

Allergen-specific immunotherapy increases plasma gelsolin levels

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ABSTRACT

Background: It has been observed that patients with allergic asthma/rhinitis have increased apoptosis of peripheral blood cells. This study was designed to explore the idea that the markers of apoptosis may help predict the response of allergen immunotherapy.

Methods: The Allergy Department of University Hospital, Malmö, Sweden, recruited a total of 58 young adults (<35 years) with a history of birch pollen/grass pollen-induced allergic rhinitis. Their diagnoses were verified by positive skin-prick tests and the presence of serum-specific immunoglobulin E antibodies toward birch and/or grass pollen. Plasma samples were obtained from 34 patients before the start of immunotherapy and 24 patients after treatment. The control group consisted of 38 nonallergic individuals. The levels of plasma gelsolin, soluble forms of Fas (sFas) and Fas ligand (Fas-L), the chemokine CCL17 (thymus- and activation-regulated chemokine), and tissue inhibitor of metalloprotease (TIMP) 1, were measured by enzyme-linked immunosorbent assay.

Results: In patients receiving immunotherapy plasma gelsolin levels were higher relative to those without immunotherapy (the median level was 23.97 $\mu\text{g/mL}$ [range, 18–35.8 $\mu\text{g/mL}$] versus 21.2 $\mu\text{g/mL}$ [range, 13.9–29.8 $\mu\text{g/mL}$]; $p = 0.012$) and were similar to those of healthy controls (24.7 $\mu\text{g/mL}$ [range, 17.4–35.3 $\mu\text{g/mL}$]). Plasma levels of sFas, Fas-L, CCL17, and TIMP-1 did not differ between study groups. Only in controls did the plasma gelsolin levels inversely correlate to the levels of soluble Fas.

Conclusion: Allergen-specific immunotherapy increases plasma levels of gelsolin, an antioxidant and antiapoptotic protein.

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Allergic rhinitis is an immunoglobulin E (IgE)-mediated (allergic) reaction to aeroallergens. Grass and birch pollen exposure is one of the major causes of allergic rhinitis in many parts of the world.¹ Conventional treatment of allergic rhinitis usually begins with avoidance of allergen or symptomatic treatment, such as intranasal corticosteroid and non-sedating antihistamines. Allergen-specific immunotherapy (subcutaneous [SQ] or sublingual) is currently the only treatment that alters the abnormal immune response underlying allergic disease.^{2,3} Immunotherapy contains the specific allergen extracts interacting with the immune system to decrease allergic sensitivity. This therapy provides long-term clinical effects and decreases the risk of asthma development in patients suffering from allergic rhinitis.^{4,5} So far, the mechanisms responsible for clinical improvement have not been fully revealed.

Conflicting results have been reported concerning the cytokine patterns before and after allergen-specific immunotherapy, although a shift from T-helper cell type 2 (Th2) response toward Th1 is seen consistently.⁶ Recent data suggest that the mechanisms involved in the regulation of survival and apoptosis of inflammatory cells play an important role in the inflammatory process characterizing allergy and asthma.^{7,8} Indeed, significantly higher percentages of apoptotic mononuclear cells were found in patients with allergic asthma and/or rhinitis when compared with nonallergic subjects.⁹

Gelsolin is an antioxidant and antiapoptotic protein¹⁰ that binds actin and prevents an increase in blood viscosity because of the actin

leakage from dying cells.¹¹ Gelsolin also binds various bioactive lipids, such as lysophosphatidic acid, platelet-activating factor, sphingosine-1-phosphate, and bacterial lipopolysaccharides.^{12–14} The binding of these inflammatory mediators can potentially deplete gelsolin, resulting in impaired elimination of circulating F actin and the development of persistent inflammation.¹⁵ Several studies provided evidence that depletion of plasma gelsolin (independently of the reason) contributes to injury and adverse outcomes whereas gelsolin administration has beneficial effects.^{16–20}

To our knowledge, plasma gelsolin levels have not been investigated in patients with allergic rhinitis. Therefore, in this study we asked two questions:

1. Are plasma levels of gelsolin changed in patients with allergic rhinitis relative to matched healthy controls?
2. Does specific allergen immunotherapy have any effect on plasma gelsolin levels?

To answer these questions we analyzed plasma gelsolin in birch- or grass pollen-allergic young adults and in healthy, nonallergic subjects.

MATERIALS AND METHODS

Study Groups

The study was performed from 2009 to 2012. After inclusion patients were investigated consecutively; thus, all patients were studied pre-season and during season of the same year. The study patients were recruited from the Allergy Division at the Department of Otorhinolaryngology, Skåne University Hospital, Malmö, Sweden. This study was approved by the Ethics Committee at Lund University (LU2009/227) and informed consent was obtained from each subject.

Fifty-eight patients (<35 years), diagnosed with seasonal allergic rhinitis, were selected for the study (Table 1). All patients had a history of birch-, grass-, or birch and grass pollen-induced rhinoconjunctivitis and suffered from itchy nose and eyes, sneezing, nasal congestion, and secretion during season. The allergy was confirmed by the positive skin-prick test and presence of serum-specific anti-IgE (minimum, 0.35 kU/L). None of these patients suffered from allergic symptoms or were on any regular treatment out of season, although some displayed positive skin reactions for furred animals and molds.

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Table 1 Patient demographics

Variable	Study Groups			p Value
	Healthy Controls n = 38	Allergic Nontreated with Immunotherapy n = 34	Allergic Treated with Immunotherapy n = 24	
Age, yr*	26.1 (25.2–27)	26.7 (24.6–28.9)	29.6 (26.7–32.5)	<0.05#
Gender (M/F)	22/16	16/18	15/9	
Allergy				NS
Birch	—	24	16	
Grass	—	30	23	
Both	—	20	14	
Asthma		12	14	NS
Allergen-specific IgE, kU/L	—	20.4 (27.4)	16.6 (25.3)	NS

*Mean (range).

#Significant difference between controls and patients treated with specific immunotherapy.

NS = not significant.

All patients had normal lung function with forced expiratory volume in 1 second of >80% of predicted. Some patients reported mild or moderate exercise-induced and allergic asthma classified according to the Allergic Rhinitis and Its Impact on Asthma.¹ Patients categorized as having asthma, as the predominant symptom, were not included in this study. The control group consisted of 38 healthy subjects having no allergic symptoms outside or during the pollen season. They were skin-prick test negative to all standard allergens, had no serum IgE antibodies, and had normal lung function.

Skin-Prick Tests

Skin-prick tests were performed with nine standard aeroallergen extracts (birch, timothy, mugwort, cat dander, dog dander, horse dander, *Dermatophagoides pteromyssinus*, *Cladosporium herbarum*, and *Alternaria* using Soluprick SQ ALK (ALK-Abelló, Hørsholm, Denmark). The results were read after 15 minutes, measuring the largest diameter of the wheal and its perpendicular diameter, and the product was expressed in millimeters squared. Skin reactions were considered positive when >9 mm.²

Immunization Protocol for Allergic Patients

Patients (n = 24) in the allergen-specific immunotherapy group were injected SQ with incremental doses of birch pollen vaccine (Alutard; ALK-Abelló) over 14 weeks (week 1, 50 SQ-U; week 2, 100 SQ-U; week 3, 200 SQ-U; week 4, 400 SQ-U; week 5, 800 SQ-U; week 6, 1500 SQ-U; week 7, 3000 SQ-U; week 8, 6000 SQ-U; week 9, 10,000 SQ-U; week 10, 20,000 SQ-U; week 11, 40,000 SQ-U; week 12, 60,000 SQ-U; week 13, 80,000 SQ-U; and week 14, 100,000 SQ-U). Thereafter, maintenance injections (100,000 SQ-U) were given every 6–8 weeks over 3 years. These patients finished treatment in 2012.

Sample Collection

Blood samples were obtained out of allergen season. Before sample donations, the patients went 3 days without any medication. Blood was collected in tubes containing sodium heparin (B-D Vacutainer System, Stockholm, Sweden) and was centrifuged within 30 minutes at 2000 × g at 4°C for 10 minutes. Plasma was separated and stored within 24 hours at –80°C until assayed.

Analysis of Plasma Analytes

Plasma levels of gelsolin were determined using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (product number ABIN366522, antibodies-online; GmbH, Aachen,

Germany). Assay sensitivity was 62.5 pg/mL, intra-assay precision was 4–6% and inter-assay precision was 8–12%.

Plasma levels of tissue inhibitor of metalloproteases (TIMP) 1 were measured using a commercially available sandwich ELISA kit (catalog DY970; R & D Systems, Abingdon, U.K.) according to the manufacturer's instructions. The minimum detection limit of TIMP-1 was 31.25 pg/mL.

Plasma levels of IL-4, soluble Fas (sFas)/TNFRSF6/CD95, Fas ligand (Fas-L)/TNFSF6, and CCL17/thymus- and activation-regulated chemokine (TARC) were determined using commercial quantitative enzyme immunoassays (ELISA kits, Human Quantikine; R & D Systems, Inc., Minneapolis, MN). Sensitivity was 20 pg/mL (range, 31.2–2000 pg/mL) for human sFas/TNFRSF6/CD95 ELISA and sensitivity was 8.05 pg/mL (range, 15.6–1000 pg/mL) for human Fas-L/TNFSF6 ELISA. Sensitivity was 7 pg/mL (range, 31.2–2000 pg/mL) for human CCL17/TARC. The minimum detection concentration for IL-4 was <10 pg/mL.

Statistical Analysis

The data were analyzed using the SPSS software (Version 20.0.1; SPSS, Inc., Chicago, IL). All variables were analyzed for normal distribution by the Kolmogorov-Smirnov test. The differences in the means were analyzed for their statistical significance with the one-way ANOVA combined with a multiple-comparisons procedure (Scheffé multiple range test). Tests showing *p* < 0.05 were considered to be significant. The estimation of the bivariate correlation between the variables was performed by computing the Spearman's correlation coefficient.

RESULTS

Study Subjects

The characteristics of the study groups are shown in Table 1. We recruited three independent cohorts of subjects, all <35 years of age: 34 patients with allergic rhinitis before receiving SQ immunotherapy, 24 patients treated for 3 years with specific allergen immunotherapy, and 38 controls. Patient groups were properly selected with a primary diagnosis for allergic rhinitis (Table 1). The control group of 38 nonallergic, nonsensitized subjects was selected from medical personnel and students. Of note, the patients treated with specific immunotherapy were somewhat older when compared with the nontreated patients and controls. However, we found no relationship between age and measured plasma markers within the groups.

Table 2 Plasma concentrations of measured analytes

Measured Analyte	Healthy Controls <i>n</i> = 38 Median (range)	Allergic Rhinitis Patients		<i>p</i> Value
		Without Immunotherapy	With Immunotherapy	
		<i>n</i> = 34 Median (range)	<i>n</i> = 24 Median (range)	
Gelsolin, $\mu\text{g/mL}$	24.7 (17.4–35.3)	21.2 (13.9–29.8)	24.0 (18–35.8)	<0.05
TIMP-1, $\mu\text{g/mL}$	112 (21.9–195)	101 (58.9–166.8)	102 (11.7–154)	NS
sFas, $\mu\text{g/mL}$	3360 (1474–162133)	3236 (1569–14345)	3515 (1668–70925)	NS
Fas-L, ng/mL	547.9 (35.8–9576.4)	152 (40.4–36662)	143.8 (38–4056)	NS
CCL17, pg/mL	45.4 (18.7–748.0)	43.4 (16.7–338.6)	108.4 (8.3–702.9)	NS

TIMP-1 = tissue inhibitor of metalloprotease 1; Fas-L = Fas ligand; sFas = soluble Fas; NS = not significant.

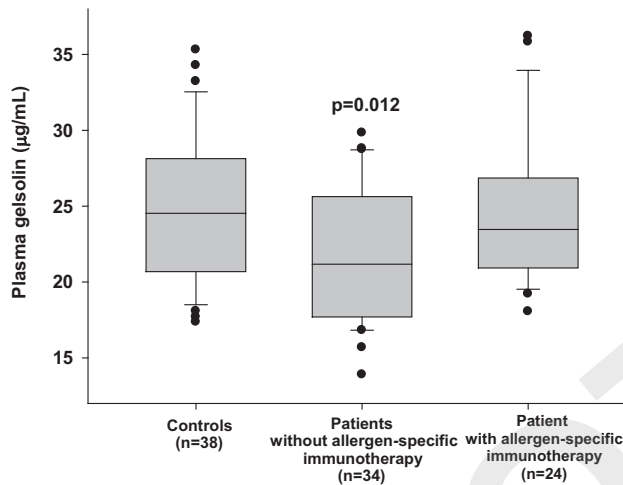


Figure 1. Plasma gelsolin levels in study groups.

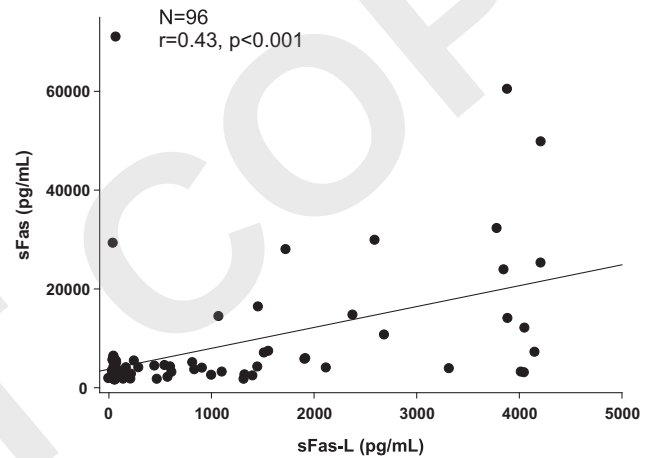


Figure 2. All cohort plasma levels of soluble Fas (sFas) correlated positively with soluble Fas ligand (Fas-L).

Plasma Levels of Measured Analytes

As shown in Table 2 and Fig. 1, patients treated with allergen-specific immunotherapy had higher levels of plasma gelsolin when compared with those without immunotherapy (the median level was 23.97 $\mu\text{g/mL}$ [range, 18–35.8 $\mu\text{g/mL}$] versus 21.2 $\mu\text{g/mL}$ [range, 13.9–29.8 $\mu\text{g/mL}$]; $p = 0.012$) and did not differ from controls (24.7 $\mu\text{g/mL}$ [range, 17.4–35.3 $\mu\text{g/mL}$]). On the other hand, plasma levels of CCL17, TIMP-1, and soluble forms of Fas and Fas-L did not differ significantly among study groups (Table 2). Notably, plasma levels of IL-4 were below detection limit in all samples (with the cutoff value of test; data not shown).

Correlations between Measured Variables

In all cohorts the sFas levels were positively correlated with sFas-L ($n = 96$; $r = 0.43$; $p < 0.001$; Fig. 2). As shown in Table 3, the healthy control plasma sFas levels were inversely correlated with levels of gelsolin ($p = 0.012$), whereas in patients not treated with allergen-specific immunotherapy sFas and sFas-L were directly correlated with gelsolin ($p = 0.01$ and $p = 0.038$, respectively). However, in patients treated with immunotherapy there was no correlation between plasma gelsolin and sFas or sFas-L levels. In patients with or without allergen-specific immunotherapy, the plasma CCL17 levels were positively correlated with sFas-L ($r = 0.57$ and $p = 0.001$, and $r = 0.58$ and $p = 0.004$, respectively).

DISCUSSION

Allergic rhinitis is a common disorder that can significantly impact the patient's quality of life.²¹ Increasing numbers of clinical trials and meta-analyses have shown positive clinical effects and safety of allergen-specific immunotherapy for the treatment of allergic rhinitis,

Table 3 Variable correlation matrix

Group/Variable	Gelsolin	sFas-L	TIMP-1
sFas			
Control, <i>n</i> = 38	−0.395*		
Treated, <i>n</i> = 24		0.43*	
Nontreated, <i>n</i> = 34	0.47#	0.363*	0.53#
sFas-L			
Control, <i>n</i> = 38			
Treated, <i>n</i> = 24			
Nontreated, <i>n</i> = 34	0.38*		
CCL17			
Control, <i>n</i> = 38			
Treated, <i>n</i> = 24		0.578#	
Nontreated, <i>n</i> = 34		0.57#	

*Correlation is significant at the 0.05 level (two-tailed).

#Correlation is significant at the 0.01 level (two-tailed).

TIMP-1 = tissue inhibitor of metalloprotease 1; sFas = soluble Fas; sFas-L = soluble Fas ligand.

specifically caused by pollens and dust mites.^{2,22} For the first time in this study, we show that the plasma levels of gelsolin, an anti-inflammatory protein, increase after allergen-specific immunotherapy. Hence, plasma gelsolin levels were significantly higher in allergic rhinitis patients treated with immunotherapy when compared with nontreated patients and did not differ statistically from controls. The cause of the gelsolin decrease in patients with allergic rhinitis and its restoration with specific immunotherapy remains unclear.

A study by Candiano and coworkers has shown that gelsolin levels in bronchial lavage are significantly up-regulated by IL-4.²³ The au-

thors showed that patients with asthma have increased amounts of IL-4 and gelsolin protein in their airways, relative to control subjects, and have speculated that IL-4-induced gelsolin may be part of a host anti-inflammatory response. Assuming that there is a link between the levels of plasma gelsolin and IL-4, we measured plasma IL-4. Unfortunately, plasma levels of IL-4 were below detection limits in all samples (with the cutoff value of test), which did not allow us to evaluate a putative link between plasma levels of IL-4 and gelsolin.

Park *et al.* have suggested that matrix metalloproteinases (MMPs) such as MMP-14, -2, and -9, among others, weaken the extracellular actin-scavenging system by cleaving plasma gelsolin.²⁴ TIMP-1 is a specific inhibitor of MMP-9 but has overlapping inhibitory effects on other MMPs, including MMP-2. Low levels of TIMP-1 have been implicated in airways diseases.^{25–27} We found that plasma TIMP-1 levels did not differ significantly between the study groups. Moreover, no linkage was found between plasma levels of TIMP-1 and gelsolin. Thus, the enzymic degradation and/or changes in gelsolin production can not be ruled out in the present study, which warrants further investigations.

The fact that gelsolin is also an antiapoptotic protein prompted us to measure the circulating levels of sFas-L, an inducer of apoptosis, and the levels of sFas, an inhibitor of apoptosis.^{28,29} sFas blocks apoptosis by inhibiting the binding of plasma membrane-associated Fas to Fas-L or sFas-L.³⁰ However, it still remains unclear whether the plasma concentrations of these apoptotic markers change concomitantly.

The cell surface expression of Fas and Fas-L in allergy has been widely examined; however, soluble forms of these markers have been less extensively studied. Kato *et al.* found that allergic rhinitis is an sFas-reduced disease compared with isolated bronchial asthma.³¹ Kinikli and coworkers found no difference in levels of serum sFas between controls and patients with allergic rhinitis who were treated or not treated with immunotherapy.³² In support of this data, plasma levels of soluble forms of Fas and Fas-L did not differ significantly among our study groups (Table 2).

Next, we sought to evaluate the relationship between plasma levels of sFas and sFas-L. A positive correlation between plasma sFas and sFas-L levels in our cohort supports a direct link between these two markers and points to their importance for regulation of the apoptosis during health and disease. Interestingly, in healthy controls circulating plasma levels of sFas inversely correlated with levels of gelsolin, whereas in allergic rhinitis patients sFas and sFas-L directly correlated with gelsolin but there was no correlation between plasma gelsolin and sFas or sFas-L levels in patients after immunotherapy. Observed correlations need to be interpreted with caution and warrants further investigation. Nonetheless, this indicates that higher plasma levels of gelsolin but lower levels of sFas can be viewed as beneficial to the subject.³³ Increased apoptosis of peripheral blood mononuclear cells has been established in patients with allergic asthma/rhinitis.⁹ Along with these results, our data in allergic rhinitis patients without immunotherapy not only show lower levels of antiapoptotic protein, gelsolin, but also reveal a direct link between plasma levels of gelsolin and soluble forms of Fas and Fas-L, markers of apoptosis and systemic inflammation.

Because allergen-specific immunotherapy is shown to shift Th2 response toward Th1⁶ and CCL17/TARC is a chemokine that attracts Th2 cells,³⁴ we aimed to measure plasma levels of CCL17. However, plasma levels of CCL17 did not significantly differ between study groups. Furthermore, no correlation was found between gelsolin and CCL17 levels. However, in rhinitis patients, independently of immunotherapy, plasma levels of CCL17 significantly correlated with Fas-L. This correlation probably indicates activation of inflammatory cells, which are major sources of these markers.

In summary, the data from our study show that plasma gelsolin levels are lower in young adults with allergic rhinitis. Plasma gelsolin circulates in the blood of healthy individuals at a concentration of 200 ± 50 mg/L¹⁷ but can decrease during acute injury and inflammation because of cell apoptosis and/or proteolysis. Lower plasma

gelsolin levels have been found in patients with adult respiratory distress syndrome, acute liver failure, rheumatoid arthritis, myocardial infarction, septic shock, and allogeneic stem cell transplantation.^{15–17,19} Decreased gelsolin concentrations appear to reliably segregate patients at particularly high risk of secondary complications.^{18,20}

Although allergic rhinitis patients may appear asymptomatic during periods of low allergen exposure, chronic activation of inflammatory cells and mediators has been observed in nasal passages during symptom-free periods.¹ It is evident that repeated exposure to nasal allergens leads to long-term local and systemic inflammation.³⁵ Gelsolin is a broad-spectrum anti-inflammatory molecule; therefore, its depletion may reflect ongoing inflammation and airway remodeling in allergic rhinitis. Additional larger-scale studies including older patients are needed to replicate our findings. We believe that the evaluation of plasma gelsolin levels together with other biomarkers may help to assess the effectiveness of specific immunotherapy in patients with seasonal allergic rhinitis.

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