Oral Presentation 4

· **Date:** May 13, Saturday 2017

· **Chairs:** Moo-Young Oh (Inje Univ.), Jung-Won Park (Yonsei Univ.)

OP-37

The Prevalence of Self-reported Allergic Diseases and IgE Level, based on Demographic and Environmental Data from the 2010 KNHANES

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Purpose: Allergic diseases are associated with demographic and environmental factors. We aimed to determine the significant factors contributing to the prevalence of allergic diseases, total (tIgE) and specific immunoglobulin E (sIgE) levels.
Methods: We analyzed data collected by the 2010 Korea National Health and Nutrition Examination Survey for 2,342 subjects (unweighted), representing 16,003,645 subjects, who underwent serum tests for tIgE and sIgE to Dermatophagoides farinae, dog, and Blattella germanica, by considering the sample weight and stratification.
Results: Total prevalence of self-reported allergic diseases was 37.6%. The individual prevalence of allergic rhinitis and atopic dermatitis decreased with age, but that of asthma was not affected by it. The prevalence of self-reported allergic disease was significantly associated with various factors (age, professional occupation, living in urban area, and depression) according to the type of allergic disease. The tIgE level decreased with age, but later increased. The elevation of tIgE was significantly associated with male gender, type of occupation, obesity, and smoking status. However, risk factors for sIgE to each allergen were quite different. Sensitization to D. farinae was higher with young age. Sensitization to B. germanica was significantly higher with male gender, residing in a house, and glucose intolerance. Young age and smoking status were significantly associated with sensitization to dog.
Conclusion: Various demographic and environmental factors were significantly associated with the prevalence of self-reported allergic diseases and levels of tIgE and sIgE to D. farinae, B. germanica, and dog in South Korea.

Key Words: Allergic disease, sensitization, immunoglobulin

OP-38

A genome-wide association study for asthma exacerbations and effects of cigarette smoke

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Despite the success of inhaled corticosteroid (ICS) therapy, about 10% of asthmatics continue to suffer from uncontrolled symptoms, which are defined as refractory asthma (RA), such as frequent exacerbation of asthmatic symptoms. Cigarette smoke has been regard as one of major contributing factor of asthma exacerbation. However, genetic factor of exacerbation and cigarette smoke has not been so far evaluation. The objective of this study was to identify genetic risk factors of asthma exacerbations using a genome-wide association study (GWAS) according to smoking status in asthmatics. The genome-wide genotyping was performed using Illumina Human660W-Quad BeadChip in 608 asthmatics followed up more than 1 years. Genome-wide associations between the genotypes and exacerbation frequency in the 1st year of follow-up were calculated using PLINK software. The results showed MYT1L, GUCY2D, RPL18AP17, ZFP42, CYP4F22 were significantly associated with asthma exacerbation. Furthermore, the genetic risk factors of the exacerbations were remarkably different between smokers and non-smokers; GUCY2D, RN7SL97P, LOC101927605 showed the most significant association with exacerbation in non-smokers, in contrast, LOC100419079, FRMD4A, EXTL2 were top-ranked in smokers. Especially, some genes including LRRTM4, LOC101927605, LOC105375195, LINC00445, CCSER1 showed opposing effects on the asthma exacerbation according to smoking status. Our findings suggest that interaction between genetic factors and smoking status is important in asthma exacerbation, and that the interaction should be regarded in genetic study for asthma exacerbation and RA.

Funding: The DNA samples were provided by a BioBank at Soonchunhyang University Hospital, and funded 2016-ER7402-00

Key Words: Asthma exacerbation, Smoke, SNPs

OP-39

Inverse relationship between the relative abundance of Firmicutes in airway microbiome and bronchial hyperresponsiveness in asthma phenotypes in children

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Background: The airway microbiome plays an important role in the development of immune system and asthma. Diverse asthma phenotypes have been identified in children. However, studies on the effect of airway microbiome on asthma phenotypes are lacking.
Objectives: We investigated the composition of airway microbiome according to childhood asthma phenotypes and relationship among airway microbiota, lung function, and bronchial hyperresponsiveness.
Methods: Thirty-one healthy control participants (mean age, 7.1 years), 30 children with asthma in remission (mean age, 7.6 years), and 31 children with asthma (mean age, 8.0 years) were enrolled between June, 2014, and January, 2016. Samples for airway microbiome were acquired by nasopharyngeal swabs. High-throughput sequencing was used to examine the structure and functional dynamics of the airway microbiome with respect to asthma phenotypes. Pulmonary function tests and methacholine challenge tests were performed.
Results: The proportion of Firmicutes was highest in the asthma group compared to that in the control and asthma remission groups. The relative abundance of Firmicutes was negatively associated with FEV1 % predicted (P = 0.032), FEF25-75% % predicted (P = 0.016), and methacholine PC20 levels (P = 0.027). The relative abundance of Firmicutes was inversely associated with blood eosinophil percentages (P = 0.016), but not with total serum IgE levels.
Conclusions: The relative abundance of Firmicutes is inversely associated with lung function, bronchial hyperresponsiveness, and eosinophil percentages. Airway microbiome might affect the prognosis of asthma through the effect on lung function with allergic inflammation.

Key Words: Airway, Microbiome, Childhood asthma

OP-40

Airway epithelial phosphoinositide 3-kinase delta contributes to the modulation of fungi-induced innate immue response

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Respiratory fungal exposure is known to be associated with severe allergic lung inflammation. Airway epithelium is an essential controller of allergic inflammatory process. An innate immune recognition receptor, NLRP3 inflammasome, and phosphoinositide 3-kinase (PI3K)-δ in airway epithelium are critically involved in various inflammatory processes in lung. We investigated the role of NLRP3 inflammasome in fungi-induced allergic lung inflammation and examined the regulatory mechanism of NLRP3 inflammasome assembly/activation focusing on PI3K-δ isoform in airway epithelium. We utilized two in vivo models induced by exposure to Aspergillus fumigatus (Af) and Alternaria alternata (Aa) as well as Af-exposed in vitro experimental system. We also checked expression of NLRP3 protein in lung tissues from allergic bronchopulmonary aspergillosis (ABPA) patients. Assembly/activation of NLRP3 inflammasome was remarkably increased in the lung of Af-sensitized/challenged mice. Elevation of NLRP3 inflammasome assembly/activation was also observed in Af-stimulated epithelial cells. Similarly, pulmonary expression of NLRP3 in patients with ABPA was increased compared to that in healthy subjects. Importantly, neutralization of NLRP3 inflammasome-derived IL-1β alleviated various pathophysiologic features of Af-induced allergic inflammation. Furthermore, blockade of PI3K-δ improved Af-induced allergic inflammation through modulation of NLRP3 inflammasome assembly/activation, especially in epithelial cells. NLRP3 inflammasome was also implicated in Aa-induced eosinophilic allergic inflammation, which was improved by blockade of PI3K-δ. These findings demonstrate that fungi-induced assembly/activation of NLRP3 inflammasome in airway epithelium may be modulated by PI3K-δ isoform. Inhibition of PI3K-δ may have potential for treating fungi-induced severe allergic lung inflammation in humans.

Key Words: Phosphoinositide 3-kinase δ, Innate immue response, Fungus

OP-41

Analysis of the microbiome and metabolome for adult asthma

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Introduction: Recent studies suggest that microbiomes of the lung contribute to the pathogenesis of asthma. However, the relationship between the microbiomes and their metabolites in adult asthma has not been fully investigated.
Methods: The microbiomes of sputum and metabolomes of sputum and plasma have been studied on total 20 subjects consists of 6 adult asthma(AA) and 14 healthy controls(HC). Bacterial DNAs were extracted from both whole cells and supernatants in order to sequence the variable region V3-4 of 16s ribosomal RNA gene.Paired end reads were demultiplexed and analyzed using QIIME. A GC-TOF-MS method was performed for an untargeting metabolomic profiling in sputum and plasma in both group.
Results: Of the AA group, 50% were female and mean age was 58.5 years (female 57.2%; mean age 50.3 years in HC).Comparing the whole sputum and sputum supernatant, general microbiome composition were not significantly different between two specimens.No difference in bacterial richness was observed between the AA and HC while alpha diversity showing significant decrease in asthma patients (P-value < 0.05). When sputum whole cells were analyzed, Firmicutes were relatively reduced while Proteobacteria increased in AA compared to HC. In Genus level, AA showed had more Moraxella, Haemophilus, and Fusobacterium but less Neisseria, Streptococcus and Prevotella. There were statistically significant changes in six metabolites (leucin, aspartic acid, 5-oxoproline, glutamic acid, phenylalanine, cholesterol) of sputum and three metabolites (proline, linoleic acid, acetic acid) of plasma in AA compared to HC (P-value < 0.05).Upon sputum microbiome and metablome correlation analysis, positive correlation was observed for Prevotella with myo-inositol.
Conclusion: In asthmatic airways, airway microbiome showed significant alterations compared to healthy control and these alteration was correlated with the change in metabolomes in part.

(This research was supported by a fund (code: HD16A1543) by Research of Korea Centers for Disease Control and Prevention.)

Key Words: Microbiota, Asthma, Metabolomics

OP-42

Nintedanib ameliorated airway remodeling by inhibiting angiogenesis of bronchial vessels

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Background/Objective: Nintedanib is a multi-tyrosine kinase receptor inhibitor recently approved for treatment of idiopathic pulmonary fibrosis. Although angiogenesis is a key process involved in airway structural changes in patients with bronchial asthma, the effect of nintedanib targeting the angiokinase pathway on airway remodeling has not been evaluated.
Methods: We used a 3-month ovalbumin (OVA) challenge mouse model of airway remodeling. Nintedanib was orally administrated during the challenge period, and the effects were examined the typical pathophysiologic features of asthma. Also, we measured the number of blood vessels around the airway and α-smooth muscle actin area was evaluated around vessels. The expression of growth factor receptors was analyzed in mice lung tissues.
Results: The OVA challenged group showed a significant increase in typical features of asthma including airway inflammation and remodeling compared to those in the control group. It was sufficiently suppressed by nintedanib compared to that by OVA. Moreover, the number of blood vessels and ASM area around vessels was significantly decreased by nintedanib. Also, nintedanib effectively suppressed the phosphorylation of vascular endothelial growth factor/ platelet derived growth factor subunit2/fibroblast growth factor3 receptors in the mice lung.
Conclusions: Nintedanib effectively ameliorated airway remodeling in an OVA-induced chronic asthma model. These results suggest that nintedanib could be a new treatment agent targeting airway remodeling in patients with severe asthma.

Key Words: Nintedanib, Airway remodeling, asthma

OP-43

Exploration of plasma metabolomics profiles in adult and elderly asthma

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Background: Asthma in adults and the elderly differs from childhood asthma and is an increasing important health issue. Distinct metabolism pathway and metabolite patterns might be involved in the pathogenesis of adult and elderly asthma. We investigated differential alteration of metabolomics profiles in the plasma of young adult and elderly asthmatics.
Methods: Thirty patients with young adult asthma (18-45yrs old), 30 patients with elderly asthma (over 65yrs old), 10 young adult control subjects and 10 elderly control subjects were enrolled for the study. Plasma was collected from the subjects and metabolomics profiles were analyzed simultaneously using ultra-performance liquid chromatograpghy quadrupole time of flight mass spectrometry (UPLC-q-TOF-MS) method with after isopropyl alcohol extraction.
Results: Multivariate analysis revealed metabolomics profiles were discriminated by age group rather than by asthma morbidity. Altered patterns of metabolite in asthmatics were observed in the young adult group more clearly than in the elderly group. Biomarkers were selected and identified in the metabolite lists showing significant difference between asthma and control. Compared with control subjects, young adult asthmatics showed lower level of bilirubin, cholesterol fragment, triglyceride and sphingolipid metabolite, higher level of some phosphatidylcholine and phosphatidylethanolamine.
Conclusion: Plasma metabolomics profiles showed different patterns according to age group. Young adult asthmatics showed metabolite changes in the plasma. Further research is warranted to validate their clinical and functional relevance.
Finding: This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (fund code 2015-ER6604-00)

Key Words: Asthma, Metabolomics

OP-44

Respiratory epithelial CD93 is released to serum in OVA-induced asthma murine model

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Background: CD93 is a one of membrane-associated glycoprotein on the surface of cells involved in the inflammatory cascade, and it can be released to serum, and becomes soluble form (sCD93). CD93 is receiving renewed attention as a biomarker of inflammation in various inflammatory and immune-mediated diseases.
Objective: We aimed to evaluate the potential of CD93 as a biomarker for allergic inflammation in OVA-induced asthma murine model.
Methods: To induced asthma murine model, mouse was sensitized with OVA (20 μg) by intraperitoneally injection twice and challenged with OVA (30 μg) by intranasally thrice consecutively. After two days, mice were sacrificed.
Results: The OVA-induced asthma murine model demonstrated typical allergic asthma features with increased airway hyper-responsiveness, increased levels of Th2 cytokines, and increased inflammatory cell infiltration in histological examination, compared to the control group. The CD93 level in lung homogenates assessed by enzyme-linked immunosorbent assay (ELISA) and real-time PCR decreased in OVA-induced asthma model, compared to control group. Immunohistochemical stain also showed CD93 expression in respiratory epithelial cells decreased in OVA-induced asthma model, consistent with the CD93 level in lung homogenates. In contrast, the CD93 level in serum increased in OVA-induced asthma model, compared to control group. Dexamethasone restored these effects of OVA on both respiratory epithelial cell and serum. In addition, LPS did not affect the levels of CD93 in neither respiratory epithelial cell nor serum.
Conclusion: This study showed that respiratory epithelial CD93 is released to serum by allergic airway inflammation in OVA-induced asthma murine model.

Key Words: Asthma, CD93, allergic inflammation

OP-45

LTE4 overproduction in mice fed a high-fat diet

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Background: Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, chronic rhinosinusitis/nasal polyps, and respiratory reactions to aspirin. Induction of 5-lipoxygenase (5-LO) pathway, which converts arachidonic acid to the cysteinyl leukotrienes (CysLTs) through inhibition of cyclooxygenase-1 (COX-1), is a hallmark in the pathogenic mechanism of AERD. However, the precise role of CysLT overproduction in AERD is still unclear.
Objective: To understand the mechanism of LTE4 overproduction in mice fed a HFD
Methods: Mice were fed a regular diet or high-fat diet for 5 weeks with/without aspirin. Airway hyper-responsiveness (AHR) was measured according to methacholine dosage. Cytokines and LTE4 were measured by using enzyme-linked immunosorbent assay (ELISA) in bronchoalvelar lavage fluid (BALF). H&E-stained lung tissue was analyzed.
Results: Mice fed a HFD with aspirin increased AHR to methacholine challenged in a dose dependent manner. BAL cellularity showed that the HFD induces airway inflammation through increased macrophage number. The production of IFN-γ was significantly enhanced by HFD but IL-4 and IL-5 were not. LTE4 also increased in BALF after mice fed a HFD and its production was more enhanced by aspirin administration. Histological analysis of the lungs also showed relatively thick epithelium.
Conclusion: These findings suggest that aspirin may contribute to LTE4 overproduction in obese patients leading to promote airway inflammation in the pathogenic mechanism of AERD.

Key Words: High fat diet, Leukotriene, Asthma

OP-46

Imbalance between mitochondrial dynamics and mitophagy affects the pathogensis of severe asthma with fungal sensitization

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Nowadays, impaired processes of mitochondrial dynamics linked to mitophagy have been accepted as a pathogenic contributor to various disorders. However, there is little information on mitochondrial dynamics and mitophagy in the pathogenesis of bronchial asthma, especially fungus-induced allergic airway inflammation. The typical asthmatic features of Aspergillus fumigatus (Af-exposed mice) were refractory to the treatment with oral dexamethasone, whereas they were improved significantly by the administration of mitochondrial reactive oxygen species (ROS) inhibitor, NecroX-7. In addition, electron-microscopic analysis revealed that in lung cells from Af-exposed mice, the mitochondria were dramatically elongated, fused each other compared to the finding in cells from control mice. The levels of mitofusin (Mfn)-1 and Mfn-2, mitochondrial fusion proteins, were significantly increased in BAL cells, primary cultured tracheal epithelial cells, and lung tissues of Af-exposed mice. The increases in Mfn-1 and Mfn-2 levels and morphological changes did not respond to oral dexamethasone, but NecroX-7 decreased the expression of mitofusins and restored the morphology of mitochondria. We also found that in vivo administration of siRNA targeting Mfn-2 modestly improved the asthmatic manifestations and mitochondrial dynamics in Af-exposed mice. We also found that the levels of the mitochondrial fission related protein (Drp-1) and mitophagy related indicators (PINK-1 and parkin) were increased in Af-exposed mice. These findings indicate that the imbalance of mitochondrial dynamics and mitophagy may be induced by fungal allergen stimulation in lung cells and it may be one of the molecular mechanisms for the pathogenesis of steroid-resistant allergic airway inflammation.

Key Words: Mitochondrial dynamics, mitophagy, Severe ashtma

OP-47

The impact of epithelial barrier, nectin-4 on asthma

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Background: Nectin is the Ca2+-independent immunoglobulin-like molecules consisting of four members that recruitment of the seproteins is mediated by afadin, an actin ?lament binding protein that connects nectins to the cytoskeleton. The biological significance of nectin-4/afadin activation in asthma and its clinical potential as a therapeutic target were not fully described.
Objective: we aimed to elucidate the role of nectin-4/afadin on airway hyperresponsiveness and inflammation using a murine asthma model and to find relationship between nectin-4 and clinical variables in patient s with asthma.
Methods: Using mice sensitized and challenged with OVA, as well as mice sensitized and challenged with saline, we investigated whether nectin-4, and Src/Rac/JNK pathway were involved in the pathogenesis of bronchial asthma by western blotting and Immunohistochemical staining. Moreover, we also checked relationship between the levels of nectin-4 levels in blood from asthmatic patients and clinical variables. Results: The OVA-OVA mice showed that the protein of nectin-4/afadin in lung tissue was significantly increased and the protein of Src/Rac/JNK pathway were increased. The plasma nectin-4 levels were significantly decreased in non-treated asthmatic patients compared to those of control subjects, and anti-asthmatic treatment were recovered to normal levels. The plasma nectin-4 level was correlated with FEV1 and methacholine PC20.
Conclusion: These findings thus raise the possibility that nectin 4 is involved in asthma pathogenesis.

Key Words: Nectin-4, bronchial asthma, epithelial barrier

OP-48

Combination of clopidogrel & montelukast attenuated airway inflammation through platelet-eosinophil combination

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Background & Objective: Platelets contribute to asthma pathogenesis by amplifying the production of cysteinyl leukotrienes (CysLT), priming leukocytes for activation. We investigated the combination of antiplatelet drug (clopidogrel) and montelukast in asthma treatment using an asthma mouse model
Materials & methods: BALB/c mice were injected intraperitoneally ovalbumin (OVA) on days 0, 14, followed by primary challenge with OVA 0.2% (days 28-30) and secondary challenge with OVA 1% (days 42-44). Mice were either administered clopidorgrel hydrogen sulfate (10mg/kg), montelukast sodium hydrate (10mg/kg) or both drugs with the 6-hour interval for 30 minutes before OVA (1%) challenges on days 42-44. On days 46, mice were assayed for airway hyperresponsiveness (AHR), and samples were collected. Cytokines in bronchoalveolar lavage fluid (BALF) were measured by ELISA kits. Platelet-eosinophil combination (PEC), P-selectin in whole blood and BALF were assessed by flow cytometry and immunohistochemistry. To induce PEC, the isolated platelets and eosinophils from mouse were primed with montelukast, clopidogrel, or both and co-cultured, followed by stimulation with adenosine diphosphate (ADP) 10 μM.
Results: Combination of montelukast & clopidogrel attenuated the increased AHR at higher concentration of methacholines, the increased eosinophil counts more effectively than single treatment ($P<0.05$ for each). The levels of interleukin (IL)-4, IL-13, eosinophil peroxidase (EPX) were reduced in BALF from the mice treated with montelukast & clopidogrel simultaneously ($P<0.05$ for each). Combination of montelukast & clopdiogrel reduced PEC formation in whole blood and BALF ($P<0.05$ for each). Piming with montelukast & clopidogrel tend to reduce the ADP-induced PEC formation and P-selectin expression on the platelet-eosinophils aggregates.
Conclusions: These findings suggest the additional effects of clopidogrel to montelukast in asthma treatment possibly through modulation of PEC.

Key Words: Asthma, Clopidogrel, Platelet