

The production of interferon- γ in response to a major peanut allergy, *Ara h* II, correlates with serum levels of IgE anti-*Ara h* II

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Abstract

The current study was undertaken to examine the potential role of T cells in the pathogenesis of peanut allergy. Peripheral blood mononuclear cells (PBMCs) from patients with peanut allergy, patients with asthma, and nonatopic normal control subjects were assessed for proliferation after stimulation with a 17 kd major peanut allergen (*Ara h* II), ovalbumin, casein, soy, and *Candida albicans*. We found that *Ara h* II and *C. albicans* induced significantly higher levels of proliferation than ovalbumin, casein, and soy. Because interferon- γ (IFN- γ) and interleukin-4 (IL-4) play critical roles in IgE regulation, we assessed the production of these cytokines after stimulation with *C. albicans* and *Ara h* II. *C. albicans* stimulated similar levels of IFN- γ in all three study groups. In contrast, after stimulation with *Ara h* II, culture supernatants from PBMCs of subjects with peanut allergy contained significantly lower levels of IFN- γ than did the PBMCs of the two control groups ($p = 0.02$). More important, there was a significant ($p = 0.05$) inverse correlation between the serum IgE anti-*Ara h* II levels and IFN- γ production by PBMCs from the respective peanut-allergic patients. IL-4 protein was not detected in culture supernatants of PBMCs stimulated with *Ara h* II. However, amplification of cytokine gene transcripts by polymerase chain reaction did demonstrate IL-4 expression in *Ara h* II-stimulated PBMCs from both patients with peanut allergy and control subjects. These data suggest that the level of IFN-

γ production in response to *Ara h* II may be an important factor in determining the development of peanut-specific IgE responses. (J ALLERGY CLIN IMMUNOL 1994;93:93-9.)

Ara h II	Second major peanut allergen
cDNA	Complementary DNA
cpm	Counts per minute
IFN-γ	Interferon- γ
IL-4	Interleukin-4
m-RNA	Messenger RNA
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction

Key words: [Peanut allergy](#), [IgE](#), [food allergy](#), [interleukin-4](#), [interferon gamma](#)

More than 80% of allergic reactions to foods in children are caused by eggs, peanuts, cow's milk, and soy. ^{1, 2} Peanuts, however, are the most common cause of fatal and near-fatal food-induced anaphylaxis. ^{3, 4} Unlike eggs, cow's milk, and soy, once established, peanut allergy persists indefinitely. ⁵ Currently there are no curative therapies for peanut allergy or other food allergies. An understanding of the immune mechanisms that control the production of IgE antibody to peanut allergen(s) is essential for the development of new therapies for this condition.

Recently there have been several major breakthroughs in our understanding of the regulation of IgE synthesis in human beings. ⁶ In particular, it has been demonstrated that interleukin-4 (IL-4) acts as an isotype switch factor that commits B cells to the IgE pathway. ^{7, 8} In contrast, interferon- γ (IFN- γ) inhibits in vivo and in vitro IgE synthesis. ⁹⁻¹² Although several recent studies have demonstrated that allergen-specific T-cell clones from patients with inhalant allergy produce increased levels of IL-4 and decreased levels of IFN- γ , ^{13, 14} no comparable studies have examined the cytokines induced by food allergens. Furthermore, previous studies on the in vitro modulation of T cells by inhalant allergens have focused only on their capacity to induce total IgE responses rather than antigen-specific IgE responses. The current study was thus carried out to examine T-cell responses to food allergens, with a particular focus on the second major peanut allergen (*Ara h* II). ¹⁵

METHODS

Subjects

Approval for this study was obtained from the institutional review board at the National Jewish Center for Immunology and Respiratory Medicine. Nine subjects with peanut allergy and 12 nonallergic control subjects were studied. All nine subjects with peanut allergy (median age, 31 years; range, 6 to 53 years) had a positive immediate prick skin test reaction to peanut and either a positive double-blind placebo-controlled food challenge (7/9 patients) or a convincing history of peanut-induced anaphylaxis. All nine patients also had a history of mild to moderate asthma, and one of the subjects with peanut allergy had mild eczema. Two control groups were studied: six subjects with mild to moderate asthma (median age, 33 years; range, 25 to 44 years) and six nonatopic healthy normal subjects (median age, 34 years; range, 30 to 46 years). Two of the asthmatic control subjects also had mild atopic dermatitis. None of the patients in the study were receiving steroids orally.

Antigens

Ara h II was prepared from crude peanut extract by a preparative anion-exchange chromatography as previously described.¹⁵ Ovalbumin, casein, and soybean were purchased from Sigma Chemical Co., St. Louis, Mo. *Candida albicans* antigen was purchased from Hollister-Stier, Spokane, Wash.

Lymphocyte stimulation studies

Donor peripheral blood mononuclear cells (PBMCs) were isolated from heparinized venous blood by density gradient centrifugation on Ficoll-Hypaque medium (Pharmacia Fine Chemicals, Piscataway, N.J.), washed three times in Hanks' balanced salt solution (Gibco, Grand Island, N.Y.), and resuspended at 1.0×10^6 cells/ml in AIM medium (Gibco) supplemented with 2 mmol/L L-glutamine, 1.5 mmol/L sodium pyruvate, 15 mmol/L hydroxyethyl piperazine ethanesulfonic acid (HEPES), 50 µg/ml streptomycin, and 100 U/ml penicillin but no serum. Cells were cultured with antigen at 37° C in a 5% carbon dioxide humidified atmosphere for varying durations up to 6 days. Proliferation assays were performed in triplicate in 96-well flat-bottomed microtiter plates with 2×10^5 cells/well. Methyl-[³H]-thymidine (Amersham, Arlington Heights, Ill.), 0.8 µCi, was added to each well, and the plate was incubated for 6 hours before harvesting. The results were expressed either as total counts per minute (cpm) or as stimulation indexes equal to mean cpm in antigen-stimulated cultures divided by mean cpm in unstimulated cultures.

Assay of PBMCs for cytokine production

PBMCs from six patients and 12 control subjects were suspended at 1×10^6 cells/ml in AIM serum-free media (Gibco). One-milliliter cultures were incubated in 12 × 75 mm polystyrene round-bottom tubes (Falcon, Franklin Lakes, N.Y.). After 6 days the supernatants were harvested and stored at -80° C. IFN-γ concentrations were determined with a commercially available ELISA (Endogen, Boston, Mass.) specific for human IFN-γ with a lower limit of sensitivity of 5 pg/ml IFN-γ per milliliter. IL-4 concentrations in the supernatants were determined by a commercially available two-site sandwich IL-4-specific ELISA from R & D, Minneapolis, Minn., which uses mouse monoclonal antibodies to human IL-4 coated onto the microtiter plate provided in the kit and a horseradish peroxidase-conjugated polyclonal anti-IL-4 as the developing reagent. The sensitivity of this assay was 5 pg/ml. In this assay culture supernatants were assayed undiluted or were concentrated 10-fold with a Centricon-10 unit (Amicon, Beverly, Mass.).

Analysis of cytokine gene transcripts

A previously described semiquantitative polymerase chain reaction (PCR) technique was used to estimate the proportion of cytokine messenger RNA (mRNA) produced by T cells. ¹⁶ In these experiments 2 µg of total RNA prepared from PBMCs stimulated for various time intervals with antigen was used for the synthesis of first-strand complementary DNA (cDNA) and subjected to amplification with the PCR with either β-actin, IL-4, or IFN-γ primers according to the manufacturer's recommendation (Clontech, Palo Alto, Calif.). The amount of product was measured by incorporation of phosphorus 32-end-labeled 3' primers added to the reactions (~1 × 10⁶ cpm each). For each cDNA preparation PCR was initially carried out with a β-actin primer pair. After incorporated radioactivity into the β-actin bands was measured, the amount of cDNA used for IL-4 and IFN-γ amplification was adjusted so reaction mixtures from each donor had similar amounts of β-actin RNA. Thus the amount of cDNA used for each reaction varied from one fortieth to one tenth of the total cDNA mixture. The PCR technique employed 25 cycles of amplification in the analysis for IFN-γ and 32 cycles for IL-4; 23 cycles of amplification were used in the analysis of β-actin to ensure that the amount of product synthesized was proportional to the amount of each cytokine mRNA in the original preparation. In separate experiments we analyzed the quantitative nature of the PCR technique by examining input cDNA mixture versus amount of amplified PCR product obtained. There was a direct correlation between the PCR product amplified and the amount of mRNA analyzed.

ELISA for IgE anti-Ara h II

A biotin-avidin ELISA was used to quantify IgE anti-peanut protein antibodies, as previously published. ^{15, 17} The upper two rows of a 96-well microtiter plate (Gibco, Santa Clara, Calif.) were coated with 100 µl each of equal amounts (1 µg/ml) of anti-human IgE monoclonal antibodies 7.12 and 4.15 (kindly provided by Dr. A. Saxon, Los Angeles, Calif.). The remainder of the plate was coated with Ara h II at a concentration of 1 µg/ml in coating buffer (0.1 mol/L sodium carbonate-bicarbonate buffer, pH 9.5). The plate was incubated at 37° C for 1 hour and then washed five times with phosphate-buffered saline solution, pH 7.4, containing 0.05% polysorbate 20 (Sigma Chemical Co., St. Louis, Mo.) immediately and between subsequent incubations. The upper two rows used a secondary standard reference to generate a curve for IgE, ranging from 0.05 to 25 ng/ml.

The serum pool and patients' samples were diluted (1:20 vol/vol) and dispensed in duplicate in the lower portion of the plate. After incubation for 1 hour at 37° C and washing, biotinylated affinity-purified goat anti-human IgE (KPL, Gaithersburg, Md.) (1:1000 vol/vol phosphate-buffered saline solution) was added to all wells. Plates were incubated for 1 hour at 37° C and washed, and 100 µl horseradish peroxidase-avidin conjugate (Vector Laboratories, Burlingame, Calif.) was added for 30 minutes. After being washed the plates were developed by the addition of a buffer containing Ø-phenylenediamine (Sigma Chemical). The reaction was stopped by the addition of 100 µl 2N hydrochloric acid to each well, and absorbence was read at 492 nm (Titertek Multiscan, Flow Laboratories, McLean, Va.). The standard curve was plotted on log-logit scale by means of simple linear regression, and values for the pooled and individual patient samples were read from the curve as nanogram equivalent units per milliliter (nanograms per milliliter). ^{15, 17}

RESULTS

Proliferative responses to food allergens

In pilot studies we assessed proliferative responses of PBMCs from the three different study groups, daily for up to 6 days, to the following antigens: *Ara h* II, ovalbumin, casein, soybean, and *C. albicans*, a common microbial antigen. Dose-dilution curves for each of the food antigens were also performed with concentrations of 1, 10, and 25 µg/ml. Optimum proliferation with *Ara h* II occurred at 10 µg/ml and was the concentration used in all subsequent experiments. Peak proliferative responses to antigens were observed on day 6. All three study groups showed significantly greater ($p < 0.05$) proliferation to *Ara h* II and *C. albicans* than to ovalbumin, casein, and soy (Table I).

TABLE I. Proliferation response of patients with peanut allergy and control subjects to five antigens

Study group	Total [³ H]thymidine incorporation (stimulation index) response				
	<i>Ara h</i> II	<i>C. albicans</i>	Ovalbumin	Soy	Casein
Peanut allergy	10,257 ± 6484 (7.3)	25,777 ± 2184 (19)	2184 ± 1031* (1.2)	3409 ± 989* (3.5)	4053 ± 15* (2.6)
Normal	11,525 ± 4395 (4)	44,100 ± 11,553 (21)	3092 ± 1154* (2.1)	5172 ± 2055* (3)	4268 ± 1180* (2.8)
Asthma	8220 ± 2036 (11)	8757 ± 1404 (13)	1056 ± 283* (1.3)	5099 ± 1748* (3)	2824 ± 1276* (3.6)

PBMCs were incubated for 6 days with either *Ara h* II (10 µg/ml), *C. albicans* (6500 protein nitrogen units/ml), ovalbumin (25 µg/ml), soy (25 µg/ml), or casein (25 µg/ml) and then assessed for [³H]thymidine incorporation.

*Indicates $p < 0.05$ as compared with *Ara h* II-stimulated PBMCs.

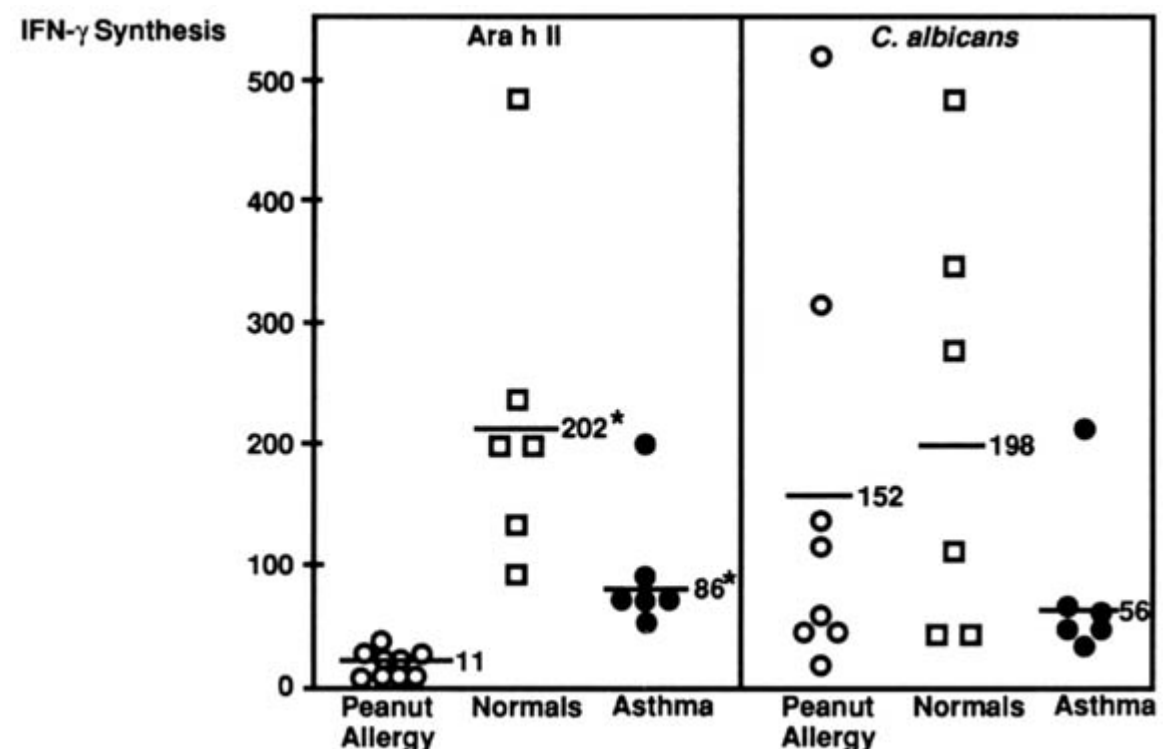
IFN-γ and IL-4 synthesis in response to *Ara h* II

In the following experiments we compared *Ara h* II and *C. albicans* for their capacity to induce IFN-γ and IL-4 synthesis. Preliminary studies examining the time course of IFN-γ production by PBMCs stimulated with these two antigens revealed maximum levels of IFN-γ in culture supernatants on days 5 and 6. Day 6 was therefore chosen for comparison between each patient population. Because proliferative responses to these antigens differed from donor to donor, the levels of IFN-γ were normalized to the stimulation index by dividing absolute values of IFN-γ (in picograms per milliliter) in the culture supernatant by the corresponding stimulation index for each culture.

We compared IFN-γ synthesis by PBMCs from patients with peanut allergy patients with asthma, and nonatopic healthy normal subjects stimulated with *Ara h* II and *C. albicans* (Fig. 1). Stimulation with *C. albicans* resulted in the secretion of similar levels of IFN-γ into the culture supernatants of PBMCs from all three groups. In contrast, although *Ara h* II stimulated similar levels of PBMC proliferation to *Ara h* II in all three study groups, it induced significantly less IFN-γ production in patients with peanut allergy as compared with either patients with asthma ($p = 0.02$) or nonatopic healthy normal subjects ($p = 0.02$).

FIG. 1 Production of IFN-γ after stimulation with *Ara h* II and *C. albicans*. PBMCs (1×10^6)

cells/ml) from nine patients with peanut allergy, six nonatopic control subjects, and six patients with asthma were cultured in the presence and absence of *Ara h* II for 5 days. Culture supernatants were then assayed for IFN- γ levels. Culture supernatants from *Ara h* II-stimulated PBMCs of patients with peanut allergy contained significantly less IFN- γ (asterisk, $p = 0.02$) than supernatants from *Ara h* II-stimulated PBMCs of the two control groups. In contrast, *C. albicans* induced similar levels of IFN- γ in all three study groups.



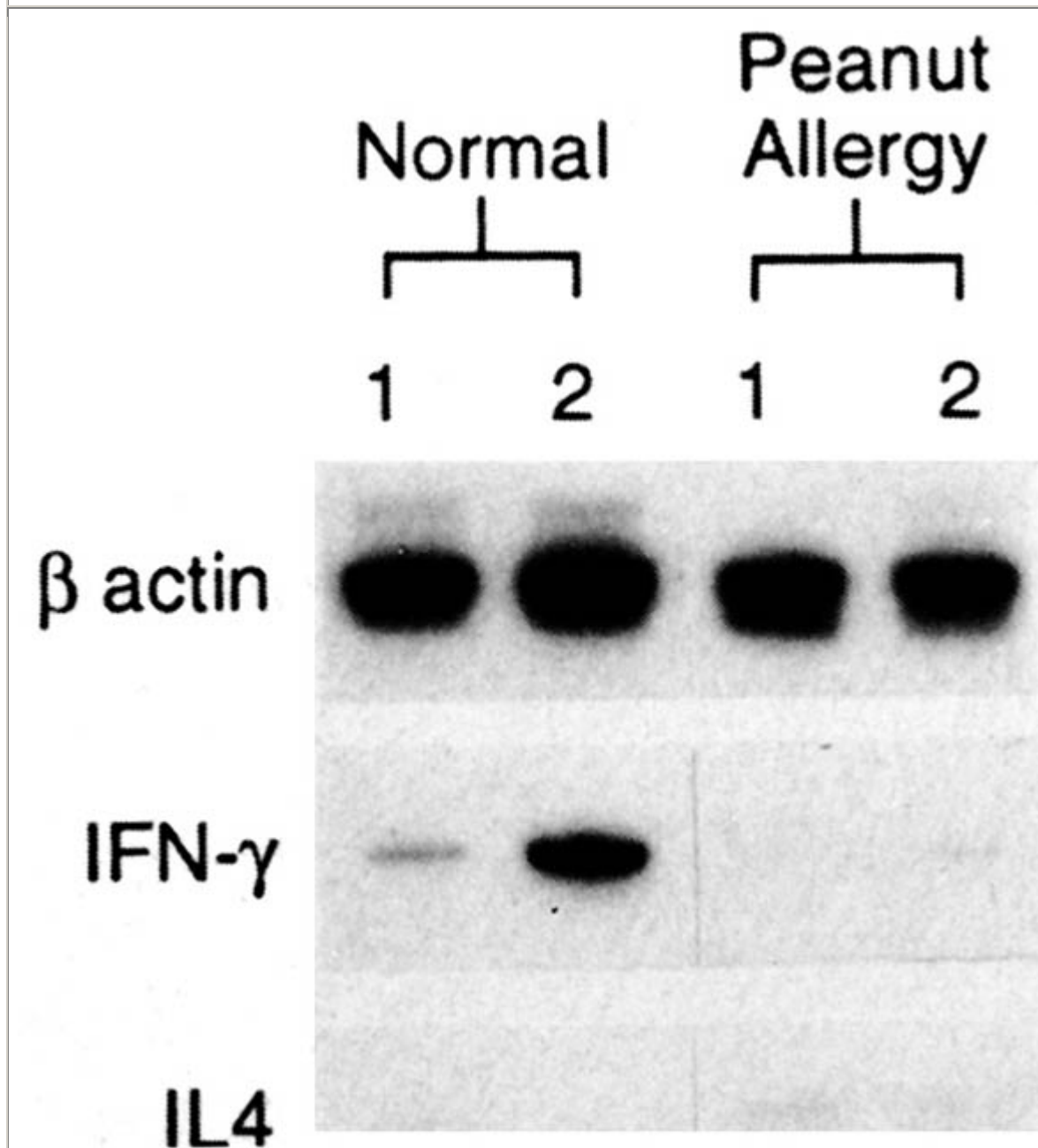
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Using a commercially available ELISA with a sensitivity of 5 pg/ml, we were unable to detect IL-4 in either unconcentrated or 10-fold concentrated culture supernatants of *Ara h* II-stimulated PBMCs from any of the three study groups. In these latter experiments supernatants were analyzed daily for up to 6 days of *Ara h* II stimulation. This was not due to an inability of their cells to produce IL-4, because stimulation of *Ara h* II cultured PBMCs from peanut-allergic and normal subjects on day 6 of culture with 10^{-8} mol/L phorbol 12-myristate 13-acetate and 5×10^{-8} mol/L ionomycin for 24 hours resulted in 250 180 pg/ml and 135 65 pg/ml of IL-4, respectively, in these two study groups.

Because the frequency of IL-4-producing cells in peripheral blood is very low, we also studied IL-4 cytokine gene expression with a semiquantitative PCR technique, after *Ara h* II stimulation. In these experiments RNA isolated from *Ara h* II-stimulated PBMCs at several time points were used for cDNA synthesis and subjected to PCR with primers specific for IL-4, IFN- γ , and β -actin. A similar level of β -actin was seen at all time points for the four donors (two peanut-allergic and two nonatopic normal donors) studied. IL-4 gene transcripts in PBMCs from either nonatopic control subjects or patients with peanut allergy were not detectable at 18, 24, or 48 hours after *Ara h* II stimulation. However, after 4 days of *Ara h* II stimulation, IL-4 gene transcript expression was observed in PBMCs from both peanut-allergic and nonatopic subjects (■Fig. 2). In contrast, IFN- γ gene expression could be detected by 18 hours of *Ara h* II stimulation and continued to rise until day 4 of culture.

IFN- γ , but not IL-4, gene expression appeared to be greater in *Ara h* II-stimulated PBMCs from normal control subjects as compared with patients with peanut allergy.

FIG. 2. Induction of cytokine gene transcripts by *Ara h* II. Expression of IL-4, IFN- γ , IL-2, and β -actin gene transcripts were analyzed by semiquantitative PCR in PBMCs cultured for 4 days within 10 μ g/ml *Ara h* II as described in the Methods. Numbers 1 and 2 refer to two different peanut allergic and two normal subjects in each study group.



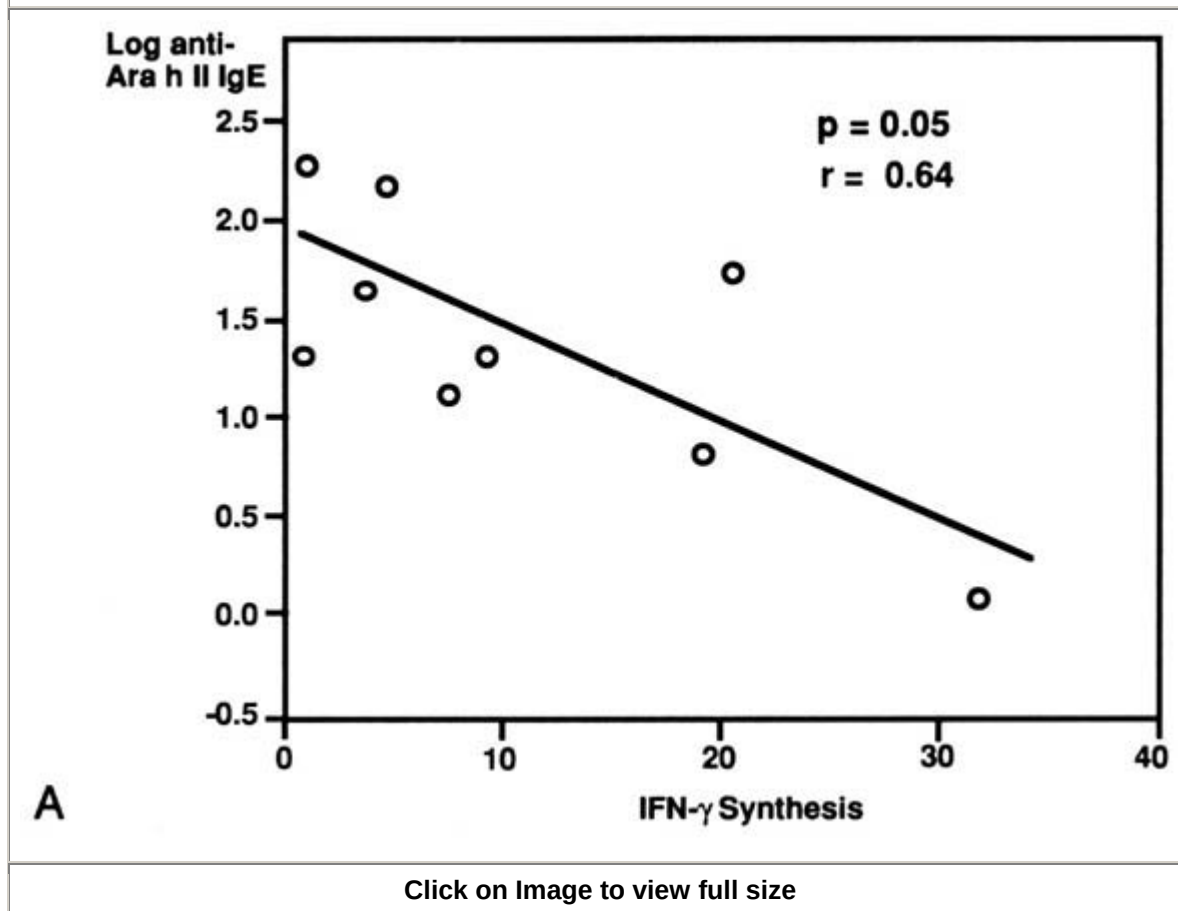
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Correlation of serum IgE anti-*Ara h* II with IFN- γ production

Because IFN- γ is a potent inhibitor of IgE synthesis, it was of interest to determine whether there was a correlation between decreased IFN- γ synthesis after *Ara h* II stimulation and increased serum IgE anti-*Ara h* II levels in patients with peanut allergy. Fig. 3 shows a regression analysis between in vitro synthesis of IFN- γ by PBMCs after stimulation with

Ara h II versus the log of the respective serum IgE anti-*Ara h* II levels. A significant inverse relationship was observed between these two parameters with a correlation coefficient (r) of 0.64 and a p value of 0.05. In contrast, there was no correlation between culture supernatant IFN- γ levels and total IgE anti-*Ara h* II levels of patients with peanut allergy ($p = 0.25$; $r = 0.29$). These data suggest that the ability of T lymphocytes to synthesize IFN- γ in response to *Ara h* II may play a role in controlling the in vivo synthesis of IgE antibody to *Ara h* II.

FIG. 3. Correlation of serum IgE anti-*Ara h* II with IFN- γ production. Levels of IFN- γ synthesis were normalized to respective lymphocyte stimulation indexes. A significant inverse correlation ($p = 0.05$) was observed between in vitro synthesis of IFN- γ by PBMCs after stimulation with *Ara h* II and the log of the respective serum IgE anti-*Ara h* II levels (**A**). In contrast, IFN- γ synthesis did not correlate with serum IgG anti-*Ara h* II levels (**B**).



DISCUSSION

Numerous studies, particularly those by Sampson et al., have demonstrated the importance of IgE-dependent hypersensitivity reactions in the pathogenesis of food allergy. [18](#) Peanuts are the most common cause of food-induced anaphylaxis. [3, 4](#) To date, however, studies characterizing various food allergens have not demonstrated what makes peanuts such potent allergens as compared with other foods such as eggs, milk, or soy products. Other potential factors need to be considered. In this regard the host's

immunologic reactivity, that is, the nature of the lymphocytes and cytokines stimulated in response to a particular antigen, may also play an important role.

The current report is the first study of lymphocyte reactivity to the major peanut allergen, *Ara h* II. As compared with ovalbumin, casein, and soy, *Ara h* II was significantly more potent in its ability to induce proliferation of lymphocytes in vitro. Our findings are consistent with those of Kondo et al., ¹⁹ whose recent report in this JOURNAL indicated very low levels of proliferation in response to ovalbumin and casein (mean of 800 cpm above background level in their food-allergic group). Several explanations for these observed differences between lymphocyte responses to *Ara h* II as compared with the other common food allergens tested are possible. First, the precursor frequency of circulating lymphocytes to specific food allergens may differ. Thus one possibility is that a higher frequency of circulating lymphocytes is reactive with *Ara h* II than with ovalbumin, milk, or soy. This explanation may account for the clinical observation that patients with peanut allergy have a higher prevalence of systemic reactions. Second, there may be as yet undefined antigenic differences in peanut allergens, as compared with other food allergens, which result in their capacity to induce higher levels of immune activation. Such analyses await the further purification and identification of the various allergens that contribute to peanut allergy.

To better understand the potential mechanisms underlying the induction of peanut-specific IgE responses, we examined the IFN- γ and IL-4 levels induced by a purified major peanut allergen, *Ara h* II, as compared with *C. albicans*, a common microbial antigen. Our present results indicate that PBMCs from patients with peanut allergy and nonatopic normal subjects synthesized similar levels of IFN- γ in response to *C. albicans*. In contrast, PBMCs from patients with peanut allergy as compared with nonatopic normal subjects secreted significantly less IFN- γ in response to stimulation with *Ara h* II. Because our patients with peanut allergy had a history of mild to moderate asthma, we also examined the capacity of PBMCs from a group of comparable patients with asthma to produce IFN- γ in response to *Ara h* II. Our results indicate that PBMCs from patients with asthma produced significantly more IFN- γ than PBMCs from patients with peanut allergy. Thus the inability to produce IFN- γ in response to *Ara h* II appears to be a specific feature of patients with peanut allergy.

Interestingly, we were unable to measure any detectable levels of IL-4 protein in the culture supernatants of *Ara h* II-stimulated PBMC culture either from patients with peanut allergy or control subjects. However, with a more sensitive technique to detect cytokine express, a semiquantitative PCR technique, cytokine gene transcripts for IL-4 were found in *Ara h* II-stimulated PBMCs from patients with peanut allergy and control subjects (Fig. 3). These data suggest that the undetectable levels of IL-4 in culture supernatants of PBMCs stimulated with *Ara h* II is due to a low precursor frequency of IL-4-producing cells in these bulk cultures.

The potential importance of IFN- γ production in determining the synthesis of IgE-specific *Ara h* II antibodies is supported by our current findings of a highly significant inverse correlation between IFN- γ synthesis by PBMCs stimulated in vitro by *Ara h* II with serum anti-*Ara h* II IgE levels in patients with peanut allergy. To date, most studies of IFN- γ have focused on its effects on non-antigen-specific total IgE synthesis. The recent study by Hayglass and Stefura ²⁰ provides further evidence of an important role for IFN- γ in the downregulation of allergen-specific IgE responses. These investigators demonstrated that in mice given immunotherapy with modified ovalbumin decreased ovalbumin-specific IgE

levels developed. More important, this effect was abrogated by giving the mice anti-IFN- γ antibodies. These data may suggest that immunotherapy inhibits allergen-specific IgE antibody responses through the induction of IFN- γ .

Taken together with this latter study, our present study suggests that PBMCs from subjects with peanut allergy respond differently than PBMCs from nonatopic subjects to *Ara h* II. We postulate that decreased IFN- γ production in response to *Ara h* II may contribute to sustained IgE levels to this important food allergen in these patients. The development of new forms of treatment directed at augmentation of IFN- γ production in response to peanut allergen may provide an important new direction in the therapy of this potentially fatal illness.

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Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy

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Xiu-Min Li, MD^a, Kamal Srivastava, MPhil^a, Alexander Grishin, PhD^a, Chih-Kang Huang, MS^a, Brian Schofield, JD^b, Wesley Burks, MD^c, Hugh A. Sampson, MD^a

Genetic susceptibility to food allergy is linked to differential T_H2-T_H1 responses in C3H/HeJ and BALB/c mice

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Vivian Morafo, PhD*, Kamal Srivastava, MPhil*, Chih-Kang Huang, MS, Gary Kleiner, MD, PhD, Soo-Young Lee, MD, Hugh A. Sampson, MD, and Xiu-Min Li, MD

Modification of T-cell receptor V β repertoire in response to allergen stimulation in peanut allergy

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Petros Bakakos, MD^a, John L. Smith, PhD^b, John O. Warner, MD^a, Gillian Vance, MRCP^a, Christine T. Moss, BSc^b, Elizabeth Hodges, PhD^b, Stuart Lanham, PhD^b, W. Martin Howell, PhD^b

A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses

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