646 Multi-omic Analysis Enhances Prediction Of Infantile Wheezing

Ramin Beheshti, MD[1], Steven Hicks[1], Patrick Frangos[1]; [1]Penn State Health Milton S. Hershey Medical Center.

RATIONALE: The pathophysiology of wheezing is multifactorial. The objective of this study is to explore the ability of medical, demographic, environmental, and immunologic factors to prospectively identify infants at risk for wheezing.

METHODS: This longitudinal cohort study involved 113 term infants. Infants were identified as wheezing (n=10) or non-wheezing (n=113) based on parental report on the International Study of Asthma and Allergies in Childhood Questionnaire and confirmed by review of medical records. Medical/demographic traits were collected by standardized surveys. Saliva samples were collected from all infants at 6 month and multi-omic analyses were used to quantify cytokines (ELISA), microRNA (RNAseq), and microbiome/virome (RNAseq) features.

RESULTS: Infants who developed wheezing were more likely to be delivered via cesarean section (p=0.007), and to attend daycare (p=0.010). Multi-omic analyses identified saliva cytokines (IL-18, p=0.049), miRNAs (miR-30c-5p, p=0.0076; miR-211-5p, p=0.020), bacteria (Elusimicrobia, p=0.0052), and viral phage species (Mycobacterium phage, p=0.0079) that differed between infants who developed wheezing and peers that did not wheeze. A logistic regression using infant traits did not differentiate infants who developed wheezing (X2 =7.0; p=0.79). Addition of environmental exposures accounted for 28% of variance (X2 =17.8; p=0.007), whereas addition of five saliva features accounted for 61% of variance (X2 =38.4; p=0.0001) between wheezing and non-wheezing groups. The five saliva features identified infants at risk for wheezing with 90% sensitivity and 85% specificity (AUC =0.917) without the aid of infant traits or environmental factors.

CONCLUSIONS: Multi-omic analysis of saliva may enhance the ability to identify infants at risk of wheezing.

647 Nasal airway microRNA profiling of infants with severe bronchiolitis and risk of childhood asthma: A multicenter prospective study

Zhaozhong Zhu, ScD[1], Robert Freishtat[2], Brennan Harmon[2], Andrea Hahn[2], Stephen Teach, MD[3], Marcos Pérez-Losada[4], Kohei Hasegawa, MD MPH[1], Carlos Camargo, MD, DrPH[1]; [1]Massachusetts General Hospital, [2]Children's National Hospital, [3]Children's National Hospital, [4]George Washington University.

RATIONALE: Severe bronchiolitis (i.e., bronchiolitis requiring hospitalization) during infancy is a major risk factor for childhood asthma. However, the exact mechanism linking these common conditions remains unclear. We examined the longitudinal relationship between nasal airway microRNAs (miRNAs) during severe bronchiolitis with the risk of developing asthma.

METHODS: In a 17-center prospective cohort study of infants with severe bronchiolitis, we profiled their nasal miRNA at hospitalization using small RNA sequencing. First, we investigated the relationship of miRNAs with the risk of developing asthma by age 6 years and identified differentially expressed miRNAs (DEmiRNAs). Second, we characterized the DEmiRNAs based on their association with asthma-related clinical features, and the expression level by tissue and cell types. Third, we conducted pathway analysis by integrating DEmiRNAs and their mRNA targets.

RESULTS: In 575 infants (median age, 3 months), we identified 23 DEmiRNAs associated with asthma development (e.g., has-miR-29a-3p, has-let-7b-5p; FDR<0.10), particularly in infants with respiratory syncytial virus infection ($FDR_{interaction}$<0.05). These DEmiRNAs were associated with 13 asthma-related clinical features (FDR<0.05)—e.g., infant eczema and corticosteroid use during hospitalization. These DEmiRNAs were also highly expressed in lung tissue and immune cells (e.g., T_H cells, neutrophils) (all FDR<0.001). Third, targets of DEmiRNAs were enriched in asthma-related pathways (FDR<0.05)—e.g., toll-like receptor, PI3K-Akt, Fc?R, and MAPK signaling pathways.

CONCLUSIONS: In a multicenter cohort of infants with severe bronchiolitis, we identified nasal miRNAs during severe bronchiolitis that are associated with major clinical features, immune response, and risks of asthma development.

648 Evaluation of a Panel of Cellular Biomarkers for Immune Dysregulation in Inborn Errors of Immunity

Priya Patel, MD[1], Boglarka Ujhazi[1], Melis Yilmaz[1], David Potts[1], Maryssa Ellison[1], Cristina Meehan[1], Sumai Gordon[1], Rachel Cruz[1], Irmel Ayala[2], Don Eslin[3], Erin Cockrell[3], Felipe Rico, MD[4], Jennifer Mayer, MD[2], Mei Sing-Ong[5], Anna Meyer, MD, PhD[6], Charles Hauk[2], Joseph Dasso, MD, PhD[1], Emma Westermann-Clark, MD[7], Panida Sriaroon, MD FAAAAI[7], Kriztian Csomos[1], Jolan Walter, MD, PhD[7]; [1]University of South Florida Morsani College of Medicine, [2]Johns Hopkins All Children's Hospital, [3]St Joseph's Children's Hospital, [4]University of South Florida Health, [5]Harvard Medical School, [6]National Jewish Health, [7]University of South Florida.

RATIONALE: Inborn errors of immunity (IEI) may present with immune dysregulation due to a variety of impairments in tolerance mechanisms. Several lymphocyte subsets have been proposed as biomarkers for immune dysregulation, but their importance in pathomechanisms and monitoring disease activity is unclear.

METHODS: Patients with IEI linked to immune dysregulation were enrolled through referrals and/or from our Jeffrey Modell Foundation registry (over 850 cases [2016 to 2022]). Peripheral blood samples were tested by flow cytometry for biomarkers of immune dysregulation including TCRab CD4-CD8- (DN), T follicular helper (Tfh), regulatory T (Treg) and CD19hiCD21lo B cell subsets.

RESULTS: Forty-one IEI patients were identified with ALPS (n=4) or variants in CTLA4 (n=16), NFKB1 (n=9), PI3K (n=8), RAG (n=1) and 22q11del (n=3). Extensive immune phenotyping was available for 78 timepoints from 31 of 41 patients. Compared to healthy donors, expansion was noted in Tfh (52 timepoint; 26 patients), CD19hiCD21lo B (36 timepoints; 21 patients) and DN (32 timepoints; 19 patients) cell populations. A reduction in Treg compartment was observed (42 timepoints; 23 patients). The relative contribution of the four biomarker subsets in specific disorders were variable. Notable was the dual expansion of Tfh and CD19hiCD21lo B cells in patients with NFKB1 variant, whereas DN T cells correlated with Tfh expansion only in CTLA4 deficient patients.

CONCLUSIONS: Our study investigates the utility of cellular biomarkers of immune dysregulation. Recognition of specific subsets of immune dysregulation may help monitor disease activity and individualize treatment strategies in IEI.

SUNDAY