditions mediate the increase in surface CRTH2 expression. This priming effect might make the eosinophils 'high responder cells' to PGD2.

It is likely that the PGD2-CRTH2 system is involved in allergic skin diseases, such as atopic dermatitis, although a further study with a larger sample size for acute urticaria, chronic urticaria, and prurigo nodularis is needed for determining differences in the activation status of eosinophils with regard to CRTH2 between acute and chronic skin diseases with eosinophilia.

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