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EPITHELIAL SIGNATURES IN RESPIRATORY DISEASE

Akademisk avhandling
Som för avläggande av Medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i sal Europa,
Konferenscentrum Wallenberg, Medicinaregatan 20 Göteborg, den 16 december 2021,
klockan 9.00.

av Elisabeth Ax

Fakultetsopponent:
Irene Heijink, Prof. Dr.
University of Groningen, Nederländerna

Avhandlingen baseras på följande delarbeten

I. Jevnikar, Z., Östling, J., Ax, E., Calvén, J., Thörn, K., Israelsson, E., Öberg, L., Singhania, A., Lau, L.C.K., Wilson, S..J, Ward, J.A., Chauhan, A., Sousa, A.R., De Meulder, B., Loza, M.J., Baribaud, F., Sterk, P.J., Chung, K.F., Sun, K., Guo, Y., Adcock, I.M., Payne, D., Dahlén, B., Chanez, P., Shaw, D.E., Krug, N., Hohlfeld, J.M., Sandström, T., Djukanovic, R., James, A., Hinks, T.S.C., Howarth, P.H., Vaarala, O., van Geest, M. & Olsson, H.; Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes study group, 2019, Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation, Journal of Allergy and Clinical Immunology

II. Ax, E., Jevnikar, Z., Cvjetkovic, A., Malmhäll, C., Olsson, H., Rådinger, M. & Lässer, C., 2020, T2 and T17 cytokines alter the cargo and function of airway epithelium-derived extracellular vesicles, Respiratory Research

III. Ax, E., Weidner, J., Winslow, S., Lässer, C., Jevnikar, Z., Olsson, H. & Rådinger, M., Th17 cytokines mediate airway epithelial barrier dysfunction – A possible role for miRNAs, In manuscript

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Abstract
The human airway epithelium protects us against harm and helps maintain immune homeostasis. In respiratory diseases such as asthma and COPD, the functions of the epithelium are altered and can cause or contribute to disease progression. Moreover, the type of airway inflammation, or endotype, can differ between individuals. Not all patients respond to currently available treatments, therefore an increased understanding of these endotypes can be used to develop novel treatments and biomarkers.

In this thesis, responses of the airway epithelium in different inflammatory environments are investigated using a primary cell-based model system. Three levels of epithelial signatures are established; gene expression, extracellular vesicle proteome, and miRNA expression. In Paper I, a subtype of asthma patients with increased activation of IL-6 trans-signaling in airway epithelium is identified. These patients demonstrate increased inflammation, epithelial barrier damage, and higher incidence of asthma exacerbations. This suggests that these patients could benefit from blocking of the IL-6 trans-signaling pathway. In Paper II, the proteomes of extracellular vesicles from epithelial cells stimulated with T2 and Th17 cytokines show differences in proteins related to airway disease-relevant processes. This is exemplified through the ability of vesicles released under Th17 inflammatory conditions to promote neutrophil migration. These findings enhance the knowledge about the contribution of epithelial extracellular vesicles in airway disease. In Paper III, Th17 cytokines are shown to disrupt the airway epithelial barrier and induce the expression of miRNAs predicted to target barrier-related genes. Two miRNAs are identified as possible candidates that cause decreased levels of mRNAs encoding barrier-forming proteins. This highlights the role of miRNAs as master regulators of expression of proteins involved in important airway epithelial functions.

Altogether, these studies show the fine-tuned responses of the airway epithelium in possible inflammatory endotypes. The results contribute to the understanding of endotype-specific processes local to the airways. Increased knowledge of these processes will enable further research that ultimately will improve the lives of patients with respiratory disease.

Keywords: airway epithelium, inflammation, gene expression, extracellular vesicles, miRNA

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