EAAS 1: Climate change, air pollution and allergy

Claudins as airway cell barrier contribute to airway inflammation in asthma following air pollutants exposure

Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea

An Soo Jang

The lung is continuously exposed to a variety of allergens as well as to exogenous environmental insults such as air pollutants, viruses, and thus, the innate and adaptive immune response plays a critical role in protecting the pulmonary system from asthma (1). Many structural cells containing epithelial cells and endothelial cells involved in this immune response.

Allergic inflammation develops in tissues that have large epithelial surface areas that are exposed to the environment, such as the lung, skin and gut (2). Barrier dysfunction in the lung and skin allows allergens to activate the epithelium and produce cytokines that are permissive for the induction and development of T helper type 2 responses, such as interleukin-33 (IL-33)(3-5).

Tight junctions act as a semipermeable barrier (or gate) to the paracellular transport of ions, solutes and water, as well as cells, and are considered to function as a fence that divides apical and basolateral domains of plasma membranes (1, 6). In addition, like other cell-cell and cell-extracellular matrix junctions (7), tight junctions coordinate a variety of signaling and trafficking molecules regulating cell differentiation, proliferation and polarity, there by serving as multifunctional complex (7-9). These functions of tight junctions are critical for epithelial and endothelial cell sheets to establish distinct tissue compartments within the body and maintain homeostasis. Cell-cell junctions not only function as the sites of attachment between epithelial and endothelial cells but also serve as signaling structures that communicate cell position, limit growt and apoptosis, and regulate vascular homeostasis (10, 11).

Claudins are structural molecules of tight junctions. There are 27 claudins known, and expression of different claudins is responsible for changes in the electrolyte and solute permeability in cells layers (12). Claudins 1, 3, 4, 5, 7, 8 and 18 are expressed in human bronchi and bronchioles (13-17). An integral membrane protein, Claudin 5 (CLDN5), is a critical component of endothelial tight junctions that control

pericellular permeability. CLDN5, while expressed weakly in the epithelium, is expressed strongly in endothelium of normal lung and is intense in endothelium in usual interstitial pneumonia (18).

Ambient ozone is a common environmental air pollutant with considerable impact on public health. Ozone significantly contributes to both human morbidity and mortality, accounting for an estimated 800 premature deaths, 4,500 hospital admissions, and 900,000 school absences annually (19). Ozone inhalation has been shown to cause airway inflammation, epithelial injury, and reduced lung function in both animal and human studies (20). Ozone is highly reactive and oxidizes proteins and lipids in the fluid-lined compartment of the lung. This initiates inflammation and increases lung permeability through cytotoxic mediators, including pro-inflammatory cytokines and reactive oxygen and nitrogen intermediates such as peroxynitrite (21-22). Distal structures of the lung, including the terminal bronchioles, the bronchiole-alveolar duct junction, and the proximal alveolar regions, are considered the primary targets of ozone (23).

Ozone is a ubiquitous urban air pollutant known to cause damage to the alveolar epithelium (19). Epidemiological data indicate that individuals with chronic inflammatory diseases, such as asthma or chronic obstructive pulmonary disease, are hypersensitive to ozone, exhibiting increased morbidity and mortality (24, 25). Acute inhalation of ozone causes structural alterations in the lung, including disruption of the alveolar epithelial barrier that leads to alveolar epithelial type II cell hypertrophy and hyperplasia. Recruitment of inflammatory cells into the lung following ozone exposure presents another risk for tissue damage through the release of toxic mediators from activated macrophages and neutrophils, including cytokines, reactive oxygen and nitrogen species, and proteolytic enzymes (20). Although ozone-induced inflammation and oxidative stress in alveolar epithelial regions of the lung have been well characterized, the response of epithelial cells in the terminal bronchioles is poorly understood. As airway function is known to be altered by low-level ozone exposure, it seems likely that injury to the bronchiolar epithelium is important in the pathogenic response to this pulmonary irritant (26).

The connection between air pollutants and barrier function and the impact of the PM on asthma development has not been studied thoroughly. So far, PM-induced disruption of barrier function in a bronchial epithelial cell line and blood in patients with asthma have been not reported. Although there is some evidence of epithelial barrier dysfunction in asthma (27, 28), it is still not clear whether PM may have an influence on TJ in asthma.

However, there is few data on the role of CLDNs in the lung following ozone and PM exposure. In this study, we hypothesized that ozone and PM exposure would differentially affect CLDNs including CLDN3, CLDN4, CLDN5, CLDN7, and CLDN14 in the lung tissue of ozone and PM exposure mouse model, and primary human lung epithelial cells. And its antioxidant genes Nrf2, Keap1, reactive oxygen species, and cytokines concentration such as IL-1β, IL-18, TNF-α and IL-4 involved in pathogenesis of this mechanism. Moreover, we also determined the levels of CLDN4, CLDN5, CLDN7 levels in blood from asthmatic patients compared with healthy controls.

References

1. Dejana E. Endothelial cell-cell junction: happy together. Nat Rev Mol Cell Biol 2004;5:261-70.
2. Islam SA, Luster AD. T cell homing to epithelial barriers in allergic disease. Nat Med 2012;18:705-15.
3. Cookson, W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nat Rev Immunol 2004;4:978-88.
4. Eiwegger, T. & Akdis, C.A. IL-33 links tissue cells, dendritic cells and Th2 cell development in a mouse model of asthma. Eur J Immunol 2011;41:1535-8.
5. Hammad, H. etal.HousedustmiteallergeninducesasthmaviaToll-likereceptor4triggeringofairwaystructuralcells. Nat Med 2009;15,410-6.
6. S. Tsukita, M. Furuse and M. Itoh, Multifunctional strands in tight junctions. Nat Rev Mol Cell Biol 2001;2: 285-93.
7. Chen X, Gumbiner BM. Crosstalk between different adhesion molecules. Curr Opin Cell Biol 2006;18:572-8.
8. Schneeberger EE,Lynch RD, The tight junction: a multifunctional complex. Am J Physiol Cell Physiol 2004; 286:C1213-C28.
9. Ivanov AI, Nusrat A, Parkos CA. Endocytosis of the apical junctional complex: mechanisms and possible roles in regulation of epithelial barriers. Bioessays 2005;27:356-65.
10. Dejana E. Endothelial cell-cell junction: happy together. Nat Rev Mol Cell Biol 2004;5:261-70.
11. Piontek J, Fritzsche S, Cording J, Richter S, Hartwig J, Walter M, et al. Elucidating the principles of the molecular organization of heteropolymeric tight junction strands. Cell Mol Life Sci 2011;68:3903-18.
12. Soini Y. Claudins in lung diseases. Res Res 2011;12:70
13. Coyne CB, Gambling TM, Boucher RC, Carson JL, Johnson LG: Role of claudin interactions in airway tight junctional permeability. Am J Physiol Lung Cell Mol Physiol 2003;285:L1166-78.
14. Mazzon E, Cuzzocrea S: Role of TNF-alpha in lung tight junction alteration in mouse model of acute lung inflammation. Respir Res 2007;8:75.
15. Daugherty BL, Mateescu M, Patel AS, Wade K, Kimura S, Gonzales LW, Guttentag S, Ballard PL, Koval M: Developmental regulation of claudin localization by fetal alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 2004; 287:L1266-73.
16. Kaarteenaho R, Merikallio H, Lehtonen S, Harju T, Soini Y: Divergent expression of claudin -1, -3, -4, -5 and -7 in developing human lung. Respir Res 2010; 11:59.
17. Kaarteenaho-Wiik R, Soini Y: Claudin-1, -2, -3, -4, -5, and -7 in usual interstitial pneumonia and sarcoidosis. J Histochem Cytochem 2009; 57:187-95.
18. Kaarteenaho-Wiik 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. Al-Hegelan M, Robert MT, Christian C, John WH. Ambient ozone and pulmonary innate immunity. Immunol Res 2011;49:173-91.
20. Uysal N, Schapira RM. Effects of ozone on lung function and lung diseases. Curr Opin Pulm Med 2003;9: 144-50.
21. Laskin DL, Fakhrzadeh L, Laskin JD. Nitric oxide and peroxynitrite in ozone-induced lung injury. Adv Exp Med Biol. 2001;500:183-90.
22. Roberts RA, Laskin DL, Smith CV, Robertson FM, Allen EMG, Doorn JA, et al. Nitrative and oxidative stress in toxicology and disease. Toxicol Sc 2009;112:4-16.
23. Laskin DL, Sunil VR, Gardner CR, Laskin JD. Macrophages and tissue injury: Agents of defense or destruction? Annu Rev Pharmacol Toxico 2011;51:267-88.
24. Desqueyroux H, Pujet JC, Prosper M, Le Moullec Y, Momas I. Effects of air pollution on adults with chronic obstructive pulmonary disease. Arch Environ Health 2002;57:554-60.

25. Zanobetti A, Schwartz J. Ozone and survival in four cohorts with potentially predisposing diseases. Am J Respir Crit Care Med 2011;184:836-41.
26. Sunil VR, Vayas KN, Massa CB, Gow AJ, Laskin JD, Laskin DL. Ozone-Induced Injury and Oxidative Stress in Bronchiolar Epithelium Are Associated with Altered Pulmonary Mechanics. Toxicol Sci 2013;133:309-19.
27. Sweerus K, Lachowicz-Scroggins M, Gordon E et al. Claudin-18 deficiency is associated with airway epithelial barrier dysfunction and asthma. J Allergy Clin Immunol 2016;139:72-81.e1.
28. 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.