Elevated Levels of Intelectin-1, a Pathogen-binding Lectin, in the BAL Fluid of Patients with Chronic Eosinophilic Pneumonia and Hypersensitivity Pneumonitis

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Abstract:
Objective  Human intelectin-1 (hITLN-1) binds to galactofuranosyl residues, which are present in the microbial cell wall, but which are absent in mammalian tissues, and has been suggested to play an immunological role against microorganisms. However, the involvement of hITLN-1 in the pathogenesis of diffuse pulmonary diseases remains unknown. The aim of this study was to compare the hITLN-1 concentrations in the bronchoalveolar lavage (BAL) fluid of patients with diffuse pulmonary diseases.

Methods  The cell components and concentrations of hITLN-1 were analyzed in the BAL fluid of 8 patients with idiopathic chronic eosinophilic pneumonia (ICEP), 3 patients with drug-induced eosinophilic pneumonia, 4 patients with hypersensitivity pneumonitis (HP), 11 patients with sarcoidosis, 9 patients with cryptogenic organizing pneumonia, and 5 patients with idiopathic fibrosing interstitial pneumonia (fibrosing nonspecific interstitial pneumonia or usual interstitial pneumonia).

Results  The hITLN-1 concentrations in the BAL fluid of patients with ICEP and HP were higher than in those with other diseases. In the ICEP group, no significant difference was observed in the hITLN-1 concentrations of patients with or without a history of bronchial asthma.

Conclusion  The results of the present study suggest that hITLN-1 may be involved in the pathogenesis of ICEP and HP, and that an increase in the hITLN-1 concentration in the BAL fluid may represent a new biomarker for these diseases.

Key words: pathogen-binding lectin, intelectin-1, BAL fluid, idiopathic chronic eosinophilic pneumonia, hypersensitivity pneumonitis

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Introduction

The lung is directly open to the external environment through the airways. Thus, inhaled pathogens may be involved in the pathogenesis of diffuse pulmonary diseases. Moreover, antimicrobial molecules in respiratory tract secretions, which participate in innate immunity, may induce excessive host responses, resulting in lung inflammation.

Intelectin (ITLN) is a Ca2+-dependent lectin that is constitutively expressed in the small intestine (1, 2). ITLN binds to galactofuranosyl residues, which are present in the microbial cell wall, but which are absent in mammalian tissues, and has been suggested to play an immunological role against microorganisms (1, 2). hITLN-1 was previously shown to be expressed in human airway epithelia (3, 4) and a differential proteomic analysis of the bronchoalveolar lavage (BAL) fluid in asthmatic patients revealed the upregulated expression of the hITLN-1 protein (5). A possible association between a single-nucleotide polymorphism in hITLN and asthma susceptibility was also reported (6). In addition, a study using a mouse model of allergic asthma re-
vealed that ITLN is required for the expression of IL-13-induced monocyte chemotactic protein-1 and -3 in lung epithelial cells and that it promotes allergic airway inflammation (7). Recently, Watanabe et al. reported that hITLN-1 was detectable in BAL fluid by an ELISA and that the concentration in inhaled corticosteroid-naïve asthma patients was higher than that in patients receiving inhaled corticosteroids (8). These studies suggest the involvement of intereelint-1 in eosinophilic airway inflammation. However, the involvement of hITLN-1 in the pathogenesis of diffuse pulmonary diseases, including eosinophilic lung diseases, remains unknown.

Chronic eosinophilic pneumonia (CEP), an eosinophilic lung disease, is characterized by the prominent accumulation of intraalveolar eosinophils, which have profound roles in the immune and inflammatory responses, and is highly responsive to oral glucocorticoid therapy. In most cases, the etiology of CEP is unknown (idiopathic CEP: ICEP); however, some patients develop drug-induced eosinophilic pneumonia (drug-EP). In many cases, the clinical features of ICEP are similar to those of cryptogenic organizing pneumonia (COP) (9). Although previous studies have analyzed cell populations in the BAL fluid of CEP patients (10, 11), the pathogenesis of CEP, including the contribution of microorganisms or their components, has not yet been elucidated in detail.

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is another immunologically-induced lung disease that results from airway exposure to dispersed organic particles to which the individual has previously been sensitized. An increase in BAL lymphocytes, lung granulomatous inflammation, and serum-precipitating IgG antibodies against the offending antigens supports this diagnosis (12, 13). However, the differential diagnoses of HP are quite broad, including sarcoidosis and fibrosing interstitial pneumonias [fibrosing nonspecific interstitial pneumonia (fNSIP) and usual interstitial pneumonia (UIP)] (12, 13). In this study, we hypothesized that interactions between hITLN-1 and microorganism-derived galactofuranosyl residues may be involved in the pathogenesis of ICEP and HP and measured the concentration of hITLN-1 in the BAL fluid of patients with these diseases. The results were compared with those of patients with drug-EP, COP, sarcoidosis, fNSIP and UIP.

Materials and Methods

This retrospective study involved the analysis of the existing clinical and laboratory data of patients who underwent bronchoscopic examinations between January 2002 and August 2008. The Ethical Committee of National Hospital Organization Kochi Hospital approved the research plan, including the measurement of the hITLN-1 concentrations in residual BAL fluid that had been stored after clinical use without individual consent (Approval no. H22-4, 13/7/2010). All data were anonymized before being included in the study database.

Patient selection

Eight patients with ICEP, 3 patients with drug-EP, 4 patients with HP, 11 patients with sarcoidosis, 9 patients with COP, and 5 patients with idiopathic fibrosing interstitial pneumonias [fNSIP (3 patients) and UIP (2 patients)] were sequentially selected for this study. Patients with ICEP were diagnosed based on: (a) respiratory symptoms of more than 2 weeks in duration, (b) multiple foci of infiltrates in the peripheral lung fields on chest imaging, (c) BAL eosinophilia, and (d) the absence of possible causes, including suspicious drugs (9). Patients with drug-EP were diagnosed based on: (a) fever or some respiratory symptoms, (b) diffuse infiltrates on chest imaging, (c) BAL eosinophilia, (d) accompanying cutaneous drug reactions, a positive reaction on a lymphocyte stimulation assay or the recurrence of symptoms with re-exposure to the drug (11, 14). HP (1 mushroom worker, 1 greenhouse worker, 1 patient who was serum-positive for anti-Trichosporon cutaneum antibodies, and 1 patient who was exposed to unknown pathogenic particles at home) was diagnosed based on the following factors: (a) clear evidence of exposure, (b) clinical behavior consistent with HP, (c) BAL lymphocytosis, (d) poorly defined small round centrilobular nodules, ground-glass opacities and reticular opacities on HRCT, (e) improvements after refuge from the suspected environment, and (f) histological findings typical of HP, such as noncaseating granulomas with multinucleated giant cells and the infiltration of lymphocytes (13). The different types of idiopathic interstitial pneumonias were classified according to the official American Thoracic Society/European Respiratory Society Statement 2013 (15). Patients with sarcoidosis were diagnosed based on their clinical background and histological findings, such as noncaseating epithelioid granuloma, which consisted of radically-arranged epithelioid cells surrounded by lymphocytic infiltrations (16). Table 1 shows the clinical characteristics of the study subjects.

BAL and fluid processing

BAL was performed before treatment. The tip of the bronchoscope was placed into the subsegmental bronchus of the right middle lobe or into the affected segment of the lung in patients with peripheral opacities. Fifty milliliters of sterile physiological saline solution was instilled through the bronchoscope, and the fluid was retrieved by gentle hand suction applied to each syringe. The procedure was repeated three times and pooled BAL fluid was centrifuged at 250×g for 10 minutes to obtain the cell preparation. Differential counts were performed by microscopic examinations using May-Grünwald-Giemsa-stained cells collected on a glass slide using a Cytospin 2 cytocentrifuge (Shandon Southern Instruments, Sewickley, USA). The supernatant fluid was stored until use at -80°C.

Bacterial, fungal, and mycobacterial cultures and identifications were also performed immediately after the broncho-
scoposcopic examination on pooled BAL fluid using standard procedures in a clinical microbiology laboratory.

**Measurement of ITLN-1 in BAL fluid**

An affinity-purified rabbit anti-intelectin polyclonal antibody was prepared as described previously (17). Recombinant hITLN-1 as the standard was purified from hITLN-1-transfected RK-13 cells using galactose-Sepharose (2). The concentration of intelectin-1 was measured by a sandwich ELISA, as described previously (18). The assay ranges for ITLN-1 were 0.1-100 ng/mL. Values below the limit of detection were given a value of zero in the statistical analyses. The albumin concentration and the ratio of hITLN-1/albumin were not measured.

**Statistical analysis**

Data were expressed as the mean values±SD. Since the data including hITLN values were neither a normal distribution nor a lognormal distribution, the nonparametric Mann-Whitney U test was employed for comparisons between groups. Spearman’s rank correlation (rho) was calculated to evaluate the relationships between hITLN-1 and the cellular components of the BAL fluid or other clinical data. P values of <0.05 were considered to indicate statistical significance.

### Results

**The clinical and BAL fluid cell characteristics of the study subjects**

A female predominance was observed for HP and sarcoidosis, as reported previously (16, 19, 20). No significant differences were observed in the ages of patients in the ICEP, HP, COP, and fNSIP/UIP groups, while the patients in the sarcoidosis group were slightly younger than the patients in the COP and fNSIP/UIP groups. No differences in smoking history were seen among patients of the ICEP, drug-EP, HP, COP, and sarcoidosis groups, while most patients in the fNSIP/UIP group were current or ex-smokers. Half of the patients in the ICEP group had a history of bronchial asthma, and two patients were treated irregularly with inhaled corticosteroids. Most patients in the ICEP and drug-EP groups required systemic steroid therapy. In contrast, the patients in the HP group were more likely to recover without steroid therapy after being removed from the environment that was suspected to have caused HP (Table 1).

The characteristics of cell components in the BAL fluid of the patients in the six subject groups are summarized in Table 1. The total number of cells per mL of BAL fluid in the patients of the sarcoidosis group was lower than that in the patients of the HP and COP groups. A differential cell count showed that the percentages of eosinophils in the patients of the ICEP and drug-EP groups were significantly higher in comparison to the other four groups. In addition, the percentages of eosinophils in the patients in the HP and COP groups were slightly higher in comparison to those in the patients of the sarcoidosis and fNSIP/UIP groups. The percentages of lymphocytes in the patients of the HP, COP, and sarcoidosis groups were higher than those in the patients of the ICEP and fNSIP/UIP groups, and the percentage in the patients of the drug-EP group was higher than that in the patients of the ICEP group. An analysis of the T lymphocyte subsets revealed that the CD4/CD8 ratio in the BAL fluid of the patients in the sarcoidosis group was higher than that in the patients of the ICEP, HP, COP and fNSIP/UIP groups. These results were consistent with the features of the diseases of the six subject groups (11, 21).

**The BAL fluid hITLN-1 concentration**

The hITLN-1 concentrations in the BAL fluid are shown in Fig. 1. In the present study, we used unconcentrated BAL fluid. The hITLN-1 concentrations in the patients in the ICEP (3.4±2.1 ng/mL) and HP (2.9±1.9 ng/mL) groups were significantly higher than those in the drug-EP (0.0±0.0 ng/mL), COP (0.7±0.8 ng/mL), sarcoidosis (0.4±0.4 ng/mL), and fNSIP/UIP (0.3±0.4 ng/mL) groups. No significant difference was observed in the hITLN-1 concentrations of the ICEP and HP groups. In the ICEP group, no significant difference was observed in the hITLN-1 concentrations of patients with or without a history of bronchial asthma (3.6±2.4, p<0.05...
ng/mL vs. 3.3±1.3 ng/mL). A significant positive correlation between the hITLN-1 concentration and the percentage of eosinophils in the BAL fluid was observed in the overall patient population (rho=0.316; p<0.05), but not in the individual groups (Fig. 2). No correlation was observed between the hITLN-1 concentration and other cellular components of the BAL fluid (data not shown). Positive correlations between the hITLN-1 concentration and the percentage of peripheral blood eosinophils (rho=0.440; p<0.01) and the peripheral blood eosinophil count (rho=0.424; p<0.01) were also observed in the overall study population. No correlation was observed between the hITLN-1 concentration and the serum CRP level or age (data not shown).

**Analysis of microorganisms**

All microorganisms isolated from the BAL fluid cultures were members of the normal bacterial and fungal flora of the skin (*Staphylococcus aureus*), digestive tract (*Serratia*...
Figure 2. The relationship between the hITLN-1 concentration in BAL fluid and the percentage of eosinophils in the BAL fluid. \( \rho \): Spearman’s rank correlation, hITLN-1: human intelectin-1, ICEP: idiopathic chronic eosinophilic pneumonia, drug-EP: drug-induced eosinophilic pneumonia, HP: hypersensitivity pneumonitis, COP: cryptogenic organizing pneumonia, SAR: sarcoidosis, fNSIP: fibro-brosing nonspecific interstitial pneumonia, UIP: usual interstitial pneumonia

Discussion

The results of the present study revealed that the BALF hITLN-1 concentrations were higher in patients with ICEP or HP than in patients with drug-EP, COP, sarcoidosis, or fNSIP/UIP. Although no direct evidence was obtained to suggest that hITLN-1 binds to galactofuranosyl residues, interactions between hITLN-1 and microorganism-derived galactofuranosyl residues may be involved in the pathogenesis of ICEP and HP. Previous studies reported the upregulation of ITLN transcripts in the intestine, abomasum, and lungs following infection in experimental mouse and sheep models (22-24). The increased expression of hITLN-1 was also observed in the nasal polyps of chronic polypoid sinusitis, implying that the overproduction of hITLN-1 could lead to persistent inflammation (25). In addition, asbestos, which has various effects on the host immune system, induces pleural inflammation and the expression of intelectin-1 in mesothelial cells (26-28). These findings provide additional support for our hypothesis.

No significant differences were observed in the patterns of microorganisms isolated from the BAL fluid of the different subject groups using conventional cultivation methods. However, the majority of microorganisms were uncultivated, and comprehensive serological studies on innumerable microorganisms are not practical. Thus, the involvement of unidentified microorganisms in the development of ICEP and HP cannot be denied. In addition, inhaled environmental galactofuranosyl residues may be the origins of the galactofuranosyl residues that bind to hITLN-1 in the lung.

Smoking is a major risk factor for airway epithelium injuries, and may affect immunological reactions in the pathogenic processes of various types of pulmonary diseases. Carolan et al. recently reported that the expression of hITLN-1 in the airway epithelium of smokers was lower than that in nonsmokers due to the immunomodulatory effects of smoking on the immune system, thereby suggesting its contribution to the increased susceptibility to infection observed in smokers (4). In contrast, the prevalence of smokers in the ICEP and HP groups was low (12, 29-32), although cigarette smoking is a well-known cause of acute eosinophilic pneumonia (AEP) (33). The decreased expression of hITLN-1 in the airway epithelium may repress the occurrence of ICEP and HP.

In the present study, a positive correlation between the BAL fluid hITLN-1 concentration and the percentage of eosinophils in the BAL fluid was observed in the overall
There are no reports on the presence or absence of ITLN-1 of eosinophils in the alveolar spaces is a common feature. ICEP and drug-EP are different, although the accumulation reported (38). These data indicate that the pathogenesis of and that the Th1 reaction becomes dominant over time (37). and Th2 responses coexist in immediate-type drug allergy or chemicals (35, 36). In addition, it was reported that Th1 expression of ADAM8 reflects the route of entry of antigens but not in drug-EP, suggesting that the induction of the ex- 
pression of ADAM8 is involved in inflammatory path-
processes (39, 40). Galactofuranosyl residues on mi-
croorganisms may affect interactions between hITLN and other immune response factors, thereby leading to the occur-
rence of ICEP and HP.

The present study is associated with several limitations. First, since we did not have a normal subjects group, the ef-
ects of sex, age and smoking status on the BAL fluid is not consid-
ered to be induced in drug-EP. Likewise, a disintegrin and metalloprotease (ADAM) 8 in BAL fluid was reported to be a marker of Th2 responses. The level was elevated in ICEP, but not in drug-EP, suggesting that the induction of the ex-
pression of ADAM8 reflects the route of entry of antigens or chemicals (35, 36). In addition, it was reported that Th1 and Th2 responses coexist in immediate-type drug allergy and that the Th1 reaction becomes dominant over time (37). A case of drug-EP with a granulomatous reaction was also reported (38). These data indicate that the pathogenesis of ICEP and drug-EP are different, although the accumulation of eosinophils in the alveolar spaces is a common feature.

The results of the present study suggest that an increase in the hITLN-1 concentration in the BAL fluid may rep-resent a new biomarker for ICEP and HP; however, the causative relationship between the increased expression of hITLN-1 and ICEH or HP remains unclear. Kerr et al. recently identified hITLN-1 as a prominent protein constituent of pathological mucus, which is associated with eosinophilic airway inflammation in asthma (39). They also revealed that galactofuranosyl residues increased the binding of hITLN to lactoferrin, one of the key molecules in immune and inflam-
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There are no reports on the presence or absence of ITLN-1

study population. One possible explanation is that the influ-
ence of microorganism-derived galactofuranosyl residues may weakly overlap with the pathogenesis of COP, SAR and UIP/NSIP. Another possibility is that hHTLN-1 is a disease non-specific marker of Th2 responses because hHTLN-1 was shown to be involved in inflammatory path-
ways downstream of IL-13 in a mouse model of allergic asthma and the bronchial epithelial cells of asthma pa-

patients (7, 8). It is considered to be difficult to distinguish ICEP from drug-EP based on BAL fluid cell findings alone (11). A lymphocyte stimulation assay is typically per-
fomed to evaluate the sensitivity of the T cells of patients with drug-EP to a suspected drug by measuring the prol-
eration of cells exposed to the drug in vitro. However, its sensitivity and specificity are insufficient (34). Although we only encountered three cases of drug-EP during this study, hITLN-1 was not detected in the BAL fluid of these pa-
tients. Generally, the causative drugs in drug-EP are admin-
istered intravenously or orally, not through the airway, and do not contain galactofuranosyl residues. Thus, hITLN-1-associated immune responses in the airways are not consid-
ered to be induced in drug-EP. Likewise, a disintegrin and metalloprotease (ADAM) 8 in BAL fluid was reported to be a marker of Th2 responses. The level was elevated in ICEP, but not in drug-EP, suggesting that the induction of the ex-
pression of ADAM8 reflects the route of entry of antigens or chemicals (35, 36). In addition, it was reported that Th1 and Th2 responses coexist in immediate-type drug allergy and that the Th1 reaction becomes dominant over time (37). A case of drug-EP with a granulomatous reaction was also reported (38). These data indicate that the pathogenesis of ICEP and drug-EP are different, although the accumulation of eosinophils in the alveolar spaces is a common feature.

There are no reports on the presence or absence of ITLN-1

Table 3. The Microorganisms Isolated from BAL Fluid Cultures.

| Microorganism                  | ICEP | drug-EP | HP  | COP | SAR  | NSIP/UIP |
|-------------------------------|------|---------|-----|-----|------|----------|
| Streptococcus pneumoniae      | 2    |         |     |     |      |          |
| Staphylococcus aureus         | 1    | 2       |     |     |      |          |
| Serratia marcescens           | 1    |         |     |     |      |          |
| Haemophilus parainfluenza     | 1    | 1       | 1  | 1  |      |          |
| Streptococcus acidominimus    | 1    |         |     |     |      |          |
| Streptococcus uberis          | 1    |         |     |     |      |          |
| Streptococcus mitis           | 1    | 1       |     |     |      |          |
| Streptococcus group C/G       | 1    |         |     |     |      |          |
| α-Streptococcus spp.          | 3    | 1       | 5  | 5  | 2    |          |
| γ-Streptococcus spp.          | 1    | 1       | 2  | 2  |      |          |
| Neisseria subflava            | 1    | 1       |     |     |      |          |
| Neisseria cinerea             | 1    |         |     |     |      |          |
| Neisseria spp.                | 2    | 1       | 4  | 5  | 1    |          |
| Candida albicans              | 1    | 1       |     |     |      |          |
| Candida glabrata              | 1    |         |     |     |      |          |
| Total                         | 10   | 4       | 6  | 13 | 17   | 9        |

See Table 1 for the definitions of the abbreviations. Values are presented as the absolute number of isolates.
Conclusion

The BAL fluid hITLN-1 concentration in patients with ICEP or HP was higher than that in patients with drug-EP, COP, sarcoidosis, or NSIP/UIP, suggesting that hITLN-1 may be involved in the pathogenesis of ICEP and HP, and that an increase in the concentration of hITLN-1 of BAL fluid may represent a new biomarker for these diseases. Further large-scale studies are needed to clarify the interactions between hITLN-1 and the microorganism-derived galactofuranosyl residues in ICEP and HP, and to determine whether the control of the hITLN-1 concentration represents a therapeutic target for ICEP or HP.

The authors state that they have no Conflict of Interest (COI).

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