

M. Kato
Y. Nozaki
T. Yoshimoto
Y. Tamada
M. Kageyama
T. Yamashita
F. Kurimoto
I. Nakashima

Different serum soluble Fas levels in patients with allergic rhinitis and bronchial asthma

Authors' affiliations:

M. Kato, I. Nakashima, Department of Immunology, Nagoya University School of Medicine, Nagoya

M. Kato, Department of Otorhinolaryngology Nagoya University School of Medicine, Nagoya

Y. Nozaki, Department of Internal Medicine, Nagoya University School of Medicine, Nagoya

T. Yoshimoto, Department of Internal Medicine, Social Insurance Chukyo Hospital, Nagoya

Y. Tamada, Department of Dermatology, Aichi Medical University, Aichi

M. Kageyama, T. Yamashita, F. Kurimoto, Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan

Correspondence to:

Masashi Kato
Department of Immunology
Nagoya University School of Medicine
65 Tsurumai-cho Showa-ku
Nagoya
Aichi 466-8550
Japan

Key words: allergic rhinitis; bronchial asthma; soluble Fas.

Background: The pathogeneses of allergic rhinitis and bronchial asthma are believed to be closely mutually related because of the similar dynamics of allergy-inducing cells and molecules and clinical overlap. In this study, we compared these diseases in the dynamics of cell apoptosis-regulating molecules.

Methods: Allergic rhinitis patients ($n=36$), bronchial asthma patients ($n=22$), and healthy subjects ($n=32$) were subjected to measurement of serum (soluble Fas) (sFas) levels during the stable and attack disease phases by a sandwich enzyme-linked immunosorbent assay.

Results: Serum sFas levels in patients with allergic rhinitis during the attack phase were significantly lower ($P<0.0001$) than those in healthy individuals. There were no differences between them during the attack and stable disease phases. In contrast, serum sFas levels in patients with bronchial asthma during the attack phase were higher ($P<0.0005$) than those in healthy individuals. Interestingly, the levels during the attack phase were lower ($P<0.002$) than those during the stable phase.

Conclusions: Our results suggest a different pathogenesis for allergic rhinitis and bronchial asthma at the cell apoptosis-linked step.

Date:

Accepted for publication 15 July 1999

To cite this article:

Kato M., Nozaki Y., Yoshimoto T., Tamada Y., Kageyama M., Yamashita T., Kurimoto F. & Nakashima I. Different serum soluble Fas levels in patients with allergic rhinitis and bronchial asthma.

Allergy 1999; 54: 1299–1302.

Copyright © Munksgaard 1999

ISSN 0105-4538

Cell-surface Fas is a member of the tumor necrosis factor receptor superfamily, and transmits basic signals controlling cell death (1). Recently, it was reported that Fas can occur as a soluble protein as well as a cell-surface receptor (2, 3). Soluble Fas (sFas) is generated by alternative mRNA splicing events (2–6), and was identified in the supernatants of activated human lymphocytes and several tumor cell lines (2–6). sFas was also reported to antagonize both anti-Fas and Fas ligand-mediated killing in a dose-dependent manner (2).

Clinically, serum sFas levels were reported to increase in autoimmune diseases and malignancies, and defective apoptosis due to sFas interaction with its ligand preventing signaling for apoptosis may contribute to these diseases (2, 3, 7). Previously, we reported that allergic rhinitis is a sFas-reduced disease, and suggested that sFas might play a new role in this disease (8).

To our knowledge, the dynamics of allergy-inducing cells and molecules in bronchial asthma is similar to that in allergic rhinitis (9–13). Clinically, these two diseases often overlap with each other, and their pathogeneses are believed to be closely related. In this study, we demonstrate an unexpected difference in serum sFas levels between allergic rhinitis patients and bronchial asthma patients, and suggest the possibility of different apoptosis systems in the pathogenesis of the two diseases.

Material and methods

All allergic rhinitis patients ($n=36$) showed single sensitization to Japanese cedar pollen by several kinds of radio-allergosorbent test (RAST), as described before (8). All cases of allergic rhinitis did not basically overlap with other allergic diseases. All patients with bronchial asthma ($n=22$) had a history of wheezing and met the diagnostic criteria for bronchial asthma of the American Thoracic Society (14). Atopic- or nonatopic-type bronchial asthma was identified by 5–15 kinds of RAST and/or skin prick tests. Bronchial asthma overlapped with allergic rhinitis in 8/23 patients. Healthy individuals ($n=32$) consisted of the volunteers described before (8, 15). Serum sFas levels in patients with allergic diseases and healthy individuals were measured by a sandwich enzyme-linked immunosorbent assay (Medical & Biological Laboratories Co., Nagoya, Japan) (8, 15). The results of patients with allergic diseases were compared with those of healthy subjects. These data were statistically analyzed by the Kruskal-Wallis test (intergroup analysis) or Wilcoxon's matched-pairs signed-rank test (intragroup analysis).

Results and Discussion

As shown in Fig. 1, serum sFas levels in patients with seasonal allergic rhinitis during the attack phase (season, $n=36$; 0.49 ± 0.37 ng/ml) were significantly "lower" ($P<0.0001$) than those in healthy individuals (1.32 ± 0.59 ng/ml). There were no differences between

them during the attack ($n=16$; 0.45 ± 0.33 ng/ml) and stable disease (preseason, $n=16$; 0.37 ± 0.26 ng/ml) phases (Fig. 2A). These results basically corresponded to those in our previous report of the reduction of serum sFas and soluble tumor necrosis factor receptor levels in allergic rhinitis (8, 9). In contrast, serum sFas levels in patients with bronchial asthma during the attack phase ($n=22$; 2.24 ± 0.80 ng/ml) were higher ($P<0.0005$) than those in healthy individuals (Fig. 1). These results may suggest different causes of allergic rhinitis and bronchial asthma at the step of cell apoptosis. Interestingly, the levels during the attack phase ($n=20$; 2.30 ± 0.94 ng/ml) were lower ($P<0.002$) than those during the stable phase ($n=20$;

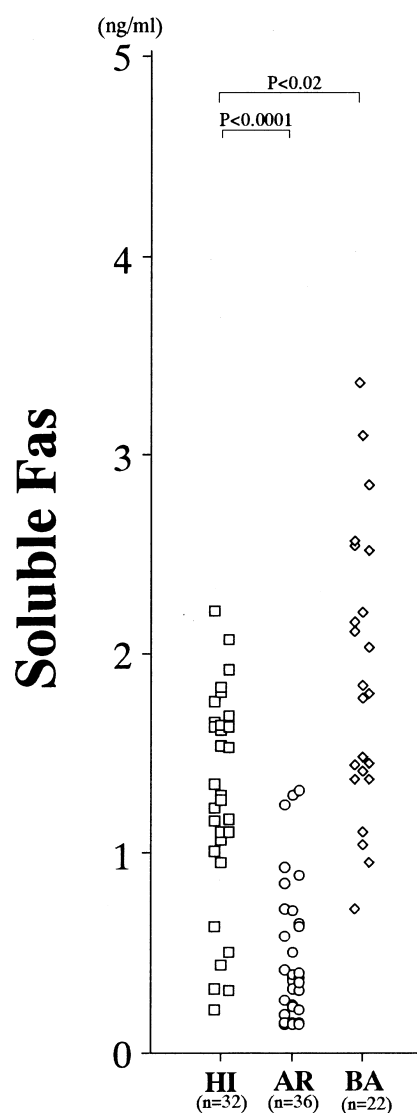


Figure 1. Serum sFas levels in allergic rhinitis patients and bronchial asthma patients during attack disease phase and in healthy individuals. HI: healthy individuals; AR: allergic rhinitis patients; BA: bronchial asthma patients.

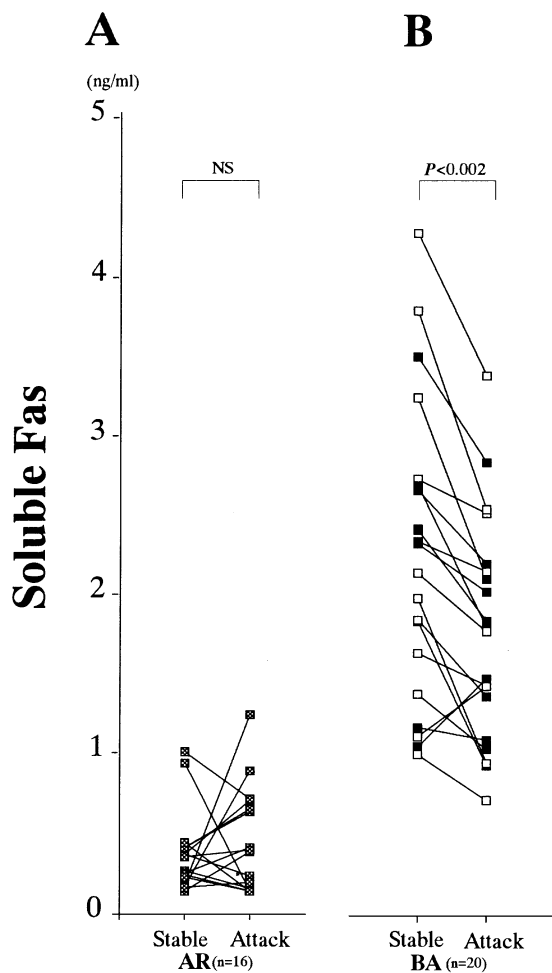


Figure 2. Serum sFas levels in allergic rhinitis patients and atopic or nonatopic bronchial asthma patients during attack and stable disease phases. A) Allergic rhinitis patients; B) atopic (■) and nonatopic (□) bronchial asthma patients.

1.87 ± 0.70 ng/ml) (Fig. 2B). High sFas levels during the attack phase and even higher levels during the stable phase were observed in both atopic ($n=8$; stable: 2.29 ± 0.80 ng/ml; attack: 1.93 ± 0.53 ng/ml) and nonatopic ($n=12$; stable: 2.32 ± 1.06 ng/ml; attack: 1.84 ± 0.81 ng/ml) bronchial asthma. Together with our findings that all atopic bronchial asthma patients were sensitized to mite, these results suggest that neither the presence, the absence, nor the type of sensitization is a major factor in sFas levels in these two diseases, although there is a possibility that some of the bronchial asthma patients classified as nonatopic type were actually sensitized to antigens yet untested.

Serum sFas levels in bronchial asthma patients with allergic rhinitis ($n=8$; stable phase: 1.36 ± 0.44 ng/ml; attack phase: 1.69 ± 0.56 ng/ml) were lower than those in

bronchial asthma patients without allergic rhinitis ($n=12$; stable: 2.21 ± 0.63 ng/ml; attack: 2.68 ± 0.94 ng/ml) during both the attack ($P<0.01$) and stable ($P<0.02$) phases. However, the levels in bronchial asthma patients with allergic rhinitis remained higher than those in simple allergic rhinitis patients during both the attack ($P<0.005$) and stable ($P<0.0001$) phases. These results suggest that each of the two disease entities has its own anti-inflammatory regulatory mechanism which may partially compete with the other's.

The mechanisms of upregulation during the stable phase and downregulation during the attack phase of serum sFas levels in bronchial asthma patients remain unknown. It was reported that serum sFas levels increased during Th1 inflammation in autoimmune diseases (2, 3) and infectious disease (15). However, we could not provide evidence that nonatopic bronchial asthma patients, some of whom may have had the Th1 inflammation, had higher serum sFas levels than atopic asthma patients. Therefore, it seems unlikely that the demonstrated difference in the serum sFas levels between allergic rhinitis and bronchial asthma patients correlates with the levels of Th1 and Th2 inflammations in the two diseases. In fact, serum sFas levels decreased during the attack phase in both atopic- and nonatopic-type bronchial asthma patients, although they remained higher than in the healthy individuals. Taken together, our results suggest that serum sFas levels might be upregulated during the chronic inflammation phase of bronchial asthma irrespective of the presence (atopy type) or absence (most of the nonatopy type) of sensitization to allergen. However, they are downregulated during the acute inflammation phase of the disease again, with or without sensitization. This might be due to the consumption of more sFas during the acute phase of inflammation than the amount produced. In any case, further investigation is needed to clarify the relationships among sFas, the regulatory mechanisms of allergic diseases in their different phases, and the pathogenesis.

In short, we provided evidence of different sFas dynamics in allergic rhinitis and bronchial asthma, and discussed its mechanisms.

Acknowledgments This study was supported in part by a Grant-in-Aid for the Encouragement of Young Scientists from the Ministry of Education, Science, Sports, and Culture of Japan.

References

1. Trauth BC, Klas C, Peters AMJ, et al. Monoclonal antibody-mediated tumor regression by apoptosis. *Science* 1989;**245**:301–305.
2. Cheng J, Zhou T, Liu C, Shapiro JP, et al. Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. *Science* 1994;**263**:1759–1762.
3. Mountz JD, Wu J, Cheng J, Zhou T. Autoimmune disease: a problem of defective apoptosis. *Arthritis Rheum* 1994;**37**:1415–1420.
4. Owen-Schaub LB, Angelo LS, Radinsky R, Ware CF, Gesner TG, Bartos DP. Soluble Fas/APO-1 in tumor cells: a potential regulator of apoptosis? *Cancer Lett* 1995;**94**:1–8.
5. Natoli G, Ianni A, Costanzo A, et al. Resistance to Fas-mediated apoptosis in human hepatoma cells. *Oncogene* 1995;**10**:1157–1164.
6. Cascino I, Fiucci G, Papoff G, Ruberti G. Three functional soluble forms of the human apoptosis-inducing Fas molecule are produced by alternative splicing. *J Immunol* 1995;**154**:2706–2713.
7. Midis GP, Shen Y, Owen-Schaub LB. Elevated soluble Fas (sFas) levels in nonhematopoietic human malignancy. *Cancer Res* 1996;**56**:3870–3874.
8. Kato M, Hattori T, Ito H, et al. Serum soluble Fas levels as a marker to distinguish allergic and non-allergic rhinitis. *J Allergy Clin Immunol* 1999;**103**:1213–1214.
9. Kato M, Hattori T, Kato Y, Matsumoto Y, Yamashita T, Nakashima I. Elevated soluble tumor necrosis factor receptor levels in seasonal allergic rhinitis patients. *Allergy* 1999;**54**:278–282.
10. Kato M, Hattori T, Kitamura M, Beppu R, Yanagita N, Nakashima I. Soluble ICAM-1 as a regulator of nasal allergic reaction under natural allergen provocation. *Clin Exp Allergy* 1995;**25**:744–748.
11. Kato M, Hattori T, Ikeda R, et al. Amount of pollen has an effect on the systemic and local levels of soluble ICAM-1 in patients with seasonal allergic rhinitis. *Allergy* 1996;**51**:128–132.
12. Gearing AJH, Newman W. Circulating adhesion molecules in disease. *Immunol Today* 1993;**14**:506–512.
13. Hashimoto S, Imai K, Kobayashi T, et al. Elevated levels of ICAM-1 in sera from patients with bronchial asthma. *Allergy* 1993;**48**:370–372.
14. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Medical Section of the American Lung Association. *Ann Rev Respir Dis* 1987;**136**:225–244.
15. Kato M, Tamada Y, Kageyama M, et al. Elevated soluble Fas levels in herpes zoster patients. *Br J Dermatol* 1998;**138**:1091.