Oral presentation 5

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· **Chairs:** Chun Geun Lee (USA), Jiu Yao Wang (Taiwan)

OP-45

The role of Sox17 in allergic airway inflammation

Eun Hee Ha, Jun-Pyo Cho[3], Hyouk-Soo Kwon[3], Hyeung Ju Park[1], So Young Park[3] Sang Joon Lah[1], Seung-Hyo Lee[1,2], In June Kim[1,2], You Sook Cho*

[1]Biomedical Science and Engineering Interdisciplinary Program, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 34141, Korea, [2]Graduate School of Medical Science and Engineering (GSMSE), Biomedical Research Center, KAIST Institute for the Bio-Century, KAIST, Daejeon, 34141, Korea, [3]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea

Asthma is a heterogeneous disease with chronic inflammation and remodeling of airway. Sox17 is regarded as a transcription factor of vascular network regulating various pro-angiogenic target genes. Recently, IL-33, a critical cytokine linking to recruitment and activation of ILC2 prior to Th2 immune responses, was reported induce up-regulation of Sox17 transcription. However, the role of Sox17 related with IL33 in the development of allergic airway inflammation was not clearly evaluated. We established conventional mouse model of asthma in WT and Sox17 endothelial conditional knock-out mice, and evaluated airway inflammation in BAL fluid and lung tissues. We sorted endothelial cells from these mice and evaluated various chemical mediators by qRT-PCR. To investigate underlying mechanism in endothelial cells, Sox17 was silenced or over-expressed in IL-33 activated HUVEC and evaluated various cytokines and chemokines. In the airway of asthmatic mice, Sox17 expression was significantly enhanced, and absence of Sox17 was resulted in down-regulation of Th2 airway inflammation. Among inflammatory cells, granulocytes and monocytes were decreased, and these were accompanied by down-regulation of cytokines and adhesion molecules in sorted endothelial cells from lung tissue. IL-33 stimulated HUVEC showed positive correlation between Sox17 expression and chemokine secretion after knock-down or over-expression of Sox17. These results demonstrated that Sox17 is involved with the development of allergic airway inflammation through IL-33 associated activation of endothelial cells.

Key Words: Sox17, Allergic airway inflammation, Endothelial activation

OP-46

Immuno-molecular Studies on Signal Transduction Pathway of Histamine Release in Indian Population

A.B. Singh, Pawan Kumar

CSIR-Institute of Genomic & Integrative Biology, Delhi University Campus, Delhi, India

Purpose: Allergy is a multifactorial disorder and about 30% population is estimated to suffer from one or the other allergic diseases. Basophils/Mast cells are primarily involved in the release of mediators e.g. Histamines, Leukotrienes and Cytokines. IgE mediated activation of the signal transduction pathway leads to chemical mediators.Studt was carried out to releasibility of histamine in Indian subjects to observe percent releasibility.
Method: As India is having largest gene pool with climatic and geographical variations through out the country, this might lead to adaptations specific for population living in particular region. Blood samples were collected from healthy subjectss attending Blood Bank and basophils isolated. The basophil activation test was carried out by repeated challenge with antigen con-A and histamine release was quantified. IgE receptor, Lyn and Syk Tyrosine Kinase expression was observed by FACS
Results: The study demonstrated releasers and non-releasers of histamine in Indian subjects. The presence of tyrosine kinases such as lyn & syk lead to releaser phenotype while in non-releases tyrosine kinases were observed to be absent. The basophils from 18.1% of subjects showed non releasibility of histamine and non-releasers had reduced serum IgE, FcER1, FcERII ($p<0.05$). Interestingly non releaser phenotypes showed absence of Lyn & Syk kinase. The role of 1L 3 gave demonstrated mutation to and established the role of non-expression of Lyn & Syk kinases. Thus less potent form of 1L 3 has been observed in non-releasers.
Conclusion: The study demonstrated that 18% of Indian population were non releasers of histamine . Non-releasers showed reduced levels of Serum IgE, FceRI, FceRII ($p<0.05$) Variations in the Expression of the Tyrosine Kinases have been observed in the different Individuals ($p<0.05$).

OP-47

Nectin-4/afadin contribute to airway inflammation and responsiveness in asthma

Pureun-Haneul Lee, Byeong-Gon Kim, Sun-Hye Lee, Jisu Hong, Ae-Rin Baek, Jong-Sook Park, June-Hyuk Lee, Sung Woo Park, Do Jin Kim, Choon-Sik, Park An-Soo Jang*

Soonchunhyang University Bucheon Hospital

Background: Nectin is calcium independent immunoglobulin-like molecules consisting of four members that recruitment of the seproteins is mediated by afadin, an actin filament 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 patients 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 be involved in the pathogenesis of bronchial asthma by western blotting and Immunohistochemical staining. Moreover, we also checked relationship between nectin-4 levels in blood from asthmatic patients and clinical variables.
Results: Nectin-4/afadin in lung tissue was significantly increased in OVA/OVA mice compared with control mice. Src/Rac/JNK pathways were involved in OVA/OVA mice. Nectin-4/afadin was co-expressed in human bronchial epithelial cells (NHBE). Nectin-4/afadin and Src/Rac/JNK were significantly increased in NHBE after house dust mite treatment, and those decreased after treatment of nectin 4 siRNA. The plasma nectin-4 levels were significantly increased in asthmatic patients compared to those of control subjects. The plasma nectin-4 level was correlated with FEV1, FEV1/FVC and methacholine PC20.
Conclusion: These findings thus raise the possibility that nectin 4/afadin be involved in asthma pathogenesis via Src/Rac/JNK pathways.

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

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Childhood Asthma is Associated with Polymorphic Markers of Cadherin-related Family Member 3 Gene

Man Fung Tang, Yu Ping Song, Alice Pik-Shan Kong[1], Agnes Sze-Yin Leung, Gary Wing-Kin Wong, Wan Yi Chan, Ronald Ching-Wan Ma[1], Juliana Chung-Ngor Chan[1], Ting Fan Leung

Departments of Paediatrics and [1]Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

Purpose: The gene encoding cadherin-related family member 3 (*CDHR3*) was recently reported to be a receptor for human rhinovirus-C, with a missense variant (rs6967330) being associated with recurrent severe asthma exacerbations in Danish preschoolers. This study investigated the associations between asthma phenotypes and single-nucleotide polymorphisms (SNPs) of *CDHR3* in Chinese children.
Methods: 892 school-age children with physician-diagnosed asthma and 1187 non-allergic controls were recruited. Ten tagging SNPs selected by HaploView 5.0 based on 1000 Genomes database for Southern Han Chinese (CHS) at pairwise r2 $\geq$ 0.8 for linkage disequilibrium (LD) and minor allele frequencies (MAFs) $\geq$ 0.01 were genotyped by Taqman genotyping assays using QuantStudio 12K Flex real-time PCR system. Genotypic and haplotypic associations with asthma phenotypes were analyzed by multivariate regression.
Results: The mean (SD) age of asthmatics and controls was 11.0 (4.1) and 13.7 (4.5) respectively. All SNPs followed Hardy-Weinberg equilibrium. Rs448025 and rs543085868 were monomorphic, while MAF of other SNPs ranged from 0.018 to 0.377. Asthma diagnosis was associated with rs6967330 under addictive (odds ratio [OR] 1.32 and 95% confidence interval [CI] 1.04-1.69; P=0.025) and dominant (OR 1.34 and 95% CI 1.03-1.73; P=0.027) models, but not with other SNPs. None of these SNPs was associated with atopy and spirometric indices. Asthma diagnosis was also associated with GAC haplotype from rs4730125, rs6967330 and rs408223 (OR 1.39 and 95% CI 1.08-1.80; P=0.012). Besides, AT haplotype of rs3887998 and rs73195657 was associated with FEV1% (β=4.210; P=0.006) and log10-transformed FVC% (β=0.019; P=0.009) among asthmatics.
Conclusions: Childhood asthma was associated with rs6967330 of *CDHR3* and a haplotype formed by rs4730125, rs6967330 and rs408223. Besides, a two-locus haplotype of rs3887998 and rs73195657 was associated with spirometric indices in asthmatics. These findings support CDHR3 to be a candidate gene for asthma susceptibility and lung function in children.

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Evaluation of human MSC treatment for airway inflammation in an acute asthma mouse model

Jung Hur, Ji Young Kang, Sook Young Lee, Young Kyoon Kim, Chin Kook Rhee*

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Purpose: Various models of experimental allergic asthma have shown that mesenchymal stem cells (MSCs)are a potential therapeutic treatment for TH2 cell-mediated inflammation. However, the mechanisms mediating the therapeutic effects and safety of MSCs are not fully understood. Using a mouse model of experimental allergic asthma, we investigated the therapeutic efficacy of human adipose-derived MSCs (hADSCs) and human bone marrow-derived MSCs (hBMSCs).
Materials and methods: We examined five groups of female BALB/c mice (control; ovalbumin [OVA]-sensitized and -challenged mice; OVA-sensitized and -challenged mice treated with phosphate-buffered saline, hADSCs or hBMSCs). Airway hyperresponsiveness (AHR), cytokine production, and lung pathology were compared among the groups.
Results: OVA-sensitized and challenged mice exhibited allergic AHR, airway inflammation, and significant increases in TH2 cytokines. Human MSC (hMSC) treatment significantly decreased AHR and bronchoalveolar lavage (BAL) counts. However, hMSC treatment increased inflammatory cell infiltration, goblet cell hyperplasia, and TH2 cytokine production.
Conclusions: The results of this study revealed that hADSC and hBMSC treatments during OVA-sensitization and -challenge suppressed AHR and BAL counts. However, these treatments significantly induced eosinophilic airway inflammation and lung histological changes. Therefore, the use of hMSC therapy should be considered carefully.

Key Words: human mesenchymal stem cell, asthma, airway inflammation

OP-50

The role of merged endoplasmic reticulum with mitochondria in the pathogenesis of inflammasome-associated severe asthma

So Ri Kim*, Yong Chul Lee, Hae Jin Park, Kyung Bae Lee, Yeong Hun Choe, Seung Yong Park, Jae Seok Jeong

Division of Respiratory Medicine and Allergy, Department of Internal Medicine, Chonbuk National University Medical School

Each asthma phenotype may have distinct observable molecular, cellular, morphological, functional, and clinical features, all of which can be possibly integrated into specific biological mechanisms, called as endotypes. Recently, one of new molecular phenotype of severe asthma has been reported as inflammasome-associated severe athma. In this study, we investigated which mechanisms contributes to NLRP3 inflammsome activation in neutrophilic severe asthma focusing on the mechanical and functional link between endoplasmic reticulum (ER) and mitochondria. The mice sensitized with OVA and LPS and then challenged with OVA (OVALPS-OVA mice) mice showed the typical features of neutrophilic asthma. Interestingly, confocal analysis and electron-microscopic findings revealed that in lung cells from OVALPS-OVA mice, the ER and mitochondria get closed each other even seemed to be united one compared to the finding of cells from control mice. An ER stress inhibitor, mitochondrial ROS inhibitor, or MCC950 significantly reduced the increases in inflammatory cytokines, mitochondrial ROS generation, NLRP3 inflammasome activation, airway inflammation, and bronchial hyperresponsiveness. Interestingly, the treatment restored the physical changes and distances of ER and mitochondria near normally. These findings indicate that the development of ER-mitochondria complex in airway inflammatory cells may be implicated in the pathogenesis of neutrophilic bronchial asthma through NLRP3 inflammasome activation, providing the novel therapeutic target for bronchial asthma.

Key Words: Inflammasome, Endoplasmic reticulum, Mitochondria

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Alternative Activated Macrophages (M2) Correlated with Symptom Severity and Promoted Th2 Responses in Allergic Rhinitis

Hongfei Lou[1], Yanran Huang[1], Yang Wang[2], Chengshuo Wang[1] and Luo Zhang[1,2]*

[1]Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China, [2]Beijing Key Laboratory of nasal diseases, Beijing Institute of Otolaryngology, Beijing, China, [3]Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China

Purpose: Macrophages play a central role in the balance and efficiency of the immune response. Their phenotype is a delicate equilibrium between the M1 and M2 profiles. This balance has been related to asthma. This study aimed to elucidate their role in allergic rhinitis (AR).
Methods: 33 AR patients and 30 healthy controls were recruited in this study. Total nasal symptom score (TNSS) was recorded when peripheral blood was taken. Macrophage phenotyping was performed by immunohistochemical (IHC) staining and flow cytometry analysis (FACS). Serum YKL-40 (M2 macrophage cytokine) were examined by Luminex. PBMCs from Der p sensitized-AR patients and healthy controls were stimulated using Der p. Next, stimulated-M2 macrophages were cocultured with naïve T cells. Experiments were undertaken to assess the function of stimulated M2 macrophages on Th cell proliferation and cytokine responses.
Results: By IHC and FACS analysis, more M2 macrophages were present in AR than in control. Serum YKL-40 levels were elevated in patients with AR and positively correlated with symptom severity. After Der p stimulation, both M2 percentages and correlated YKL-40 levels in AR patients were increased significantly higher than in controls, while the number of M1 macrophages was not different. M2 skewed subsequent naïve T cells differentiation to Th2 cells and higher IL-4 production were found in coculture supernatants in AR as compared to blank controls. However, no influence of M2 was observed in healthy controls.
Conclusion: M2 macrophages correlated with symptom severity and promoted Th2 responses in AR.

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Different clinical feature among asthmatics according to airway microbiome clusters

Young-Chan Kim[1], Boram Bae[2], Sungmi Choi[3], Kyoung-Hee Sohn[2,4], Hye Jung Park[5], Min-Gyu Kang[6], Min-Suk Yang[7], Jae-Woo Jung[8], Sang Min Lee[9], Sae-Hoon Kim[10], Sang-Heon Cho[1,2], Hana Yi[3,11], Hye-Ryun Kang[1,2]*

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Public Health Sciences, Graduate School, Korea University, Seoul, Republic of Korea, [4]Seoul National University Hospital Public Health Agency, [5]Department of Internal Medicine, Yongin Severance Hospital, Yongin, Korea, [6]Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk, Korea, [7]Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea, [8]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea, [9]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea, [10]Department of Internal Medicine Seoul National University Bundang Hospital, Seongnam, Korea, [11]School of Biosystem and Biomedical Science, Korea University, Seoul, Korea

Rationale: Several studies showed alterations of microbiota in airway of asthma patients. We focused on changes in lung microbiome from asthma patients.
Methods: Induced whole sputum of 31 healthy adult subjects and 121 adult asthmatics (mild: 55, severe: 66 patients) were obtained and V3-4 hypervariable region of the bacterial 16S rRNA gene was amplified and sequenced with the MiSeq v3 platform (Illumina®). Data were cleaned and analyzed using QIIME and Ezbiocloud 16S database. Cluster dendrogram was constructed using weighted UniFrac distance data. To select genera with significant changes in proportion among healthy control, mild and severe asthma group, Optimal microbiome-based association test (OMiAT)-based method was used to compare genus from each group. Chi-square test or Kruskal-Wallis rank sum test was used for analyzing categorical or continuous variables, respectively.
Results: There were no significant differences in alpha diversity and beta diversity among 3 groups. However, OMiAT-based method found relative proportion of Campylobacter and Selenomonas were significantly different among groups. When clustering into 5 groups based on UniFrac method, the proportion of several clinical variables were significantly different between groups; acute exacerbation per year ($p = 0.02$), Asthma control test (ACT) score ($p = 0.04$), antibiotics use within six months ($p = 0.04$), oral steroid administration ($p = 0.02$), SEB class ($p = 0.03$). According to the dominant genus in each group, group 1 had dominancy of both Streptococcus and Prevotella, group 2 showed abundant Prevotella, group 3 showed Neisseria dominant, group 4 had no specific pattern, and group 5 was Streptococcus dominant.
Conclusion: Genus level demonstrated that the proportion of Campylobacter and Selenomonas were reduced among asthma in the order from mild to severe asthma compared to the healthy controls. Several clinical factors were significantly different according to the phylogenetic clusters.

Key Words: asthma, microbiome

OP-53

Integrated Analysis of Stool Metabolome and Microbiome Profiles In Eczema And Healthy Infants

Gaik Chin Yap[1], Le Duc Huy Ta[1], James Chun Yip Chan[2], Rikky W. Purbojati[3], Daniela Isabel Moses[3], Chiung-Hui Huang[1], Dorinda Yan Qin Kioh[2], Lynette P.C. Shek[1,4], Anne Goh[4], Hugo P. S. Van Bever[1,4], Oon Hoe Teoh[5], Jian Yi Soh[1,4], Biju Thomas[4], Mahesh Babu Ramamurthy[1,4], Daniel Y. T. Goh[1,4], Christophe Lay[1,6], Shu-E Soh[1,7], Fabian Yap[6], Kok Hian Tan[8], Yap-Seng Chong[8,9], Keith M. Godfrey[10], Peter D. Gluckman[9], Stephan Schuster[3], Eric Chun Yong Chan[2], Bee Wah Lee[1]

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, [2]Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, [3]Singapore Center On Environmental Life Sciences Engineering (SCELSE), Nanyang Technological University, Singapore, [4]Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, [5]Department of Paediatrics, KK Women's and Children's Hospital, Singapore, [6]Danone Nutricia Research, Singapore, [7]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, [8]Department of Obstetrics & Gynaecology, National University of Singapore, Singapore, [9]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research Singapore, Singapore, [10]MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

Purpose: The infant intestinal microbiota is a complex ecosystem that undergoes a succession of demographic changes especially in the first year of life. Furthermore, compelling evidence with microbiota-derived metabolites has established the importance of such molecules in shaping host immune system. The aim of this study was to identify and compare intestinal microbial composition and metabolism between infants with atopic eczema and healthy controls.
Methods: From the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort, a sub-cohort of 64 subjects categorized by clinical outcome at 18 months of age: (1) non-atopic eczema (NAE) (n=15), (2) atopic eczema (AE) (n=14) and (3) healthy controls (n=35), were selected for this retrospective analysis. A total of 164 stool samples were collected at week 3, months 3, 6 and 12. Fecal samples were subjected to metabotyping using gas chromatographyh/time-off-flight mass spectrometry. Microbiota profiling was performed using metagenomic sequencing. Longitudinal multivariate analysis and correlation network were employed to study the microbial and metabolic maturation and their interactions while adjusting for possible confounders.
Results: Longitudinal analysis revealed a decreased abundance of *Firmicutes* phylum across all time-points in AE, but not NAE, compared to controls (adj <0.05). Within this phylum, further correlation analysis showed that the reduced abundance of butyric-producing bacteria (predominantly made up of *Blautia*, *Clostridium*, *Faecalibacterium* and *Butyrivibrio* genera) and acetic-producing bacteria (Streptococcus genus) was associated with a depletion of butyric and acetic acids in AE, most significant from 3 months onwards (adj $p<0.05$). Several other marker metabolites which correlated positively with butyric acid and reduced in AE compared to controls included sugar: N-Acetyl-Mannosamine; organic acids: benzoic acid, butanoic acid, succinic acid; amino acids and biogenic amines: L-Alanine, L-Tyrosine and L-Mimosine (adj $p<0.05$).
Conclusions: Differences in the gut microbiota is associated with perturbation of stool metabolites and the development of AE in infants.

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Alterations of gut microbiota associated with distinct allergic phenotypes: Data from an Asian longitudinal birth cohort study

Narissara Suratannon[1]*, Anchalee Senavonge[1], Massalin Nakphaichit[3], Wanwipa Vongsangnak[4,5], Preecha Patumcharoenpol[2], Sunee Nitisinprasert[3], Sittiruk Roytrakul[6], Yong Poovorawan[7], Nasamon Wanlapakorn[7], Pathareeyawan Srimuan[1], Jarungchit Ngamphaiboon[1], Elke Leuridan[8], Pierree Van Damme[8], Surasith Chaithongwongwatthana[9], Pantipa Chatchatee[1]

[1]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [2]Interdisciplinary Graduate Program in Bioscience, Faculty of Science, Kasetsart University, Bangkok, Thailand, [3]Department of Biotechnology, Faculty of Agro-Industry, Kasetsart University, Bangkok, Thailand, [4]Department of Zoology, Faculty of Science, Kasetsart University, Bangkok, Thailand, [5]Computational Biomodelling Laboratory for Agricultural Science and Technology (CBLAST), Faculty of Science, Kasetsart University, Bangkok, Thailand, [6]Genome technology Research Unit, National Center for Genetic Engineering and Biotechnology (BIOTEC), Pathumthani, Thailand, [7]Center of excellence in clinical virology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [8]Centre for the Evaluation of Vaccination, Vaccine and Infectious Diseases Institute, University of Antwerp-Campus DrienEiken, [9]Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Purpose: Allergic diseases usually originate in early life. The interaction between gut microbiota and host immune cells shapes the immune development and affects the manifestations of allergic phenotypes. Whether gut microbiota change is different among distinct allergic phenotypes has never been elucidated in a longitudinal birth cohort. We aimed to determine the difference of gut microbial colonization in distinct allergic diseases in infants age 9-12 months who participated in the longitudinal birth cohort.
Methods: A longitudinal population-based birth cohort study was conducted in Bangkok, Thailand. Diagnosis of allergic diseases was confirmed by allergists. The gut microbiome were analyzed using 16s amplicon sequencing method.
Results: Of the 336 children, the incidence of allergic diseases was 42/336 (12.5%). Twenty-six children aged between 9 to 12 months completed fecal collection and were analyzed compared to match healthy controls (1:1). Three atopic phenotypes including atopic dermatitis(AD) 58.8%, food allergy(FA) 17.7% and subjects who have both AD and FA(AD/FA) 23.5% were identified. Shannon index revealed that microbial diversity of allergic infants was not significant different compared to controls. However, the diversity index of FA samples was the lowest at 2.08 whereas the others were in range of 2.32-2.38. Microbial compositions between four groups were mostly similar. Interestingly, the amount of family *Erysipelotrichaceae* which was suggested to correlate with inflammation in human was significantly higher in AD and AD/FA groups than controls($p<0.05$). The relative abundance of *Bacteroidaceae* and *Enterobacteriaceae* in FA and AD/FA group was slightly higher than controls, while *Bifidobacteriaceae* was oppositely presented.
Conclusions: The changes in gut microbiota associated with atopic disease. Different allergic phenotypes have impact on shaping of microbiome in infant. This finding serves for further study in longitudinal birth cohort. Understanding the dynamic of microbial colonization patterns in allergic diseases will lead to discovering a promising clinical target for allergy prevention and treatment.

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Association of Folliculin with Epithelial Cell Activation in Aspirin Exacerbated Respiratory Disease

Hoang Kim Tu Trinh[1†], Duy Le Pham[4†], Young Woo Choi, Hyun-Mi Kim, Seung-Hyun Kim, Hae-Sim Park*

[1]Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea, [2]Department of Biomedical Sciences, The Graduate School, Ajou University School of Medicine, Suwon, South Korea, [3]Translational Research Laboratory for Inflammatory Disease, Clinical Trial Center, Ajou University Medical Center, Suwon, South Korea, [4]Department of Faculty, University of Medicine and Pharmacy at Ho Chi Minh city, Vietnam

Background and Objective: There is increasing evidence showing that epithelial cells contribute to eosinophilic airway inflammation in aspirin-exacerbated respiratory disease (AERD). Folliculin (FLCN) is essential to regulate the epithelial barrier integrity; however, the role of FLCN in AERD is underinvestigated. We elucidated the function of FLCN in AERD pathogenesis.
Materials and Methods: From Ajou Medical Center, 178 subjects with AERD, 276 subjects with aspirin tolerant asthma (ATA) and 71 normal healthy controls (NC) were included. The peripheral blood eosinophils (PBE) isolated from the subjects with asthma and were cocultured with human airway epithelia cells (HAECs), primed with cysteineyl leukotrienes (LT) E4, dexamethasone and montelukast. The serum and supernatant levels of FLCN and interleukin (IL)-8 were evaluated by ELISA. The intracellular expression of FLCN expressions was analyzed by Western blot. Knockdown of FLCN in HAEC was performed by shRNA.
Results: We detected the increased serum levels of FLCN in subjects with AERD group comparing to ATA and NC groups ($P<0.0001$ for each). Serum FLCN level could distinguish AERD from NC with 82% sensitivity (AUC=0.793, $P<0.001$). The highFLCN phenotype was defined as subjects with the FLCN level higher than cutoff value (mean+2SD from NC group). Within the asthma cohort, patients with high FLCN were associated with airway hyperresponsiveness to methacholine ($P=0.015$). In in vitro assay, exposure to LTE4 induced FLCN release significantly ($P<0.05$). FLCN and IL-8 were enhanced when HAECs were co-cultured with PBE and LTE4 in dose-dependent manners ($P<0.05$ for each), which were attenuated when FLCN was downregulated in HAEC. Dexamethasone and montelukast reduced the release of FLCN and IL-8 in the co-culture assay significantly ($P<0.05$ for each).
Conclusion: In AERD, high LTE4 and eosinophilic inflammation may trigger FLCN release from HAECs, leading to activation of HAECs. FLCN may be a potential target for AERD

Key Words: FLCN, epithelial cells, AERD

[†]Both authors contributed equally to this work.