UKE Paper of the Month Juni 2020

A prenatally disrupted airway epithelium orchestrates the fetal origin of asthma in mice

Dimitra E Zazara, Michael Wegmann, Anastasios D Giannou, Alexandra Maximiliane Hierweger, Malik Alawi, Kristin Thiele, Samuel Huber, Maike Pincus, Ania C Muntau, Maria Emilia Solano*, Petra C Arck*
** equally contributing senior authors*

J Allergy Clin Immunol. 2020; S0091-6749(20)30335-3.

ABSTRACT:

Background: Prenatal challenges such as maternal stress perception increase the risk and severity of asthma during childhood. However, insights into the trajectories and targets underlying the pathogenesis of prenatally triggered asthma are largely unknown. The developing lung and immune system may constitute such targets.
Objective: Here we have aimed to identify the differential sex-specific effects of prenatal challenges on lung function, immune response, and asthma severity in mice.
Methods: We generated bone marrow chimeric (BMC) mice harboring either prenatally stress-exposed lungs or a prenatally stress-exposed immune (hematopoietic) system and induced allergic asthma via ovalbumin. Next-generation sequencing (RNA sequencing) of lungs and assessment of airway epithelial barrier function in ovalbumin-sensitized control and prenatally stressed offspring was also performed.
Results: Profoundly enhanced airway hyperresponsiveness, inflammation, and fibrosis were exclusively present in female BMC mice with prenatally stress-exposed lungs. These effects were significantly perpetuated if both the lungs and the immune system had been exposed to prenatal stress. A prenatally stress-exposed immune system alone did not suffice to increase the severity of these asthma features. RNA sequencing analysis of lungs from prenatally stressed, non-BMC, ovalbumin-sensitized females unveiled a deregulated expression of genes involved in asthma pathogenesis, tissue remodeling, and tight junction formation. It was also possible to independently confirm a tight junction disruption. In line with this, we identified an altered perinatal and/or postnatal expression of genes involved in lung development along with an impaired alveolarization in female prenatally stressed mice.
Conclusion: Here we have shown that the fetal origin of asthma is orchestrated by a disrupted airway epithelium and further perpetuated by a predisposed immune system.

STATEMENT:

In this work, we demonstrate that a dysfunctional airway epithelium rather than a predisposed immune system determines the fetal origin of asthma in mice in a sex-specific manner. Our study pinpoints the mechanisms underlying the well-reported association of prenatal maternal stress with an increased risk for childhood asthma thereby providing insights into the fetal programming of the disease. Early detection of potential aberrations in lung development, which may subsequently lead to postnatal lung dysfunction and disease, will allow to design efficient prediction and prevention strategies.

BACKGROUND:

This work was performed at the Laboratory for Experimental Feto-Maternal Medicine under the supervision of Prof. Dr. Petra Arck and PD Dr. Maria Emilia Solano, in close collaboration with scientists from Hamburg, Borstel and Berlin. It was part of the PhD thesis of Dr. Dimitra Zazara, who is supported by a clinician scientist scholarship awarded by the Medical Faculty of the University of Hamburg. This work was funded by the German Research Foundation (KFO296, AR232/25-2 and SO1413/1-2) and State Research Funding - FV45, Authority for Science, Research and Equality, Hanseatic City of Hamburg, Germany.