RESEARCH AREA II
HIGHLIGHT

01
TITLE OF THE WORK

Deciphering the pathophysiological significance of serine peptidase inhibitor gene variants in asthma.

02
SOME BACKGROUND

Bronchial asthma is a chronic inflammatory airway disease caused by a complex interaction between an individual's genetic make-up, the environment and most likely the airway microbiota. During the last years, gene variants have been identified which are suspected to be associated with a manifestation of asthma. These genes, also known as asthma susceptibility genes, i.a. include two serine protease inhibitors (serpins): spink5 and scca1. But not every person carrying an altered gene variant develops asthma. It is a tight interaction between the genetic predisposition and noxa such as cigarette smoke or allergens which lead to the onset of the disease. Furthermore, recent studies discovered an additional putative risk factor: the bacterial composition of the airway microbiome. To shed some light on this complexity is the aim of our work.

03
WHAT DID SCIENTISTS DISCOVER?

To decipher the functional role of the networks, we modified both serpin genes in *Drosophila melanogaster* thus mimicking the situation of human carriers of variants in these genes. Of note, both serpins are expressed in airway epithelial cells of human. First results demonstrate that variation of ssca1 affects airway growth thereby leading to a decreased tolerance of hypoxia. The investigation of more relevant environmental exposures such as cigarette smoke are currently planned.
For the first time, we were able to show that the airways of wild-caught flies possess a microbial colonization. Since it is known that an altered airway microbiome may be a feature of asthma, we now ask whether variants of both serpin genes are involved in shaping the airway microbiota.

04
WHY IS IT IMPORTANT?

To understand the impact of genetic, environmental and microbiotic factors on our airway epithelium and their interdependence would contribute significantly to the comprehension of asthma pathogenesis. And an early cognition of these risk factors could contribute to an alleviation in the disease's progress, it could antagonize exacerbation, or even prevent a manifestation of the disease.

05
WHO DID THE RESEARCH?

Hanna Angstmann [a]
Christina Wagner [a]
Stephan Pfeifer [b]
Susanne Kublik [b]
Johannes Bischof [c]

[a] – Division of Invertebrate Models, Priority Research Area Asthma & Allergy, Research Center Borstel, Germany

[b] – Research Unit Comparative Microbiome Analysis, German Research Center for Environmental Health, Helmholtz Zentrum München

[c] – Institute of Molecular Life Sciences, University of Zurich

06
WHY DID THEY CHOOSE THE DESCRIBED METHODS?

Elucidation of molecular mechanisms underlying the pathophysiological alterations of the airway epithelium due to serpin dysregulation in combination with environmental and microbiotic aspects can only succeed in a model organism. *Drosophila* allows genetic manipulations constricted to the respiratory epithelium. And furthermore, it is ideally suited to study the pathophysiology of the airway epithelium.

07
DETAILS FOR SCIENTISTS – PUBLICATION

Karaaslan C., Birben E., Keskin O., Sahiner U., Sackesen C., Kalayci O. (2013) The role of SCCA1 in asthma related physiological events in the airway epithelium and the effect of promoter variants on asthma and gene function, Respiratory Medicine, 107: 368-379.

Kabesch M., Carr D., Weiland S. K., Von Mutius E. (2004) Association between polymorphisms in serine protease inhibitor, kazal type 5 and asthma phenotypes in a large German population sample, Clin Exp Allergy, 34 (3): 340-345.

Hilty M., Burke C., Pedro H., Cardenas P., Bush A., et al. (2010) Disordered Microbial Communities in Asthmatic Airways. PLoS ONE, 5(1): e8578.