Oral Abstract Session 2

Revelatory Insights for Mechanisms of Asthma

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OAS-12

An Inhaled Formulation of IGFBP-3 Peptide Attenuates Severe Neutrophilic Bronchial Asthma

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The pulmonary system has been used to deliver pharmacologically active compounds to the body. Small synthetic molecule-based therapies are commonly prescribed for chronic airway disorders such as asthma and chronic obstructive pulmonary disease (COPD). However, the small molecules are often extremely durable thus they can have side effects in other organs until metabolized by the liver and/or cleared by the kidney. For many peptides/proteins, an inability to cross the respiratory epithelium after inhaled delivery may be advantageous as it would result in a high ratio of lung to systemic bioavailability and thus would reduce off-target effects. Insulin-like growth factor binding protein 3 (IGFBP-3) blocks critical physiologic manifestations of asthma. However, there is little information on the efficacy of an inhaled IGFBP-3 peptide in severe neutrophilic asthma. In this study, we have found that the mice sensitized with OVA and LPS and then challenged with OVA (OVALPS-OVA mice) mice showed the typical features of neutrophilic asthma. Interestingly, intratracheal administration of recombinant human IGFBP-3 substantially attenuated the increases in the expression of ER markers, the pro-inflammatory cytokines, airway inflammation, and bronchial hyperresponsiveness. The administration of 4-PBA also reduced all increased parameters significantly in the lung of OVALPS-OVA mice. These findings suggest that the pharmacologic effects of the inhaled IGFBP-3 peptide on the neutrophilic asthmatic features are via the modulation of ER stress in the lung, providing the novel therapeutic target for severe neutrophilic asthma.

Key Words: Severe asthma, IGFBP-3, ER stress

OAS-13

The Impact of Claudin 5 and SOX18 on Asthma and COPD

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Background: The tight junction protein, claudin 5 (CLDN5) is critical to the control of endothelial cellular polarity and pericellular permeability. SOX-18 as an essential regulator of endothelial claudin-5 expression, as well as barrier function, blood vessel development and endothelial barrier integrity as well as in wound healing processes. However, the impact of Claudin 5 and SOX18 in bronchial asthma and COPD remains to be determined.
Methods: Fifty patients with Asthma (mean age: ±years) and thirty patients with COPD (mean age: ±years) and 25 healthy controls were enrolled to the study. Plasma CLDN5 and SOX18 level was checked in both stable and exacerbated state of patients with asthma and COPD.
Results: Claudin 5 and SOX18 in blood from exacerbated asthmatics was increased compared with those from stable asthmatics. Comparison analysis was done in patients from increase in CLDN5 and SOX18 levels from exacerbated state compared to stable state. CLDN5 was correlated with SOX18, and FEV1% predicted. SOX18 was correlated with FEV1% predicted in asthma. The ROC curves of CLDN5 and SOX18 levels differed between asthma patients and controls (AUC=0.939 and 0.840). On the other hand, the mean plasma CLDN5 and SOX18 level of patients with COPD tended to be different respectively. Although the levels of CLDN5 decreased compared to control subjects, the levels of SOX18 increased. SOX18 correlated with smoke amount and FEV1/FVC in COPD. The ROC curves of Cldn5 and SOX18 levels differed between COPD patients and controls (AUC=0.810 and 0.727).
Conclusion: Claudin 5 and SOX18 may be implicated in the pathogenesis of asthma and COPD.

Key Words: Tight junction, Claudin 5, SOX18

OAS-14

Dysregulation of Sphingolipid Metabolites Identified by Untargeted Metabolomics in Patients with AERD

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Background: Patients with aspirin exacerbated respiratory disease (AERD) are known to have poor prognosis. Metabolomics approaches allow biomarker discovery and identification of disease mechanism. This study was aimed to investigate the causal pathway of AERD using untargeted metabolomics approach.
Method: A total of 36 AERD and 38 aspirin tolerant asthma (ATA) patients were enrolled. Untargeted metabolomics profile data were generated using UHPLC/Q-ToF MS system. Balanced training and test sets were used for model validation by random forest classification. Whole blood mRNA expression of SPTLC2 was analyzed.
Results: A reliable random forest model was found for discriminating AERD form ATA (AUC=0.85, sensitivity 91.7%, specificity 66.7%). Among top 10 metabolites discriminating AERD from ATA, 4 metabolites were identified using human metabolome database and METLIN; sphingomyelin (d18:0/13:0), N-acetylvanilalanine, oleoly ethyl amide (OetA), and hexadecyl acetyl glycerol. In the pathway of sphingolipid metabolism, serum 3-ketosphingosin, serum sphingomyelin (d18:8/13:0), urine palmitic amide and urine OetA were identified. The levels of serum sphingomyelin (d18:0/13:0) were significantly decreased (P<0.001) and those of urine palmitic amide and OetA were significantly increased (P<0.001 for both) in patients with AERD. The mRNA expression of SPTLC2 was significantly higher in patients with AERD than those with ATA (P=0.012). Sputum eosinophil count and FEV1 were significantly correlated with the mRNA expression of SPTLC2 in patients with AERD (P=0.027, r=0.587 and P=0.008, r=-0.552). The levels of urine OetA were significantly correlated with % fall of FEV1 after lysine-aspirin bronchoprovocation test in patients with AERD (P=0.001, r=0.478). The levels of urine OetA were significantly increased after lysine-aspirin bronchoprovocation test in patients with AERD (P=0.022).
Conclusion: Sphingolipid metabolic pathway was identified to be related with AERD.

Key Words: Asthma, Metabolomics, Sphingolipids

OAS-15

QCT Imaging-based Structural and Functional Changes during Asthma Attacks

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Introduction: It is still yet to be investigated how airway structure and lung function are altered during an asthma attack. This study aims to investigate structural and functional difference during an asthma attack compared with post- lung function recovery.
Methods: We obtained the asthma attack (pre-) and follow-up after recovery (post-) CT images of 8 asthmatic subjects at total lung capacity (TLC) and functional residual capacity (FRC), respectively. Using Apollo segmentation and an image registration, airway structures such as wall thickness (WT), hydraulic diameter (Dh), as well as, functional variables such as fractional air-volume change (ΔVairf) and AirT% (Air-trapping percentage) at pre- and post-TLC were obtained.
Results: During the asthma attack, WT in upper segmental airways was significantly increased, whereas Dh was decreased in the upper main and lobar bronchi (p<0.05). Furthermore, compared with the recovery phase, asthma attack led to a decrease of air volume change in lower lobes with an increase in AirT% (pre: post=50 %: 28 %).
Conclusion: With the limited samples, we found that air-trapping occurs in lower lobes with significant airway narrowing and wall thickening especially in upper segmental airways during the asthma attack compared with the recovery phase.

Key Words: Asthma, Tomography, X-ray, Asthma attack

OAS-16

Is Dog Ownership in Early Childhood a Risk Factor for the Sensitization or Bronchial Hyperresponsiveness in Preschool Children? Findings from COCOA Birth Cohort Study

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Introduction: It is still debatable whether pet ownership during pregnancy or infancy is a risk factor for the development of allergic diseases. We investigated the association between dog ownership in early childhood and sensitization and bronchial hyperresponsiveness (BHR) in preschool children.
Methods: The Cohort for Childhood Origin of Asthma and Allergic diseases (COCOA) is a general population-based birth cohort study. Overall 2,358 children from cohort study were enrolled in the analysis. Information on the allergic symptom, diagnosis, and given treatment was collected at each follow up physicians' records. Dog ownership was asked by the questionnaires. Skin prick tests (SPT) were performed at age 3 and 7 years old and bronchial provocation test was conducted at age 7.
Results: Sensitization to dog at age 3 and 7 was not differ between dog ownership group and non-ownership group. Compared with non-ownership, dog ownership during early life (before age 1 year) was associated with lower rate of sensitization to inhalant allergens at age 7 (26.1%, 47.9%, P<0.01).
Dog ownership increased a risk of BHR in non-atopic children at age 7 (OR=2.64; 95% CI 1.24-5.63) but no association was evident in atopic children.
Conclusion: Dog ownership during pregnancy or infancy reduced a risk of sensitization to inhalant allergen and increased a risk of BHR in non-atopic children.

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Key Words: Dog, Infancy, Sensitization

OAS-17

A Novel Function of TGF-β1 in Leukotriene C4 Synthase Expression in AERD Patients

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Background: Cysteinyl leukotriene (CysLT) overproduction and airway eosinophilia are hallmarks of aspirin-exacerbated respiratory disease (AERD), however, the mechanisms how CysLT to induce airway remodeling have not been completely understood.
Objective: To demonstrate the functional effect of transforming growth factor beta 1 (TGF-β1) in the airway inflammation of AERD.
Methods: AERD (n=235)/aspirin-tolerant asthma (ATA, n=403) patients, and healthy control subjects (HC, n=265) were enrolled. Serum TGF-β1 level was measured using ELISA and urinary LTE4 level was quantified using UHPLC system. The effect of TGF-β1 on eosinophils was investigated in ex vivo/in vivo models.
Results: Serum TGF-β1 levels were significantly higher in AERD than in ATA patients (P=.001) with a positive correlation with urinary LTE4 level. TGF-β1 treatment on peripheral eosinophils enhanced leukotriene C4 synthase (LTC4S)/cysteinyl leukotriene receptor 1 (CysLTR1) expression (not CysLTR2) and cysteinyl leukotriene E4 (LTE4) production, which were replicated in our in vivo model: TGF-β1 treatment in mice could enhance the expression of LTC4S/CysLTR1(not CysLTR2) and increased LTE4 level in bronchoalveolar lavage fluid. In addition, LTE4 sequentially induced eosinophil degranulation including eosinophil-derived neurotoxin (EDN) release through the ERK-p38 pathway, and EDN stimulated airway epithelial cells to release TGF-β1.
Conclusions: These findings suggest that TGF-β1 contributes to CysLT production. Moreover, eosinophil degranulation induced by LTE4 further activates airway epithelial cells, enhancing persistent CysLT mediated type-2 airway inflammation in ARED.

Key Words: Aspirin-exacerbated respiratory disease, Leukotriene C4 synthase, Transforming growth factor beta 1

OAS-18

NEK7-NLRP3 Binding is Essential in the Assembly of NLRP3 Inflammasome in the Pathogenesis of House Dust Mite-Induced Asthma

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NLRP3 inflammasome, consisting of NLRP3, the adaptor protein ASC, and the protease caspase-1, is responsible for the production of active forms of IL-1β and IL-18. In this process, oligomerization of ASC is a key step in assembly/activation of inflammasome and, recently, NEK7, a serine and threonine kinase, has been also reported as an essential activator of the NLRP3 inflammasome. MCC 950 is a small-molecule inhibitor of NLRP3 inflammasome, however, molecular action mechanism of MCC 950 is not fully understood. We investigated the therapeutic effects of the MCC 950 and its action mechanism in house dust mite (HDM)-induced allergic lung inflammation, particularly focusing on the NLRP3 inflammasome assembly process involving ASC and NEK7. Respiratory HDM exposure into mice led to the significant increases of pulmonary NLRP3, caspase-1, and IL-1β. Furthermore, levels of ASC oligomers were elevated in lung tissues of HDM-exposed mice and we observed the cytoplasmic co-localization of immunofluorescence intensities of NLRP3 and NEK7 in bronchoalveolar lavage (BAL) cells. Notably, treatment with MCC 950 significantly reduced the HDM-induced increases of ASC oligomerization and NLRP3-NEK7 colocalization in the lung of mice, and that ameliorated the HDM-induced increases of airway inflammatory cells infiltration, airway hyper-reactivity, and pulmonary TH2 cytokines. These results suggest that MCC 950 may have potential for treating HDM-induced allergic asthma partly through the regulation of HDM-induced ASC oligomerization and NEK7-NLRP3 binding in NLRP3 inflammasome assembly.

Key Words: House dust mite, MCC 950, NEK7-NLRP3 interaction

OAS-19

Genetic Signatures of Acute Exacerbation of Asthma

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Background: Acute exacerbation (AE) is an important domain of asthma management and may be related with an ineffective response to corticosteroid.
Objective: This study aimed to find mechanisms of AE using genome-wide gene expression profile of blood cells from asthmatics and its perturbation by in vitro dexamethasone (Dex)-treatment.
Methods: We utilized lymphoblastoid B cells from 107 childhood asthmatics and peripheral blood mononuclear cells from 29 adult asthmatics who were treated by inhaled corticosteroids. We searched for a preserved co-expression gene module significantly associated with the AE rate in both asthmatic cohorts and measured expression changes of genes belong to this module after Dex-treatment.
Results: We identified a preserved module composed of 77 genes. Among them, expressions of two genes (EIF2AK2 and NOL11) decreased significantly after Dex-treatment in both cohorts. EIF2AK2, a key gene acting antiviral defense mechanism, showed significantly higher expression in asthmatics with AE. The protein repair pathway was enriched significantly in 64 genes which belong to the preserved module but showed no expression differences after Dex-treatment in both asthmatics. Among them, MSRA and MSRB2 may play key roles by controlling oxidative stress.
Conclusion: Many genes belong to the AE rate-associated and preserved module identified in blood cells from childhood and adults asthmatics showed no expression changes after in vitro Dex-treatment. This findings suggest that we may need alternative treatment options to corticosteroids to prevent AE. EIF2AK2, MSRA and MSRB2 expressions on blood cells may help us to select AE-susceptible asthmatics and to adjust treatments to prevent AE.

Key Words: Severe asthma, PBMC, Genetic signature

OAS-20

Allergic Airway Disease Has Distinct Urine Microbome-derived Extracelluar Vesicles

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Background: Urine microbome-derived extracellular vesicle (EV)s have the ability to move freely between body compartments, so it may represent the whole microbiome community. Urine EVs are recently found to have distinct pattern of bacterial diversity and abundance in relation to airway diseases. The aim of this study was to investigate the association between urine EVs in allergic airway disease and allergic biomarkers.
Methods: The subjects were randomly selected from children included in 10-12 year-old students from schools survey. Subjects with atopic asthma and allergic rhinitis were selected as allergic airway disease group (AW) according to ISAAC questionnaire and serum specific IgE to inhalant allergens. Controls were free of a history suggesting chronic rhinitis or allergic diseases and had negative serum specific IgE. Single voided urine samples were collected. Urine EVs were isolated and their DNA was extracted for 16S-rDNA pyrosequencing. Serum total IgE, eosinophil percent and FeNO were measured.
Results: A total of 43 subjects were included; 16 AW (asthma with rhinitis 6, allergic rhinitis 10) and 27 controls. Phyla Firmicutes was the most abundant in the AW while the Proteobacteria was the most abundant in the controls. The abundance of 9 genera showed moderate positive correlation with both serum total IgE and eosinophil percentage including pathogenic bacteria Escherichia-Shigella, Klebsiella and Haemophilus.
Conclusion: Urine EVs showed a significant correlation with allergy markers of IgE and eosinophil percentage. Urine EVs could be a good indicator for assessing the correlation between microbiome and allergic airway disease.

Key Words: Microbiome, Extracellular vesicles, Allergy, Asthma, Allergic rhinitis

OAS-21

Distinct Airway Microbiota of Asthma Exacerbation in Children is Associated with Inflammatory Phenotypes

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Introduction: The role of airway microbiome in asthma exacerbation is not known yet. We aimed to characterized the airway microbiota in asthmatic children with acute exacerbation and evaluate it according to airway inflammatory phenotypes.
Methods: We collected induced sputum from children with stable asthma (n=83, 67 in atopy), asthma exacerbation (n=22, all atopy) and no asthma (healthy control; n=22). Among children with stable asthma, 40 children showed eosinophilic and 45 children showed neutrophilic asthma phenotype. Among children with asthma exacerbation, 8 children showed eosinophilic and 12 children showed neutrophilic asthma phenotype. Metagenome prediction was assessed using PICRUSt and KEGG pathway.
Results: Airway microbiology was significantly different in children with asthma exacerbation compared with those with stable asthma or healthy control. When comparing airway microbiota in asthma exacerbation with those in stable asthma and control, there are prominent more or less microbiota composition in asthma exacerbation. However, when comparing airway microbiota these groups among all atopic children for excluding atopic effect, only less microbiota composition was significant in asthma exacerbation. When comparing airway microbiota in asthma exacerbation and stable asthma according to eosinophilic and neutrophilic phenotype, prominent more microbiota composition of eosinophilic phenotype in asthma exacerbation was similar with that in stable asthma. However, any significant microbiota of neutrophilic phenotype in asthma exacerbation was not similar with that in stable asthma. In metagenome prediction assessment, more lipopolysaccharide biosynthesis and less quorum sensing were found in asthma exacerbation. In neutrophilic phenotype of asthma exacerbation, necroptosis was found significantly.
Discussion: Airway microbiome in asthma exacerbation is characterized with depletion of normal airway bacteria, which could be vulnerable to acute infection.

Key Words: Asthma, Exacerbation, Microbiota

OAS-22

Heterogeneous Dynamics within Microbial Communities in Asthma

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Background: Microbiome has been suggested as potent players regulating inflammation in asthma but airway microbial dysbiosis is not specified nor successfully replicated in different population. Although microbiome interactions are recently suggested to play a role in shaping host fitness, dynamics within microbial communities of asthmatic airway is barely studied.
Objective: To characterize the interactions of airway microbiome reflecting the clinical features of asthma.
Methods: Metagenomic DNA was extracted in sputum induced from 155 participants composed of normal control, non-severe asthma, and severe asthma. The heatmap was illustrated using the percentage abundance values of top 50 genera and was drawn into a dendrogram using hclust package with a complete clustering option in the R program. The heatmap-based dendrogram was divided into three groups using the dendrogram height of 10 as the threshold. Their microbiome profiles and interactions were compared according to the clusters classified by microbial hierarchy of abundance of predominant microbes.
Results: There were three clusters (C1, C2, and C3) showing difference in microbial abundance of predominant microbiota in asthma patients. C2 and C3 showed more frequent exacerbation of asthma compared to C1. Among 91, 35, and 67 pairs of microbial interactions in C1, C2, and C3, there were 25 (27.5%), 4 (11.4%), and 10 (14.9%) pairs unique to each cluster. Correlation patterns between microbes were different according to clusters (C1 vs. C2 or C3). 'Veillonella-Rothia', 'Veillonella-Capnocytophaga', 'Veillonella-Alloprevotella' pairs showed significant positive correlation in C1 while those pairs were negatively interacted in cluster 2 and cluster 3.
Conclusion: Clustering based on microbial patterns in asthma patients showed distinct clusters with different microbial genus-genus interactions and with different associations of clinical characteristics.

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Key Words: Adult asthma, Microbiota, Sputum, Cluster analysis