＜原　著＞

Induction of Lymphocyte Antigen-specific IL-2 Responsiveness and Its Regulation in Children with Atopic Dermatitis

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Summary

IL-2 responsiveness was induced in lymphocytes from patients with cow's milk hypersensitivity specifically on stimulation with α-lactalbumin, bovine serum albumin, β-lactoglobulin and α-casein. The frequencies of the responses were 86% with α-lactalbumin, 67% with bovine serum albumin, 58% with β-lactoglobulin and 50% with α-casein.

There was no correlation between the intensity of the induced responsiveness and the specific IgE RAST scores of the sera. Although healthy infants and early pre-school children showed some responsiveness, it was usually weaker than that of atopic children. This in vitro lymphocyte phenomenon can be used to identify the etiological allergen and to monitor the clinical activity of atopic diseases. Expression of p-75-, but not p-55-IL-2 receptors, was specifically generated on patient lymphocytes stimulated with α-casein. We further investigated regulatory mechanisms of the α-casein induced IL-2 responsiveness. The medium supernatant collected from a 5 day culture of lymphocytes from healthy subjects stimulated with α-casein suppressed the IL-2 responsiveness of lymphocytes from patients but not the mite-induced IL-2 responsiveness of the same lymphocytes. The culture medium supernatant from patient lymphocytes stimulated with α-casein did not show a suppressive effect on the induction of IL-2 responsiveness. These results indicate that the culture medium supernatant of lymphocytes from healthy subjects stimulated with α-casein contained factor(s) that specifically regulate α-casein-induced IL-2 responsiveness and that the regulatory function of patient lymphocytes exerted on the induced IL-2 responsiveness was impaired.

Key Words : IL-2 responsiveness, cow's milk allergy, IL-2 receptors

Ⅰ. Introduction

It has been postulated that changes in the responsiveness of children's lymphocytes to allergens as they grow may be involved in the onset and natural resolution of allergic diseases. Assay of the allergen-activated lymphocyte response to interleukin-2 (IL-2) appears to be a useful means of assessing effector T cell function, e.g., the IgE-producing helper cells involved in disease onset, the delayed hypersensitivity response of effector T cells, and the activity of cytotoxic T cells[1),2)].

We have already reported that antigen-specific IL-2 responsiveness was induced when the peripheral lymphocytes of children with hens' egg allergy were stimulated with ovalbumin (OVA) and incubated for 5 days[3)]. In the present study, we stimulated the peripheral blood lymphocytes of children with atopic dermatitis (thought to be caused by cow's milk antigens) using α-casein and bovine serum albumin and assessed the induction of IL-2 responsiveness. We also investigated the diagnostic significance of lymphocyte

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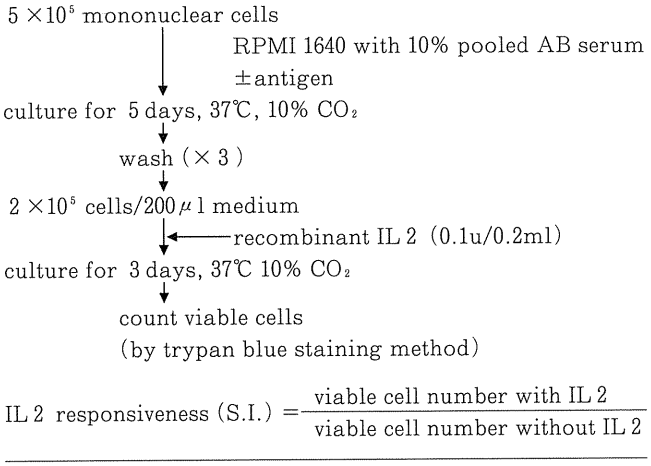

IL 2 : interleukin 2

Fig. 1 Assay for IL-2 respoosiveness in antigen-stimulated lymphocytes

responsiveness to these allergens, especially the changes in IL-2 responsiveness with age, the relationship to the IgE RAST score, and the induction of IL-2 responsiveness by other cow's milk antigens in children with milk allergy. In addition, we investigated the mechanisms regulating the induction of IL-2 responsiveness.

Ⅱ. Subjects

Peripheral blood mononuclear cells were obtained from 45 children with atopic dermatitis. Clinical findings (e.g., the IgE RAST score, skin tests, antigen challenge tests) were used to make a diagnosis, but all patients at least fulfilled Bachman's[7] definition of milk allergy. After ingestion of a small amount of milk, they showed 1) the occurrence of at least one out of eczema, hives, asthma and rhinitis, and 2) they developed gastrointestinal symptoms or abnormal behavioral. These symptoms were reproducibly induced by challenge with milk. We also obtained lymphocytes from 10 healthy age-matched non-atopic children in whom the results of the above-mentioned tests were negative as well as lymphocytes from 5 healthy adults as controls.

Ⅲ. Methods

1. Induction of lymphocyte IL-2 responsiveness by allergen stimulation (Fig. 1).

Various concentrations of BSA. β-lactoglobulin (β-LG), α-lactalbumin (α-LA), α-casein, and fetal calf serum (FCS) were added to mononuclear cells (1x10⁶/ml) separated from heparinized peripheral blood by Ficoll-Conray density gradient centrifugation[4] and placed in 5-ml culture tubes (Falcon). After incubation for 5 days in RPMI 1640 medium supplemented with 10% human pooled AB serum and readjustment of the cell count to 2 × 10⁵/0.2 ml, various concentrations of recombinant IL-2 (Takeda chemical Industries, Ltd.) were added, and culture was continued for 3 days in 96-well flat-bottom microplates (Nunc Co.). Then 50 μl of 1 % trypan blue was added and viable cells were counted after thorough stirring using a hemacytometer (the proportion of viable cells was 90% or more).

The evaluate IL-2 responsiveness, the stimulation index (SI) was calculated using the following formula:

SI = viable cell count with IL-2/viable cell count without IL-2.

SI values were determined for the patients and the controls in triplicate and were expressed as the mean error, SI values were also obtained for each of the milk antigens and were expressed as the mean ± deviation. The reason for not using thymidine (^{3}H-TdR) uptake as an index of cell division was that the time of maximum DNA synthesis varies with the antigen, the underlying disease, and its activity, making it difficult to obtain reproducible results. Accordingly, we determined the viable cell count as a means of directly evaluating cell proliferation.

2. Specific IgE RAST assay

Serum IgE RAST values for OVA, Dermatophagoides farinae (Df), and each of the various milk antigens were measured with an in vitro allergen testing kit and RAST Shionogi Isotope Reagent (Shionogi & Co., Ltd.).

3. Assessment of IL-2 receptor expression by stimulated lymphocytes using a fluorescence-activated cell sorter (FACS)

Peripheral blood mononuclear cells (1 × 10⁶)

from healthy controls and patients were stimulated with an optimal concentration of α-casein and cultured as mentioned above for 5 days. After washing, 2μl of an FITC-conjugated anti-IL-2 receptor-p55 monoclonal antibody (Becton Dickinson Immunocytochemistry Systems) or an FITC-conjugated anti-IL-2 receptor-p75 monoclonal antibody (Nichirei) was added and incubated for 30 min at 4℃. Then the cells were washed 3 times with phosphate-buffered saline (PBS), and IL-2 receptor expression was assayed by the immunofluorescence technique using FACS 440 (Becton Dickinson).

4. Analysis of the mechanism regulating the induction of IL-2 responsiveness by α-casein stimulation

The conditioned culture supernatant from healthy control lymphocytes which had been stimulated with α-casein and incubated for 5 days was added to cells with α-casein-induced IL-2 responsiveness at the start of culture, and the inhibitory effect was assessed. We have previously demonstrated that pretreatment of healthy control lymphocytes (which show no induction of IL-2 responsiveness following allergen stimulation) with antibodies to Leu 18 (CD45R), a suppressor/inducer antigen marker, causes IL-2 responsiveness to be induced5). For CD45R pretreatment of lymphocytes from healthy controls, peripheral mononuclear cells were reacted with 20 ml of an anti-Leu 18 monoclonal antibody (Becton Dickinson) at 4℃ for 30 min. After washing 3 times with RPMI 1640 as described above, α-casein was added and the IL-2 responsiveness was assayed.

5. Statistical analysis

Comparisons with the controls were performed using the two-tailed Student's t-test. IL-2 responsiveness was considered positive when there was a statistically significant difference compared with the group not subjected to antigen stimulation. In addition, disease (antigen)-specificity of IL-2 responsiveness was considered positive when there was a significantly higher response than in the healthy control group.

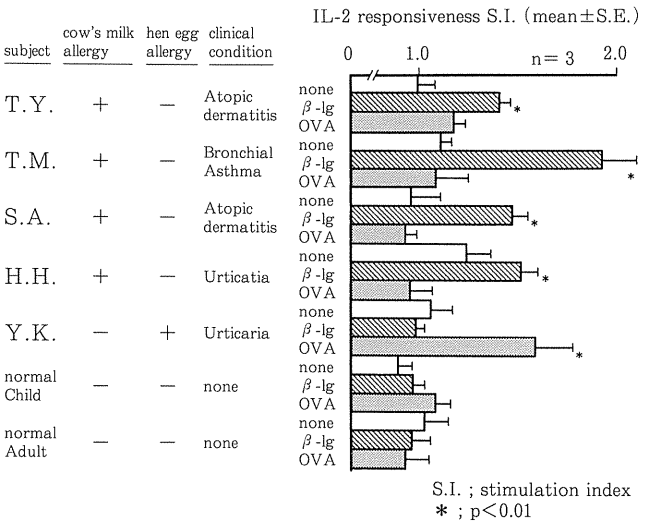

Fig. 2 Induction of IL-2 responsibeness in lymphocytes from patients with cow's milk allergy (I)

Ⅳ. Results

1. Induction of IL-2 responsiveness by β-LG in milk allergy patients

An increase of IL-2 responsiveness was induced by β-LG in 11 patients with milk allergy (SI: 1.58 ± 0.24; mean ± SD), and no OVA-induced IL-2 responsiveness was observed among these patients (1.03 ± 0.13). However, an increase of IL-2 responsiveness induced by OVA was observed in 5 patients with hen's egg allergy (1.56 ± 0.10), and there was no β-LG-induced increase in these patients. An almost maximal viable cell count was observed at the 0.1 unit/0.2 ml concentration of IL-2, and this was regarded as the optimal concentration. In the healthy control group, no IL-2 responsiveness was detected after stimulation with any of the allergens. Thus, the IL-2 responsiveness induced by β-LG stimulation in milk allergy patients appeared to be allergen-specific (Fig. 2). The optimal concentration of β-LG was 100 μg/ml (data not shown).

2. Induction of IL-2 responsiveness by α-casein in milk allergy patients

When we stimulated patient lymphocytes with

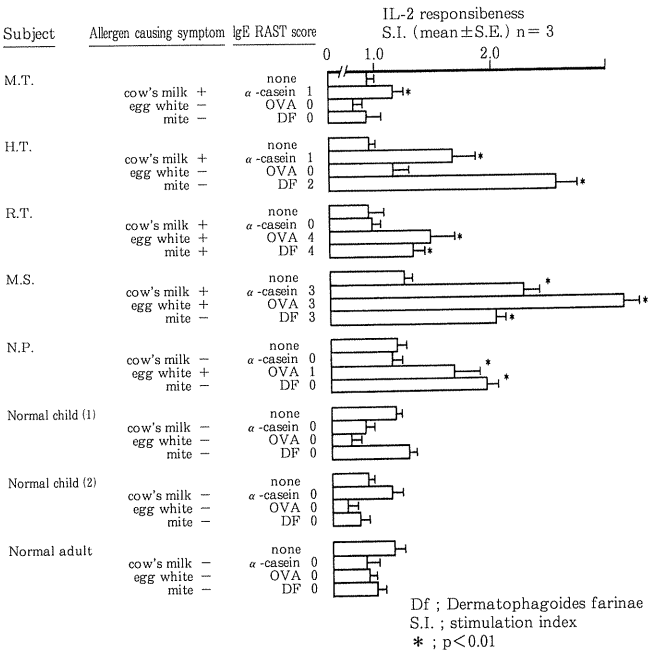

Fig. 3 Induction of IL-2 responsiveness in lymphocytes from patient with cow's milk allergy (Ⅱ)

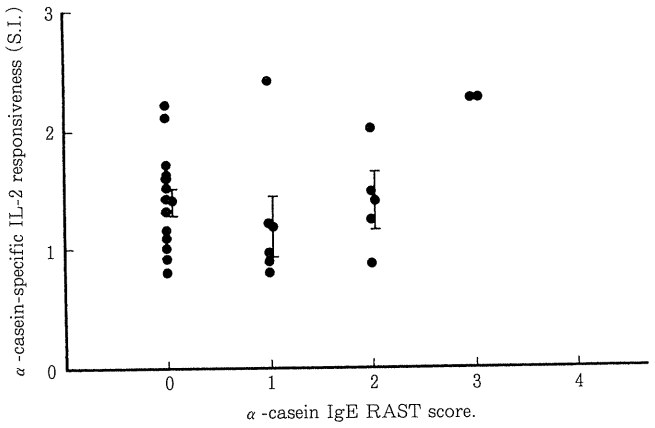

Fig. 4 Relationship between antigen-specific IL-2 responsiveness and the IgE RAST score.

α-casein in the same manner and assessed IL-2 responsiveness, there was an antigen-specific response in 7 of the patients (1.70±0.56, mean ±SD). No induction of IL-2 responsiveness by α-casein was observed in any of the 10 control subjects (0.92±0.14) (Fig. 3). The optimal concentration of α-casein was determined to be 10μg／ml.

3 . Induction of IL-2 responsiveness by other milk antigens in milk allergy patients

Induction of IL-2 responsiveness by bovine serum albumin (BSA; 8 patients, 2.06±0.32; mean±SD) and α-lactalbumin (6 patients, 1.69

Table. 1 Frequency of IL-2 responsiveness induced by protein components in patients allergic to cow's milk

BSA-specific IL-2 responsiveness	: 8 out of 12 (67%)
β-LG-specific IL-2 responsiveness	: 11 out of 19 (58%)
α-LA-specific IL-2 responsiveness	: 6 out of 7 (86%)
α-Cas-specific IL-2 responsiveness	: 7 out of 13 (54%)
OVA-specific IL-2 responsiveness	: 8 out of 17 (47%)

Fig. 5 Relationship between α-casen-specific IL-2 responsiveness and age of patients.

IgE RAST score＝0
△ : atopic dermatitis
◎ : normal indivisuals
IgE RAST score≧1
○ : atopic dermatitis

0.26) was also observed. As shown in Table 1 , increased IL-2 responsiveness was observed in 67% of the milk allergy patients after exposure to BSA, while it was seen in 58% with β-lactoglobulin, 86% with α-lactalbumin, and 54% with α-casein.

4 . Correlation between allergen-induced lymphocyte responsiveness to IL-2 and specific IgE RAST values in milk allergy patients

As shown in Fig. 4 , when we determined both the allergen-induced IL-2 responsiveness and the specific IgE RAST values in the same patients. We found no constant relationship between allergen-induced IL-2 responsiveness and the RAST score in the case of a-casein. Patients whose lymphocytes showed allergen-induced IL-2 responsiveness were found even among those with an IgE RAST score of 0. Similar findings were also obtained with the other milk antigens.

5 . Age-dependence of allergen-induced lymphocyte responsiveness to IL-2 in milk allergy patients

Figure 5 shows the relationship between age

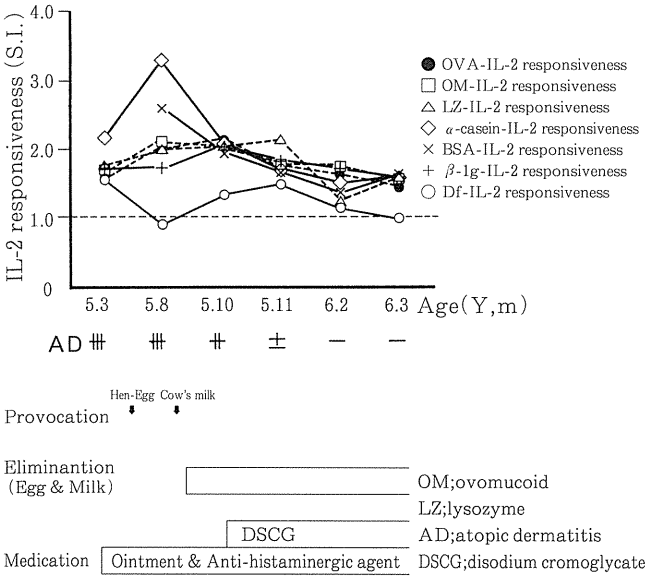

Fig. 6 Patient : R. W. 5y/o ♀ : atopic dermatitis

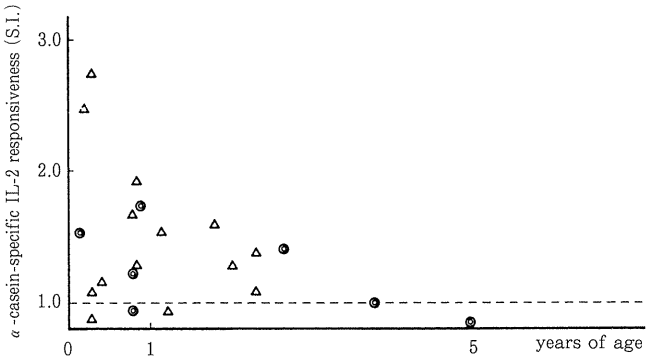

Fig. 7 Relationship between α-casein-specific IL-2 responsiveness and age of patients.
(IgE RAST score＝0)
△ : atopic dermatitis
◎ : normal individuals

and α-casein-specific IL-2 responsiveness. Healthy infants and preschool children exhibited mild IL-2 responsiveness, but the response was weaker than in the allergy patients. In the patient group, a decrease in responsiveness was observed in association with symptomatic improvement (Fig. 6). Some of the patients displayed marked induction of IL-2 responsiveness as early as 2 - 3 months after birth.

Figure 7 shown IL-2 responsiveness in patients with an α-casein-specific IgE RAST score of 0. There is relatively high responsiveness in the infants and preschool children, but as the clinical manifestations

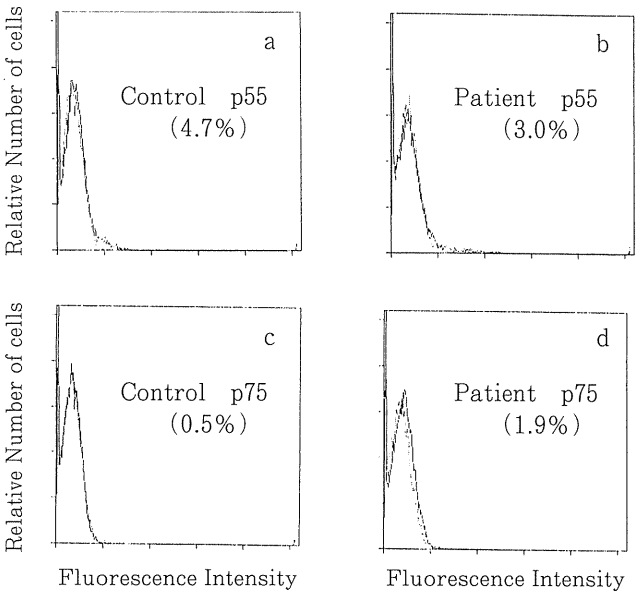

Fig. 8 Expression of IL-2 receptors (p55, p75) by α-casein-activated lymphocytes.

improve the IL-2 responsiveness also decreases. In addition, the relationship between age and the induction of IL-2 responsiveness by the various protein components of milk (i.e., α-lactalbumin, BSA and β-lactoglobulin), was similar to that described above (data not shown).

6. OVA-specific induction of IL-2 responsiveness in children with milk allergy

When we investigated OVA-specific induction of IL-2 responsiveness in patients with milk allergy, 8 (47%) out of 17 were positive (Table 1). None of the 10 non-atopic normal children were positive.

7. IL-2 receptor (p55, p75) expression by α-casein-stimulated lymphocytes

As shown by the typical example in Fig. 8 (panels a and b), lymphocytes expressing 55 kD IL-2 receptors after antigen stimulation averaged 4.7% in the normal controls and 3.0% in the patients, as opposed to 1.9% and 1.6% when the cells were not stimulated (6.8% for Con A-stimulated normal control cells). Expression was increased by antigen stimulation, but the difference between the normal controls and the patients was not significant.

In the case of the p75 IL-2 receptor after

Table. 2 Suppressive effect of α-Cs-SN on α-Cs-induced IL-2 responsiveness in patients lymphocytes

Subject	Antigen	α-Cs-SN	IL-2 responsiveness S.I. (mean±S.E.) n=3	Suppression
Patient 1 (allo)	none	−	1.16±0.16	
	α-Cs	−	2.42±0.03	
	α-Cs	+	1.21±0.09*	+
Patient 2 (allo)	none	−	1.15±0.05	
	α-Cs	−	1.49±0.05	
	α-Cs	+	1.33±0.08	−
Leu 18-treated normal lymphocytes (auto)	none	−	1.06±0.11	
	α-Cs	−	1.33±0.07	
	α-Cs	+	1.14±0.08	+

α-Cs-SN;Supernatant from α-casein-stimulated normal lymphocytes
α-Cs ; α-casein
A representative datum was shown. *p<0.01
S.I.;stimulation index

antigen stimulation, the rate of expression in the normal controls and patients was 0.5% and 1.9 %, respectively, (panels c and d), and the rates for unstimulated cells were 0.3% and 1.3% (0.5 % for Con A-stimulated normal control cells). A difference was found between p75-IL-2 receptor expression by cells from the normal controls and the patients after antigen stimulation.

8. Suppressive effect of the culture supernatant from α-casein-stimulated control lymphocytes on patient α-casein induced IL-2 responsiveness

Regarding the addition of culture supernatant from α-casein-stimulated control lymphocytes the results of 10 preliminary experiments in 10 subjects showed suppression of IL-2 responsiveness when a 50% final concentration was added.

Accordingly, we adopted 50% as the final concentration of culture supernatant for use in the experiments reported here. when we added culture supernatant from control α-casein-induced lymphocytes to lymphocytes from milk-allergy patients, we observed a suppressive effect on α-casein-induced IL-2 responsiveness in 3 out of 9 patients. When we added α-casein to control lymphocytes after pretreatment of the cells with Leu18, IL-2 responsiveness was induced, and the response was inhibited again by the addition of autologous culture supernatant (Table 2). When we stimulated

Table. 3 Suppressive effect of α-Cs-SN on α-Cs-induced IL-2 responsiveness in leu 18-treated normal lymphocytes (autologous) was specific for antigen.

Antigen	α-Cs-SN	Induced-IL-2-respons S.I. (mean±S.E.) n=3	Suppression
none	−	1.13±0.09	
α-Cs	−	1.62±0.17	
α-Cs	+	1.18±0.02*	+
Df	−	1.59±0.09	
Df	+	1.69±0.10	−

Data of ten independent experiments were pooled.
α-Cs-SN;Supernatant from culuture of α-casein-stimulated normal lymphocytes (autologous)
*p<0.01
S.I.;stimulation index

Table. 4 Supernatant from α-casein-stimulated patient lymphocytes (α-Cs-SN) failed to suppress α-casein-specific induction of IL-2 responsiveness in autologous lymphocytes.

Experiment	Subject	Antigen	α-Cs-SN	IL-2 responsiveness S.I. (mean±S.E.) n=3	Suppression
I	patient lymphocyte (autologous)	none	−	1.01±0.04	
		α-Cs	−	1.35±0.04	
		α-Cs	+	1.32±0.08	−
II	leu 18-treated normal lymphocyte (autologous)	none	−	1.06±0.11	
		α-Cs	−	1.33±0.07	
		α-Cs	+	1.14±0.08*	+

α-Cs; α-casein *p<0.01
S. I. ; stimulation index

Leu18-antibody-pretreated autologous lymphocytes with a-casein, IL-2 responsiveness was induced, and the culture supernatant from autologous lymphocytes stimulated with α-casein suppressed this response. However, the IL-2 response induced by mite antigen (Dermatophagoides farinae) was not suppressed (Table 3). Thus, suppression of the response to α-casein appeared to be antigen-specific. On the other hand, suppressive activity was observed when we added culture supernatant from the lymphocytes of children with milk allergy to the autologous response system (Table 4). Thus, there appeared to be some deficiency in the suppression of α-casein-specific IL-2 lymphocyte responsiveness in the patients with milk allergy.

V. Discussion

Although milk allergy has been known since the time of Hippocrates, research on it only started after feeding infants dairy products became widespread in the 20th century. Hamburger[6] has stated that, "since infants

Table. 5 Sensitivity to cow's milk protein component in patients of milk protein allergy

method / antigen	skin test	oral challlenge		IL-2
	A.Goldmann et. al.	A.Goldmann et. al.	E.Lebenthal et. al.	responciveness
β-lactoglobulin	24%	66%	82%	58%
α-casein	40%	57%	43%	54%
α-lactalbumin	22%	54%	41%	86%
BSG	−	−	27%	−
BSA	24%	51%	18%	67%
OVA	−	−	−	47%

BSA ; bovine serum albumin BSG ; bovine nerum globulin OVA ; ovalbumin − ; not tested

become sensitized to milk proteins, which are xenogenic proteins, and allergies become established, the use of dairy products is not advisable". Research on milk allergy has chiefly been conducted in Western countries. Bachman et al.[7] defined milk allergy as being present when ingestion of a small quantity of milk caused 1) at least one of eczema, urticaria, asthma, or rhinitis, as well as 2) gastrointestinal symptoms or abnormal behavior, with the recurrence of 1) and 2) occurring repeatedly on challenge with milk. they reported that 4 (1 %) out of 403 healthy infants followed up for 2 years were allergic to milk, but there are large differences in the reported incidence of this allergy, ranging from 0.3% to 7.5%. While this appears to be attributable to differences in age, diagnostic criteria, diet, and the method of enrolling subjects, no consensus has yet been achieved regarding the diagnostic criteria for milk allergy. In the present study, the diagnosis was limited to patients who at least exhibited atopic dermatitis and repeatedly suffered gastrointestinal symptoms after ingesting milk, and the IL-2 responsiveness of activated T cells induced by antigen stimulation was assessed for its value as an index of disease activity and a method of antigen diagnosis in atopic disease.

Cow's milk protein is composed of casein and whey proteins. Casein is comprised by α , β , γ , and κ-casein, while the whey proteins include lactalbumin and immunoglobulins. Lactalbumin further consists of β-LG, α-LA, and BSA. In a study on differences in the allergenicity of milk protein components, Ratner et al.[9] intraperitoneally and subcutaneously injected α-casein, α-LA, and β-LG into guinea pigs. Then they injected milk intravenously 3 weeks later and assessed the intensity of the allergic response. Their findings suggested that α-LA was the principal etiologic protein in milk allergy. In addition, Goldman[10] fed the same amount of casein, β-LG, α-LA, and BSA as is found in 100 ml of skim milk to 89 patients with classic milk allergy, and reported that every patient reacted to one or more of these milk protein component (β-LG, 66% ; casein, 57% , α-LA, 54% ; and BSA, 51%). They also dissolved α-casein, β-LG, α-LA, and BSA in saline at concentrations of 1000 PNU／ml and 10,000 PNU／ml, and then intradermally injected them into 85 patients, producing intradermal reaction rates of 40% for 24% for β-LG, 24% for BSA, and 22% for α-LA. Lebenthal[11] summarized the results of oral challenge studies, and reported the following positivity rates: β-LG, 82% ; α-casein, 43% ; α-LA, 41% ; BSA, 27% ; and BSA, 18%. The present study assessed T cell IL-2 responsiveness induced by α-LA, BSA, β-LG, and α-casein, and also investigated the clinical significance of these responses. The positivity rates were: α-LA, 86% ; BSA, 67% ; β-LG, 58 % ; and α-casein, 54%. Proteins with an intense antigenicity, such as α-LA and β-LG, appear to be important in the establishment of milk allergy. In addition, since it yielded higher positive rates than skin testing and the results were close to those obtained with oral challenge tests, the in vitro IL-2 responsiveness test adopted for the present study appears to be a useful method of identifying etiologic allergens and monitoring disease activity.

The lymphocytes of the milk allergy patients appeared to be specifically sensitized to β-LG antigen, since no IL-2 responsiveness was induced by stimulation with OVA. Moreover, the absence of any induction of IL-2 responsiveness when lymphocytes from normal non-atopic adults were stimulated with β-LG also seems to suggest that the induction of responsiveness was antigen-specific.

OVA-specific induction of IL-2 responsiveness

is reported to be regulated at the cellular level, and abnormalities of this regulation seem to be connected with increased OVA-induced IL-2 responsiveness and the onset of allergic disease in children, especially atopic dermatitis[3]. The same etiology may underlie the induction of IL-2 responsiveness by the various components of cow's milk protein in children with milk allergy.

Because we did not find any correlation between the induction of IL-2 responsiveness in our additional study of α-casein and the values for specific IgE, which is the major effector of type I allergy, it seems that atopic dermatitis is based on mechanisms other than type I allergy[12].

The finding of a high frequency of IL-2 responsiveness after induction by OVA in the children with milk allergy (47% vs. 0 % in normal children of a corresponding age), is a fact which should be remembered in the diagnosis and treatment of children with milk allergy.

Next, we assayed IL-2 receptor expression by lymphocytes stimulated with α-casein. The expression of p-55 IL-2 receptors was examined in both healthy individuals and allergy patients. Since IL-2 responsiveness was not induced in the healthy individuals and the patients' IL-2 responsiveness was somewhat suppressed by the culture supernatant from healthy control lymphocytes (p-55 positive), the response to IL-2 was unrelated to p-55 IL-2 receptor expression, but instead appeared to be regulated by the p-75 IL-2 receptor (the high-affinity IL-2 receptor).

After stimulating the lymphocytes of healthy controls with α-casein, the culture supernatant suppressed patient α - casein-induced IL-2 responsiveness, but patient mite-antigen-induced IL-2 responsiveness was not suppressed. In addition, culture supernatant obtained from patients in the same manner was incapable of suppressing α-casein-induced IL-2 responsiveness. Furthermore, the α-casein-stimulated lymphocytes of healthy controls did not suppress the IL-2 responsiveness of any of the children with allergy. Suppressive activity was observed with a probability of about 1／3, and since genetic restriction appeared to influence this suppressive activity, we are currently considering the HLA typing of patients and healthy controls in whom we observed suppressive activity. We would also like to attempt to devise treatments for allergic diseases and to perform a molecular biological analysis of these inhibitory factors by establishing human T cell hydridomas secreting inhibitory factors.

In children with milk allergy, assaying IL-2 responsiveness is a safe, inexpensive, and accurate diagnostic method that appears to be clinically useful.

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アトピー性皮膚炎患児における リンパ球の抗原特異的IL-2反応性の誘導と調節

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要　旨

牛乳アレルギーによるアトピー性皮膚炎患児末梢血リンパ球に各種牛乳蛋白成分を抗原とするIL-2反応性が誘導され、この反応を調節している因子はp-75 IL-2レセプターと関連があることを示した。健康者リンパ球を α-casein で培養して得られた細胞上清は凡そ1／3の確率で患者の α-casein IL-2反応性を抑制した。

キーワード：IL-2反応性、牛乳アレルギー、IL-2レセプター