Cell-surface expression of CD25, CD26, and CD30 by allergen-specific T cells is intrinsically different in cow's milk allergy

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Background: The release of T_H2 cytokines by food-specific T cells is thought to be important in the etiology of food allergy. It has been suggested that the activation state of food-specific T cells also plays a significant role, but this has not yet been studied at the single-cell level.

Objective: Differences in the expression of cell-surface markers by cow's milk protein (CMP)–specific T cells between infants with and without cow's milk allergy (CMA) were evaluated at the clonal level. In addition, expression after the spontaneous development of tolerance of cow's milk in infants with CMA was analyzed.

Methods: We established CMP-specific T-cell clones (TCCs) from blood of infants with CMA and atopic dermatitis, from atopic controls with atopic dermatitis but without CMA, and from nonatopic controls. In addition, we established TCCs from infants with CMA after they had spontaneously developed tolerance to cow's milk. Expression levels of CD25, CD26, and CD30 by each TCC were analyzed by use of flow cytometry.

Results: Cow's milk protein–specific T cells from infants with CMA expressed much higher levels of CD25 and CD30 than CMP-specific T cells from infants without CMA. Expression of CD26 was much lower than in normal controls. After development of tolerance for cow's milk, expression of CD25 and CD30 was decreased, whereas the expression of CD26 was increased to normal levels.

Conclusion: Antigen-specific T cells from patients with food allergy display an increased expression of cell-surface markers of activation compared with cells of patients without food allergy. This suggests an intrinsically stronger food-specific T-cell response in food-allergic patients, and points to the key role of food-specific T cells in the pathogenesis of food allergy. (J Allergy Clin Immunol 2002;109:357-62)

Key words: *Atopic dermatitis, T-cell clone, cow's milk, CD25, CD26, CD30, food allergy, infants, human, T_H1/T_H2 cells*

Food antigens are the main allergens that cause allergic reactions during infancy and childhood,[1,2] An important role in the pathogenesis of food allergy is attributed to food-specific T-cell reactivity. Both in allergen-stimulated PBMCs[3-6] and at the clonal level,[7] it has been shown that the food-specific T-cell response in patients with food allergy is T_H2-skewed when compared to that of food-tolerant individuals. Because the T_H2 cytokines (IL-4, IL-5, and IL-13) are important in the pathogenesis of allergic inflammation,[8,9] these results have suggested a key role for allergen-specific T cells in food allergy-related symptoms.

Several observations suggest that not only production of T_H2 cytokines, but also the activation state of food-specific T cells might play a role in the pathogenesis of food allergy. Food-specific T-cell reactivity is present in food-allergic and food-tolerant individuals, but proliferative responses of T cells in patients with food allergy are higher than those in food-tolerant patients.[10-14] In addition, patients with allergic disease have higher numbers of circulating, activated, allergen-specific T cells bearing activation markers such as CD25 and CD30.[15-18] However, these studies investigated T-cell reactivity in bulk cultures of T cells, which makes it difficult to extrapolate results to the individual T cell.

An important marker of T-cell activation is CD25 (IL-2Rα), the high affinity receptor for IL-2.[19] CD30, a member of the TNF receptor superfamily, is another marker for the activation state of a T cell.[20] The expression of CD30 by T cells has been associated with the preferential production of T_H2 cytokines.[21,22] Similarly, the expression of CD26 (dipeptidyl-peptidase IV) by T cells has been associated with T_H1 responses.[23,24] To date, no study has investigated the expression of these cell-surface markers by food-specific T cells at the single-cell level.

Cow's milk is the most common food antigen in young children, and is the etiologic factor of cutaneous symptoms in ~35% to 40% of infants with atopic dermatitis (AD).[25,26] Cow's milk allergy (CMA) in infancy is often associated with the spontaneous development of toler-

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Abbreviations used
AD: Atopic dermatitis
CMA: Cow's milk allergy
CMP: Cow's milk protein
MFI: Mean fluorescence intensity
TCC: T-cell clone
TCR: T-cell receptor
[^{3}H]-TdR: Tritiated thymidine

ance within 2-3 years.[2] The aim of this study was to investigate the cow's milk protein (CMP)–specific T-cell response in patients with CMA and AD at the clonal level, by analyzing levels of expression of cell-surface markers by the CMP-specific T cells in these patients. We used an antigen-specific T cell culturing system with autologous B cells as antigen-presenting cells to establish CMP-specific T-cell clones (TCCs) from blood. Expression of CD25, CD26, and CD30 by T cells derived from blood of infants with CMA was compared with CMP-specific T cells from age-matched control infants without CMA. In addition, we investigated the expression after the spontaneous development of tolerance for cow's milk in infants with CMA.

METHODS

Patients and control subjects

The CMP-specific TCCs described in this study were derived from blood of 5 infants with CMA and AD, and from 4 atopic control infants with AD but without CMA. These infants have been described previously.[7] Cow's milk allergy was diagnosed by complete elimination of cow's milk from the infant's diet, followed by a cow's milk challenge. The nonatopic control group comprised 3 infants prior to cardiac surgery, in the absence of hemodynamic compromise. These infants did not have any atopic disorders (eczema, asthma, or rhinitis), did not have increased total IgE levels, and were not sensitized for a panel of 12 common inhalation and food allergens as determined by CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden). They did not use systemic or topical immunomodulatory drugs. The 3 groups of infants were matched with regard to age: CMA patients (mean 7.4 months, range 4.5–10.4), atopic controls (mean 7.0 months, range 6.1-7.4), and nonatopic controls (mean 8.0 months, 6.4-9.9).

In addition, CMP-specific TCCs were established from 3 infants with AD and CMA after they had spontaneously outgrown their CMA (mean age 26.5 months, range 21.9-32.3). To control for age-related changes, CMP-specific TCCs from 3 infants with AD but without CMA at the same age (mean 26.0 months, range 19.8-38.3) were established.

All blood samples were taken after written informed consent was obtained, and the study was approved by the medical ethical committee of the University Medical Center, Utrecht.

Reagents

A mix of purified CMPs (CMP-mix) containing equal quantities of total casein, α-lactalbumin, and β-lactoglobulin (each at a concentration of 50 μg/mL) was used as antigen. Purified CMPs were kindly provided by Dr E.C.H. van Beresteijn (Netherlands Institute for Dairy Research, Ede, The Netherlands). For culturing of T-cell lines and TCCs, complete medium RPMI-1640 (Gibco, New York) was used, supplemented with 10% pooled human AB serum obtained from 10 healthy individuals with blood group AB. Epstein Barr virus–transformed B cells were cultured in RPMI-1640 (Gibco), supplemented with 10% fetal calf serum (Gibco). Established TCCs were maintained in Iscove's Modified Dulbecco's Medium (Gibco) supplemented with 2% pooled human AB serum and 5% Yssel's medium. All media were supplemented with penicillin (100 IU/mL), streptomycin (100 mg/mL), and glutamine(1 mmol/L) (Gibco).

Preparation of CMP-specific TCCs

Cow's milk protein–specific TCCs were established as described previously.[7,27] Peripheral blood mononuclear cells were isolated from heparinized venous blood, and subsequently cultured in the presence of CMP-mix. After 7 days, 50 IU/mL of both recombinant IL-2 and IL-4 (kind gift of Novartis Research Institute, Vienna, Austria) was added to the culture medium. Cultures were restimulated every 14 days with irradiated (50 Gy) autologous EBV-transformed B cells that had been preincubated overnight with CMP-mix, as antigen-presenting cells. If these cultures indicated a high CMP-specific T-cell proliferation in lymphocyte stimulation test, T cells were cloned by limiting dilution, in the presence of IL-2, IL-4, and irradiated autologous EBV-transformed B cells (10^4/well) that had been preincubated overnight with CMP-mix. All established TCCs were tested in lymphocyte stimulation test to verify CMP specificity.

Flow-cytometric analysis

Expression of CD4, CD8, T-cell receptor (TCR), CD25, CD26, and CD30 by the TCCs was analyzed by flow cytometry 2 days after a restimulation with irradiated autologous EBV-transformed B cells that had been preincubated overnight with CMP-mix. Antibodies used were FITC- conjugated mouse-anti-human CD4 (clone Leu-3a, BD Biosciences, San Jose, Calif), PE-conjugated mouse-anti-human CD8 (clone Leu-2a, BD Biosciences), FITC-conjugated mouse-anti-human α/β TCR (clone WT-31, BD Biosciences), FITC-conjugated mouse-anti-human CD25 (clone M-A251, BD Biosciences), PE-conjugated mouse-anti-human CD26 (clone M-A261, BD Biosciences), and FITC-conjugated mouse-anti-human CD30 (clone BerH8, BD Biosciences). Cells were stained, fixed in paraformaldehyde, and analyzed with FACScan (BD Biosciences). All clones were CD4+ and expressed the α/β TCR (data not presented). Expression levels of CD25, CD26, and CD30 by each TCC was measured as mean fluorescence intensity (MFI). Isotype-matched control antibodies were used to control for nonspecific binding.

CMP-specific cytokine release

CMP-specific cytokine release by the TCCs was determined as described previously.[7]

To determine CMP-specific cytokine release, 10^6 cells of each TCC were incubated with 10^6 irradiated autologous EBV-transformed B cells that had been preincubated overnight with CMP-mix. Control cultures of TCCs and EBV-transformed B cells, preincubated without antigen were prepared in parallel. Cell-free supernatants were obtained after 24 hours of culture. Cytokines (IL-4 and IFN-γ) were measured in supernatants by use of ELISA according to the manufacturer's recommendations (Central Laboratory of the Blood Transfusion Service, Amsterdam, The Netherlands).

Statistical analyses

Parametric analysis (Student *t* test) was applied to determine significant differences between patient and control groups with regard to age, mean MFI, and differences in cytokine production. Differences associated with *P* values of <.05 were considered statistically significant. Parametric analysis (Pearson's correlation)

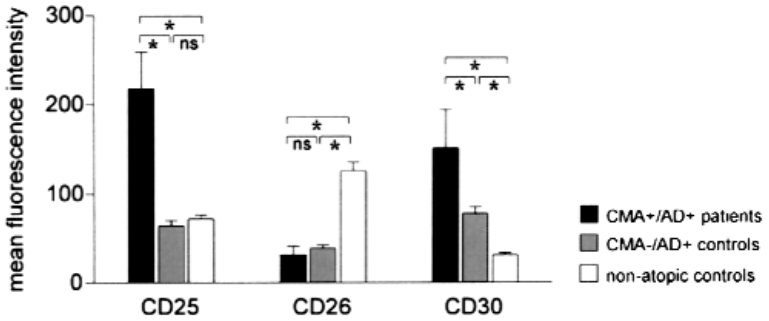

FIG 1. Mean of CD25-, CD26-, and CD30-expression by CMP-specific TCCs derived from infants with CMA and AD (*black bars*), age-matched atopic control patients with AD but without CMA (*gray bars*), and age-matched nonatopic controls (*white bars*). Expression was measured as mean fluorescence intensity by using flow cytometry, 2 days after stimulation with CMPs. *$P < .05$ (Student *t* test).

was used to test for correlation between expression of different cell-surface markers, and between surface marker expression and cytokine production.

RESULTS

Differences in expression of cell-surface markers by CMP-specific T cells from infants with CMA and controls

Differences in expression of CD25, CD26, and CD30 by TCCs (n = 13) derived from 5 infants with CMA and AD, TCCs (n = 37); from 4 atopic control infants without CMA, and TCCs (n = 74); and from 3 nonatopic control infants without CMA were analyzed. Fig 1 shows mean MFI of CD25, CD26, and CD30 expression on all CMP-specific TCCs derived from the 3 patient groups. Mean expression of CD25 was significantly higher on TCCs derived from infants with CMA (mean MFI ± SD, 218 ± 41) compared with TCCs from atopic (MFI 64 ± 6) and nonatopic (MFI 72 ± 4) infants without CMA ($P < .001$). Expression of CD30 was also significantly higher on TCCs derived from infants with CMA (MFI 151 ± 43) compared with TCCs from atopic (MFI 78 ± 7) and nonatopic (MFI 31 ± 2) infants without CMA ($P < .001$). In contrast, mean expression of CD26 was lower in infants with CMA (MFI 31 ± 10) than in nonatopic infants (MFI 126 ± 9) without CMA ($P < .001$). Comparison of both control groups showed that atopic infants without CMA had comparable expression of CD25 (MFI 64 ± 6 vs 72 ± 4, not significant), but a significantly higher expression of CD30 (MFI 78 ± 7 vs 31 ± 2, $P < .001$) and a lower expression of CD26 (MFI 39 ± 4 vs 126 ± 9, $P < .001$) than nonatopic controls.

Expression of CD25, CD26, and CD30 after the development of tolerance in patients with CMA

Expression of CD25, CD26, and CD30 on TCCs (n = 18) derived from 3 infants with CMA after they had spontaneously developed tolerance for CMP was analyzed. In addition, TCCs (n = 39) from 3 age-matched atopic controls were investigated. Results from this time point were compared with results from the first time point. Fig 2 shows mean MFIs of the expression of CD25 (Fig 2, *A*), CD26 (Fig 2, *B*), and CD30 (Fig 2, *C*). Mean expression of CD25 on CMP-specific TCCs derived from infants with CMA after they had developed tolerance to cow's milk was significantly lower compared to TCCs derived from infants during the allergic state (MFI 218 ± 41 vs 95 ± 10, $P < .01$). The same was true for the expression of CD30, which was high during the allergic state, and was significantly lower after the development of tolerance (MFI 151 ± 43 vs 47 ± 7, $P < .01$). In contrast, mean expression of CD26, which was low during the allergic state, was higher at the development of tolerance (MFI 31 ± 10 vs 88 ± 17, $P < .05$). In atopic controls, CD25 expression did not change between the two time points (MFI 64 ± 6 vs 57 ± 6). CD30 expression decreased in this group (MFI 78 ± 7 vs 31 ± 5, $P < .001$), whereas CD26 increased (MFI 39 ± 4 vs 89 ± 9, $P < .001$).

Correlation between expression of different cell-surface markers

The relation between the antigen-specific expression of the different cell-surface markers on the CMP-specific TCCs described in this study was investigated. Results showed that the expression of CD25 and CD30 was significantly correlated ($r = 0.668$, $P < .01$) in all TCCs investigated in this study (Fig 3, *A*). There was a negative correlation ($r = -0.241$, $P < .01$) between the expression of CD26 and CD30 in all TCCs (Fig 3, *B*). No significant correlation was observed between the expression of CD25 and CD26 (data not shown).

Relation between expression of CD26/CD30 and production of T_H1/T_H2 Cytokines

To investigate whether the relationship between the expression of CD26 and CD30 is associated with the production of T_H1/T_H2 cytokines in the TCCs described in this study, the correlation between the expression of CD26 and CD30 and the production of IL-4 and IFN-γ was calculated. Results showed no significant correlation between the expression of CD26 and IFN-γ, or between the expres-

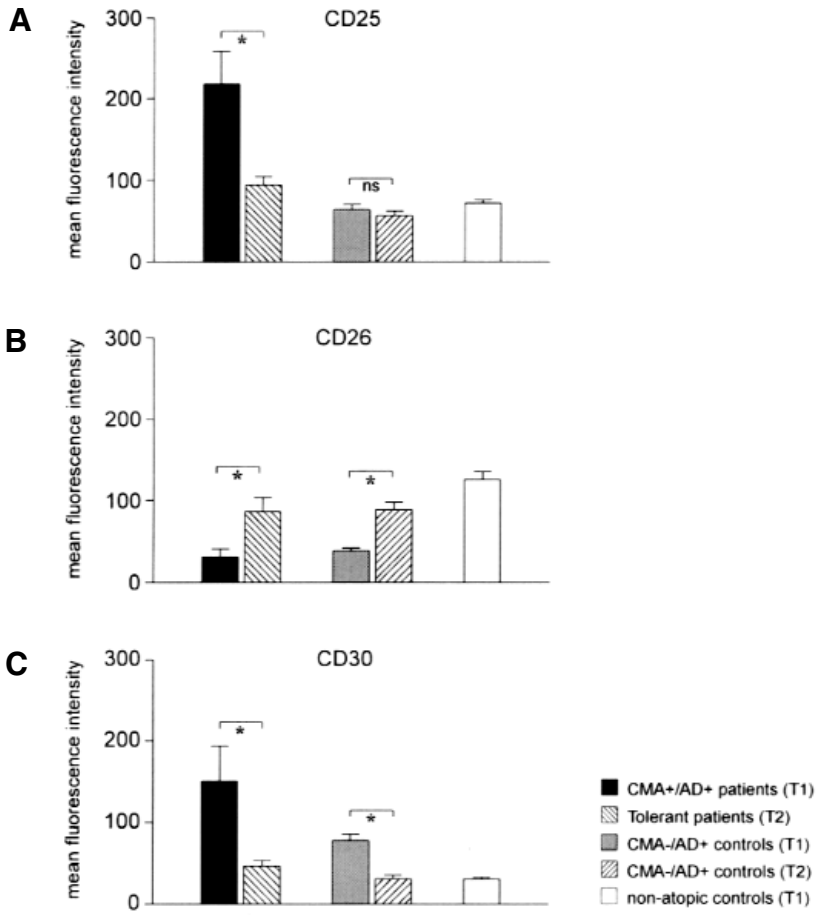

FIG 2. Mean expression of CD25 (**A**), CD26 (**B**), and CD30 (**C**) by CMP-specific TCCs derived from infants with CMA and AD, before and after the development of tolerance, and age-matched atopic control patients with AD without CMA at both time points. Nonatopic control infants from the first time point are shown as reference. Expression was measured as mean fluorescence intensity by using flow cytometry, 2 days after stimulation with CMPs. T1, First time point (before tolerance); T2, Second time point (after tolerance). *$P <$ .05 (Student *t* test).

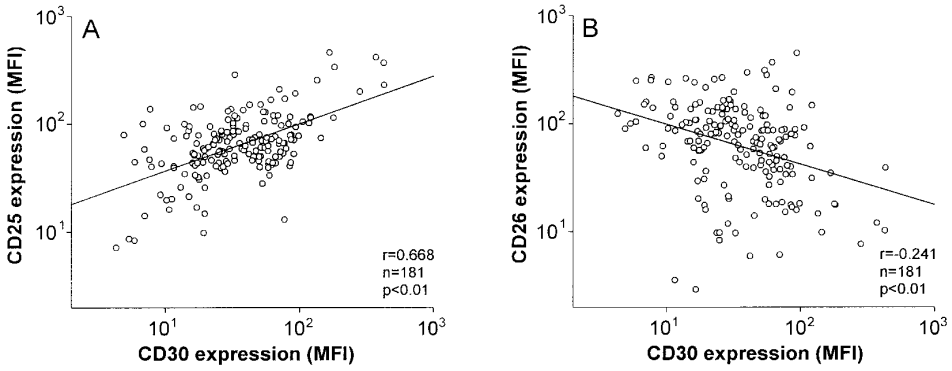

FIG 3. Correlations between expression of CD25 and CD30 (**A**) and between expression of CD26 and CD30 (**B**) by the CMP-specific TCCs investigated in this study. Expression was measured as mean fluorescence intensity by using flow cytometry, 2 days after stimulation with CMPs.

sion of CD30 and IL-4 (data not shown). In addition, we found no significant correlation between the expression of CD30 and the production of IFN-γ or between the expression of CD26 and the production of IL-4 (data not shown).

DISCUSSION

Food antigen-specific T cells are important in the etiology of allergic reactions to foods.[1] It has been shown

that food-specific T cells from food-allergic and food-tolerant individuals differ greatly with regard to the production of T_H1 and T_H2 cytokines.[3-7] In this study, we analyzed differences in food-specific T-cell reactivity with regard to expression of cell-surface markers.

The results from our study show at the clonal level that food-specific T cells from patients with food allergy express much higher levels of CD25 than food-specific T cells from patients without food allergy. CD25 (IL-2Rα) expression is regulated by IL-2, the major T-cell growth factor, and is, therefore, an important marker for the activation state of a T cell.[19] The fact that the food-reactive T cells from food-allergic patients have a much higher expression of the receptor for IL-2, suggests that the antigen-specific T-cell response in these patients is more pronounced than in patients without food allergy. From investigations in PBMCs, it is known that food-specific T cells from patients with allergy to food have a higher proliferative capacity in vitro than cells from non-food allergic patients.[10-14] This suggests that the in vivo food-specific T-cell response in patients with food allergy is intrinsically more vigorous. Our finding that allergen-specific T cells from infants with food allergy obtain a higher state of activation, might explain the food-allergic state of these patients. In this respect, the findings in the patients that had become spontaneously tolerant after cow's milk allergy are also of interest. These data suggest that in TCCs derived from these patients the expression of CD25 is significantly lower than at the allergic state, whereas no change occurs in age-matched atopic controls, again suggesting that high CD25 expression by allergen-specific T cells and allergic state might be connected.

Determination of CD30 expression by the TCCs in our study confirmed the results of the expression of CD25. Analysis of expression of CD30 showed that antigen-specific T cells from cow's milk–allergic patients have a higher CD30 expression than T cells from patients who are not cow's milk–allergic. The data suggest that expression of CD30 by CMP-specific T cells from patients who had developed tolerance spontaneously is significantly lower than at the allergic state. These results from CD30 as marker for the activation state of T cells are comparable with the results of the CD25 expression, and indicate an enhanced activated state of T cells in patients with allergic symptoms. Indeed, analysis of the expression of CD25 and CD30 showed a significant positive correlation between expression of the two markers.

Our study indicates that expression of CD26 by CMP-specific T cells from patients with CMA and AD is significantly lower than that in normal controls. Expression of CD26, the receptor for adenosine deaminase, by T cells is important for costimulatory signals, but its precise physiologic role is unknown.[28,29] Several studies have shown that absence or low levels of CD26 on T cells mediates immunologic diseases.[28-31] It is, therefore, tempting to speculate that low expression of CD26 by allergen-specific T cells from patients with food allergy contributes to the allergic state of these patients.

The expression of CD26 by T cells has been described to be preferentially associated with the release of T_H1 cytokines.[23,24] Similarly, the expression of CD30 by T cells has been associated with T_H2-mediated disease.[21,22] These associations have even led to the proposal for CD26 and CD30 as exclusive markers for T_H1 cells and T_H2 cells, respectively.[32] Several subsequent studies, however, have shown that expression of CD26 and CD30 is variable, and can be expressed by T cells on both ends of the T_H1-T_H2 spectrum, as well as T_H0 cells.[33-37] We investigated the relation between the expression of CD30 and CD26, and the production of IL-4 and IFN-γ, the hallmark T_H2-T_H1 cytokines, in the TCCs described in our study. We found no correlation between the expression of CD30 and production of IL-4, or between the expression of CD26 and IFN-γ production. In addition, we observed no association between CD30 and IFN-γ production, or between CD26 expression and IL-4 release. These results with a large number (n = 181) of TCCs confirm that on the level of the individual T cell, CD30 and CD26 can not be used as exclusive markers for T_H2 and T_H1 cells.[33,35,36]

It is of interest that we noted differences in the expression of CD26 and CD30 by T cells from the atopic and nonatopic control patients. Despite the fact that the atopic controls did not have CMA, the CMP-specific T cells showed a higher expression of CD30 and a lower expression of CD26 than the nonatopic controls. These differences indicate that expression of these markers by T cells may reflect the atopic state of a patient. It has been shown that expression of CD30 is generally increased in atopic disease, both on the surface of T cells[38,39] as well as release of its soluble counterpart.[40,41] However, studies that investigated CD30 expression on T cells mostly investigated differences in numbers of CD30-positive T cells. Our study now shows that expression levels of CD30 on individual T cells are also increased in atopic disease. The exact immunologic functions of CD26 and CD30 remain unknown; consequently, further studies are needed to clarify the exact role of CD26 and CD30 in allergy and atopic disease.

In summary, it has been established that patients with food allergy have an antigen-specific T_H2-skewed T-cell response compared with food-tolerant patients. The results from the present study show that, following stimulation, antigen-specific T cells from patients with food allergy display an increased expression of cell-surface markers of activation, compared with patients without food allergy. This result suggests an intrinsically stronger response of food-specific T cells in food-allergic patients, and points to the key role of food-specific T cells in the pathogenesis of food allergy.

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