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ORIGINAL ARTICLE

Impact of ozone on circulating tight junction protein claudin 4 and claudin 5 in patients with asthma

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Purpose: Claudins are a type of tight junction proteins in human endothelia and epithelia. Ozone brings about oxidative stress and lung inflammation in humans and experimental models. However, the impact of ozone on claudins in subjects with asthma remains poorly understood. The aim of this study was to find variations in the tight junction proteins claudin-4 and claudin-5 in subjects with asthma in relation to ambient ozone concentration.

Methods: We previously recruited 50 patients with stable/exacerbated asthmatics and 25 controls. Furthermore, to examine the influence of ozone concentration, we reanalyzed 18 patients with stable or exacerbated asthma and 3 controls. The plasma claudin-4 and claudin-5 levels in response to high concentrations of ozone were compared to stable/exacerbated asthma, and controls.

Results: The lung functions were significantly lower in subjects with asthma than those in controls. Blood eosinophil proportions were significantly higher in exacerbated asthmatics than in subjects with stable asthma. In high concentration period of ozone, plasma claudin-4 levels were significantly higher in subjects with exacerbated asthma (0.44 ± 0.30 ng/mL, $P = 0.005$) or stable asthma (0.38 ± 0.31 ng/mL, $P = 0.009$) compared to those in control subjects (0.16 ± 0.1 ng/mL). Plasma claudin-5 levels were lower in subjects with stable asthma (2.97 ± 1.38 ng/mL, $P = 0.011$) than in control subjects (6.92 ± 3.9 ng/mL), and higher in subjects with exacerbated asthma (7.49 ± 4.23 ng/mL, $P < 0.001$) than those with stable asthma.

Conclusion: These results reveal that claudins be changed in patients with asthma following ozone exposure in subjects with asthma. (*Allergy Asthma Respir Dis 2024;12:134-139*)

Keywords: Ozone, Tight junction, Claudin, Bronchial asthma

INTRODUCTION

Ozone exposure has known an important role in the pathogenesis of chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD).[1-3] Ozone exposure causes irritation, airway hyperreactivity (AHR), inflammation of the airways, and destruction of alveoli, the gas exchange area of the lung in humans and mice.[1-4] Ozone is highly reactive and oxidizes proteins and lipids in the fluid-lined compartments of the lung.[5,6] This initiates inflammation and increases lung permeability through cytotoxic mediators, including proinflammatory cytokines and reactive oxygen and nitrogen intermediates such as peroxynitrite.[5,6] A recent epidemiologic study revealed that short-term exposure to ozone increased the risk of asthma mortality.[7] Chronic ozone exposure leads to a progressive loss of the gas-exchanging alveoli associated with chronic inflammation, fibrosis, and terminal respiratory failure, observed in patients with COPD and asthma.[8] The airway epithelium as a physical barrier act in first mucosal immunity line of defense against external environment.[9,10] Tight junctions (TJs) and adherens junctions (AJs), fluid, mucus, surfactant proteins, and motility of cilia are critical for barrier control and innate responses.[11] Ozone impairs epithelial protein leading to airway inflammation.[12]

Claudins are 27 known structural proteins of TJs. The function of different claudins is responsible for solute exchanges and electrolyte transmission in cell layers.[13] The impact of claudin-4 has been reported in lung injury,[14] cancer,[15] and fibrosis.[16] Claudin-5, while weakly expressed in the epithelium, is strongly expressed in

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normal lung endothelium and is upregulated during interstitial pneumonia and asthma.[17,18]

Ozone exposure to mice has increased airway inflammation and bronchial hyperresponsiveness compared to control mice. The protein expression of claudin-3 and claudin-4 as well as reactive oxygen species (ROS), Nrf2, and Keap1 increased, and lung protein expression of claudin-14 decreased in mice exposed to ozone compared to control mice.[19] This suggests that claudins are involved in airway inflammation following ozone exposure, suggesting that ozone affects TJ proteins through oxidative mechanisms.[19]

Therefore, in this study we hypothesized that ozone exposure would differentially affect claudins, including claudin-4 and claudin-5, in patients with asthma. The plasma claudin-4 and claudin-5 levels in response to ozone concentration were compared among patients with stable and exacerbated asthma, and controls subjects.

MATERIALS AND METHODS

1. Study population

We previously recruited 50 patients with stable or exacerbated asthma and 25 controls.[17]

All subjects had a clinical diagnosis of asthma that was supported by one or more of the following criteria: variability in the maximum diurnal peak expiratory flow greater than 20% over the course of 14 days; an increase in the forced expiratory volume in 1 second (FEV_1) greater than 12% after inhalation of 200–400 μg albuterol; or a positive PC_{20} response, defined as a 20% reduction in FEV_1 in response to an inhalation of methacholine. Asthma exacerbation is defined by the Global Initiative for Asthma[20] guidelines as episodes of progressive increases in shortness of breath, coughing, wheezing, or chest tightness, or some combination of these symptoms, accompanied by decreases in expiratory airflow and use of systemic corticosteroids (tablets, suspension, or injection) or an increase from a stable maintenance dose, for at least 3 days, and a hospitalization or emergency department visit requiring systemic corticosteroids because of asthma. These healthy control subjects were included based on the following criteria: negative responses on a screening questionnaire for respiratory symptoms and other allergic diseases, FEV_1 values greater than 80% of predicted values, PC_{20} methacholine values >16 mg/mL, and normal findings in simple chest radiographs. The exclusion criteria included respiratory infection during sputum induction, COPD, vocal cord dysfunction, obstructive sleep apnea, Churg–Strauss syndrome, cardiac dysfunction, allergic bronchopulmonary aspergillosis, or poor compliance with treatment.

Furthermore, to examine the influence of ozone high concentration, we reanalyzed 18 patients with stable or exacerbated asthma and 3 controls. The biospecimens and data used for this study were provided by the biobank of Soonchunhyang University Bucheon Hospital, a member of the Korea Biobank Network. This study was approved by the Institutional Review Board of Soonchunhyang University (SCHBC-2014-10-011).

2. Ozone concentration

The average ground-level ozone concentrations in Gyeonggi-do, South Korea, were obtained for the period 2006–2014 from the

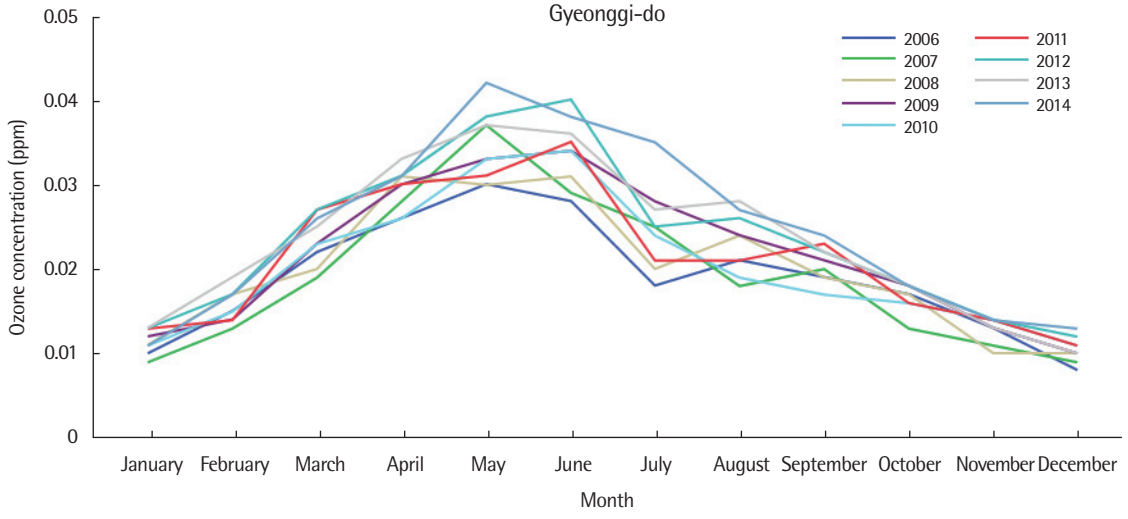

Fig. 1. Average yearly ozone levels in Gyeonggi-do, South Korea. Average ground-level ozone concentrations in Gyeonggi-do, South Korea, during 2006–2014.

Korea Environment Corporation (https://airkorea.or.kr) (Fig. 1). Ozone concentration levels were high in May, June, July, and August compared with other months.[21] We reanalyzed claudin-4 and claudin-5 in patients with asthma and control subjects in high concentration of ozone group based on the sample collected date.

3. Spirometry

Spirometry was performed in accordance with the standards of the American Thoracic Society/European Respiratory Society using established reference values with modifications.[22] Spirometry was performed before and after bronchodilator use. Baseline forced vital capacity (FVC) and FEV_1 measurements were obtained in the absence of bronchodilator use (within 8 hours). Basal and post-bronchodilator FEV_1 and FVC values were measured using the Vmax Series 2130 Autobox Spirometer (Sensor Medics, Yorba Linda, CA, USA).

4. Allergy skin tests

Common inhalant allergens, including dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat fur, dog fur, cockroach, grass, tree pollen (mixed), ragweed, mugwort, and *Alternaria* and *Aspergillus* spp. (Bencard Co., Brentford, UK) were used for the skin prick test. Atopy was defined as having an allergen-induced wheal reaction equal to or greater than that caused by histamine (1 mg/mL) or equal to or greater than 3 mm in diameter. The total IgE level was measured using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden).

5. Enzyme–linked immunosorbent assay

Protein levels of claudin-4 or claudin-5 in human plasma were measured by enzyme-linked immunosorbent assay (USCN, R&D System, Minneapolis, MN, USA). To compare results from different plates, test sample optical density (OD) were adjusted relative to the positive and negative control samples supplied in each kit. The mean OD of duplicate wells was calculated. The index value of each tested serum was defined by the following formula: index = (OD of tested serum–OD of negative control)/(OD of positive control–OD of negative control) × 100. A low detection limits were set at 0.066 ng/mL or 0.156–10 ng/mL for claudin-4 or claudin-5, respectively on the basis of the manufacturer's recommendation.

6. Statistical analysis

The data were double-entered into IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Data are expressed as mean ± standard deviation (SD) or standard error of the mean. Group differences were compared using a 2-sample *t*-test or Mann-Whitney *U*-test. Statistical significance was determined at $P < 0.05$.

RESULTS

1. Patients with asthma characteristics in high concentration of ozone

Clinical data of 50 asthma patients and 25 control subjects are presented, as previously described.[17,23] The clinical characteristics of high concentration of ozone group of 18 stable asthma patients (mean age ± SD, 53.8 ± 15.2 years), 18 patients with exacerbated asthma (mean age ± SD, 57.6 ± 13.0 years), and 3 control subjects (mean age ± SD, 68.9 ± 5.3 years) are summarized in Table 1. Initial FEV_1% predicted, FVC% predicted, and FEV_1/FVC values in patients with asthma were significantly lower than those in control subjects. Blood white blood cell proportions in patients of exacerbated asthma were significantly higher than in those in control subjects. Body mass index (BMI) did not vary between asthmatic patients and control subjects. The duration of asthma was 5.12 ± 3.22 years in asthmatic patients, and the exacerbation rate per year during follow-up was 6.96% ± 3.96%. FEV_1% predicted, FVC% predicted, and FEV_1/FVC were lower in exacerbated asthma than in stable asthma.

2. Alterations of claudin–4 levels in patients with asthma during high concentration of ozone

In our previously study,[23] the mean plasma claudin-4 levels were significantly higher in patients with stable (0.314 ± 0.044 ng/mL) and exacerbated (0.451 ± 0.061 ng/mL) asthma than in control subjects (0.166 ± 0.030 ng/mL). When ozone concentration was high, the mean plasma claudin-4 level was 0.44 ± 0.30 ng/mL in patients with exacerbated asthma and 0.38 ± 0.31 ng/mL in those with stable asthma, and that of healthy controls was 0.16 ± 0.1 ng/mL (Fig. 2A). Thus, in high concentration period of ozone, the plasma claudin-4 level were significantly higher in patients with stable and exacerbated asthma relative to those control subjects.

3. Alterations of claudin–5 levels in patients with asthma in high concentration of ozone

Our previous analysis of the plasma claudin-5 levels decreased in patients with stable asthma compared with those in control subjects, during exacerbation, claudin-5 levels were similar to those in

Table 1. Clinical characteristics of control subjects and patients with stable and exacerbated asthma when it is in high ozone concentrations

Characteristic	Control subjects	Asthma patients	
		Stable	Exacerbation
No. of subjects	3	18	18
Sex, male:female	0:3	6:12	8:10
Age of asthma onset (yr)	-	47 (20–73)	47 (23–74)
Asthma duration (yr)	-	5.12±3.22	6.63±3.61
Smoking, NS:ES:CS	3:0:0	13:3:2	9:6:3
Smoke amount, pack years	-	7.30±14.38	10.73±15.70
Body mass index (kg/m^2)	24.92 (23.24–27.39)	24.46 (20.89–30.36)	24.98 (20.31–30.36)
Lung function			
FEV_1 (% predicted)	125 (116–151)	79 (59–140)*	62 (22–83)*
FVC (% predicted)	106 (91–123)	82 (51–148)*	62 (26–81)*,†
FEV_1/FVC ratio	89 (81–92)	76 (62–87)*	68 (39–80)*
PC_{20} (mg/mL)	-	9.28±10.47	11.86±10.66
Total IgE (kU/L)	42.80±89.12	385.92±651.99	432.02±702.41
Atopy	0 (0)	6 (33.3)	8 (44.4)
Asthma attack frequency (yr)	-	3.44±3.25	3.90±3.24
Duration of exacerbation during follow-up (yr)	-	5.12±3.22	6.96±3.96
Blood WBC/μL	6,200 (5,820–7,000)	7,300 (3,600–13,200)	11,920 (4,700–14,460)*,†
Blood eosinophils (%)	2.20±1.30	4.29±5.00*	5.00±5.52*
Blood neutrophils (%)	64.1 (63.8–68.9)	51.9 (38.9–83.2)	65.4 (10.2–93.4)

Values are presented median (range), mean±standard deviation, or number (%).
NS, nonsmoker; CS, current smoker; ES, ex-smoker; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC_{20}, provocative concentration of methacholine causing a 20% fall in FEV_1; IgE, immunoglobulin E; WBC, white blood cell.
*P<0.01 compared with control subjects. †P<0.05 compared with patients with stable asthma.

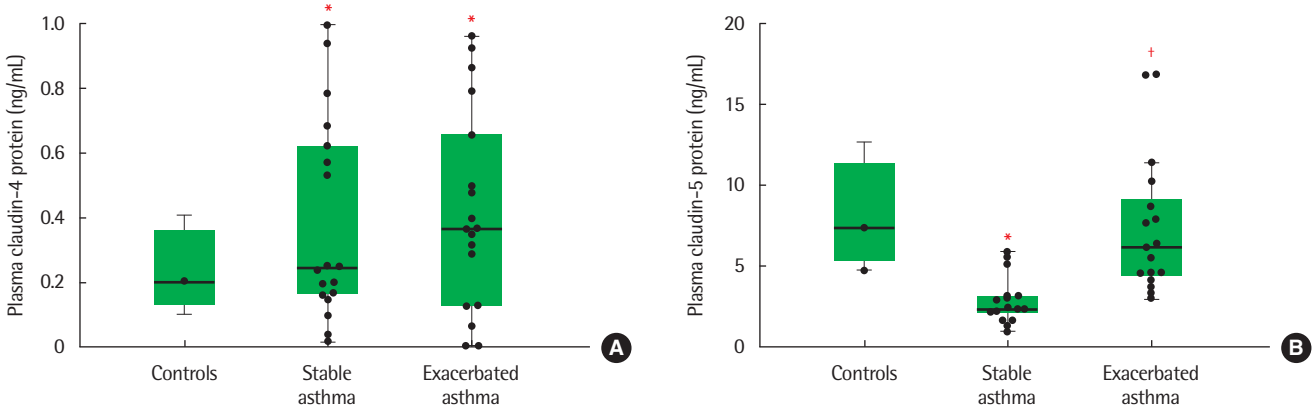

Fig. 2. Plasma claudin-4 (A) and claudin-5 (B) levels in control subjects (n=3), stable asthma patients (n=18), and exacerbated asthma patients (n=18) in high concentration of ozone. Values are presented as mean±standard deviation. *P<0.01 compared with control subjects. †P<0.01 compared with stable versus exacerbated asthma.

control subjects.[17] When ozone concentration was high, the mean plasma claudin-5 level was 7.49±4.23 ng/mL in patients with exacerbated asthma and 2.97±1.38 ng/mL in those with stable asthma (Fig. 2B) (P<0.05), and that of healthy controls was 6.92±3.9 ng/mL (Fig. 2B). Thus, the plasma claudin-5 level were lower in subjects with stable asthma than in control subjects and higher in subjects with exacerbated asthma than those with stable asthma.

DISCUSSION

Ozone exposure causes bronchoconstriction in humans and AHR in rodents and humans.[24,25] Mice and humans exposed to

ozone exhibit a dose-dependent increase in airway resistance to methacholine aerosol, as measured by invasive plethysmograph.[25] Chronic ozone exposure causes chronic lung inflammation, emphysema, and interstitial fibrosis, with progressive loss of lung function in humans and rodents.[26] Furthermore, ozone enhances the development of chronic lung diseases such as allergic and nonallergic asthma, COPD, and emphysema.[26] Our previous studies showed that ozone could induce airway obstruction in a concentration-dependent manner[27,28] and alveolar epithelial proliferation and nitric oxide synthase may be involved in airway obstruction in mice exposed to ozone.[27,28] Long-term ozone exposure increases the ratio of interleukin-4 to interferon-gamma in goblet cells, myofibroblasts, and smooth muscle cells, suggesting that prolonged ozone exposure leads to airway remodeling.[27-29]

In our study,[19] ROS, Nrf2, and Keap1 were increased in ozone-exposed mice and epithelial cells, suggesting that ozone can activate antioxidant mechanisms to alleviate ozone-induced toxic reactions in the lungs. Claudins might be involved in airway inflammation following ozone exposure, suggesting that ozone affects tight junction proteins, various claudins, proinflammatory cytokines, and ROS, which may result in tight junction barrier permeability, leading to AHR. The effects of ozone on bronchoconstriction and AHR raise the possibility that ozone may be involved in a specific type of asthma, namely the neutrophilic inflammatory phenotype.[30] However, the evidence linking neutrophilic asthma to ozone exposure as a constituent of pollution is unclear, although exacerbation of asthma following a peak increase in levels of environmental ozone has been reported.[31] In our study, patients with exacerbated asthma had higher levels of leukocytes than those with stable state asthma, suggesting that neutrophils may be involved in airway inflammation following ozone exposure.

The integrity of the epithelial barrier depends on TJs and AJs, which insure apicobasal cell polarity, but also on mucus, fluid, and function of the cilia.[11,32] Tight junction proteins such as the claudin family, occludin, and tricellulin and several scaffolding proteins, such as zonula occludens (ZO)-1, ZO-2, ZO-3, and multi-PDZ (PSD95/DLG1/ZO-1) domain protein 1 have been identified in the TJs.[33,34] E-cadherin, as well as TJs, were reduced in patients with asthma.[35] The epithelial barrier disintegrates not only in the lower airways of patients with asthma[11] but also in the nasal mucosa in allergic rhinitis due to house dust mites,[35] leading to reduced occludin and ZO-1 levels. Ozone exposure disrupts TJ proteins and the functioning of the respiratory barrier.[19,36]

The mean plasma claudin-5 level was higher in exacerbated COPD patients than in patients with stable COPD.[37] The plasma claudin-5 levels of COPD subjects were correlated with the amount of smoking and forced expiratory volume in one second (FEV_1%, predicted).[37] The average ground-level ozone concentration in Gyeonggi-do, South Korea, was obtained for 2006–2014 from the Gyeonggi-do Meteorological Agency. Ozone concentration was higher in June, July, and August than in other months. The authors recruited control subjects and asthmatics during same period.

In our study, plasma claudin-4 levels were significantly higher in exacerbated asthma patients compared to stable asthmatic patients and control subjects. Plasma claudin-5 levels were decreased in patients with stable asthma compared to controls and were increased in those with exacerbated asthma compared to stable asthma patients. We reported that plasma claudin-5 levels decreased in patients with stable asthma compared with those in control subjects, suggesting that asthma therapy can decrease plasma claudin-5 levels.[17] In this study we have analyzed claudin-4 and claudin-5 level relating to ozone concentration can be a factor affecting exacerbation of asthma. Although, the authors did not ozone concentration with serial monitoring for patients with asthma during daily life, therefore this result suggests indirect reflection for ozone effect on circulating claudins in patients with asthma. Growing evidence indicates that exposure to air pollution contributes to obesity and cardiometabolic disease risk in adults. Higher exposure to regional air pollutants was associated with higher fasting serum lipid measures. These associations were more pronounced in obese participants, suggesting that obesity may exacerbate the effects of air pollution exposure on lipid levels in young adults.[38] Diesel exhaust particle (DEP)-exposed obese mice group had increased airway responses and inflammation compared to the DEP-exposed nonobese group, indicating that diesel particulates and obesity may be cocontributors to asthma.[39] In our study, although BMI did not differ between asthmatic patients and control subjects, Further studies would be needed to clarify association of BMI and ozone level in many patients with asthma.

In conclusion, ozone is one of the pollutants contributing to asthma exacerbation, and claudins may be involved in airway inflammation following ozone exposure in patients with asthma.

REFERENCES

1. Lee KY, Wu SM, Kou HY, Chen KY, Chuang HC, Feng PH, et al. Associ-

ation of air pollution exposure with exercise-induced oxygen desaturation in COPD. Respir Res 2022;23:77.
2. Albano GD, Gagliardo RP, Montalbano AM, Profita M. Overview of the mechanisms of oxidative stress: impact in inflammation of the airway diseases. Antioxidants (Basel) 2022;11:2237.
3. Wiegman CH, Michaeloudes C, Haji G, Narang P, Clarke CJ, Russell KE, et al. Oxidative stress-induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2015;136:769-80.
4. Acute Respiratory Barrier Disruption by Ozone Exposure in Mice. Acute respiratory barrier disruption by ozone exposure in mice. Front Immunol 2019;10:2169.
5. Patial S, Saini Y. Lung macrophages: current understanding of their roles in ozone-induced lung diseases. Crit Rev Toxicol 2020;50:310-23.
6. Roberts RA, Smith RA, Safe S, Szabo C, Tjalkens RB, Robertson FM. Toxicological and pathophysiological roles of reactive oxygen and nitrogen species. Toxicology 2010;276:85-94.
7. Liu Y, Pan J, Zhang H, Shi C, Li G, Peng Z, et al. Short-term exposure to ambient air pollution and asthma mortality. Am J Respir Crit Care Med 2019;200:24-32.
8. Shah PL, Herth FJ, van Geffen WH, Deslee G, Slebos DJ. Lung volume reduction for emphysema. Lancet Respir Med 2017;5:47-56.
9. Georas SN, Rezaee F. Epithelial barrier function: at the front line of asthma immunology and allergic airway inflammation. J Allergy Clin Immunol 2014;134:509-20.
10. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. J Allergy Clin Immunol 2014;134:499-507.
11. Price ME, Sisson JH. Redox regulation of motile cilia in airway disease. Redox Biol 2019;27:101146.
12. Rothenberg ME, Saito H, Peebles RS Jr. Advances in mechanisms of allergic disease in 2016. J Allergy Clin Immunol 2017;140:1622-31.
13. Soini Y. Claudins in lung diseases. Res Res 2011;12:70.
14. Kage H. Claudin heterogeneity and control of lung tight junctions. Annu Rev Physiol 2013;75:551-67.
15. Jin W, Rong L, Liu Y, Song Y, Li Y, Pan J. Increased claudin-3, -4 and -18 levels in bronchoalveolar lavage fluid reflect severity of acute lung injury. Respirol 2013;18:643-51.
16. Lappi-Blanco E, Lehtonen ST, Sormunen R, Merikallio HM, Soini Y, Kaarteenaho RL. Divergence of tight and adherens junction factors in alveolar epithelium in pulmonary fibrosis. Hum Pathol 2013;44:895-907.
17. Moon KY, Lee PH, Kim BG, Park CS, Leikauf GD, Jang AS. Claudin 5 in a murine model of allergic asthma: its implication and response to steroid treatment. J Allergy Clin Immunol 2015;136:1694-6.e5.
18. Kaarteenaho R, Soini Y. Claudin-1, -2, -3, -4, -5, and -7 in usual interstitial pneumonia and sarcoidosis. J Histochem Cytochem 2009;57:187-95.
19. Kim BG, Lee PH, Lee SH, Park CS, Jang AS. Impact of ozone on claudins and tight junctions in the lungs. Environ Toxicol 2018;33:798-806.
20. Becker AB, Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. Curr Opin Allergy Clin Immunol 2017;17:99-103.
21. Yeo MJ, Kim YP. Long-term trends of surface ozone in Korea. J Clean Prod 2021;294:125352.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
23. Lee PH, Kim BG, Lee SH, Lee JH, Park SW, Kim DJ, et al. Alteration in claudin-4 contributes to airway inflammation and responsiveness in asthma. Allergy Asthma Immunol Res 2018;10:25-33.
24. Sokolowska M, Quesniaux VFJ, Akdis CA, Chung KF, Ryffel B, Togbe D. Acute respiratory barrier disruption by ozone exposure in mice. Front Immunol 2019;10:2169.
25. Kong X, Bennett WC, Jania CM, Chason KD, German Z, Adouli J, et al. Identification of an ATP/P2X7/mast cell pathway mediating ozone-induced bronchial hyperresponsiveness. JCI Insight 2021;6:e140207.
26. Mumby S, Chung KF, Adcock IM. Transcriptional effects of ozone and impact on airway inflammation. Front Immunol 2019;10:1610.
27. Michaudel C, Mackowiak C, Maillet I, Fauconnier L, Akdis CA, Sokolowska M, et al. Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33. J Allergy Clin Immunol 2018;142:942-58.
28. Lee PH, Park S, Lee YG, Choi SM, An MH, Jang AS. The impact of environmental pollutants on barrier dysfunction in respiratory disease. Allergy Asthma Immunol Res 2021;13:850-62.
29. Cho HY, Jedlicka AE, Chang FH, Marzec J, Bauer AK, Kleeberger SR. Transcriptomics underlying pulmonary ozone pathogenesis regulated by inflammatory mediators in mice. Antioxidants (Basel) 2021;10:1489.
30. Chung KF. Neutrophilic asthma: a distinct target for treatment? Lancet Respir Med 2016;4:765-7.
31. Madani NA, Carpenter DO. Patterns of emergency room visits for respiratory diseases in New York State in relation to air pollution, poverty and smoking. Int J Environ Res Public Health 2023;20:3267.
32. Ivanov AI, Naydenov NG. Dynamics and regulation of epithelial adherens junctions: recent discoveries and controversies. Int Rev Cell Mol Biol 2013;303:27-99.
33. De Benedetto A, Rafaels NM, McGirt LY, Ivanov AI, Georas SN, Cheadle C, et al. Tight junction defects in patients with atopic dermatitis. J Allergy Clin Immunol 2011;127:773-86.e1-7.
34. Sugita K, Steer CA, Martinez-Gonzalez I, Altunbulakli C, Morita H, Castro-Giner F, et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. J Allergy Clin Immunol 2018;141:300-10.e11.
35. Wawrzyniak P, Wawrzyniak M, Wanke K, Sokolowska M, Bendelja K, Rückert B, et al. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients. J Allergy Clin Immunol 2017;139:93-103.
36. Tan HT, Hagner S, Ruchti F, Radzikowska U, Tan G, Altunbulakli C, et al. Tight junction, mucin, and inflammasome-related molecules are differentially expressed in eosinophilic, mixed, and neutrophilic experimental asthma in mice. Allergy 2019;74:294-307.
37. Kim BG, Lee PH, Lee SH, Baek AR, Park JS, Lee J, et al. Impact of the endothelial tight junction protein claudin-5 on clinical profiles of patients with COPD. Allergy Asthma Immunol Res 2018;10:533-42.
38. Kim JS, Chen Z, Alderete TL, Toledo-Corral C, Lurmann F, Berhane K, et al. Associations of air pollution, obesity and cardiometabolic health in young adults: the Meta-AIR study. Environ Int 2019;133(Pt A):105180.
39. Moon KY, Park MK, Leikauf GD, Park CS, Jang AS. Diesel exhaust particle-induced airway responses are augmented in obese rats. Int J Toxicol 2014;33:21-8.