THE MODULATORY EFFECTS OF INTERLEUKIN-4 AND INTERFERON-GAMMA PRODUCTION BY T-HELPER CELLS ON IgE SYNTHESIS IN CHILDREN WITH ATOPIC DISEASE

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ABSTRACT

Interleukin-4 (IL-4) is produced by T-helper cells type 2 (TH2) and induces IgE synthesis. T-helper cells type 1 (TH1) produce interferon-gamma (IFN-gamma) which suppresses TH2 and reduces IL-4 induced IgE production. In this study, we demonstrated that the levels of specific IgE in the serum of atopic children (n=20) were elevated while IL-4 production was increased and IFN-gamma secretion was reduced, compared to those of control group. Interleukin-4-induced IgE synthesis by peripheral blood mononuclear cells of atopic children in vitro was blocked in the presence of IFN-gamma. In addition, levels of soluble CD23 which is specifically induced by IL-4 were significantly elevated in our atopic patients. The data indicate that enhanced production of IL-4 and lowered IFN-gamma secretion by T-helper cells correlate with the elevated specific IgE levels in the serum of atopic children.

Key words: Atopy, IgE Synthesis, T-Helper Cells, Cytokines, Interleukin-4, Interferon-Gamma, Soluble CD23.

INTRODUCTION

IgE synthesis is modulated by the cytokines which are produced by T-helper cells. Interleukin-4 (IL-4) activates B cells to synthesize IgE.(1,2,3)
Modulatory Effects of Interleukin-4

Interleukin-5 (IL-5) and soluble CD23 enhance the IgE-inducing effect of IL-4, while alone are ineffective to stimulate IgE synthesis by B cells (5).

Interferon-gamma (IFN-gamma) blocks the IL-4 induced IgE production and acts as an antagonist of IL-4(1).

In this study, we examined the nutritive and inhalative allergens by measuring the levels of specific IgE in the serum and the levels of IL-4 and IFN-gamma in the stimulated peripheral blood mononuclear cells (PBMCs) of 20 children with established atopic disease and 15 healthy children. In addition, we measured the levels of IgE production by PBMCs of atopic patients in the presence of IFN-gamma.

SUBJECTS AND METHODS

We selected 20 children (2-6 years of age, mean 4.2, 10m, 10f) with atopic disease such as atopic dermatitis, asthma and allergic rhinitis and 15 healthy children without allergic symptoms or a family history of atopy (2-6 years of age, mean 4.4, 10m, 10f) as control group. All 20 atopic children had positive skin prick tests for nutritive or inhalative allergens. PBMCs of atopic patients and healthy subjects were isolated from sodium heparinized whole blood by centrifugation over Ficoll/Hypaque and cultured with phytohaemagglutinin (PHA) 10 μg/ml (Welcome Laboratories, Beckenham, U.K.) as a stimulant. In addition, PBMCs of atopic children in cell culture were incubated with IFN-gamma 250 U/ml.

We measured IL-4 (DPC, Bad Nauheim, Germany), IFN-gamma (DPC, Bad Nauheim, Germany), s-CD23 (Sigma Chemical Co) and IgE production by PBMCs ELISA (Behring-Hochst, Marburg, Germany) and specific IgE in serum for nutritive and inhalative allergens by radioimmuno- assay method (Pharmacia, Uppsala, Sweden).

RESULTS

We recruited 20 children with atopic disease. Fifteen of these children had atopic dermatitis, 16 had asthma and 6 had allergic rhinitis. All of them had positive skin prick tests for one or more allergens. PHA stimulated PBMCs of these patients showed a significantly higher IL-4 secretion (490-1080 pg/ml, mean 712) than in the control group (6-42 pg/ml, mean 18.6) and lower IFN-gamma production (11-48 U/ml, mean 28.2) than in healthy children (79-220 U/ml, mean 124). The levels of specific IgE in serum were higher (4.8-17.6 KU/l, mean 12.4) than in the control group (<3.5 KU/l). In PBMCs of atopic children levels of IL-4-induced IgE production were lower (0.8-1.9 ng/ml, mean 1.2) with the presence of IFN-gamma (250 U/ml), compared to that in the medium (5.6-12.4 ng/ml, mean 9.8).

Soluble CD23 levels were increased in atopic patients (240-1060 pg/ml, mean 940) in comparison to the control group (42-780 pg/ml, mean 82).

DISCUSSION

Interleukin-4 induces IgE synthesis in stimulated PBMCs as well as in tonsil and spleen cells isolated from normal subjects in vitro (1,2,3,4,5). Interferon-gamma blocks IL-4-induced IgE synthesis (1).

In the present study, we demonstrated that the children with atopic disease had enhanced IL-4 production and reduced IFN-gamma secretion which corresponds to elevated specific IgE synthesis for nutritive or inhalative allergens.

Expression and subsequent release of CD23 from B cells and monocytes are induced by IL-4(7,8,9,10). Soluble CD23 enhances IgE synthesis by B cells from atopic subjects(11), but is ineffective in inducing IgE synthesis in the absence of IL-4(5,6).

The increased levels of s-CD23 in our atopic patients supports the notion that increased IL-4 production is responsible for elevated s-CD23 levels and may contribute to the enhanced IgE production.

In addition, we observed that stimulated PBMCs of atopic patients showed reduction of IFN-gamma secretion, compared to that of control group and demonstrated that IL-4-induced IgE production by PBMCs of atopic children in vitro was strongly inhibited in the presence of IFN-gamma.

This inhibitory effect confirms the fact that IL-4 and IFN-gamma play an antagonistic role in the regulation of IgE production.

We conclude that disturbed balance between TH1 (IFN-gamma) and TH2 (IL-4) activity plays an
important role in the pathogenesis and development of IgE-mediated atopic disease.

REFERENCES