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The Pathophysiology of Atopic Dermatitis

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INTRODUCTION

Patients with atopic dermatitis (AD) show a variety of humoral and cell-mediated immune dysfunctions, including an elevation of serum IgE level, multiple positive immediate skin tests to a variety of antigens, reduced responsiveness to contact allergens, and cutaneous anergy to intradermally administered microbial antigens (1, 2). Transfer of atopic disorders via bone marrow transplantation suggests that IgE-related immunological abnormalities underlie the pathogenesis of AD (3). The skin lesion of AD is infiltrated by activated $CD4^+$ T cells and IgE-bearing antigen-presenting cells (APC) such as Langerhans cells (LC), dendritic reticulum cells, and monocytes/macrophages (4–7). These findings suggest that the interaction between activated T cells and IgE-bearing APC plays a crucial role in the formation of skin lesions in AD.

The low-affinity receptor for the Fc region of IgE (FcεRII/CD23) is a 45–49kD membrane glycoprotein that bears marked homology with various animal lectins (8–15). FcεRII is induced by interleukin 4 (IL-4) in various cell types including B cells, T cells, monocytes and eosinophils, and may play a major role in IgE-related immune responses (16–21). For example, this receptor participates in parasite killing by eosinophils (22) and is engaged in antigen focusing on B cells and LC (23, 24). IFN-γ inhibits the expression on IL-4-stimulated T and B cells (25, 26), whereas monocytes and LC are stimulated to express FcεRII by IFN-γ (27–29). IFN-α suppresses FcεRII expression on B cells, monocytes and LC (30).

We have raised a monoclonal antibody (Mab) specific for FcεRII on human lymphocytes, H107(9), and have used this Mab to study the role of $FcεRII^+$ lymphocytes in the formation of skin lesions in AD.

SUBJECTS AND METHODS

We studied 95 patients with AD (aged 12–48 years; 51 men, 44 women), 26 patients with eczematous dermatitis (ED) (aged 18–75 years; 15 men, 11 women), and 42 healthy non-atopic volunteers with low serum IgE levels (less than 250 IU/ml) (aged 22–44 years; 25 men, 17 women). The diagnosis af AD was based on the following three criteria: (i) a focal or generalized maculopapular, lichenified, pruritic skin rash that showed predilection for the flexural areas of the extremities, and the face and neck; (ii) chronic or chronically relapsing course; and (iii) a positive family and/or personal history of respiratory atopy or eczema.

ED included generalized exfoliative dermatitis (five patients), autosensitization dermatitis (n=6), contact dermatitis (n=8), nummular eczema (n=4) and hand eczema (n=3). The patients with ED did not have a personal atopic history and were chosen as controls because the clinical and histological pictures of AD are both similar to those of ED. Serum IgE levels in ED patients were variable; some of the patients with severe to moderate ED had increased serum IgE levels, which occurs independently of the atopic diathesis (31).

None of the patients had received any treatment for at least 1 week before the study, had taken oral steroids, or had evident systemic disease.

Examinations of the peripheral blood from subjects with respiratory allergy (allergic rhinitis and/or asthma) were performed when they were free from respiratory attacks, in order to avoid the influence of active allergy of the frequency of $FcεRII^+$ cells (32).

Cutaneous index (CI) was quantified by determining the extent of body involvement, based on Lund & Browder's law (33). Since CI in patients with AD on the frequently involved sites (face, neck and flexural areas of extremities) was approximately 10% of the body surface, we divided the patients tentatively into: severe group, with CI > 50%; moderate group, with CI 50–10%; and mild group, with CI < 10%.

Reagents used throughout these studies, isolation of peripheral blood mononuclear cells (PBMC), immunofluorescence staining, blood and tissue analyses, and statistical analysis were described previously (34, 35).

THE PROPORTION OF $FcεRII^+$ LYMPHOCYTES CORRELATES WITH THE EXTENT OF SKIN LESIONS

% $FcεRII^+$ PBMC from patients with severe and moderate AD were ~6 and ~5, respectively, which is three- to four-fold higher than the value of normal non-atopic individuals (~1.5). The percentage for the severe and moderate ED group (~2.5%) was not significantly different from those for the mild ED (~2.2%) and AD (~2.3%) groups. A linear regression analysis showed that the percentage of $FcεRII^+$ PMBC did not correlate with the total IgE content in the serum. These findings suggested that the increase in $FcεRII^+$ mononuclear cells in the peripheral blood was an indication of the presence of extensive AD.

In severely and moderately affected AD patients, the majority of $FcεRII^+$ PBMC were B cells (Bε cells) representing at least half of all peripheral blood B cells. About 10% of $FcεRII^+$ PBMC bore the Leu 4 marker and these Tε cells comprised about 1% of peripheral T cells. However, virtually all $FcεRII^+$ PBMC in the mild AD, severe to mild ED and normal groups were considered to be B cells. These Bε cells comprised one-fourth to one-fourth of all peripheral Bells. These data on B cells agreed essentially with the findings by Suemura et al. (10) in which Bε cells comprised half of the peripheral blood B

cells in normal individuals and all B cells expressed FcεRII in atopic subjects.

The proportion of FcεRII$^+$ monocytes was increased significantly in AD patients, compared with normal subjects, and up to 50% of monocytes were FcεRII$^+$ in severely affected AD patients.

When the phenotype of Tε cells was examined in the severe and moderate AD groups, Tε cells preferentially expressed the CD8 suppressor/cytotoxic marker. Proportions of Tε cells with CD8 in these groups were ~0.4% and ~0.25%, respectively, and were significantly higher than those with CD4 in the corresponding groups (0.1±0.1% in both groups) ($0.025>P$).

The in-patients from the severe and moderate AD groups were placed on a daily regimen of topical corticosteroid and oral antihistamine. At the end of the 2-month treatment, the patients were classified as improved or unchanged, based on the evaluation of pre- and post-therapeutic CI. The post-therapeutic proportion of FcεRII$^+$ PBMC was reduced to less than half of the pre-therapeutic value in the improved group due to the overall decrease in Tε and Bε cells. Since the proportion of CD20$^+$ cells was also reduced, consistent with the improvement in dermatitis, percentages of Bε cells in CD20$^+$ cells were unchanged before and after treatment. On the other hand, frequencies of FcεRII$^+$ PBMC and of Tε and Bε cells before and after treatment did not differ significantly in the unchanged group.

These results demonstrated a significant correlation between the proportion of FcεRII$^+$ PBMC and the extent of the dermatitis. The activation of lymphocytes seems to be associated with *in vivo* generation of FcεRII. In atopic patients sensitive to grass pollen, exposure to antigen rather than the elevated level of total serum IgE is responsible for the larger numbers of FcεRII$^+$ lymphocytes in the peripheral blood(32). AD patients are occasionally sensitive to environmental allergens such as house dust mites and moulds and food allergens (1). It is reported that mite allergens produce eczematous lesions when patch tested on normal-appearing sking and induce *in vivo* proliferation and IL-2 production by T cells in AD patients with elevated RAST scores to these allergens (36, 37). While the role of environmental and food allergens in the elicitation of skin lesions in AD is still not fully explored, it is likely that daily exposure to the allergens sustains skin inflammation and activates T cells in the presence of IgE-bearing APC in the lesions of AD, resulting in the expression of FcεRII on activated T cells.

INFILTRATION OF FcεRII$^+$ T CELLS IN THE SKIN LESIONS

In acute AD lesions, FcεRII$^+$ were found scattered around the vessels in the upper dermis and sparsely distributed in the epidermis. Some of the cells co-expressed FcεRII and the Leu 1 marker, suggesting that these cells were Tε cells. With the use of anti-Leu 4 antibody instead of anti-Leu I antibody, similar results – but inferior staining patterns – were obtained.

Counting of the stained cells in AD lesions revealed that some 2–5% of the infiltrating mononuclear cells bore FcεRII. Acute lesions were infiltrated with significantly higher numbers of FcεRII$^+$ mononuclear cells than were chronic lesions. Regression analysis revealed that the proportion of FcεRII$^+$ cells in the skin lesion correlated with neither CI, the percentage of FcεRII$^+$ PBMC, nor with the serum IgE level. Half or more of the H107-reactive cells were positive for CD5 in both acute and chronic skin lesions. Means of CD8$^+$ and CD4$^+$ Tε cells among infiltrating mononuclear cells in acute lesions were about 1%. Of note was the finding that CD8$^+$ Tε cells were always found in acute lesions, whereas the infiltration of CD4$^+$ Tε cells was occasional. On the other hand, chronic lesions contained up to 0.5% of CD8$^+$ Tε cells and of CD4$^+$ Tε cells, suggesting the lack of a tendency for predominant infiltration of T cells with the particular phenotype. OKT6$^+$ cells were not reactive with H107 in either epidermis or dermis.

ED lesions did not always contain FcεRII$^+$ cells. When present, most of these cells seemed to be on non-T-cell lineages. H107-reactive cells were absent in normal-appearing skin from AD and ED patients and in the skin of normal non-atopic individuals.

Because the FcεRII on lymphocytes is an activation antigen (19--21), subpopulations of T cells might have been activated by a local endogenous or exogenous antigen to express FcεRII. Alternatively, subsets of peripheral blood T cells bearing FcεRII preferentially migrated to the AD lesion after antigenic stimulation at extracutaneous sites. High proportions of FcεRII$^+$ cells in acute vis-à-vis chronic lesions suggested that antigenic stimulation was more extensive in the former.

ABERRANT CONTROL IN THE *IN VITRO* EXPRESSION OF FcεRII/CD23 ON PERIPHERAL BLOOD T CELLS IN AD

A critical question arising from the above-mentioned results is whether FcεRII expression on T cells, especially on those with CD8, is intrinsic to atopic lymphocytes following stimulation or secondary to abnormal production of stimuli that induce FcεRII.

When PBMC were cultured in medium alone, or stimulated with IL-4 or PHA-P, various proportions of lymphocytes expressed FcεRII over the 7-day culture. In patients with severe AD and normal individuals, maximum levels of FcεRII expression were obtained 3 days after stimulation of the cells with IL-4 at 100 U/ml or with PHA-P at 5μg/ml. The course of this expression gradually declined thereafter in both groups. IL-4- and PHA-P-induced expressions of FcεRII in all patients with moderate and mild AD, and those with ED showed essentially the same time course.

Levels of the specific FcεRII expression in T cells on day 3 were ~6% in T cells and ~60% in B cells in IL-4-culture and were ~5% in T cells in PHA-culture. These values were comparable among all group, whereas the value in B cells was specifically higher in AD than in other groups. Specific induction of Bε cells was not detected in PHA-culture.

In PBMC cultured with IL-4 for 3 days, both CD4$^+$ and CD8$^+$ Tε cells were generated in all groups. Comparisons of the CD8/CD4 ratio in IL-4-induced Tε cell populations revealed that both severely and mildly affected AD patients had significantly high ratios compared with ED patients and nor-

mal individuals. Since CD8/CD4 ratios in PBMC before and after incubation with IL-4 were comparable among atopics and non-atopics, this increased ratio was not a reflection of a large number of $CD8^+$ T cells in atopics. The same results were obtained upon incubation of PBMC with PHA-P. This suggested that atopic donors tended to generate $CD8^+$ Tε cells in higher proportions than non-atopic donors when T cells were stimulated with appropriate stimuli to express FcεRII. Levels of FcεRII expression in culture containing 500 U/ml of IFN-γ declined to ~50% of the levels induced by IL-4 alone in both AD and normal individual groups. Proportions of Tε cells and Bε cells were significantly decreased by the addition of IFN-γ. On the other hand, neither PGE_2 nor IFN-α exerted any obvious effect on FcεRII expression in lymphocytes in either group.

DISCUSSION

In normal individuals, IL-4 production is limited to a comparably small population of $CD4^+$ T cells, in contrast to IFN-γ and IL-2 production in which one-third to more than half of peripheral $CD4^+$ T cells are engaged (38). Such limitation seems to selectively regulate the effect of IL-4 on immune responses. On the other hand, atopic patients have regulatory abnormalities in lymphokine production as exemplified by a defect in IFN-γ production by circulating T cells and the increased prevalence of IL-4-producing T cells (39, 40). Analysis of the inflammatory infiltrate in patients with vernal conjunctivitis at clonal level shows a higher frequency of T cells producing IL-4, compared with those secreting IFN-γ (3). Thus, it is possible that abnormal production and/or regulation of IL-4 and IFN-γ by T cells in response to allergen in skin and mucous membrane plays a role in the pathogenesis of atopic disorders.

Recent studies (5–7) have reported that APC – including LC in lesional areas of AD – bear IgE on the cell surface, suggesting FcεRII expression on these cells. By immunofluorescent staining, the allergen from house dust mites locates on LC partly via IgE bound to FcεRII at these sites (41). Environmental allergen may be presented so as to select T cells with abnormal profiles of cytokine production in skin lesions of AD. Since *in vitro* FcεRII expression on T cells was regulated by the reciprocal activity of IL-4 and IFN-γ, such an event, in turn, provides a milieu for the preferential expression of FcεRII on T cells. Although the role of $FcεRII^+$ lymphocytes in AD remains speculative, in the light of the pleiotropic functions of FcεRII, it is possible that these cells modulate cutaneous inflammatory reactions.

Polyclonal activation of peripheral T cells is associated with the generation of $FcεRII^+$ cells bearing not only helper/inducer but also suppressor/cytotoxic phenotypes. On the other hand, several studies (19, 20) have demonstrated that FcεRII is expressed exclusively on $CD4^+$ T cells when peripheral blood cells from allergic donors are stimulated with allergen with or without IL-4. Patients with AD, however, had a greater tendency for FcεRII expression on $CD8^+$ T cells, as compared with non-atopic subjects. Therefore, differences in the way of stimulation, i.e. polyclonal vs. allergen-specific, and in the selection of donors, i.e. atopics vs. non-atopics, may in part determine the types of T cells that express FcεRII. The assumption that an allergen-specific inflammation occurs in atopic lesions (3) predicts an overwhelming number of $CD4^+$ Tε cells in the lesions. The preferential appearance of $CD8^+$ Tε cells in the peripheral blood and skin lesion in AD suggests the concomitant occurrence of polyclonal activation of inflammatory cells partly by IL-4 produced by allergen-specific T cells. We speculate that $CD8^+$ Tε cells may adversely affect skin inflammation by enhancing IgE production. In rodents, Marcelletti & Katz (42) have identified $CD8^+$ Tε cells that disturb the regulatory function $CD4^+$ Tε cells concerned with IgE synthesis with resultant enhancement of IgE production.

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