Editorial
Allergy Asthma Immunol Res. 2018 January;10(1):4-5.
https://doi.org/10.4168/aair.2018.10.1.4
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Claudin may be a Potential Biomarker for Epithelial Barrier Dysfunction in Asthma

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Asthma is a chronic inflammatory disorder of the airway, which is associated with interactions between the airway epithelium and inhaled substances from the environment including allergens, microbes, pollutants, and tobacco smoke.[1] Epithelial cells form a barrier against the outside environment and the epithelium has airway surface fluids, mucus, and apical junctional complexes between neighboring cells.[2] The epithelial barrier has physical, chemical, and immunological protective mechanisms with innate immunological mechanisms to maintain barrier homeostasis and minimize inflammation.[3]

It has been shown that airway epithelial cells have important roles in the pathogenesis of asthma.[1] In asthmatic patients, epithelial injury with disruption of tight junction proteins has been confirmed using bronchial biopsy specimens.[4] Functional studies using epithelial cultures have demonstrated increased permeability and sensitivity to environmental and oxidative stresses in asthmatic patients,[5,6] which may promote allergic sensitization and reduce the threshold for epithelial damage and activation of a type 2 response.[7,8] To our knowledge, few studies exist linking epithelial dysfunction to asthma severity and exacerbation. Xiao *et al.*[9] reported that the barrier function was reduced with significantly lower transepithelial electrical resistance in moderate to severe asthma patients. Bronchial epithelial cells from asthmatic patients responded abnormally to viral infections as the main triggers of asthma exacerbation which may potentiate airway inflammation.[10,11]

Tight junctions and adherens junctions are macromolecular complexes that bind together in the intercellular space and have intracytoplasmic protein-to-protein interactions. Tight junctions consist of various proteins including occludin, claudin, tricellulin, and junctional adhesion molecules. Claudins are core tight junction proteins expressed in a tissue and cell type selective manner and interact in the extracellular space.[2,12] Currently, 27 claudins are known to be expressed in humans. Claudins 1, 3, 4, 5, 7, 8, and 18 are expressed in human bronchial regions and bronchioles. Four major claudins (3, 4, 7, 18) are expressed in lung epithelial cells.[12-14] Sweers *et al.*[15] demonstrated that claudin 18 levels are reduced in patients with asthma and knockdown of claudin 18 increased epithelial permeability. Claudin 4 has been shown to serve as a selective sodium barrier or as a barrier-forming claudin.[16,17] Although several reports have been published suggesting the potential role of claudin in other lung diseases, including acute respiratory distress syndrome and lung cancer,[18,19] the role of claudin 4 in patients with asthma is not clear. In the current issue of *Allergy, Asthma and Immunology Research*, Lee *et al.*[20] report a role of claudin 4 in the airway inflammation of asthma. In particular, the authors observed significantly higher plasma levels of claudin 4 in asthmatic patients than in controls, which further increased during asthma exacerbation. A negative correlation was found between claudin 4 levels and FEV1 (%). In addition, they demonstrated the functional role of claudin 4 and the effect of steroid treatment using a mouse model of allergic asthma. These findings suggest that claudin 4 may be a potential biomarker to predict the severity of airway inflammation in asthmatic patients. Regulation of claudin 4 may be a new therapeutic target for asthma.

In conclusion, epithelial barrier dysfunction via claudin 4 may be associated with airway inflammation. Further studies are needed to investigate the exact mechanisms how claudins contribute to airway inflammation and exacerbation.

ACKNOWLEDGMENTS

This work was supported by KHIDI funded by the Ministry and Health & Welfare, Republic of Korea (HI16C0992).

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Received: September 5, 2017; Accepted: September 21, 2017
• There are no financial or other issues that might lead to conflict of interest.

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