AB90 Abstracts

RhinoVirus Infection Results in Increased and More Persistent Dysregulation of Gene Expression

Huyen-Tran Nguyen, MD1, Peter W. Heymann, MD2, Mark Lindsey3, Umasundari Sivarupasad, PhD3, Mario Medvedovic, PhD3, Naim Mahi4, Thomas A. E. Platts-Mills, MD, PhD, FAAAAI FRS2, Ronald B. Turner, MD5, John W. Steinke, PhD, FAAAAI2, Judith A. Woodfolk, MBChB, PhD, FAAAAI2, Larry Borish, MD, FAAAAI5, Gurjit K. Khurana Hershey, MD, PhD, FAAAAI3, 1Cincinnati Children’s Hospital Medical Center, Division of Allergy and Immunology, Cincinnati, OH, 2Division of Asthma, Allergy & Immunology, University of Virginia Health System, Charlottesville, VA, 3Cincinnati Children’s Hospital Medical Center, Division of Asthma Research, Cincinnati, OH, 4University of Cincinnati, Department of Environmental Health, Cincinnati, OH, 5University of Virginia Health System, Division of Infectious Diseases, Charlottesville, VA.

RATIONALE: RhinoVirus is associated with 50-90% of asthma exacerbations in adults and children. We hypothesized that gene expression in asthmatics would be significantly dysregulated compared to non-asthmatics following RhinoVirus infection.

METHODS: Adults (20-33 years old), 5 with allergic asthma and 6 without (controls), were inoculated with RhinoVirus-16 and nasal epithelial samples were obtained 7 days prior to (T0), 2 days after (T1), and 7 days after inoculation (T2). RNA was extracted and used for RNA-seq analysis. Differential gene expression analysis was performed based on the negative-binomial statistical model of read counts as implemented in the edgeR Biocductor package.

RESULTS: At baseline, 57 genes were differentially expressed in asthmatics compared to controls (p adj < 0.05). In non-asthmatic controls, 62 genes were significantly altered from T0 to T1, including 27 genes whose expression changed at least 3-fold. Interestingly, in asthmatics, 1329 genes were significantly altered from T0 to T1, including 550 genes whose expression changed at least 3-fold. In controls, only 3 genes remained at least 3-fold dysregulated at T2, while in asthmatics, 50 genes still demonstrated at least a 3-fold change in expression even 7 days later.

CONCLUSIONS: Healthy individuals with asthma have a substantially different response to RhinoVirus infection than non-asthmatic healthy controls. The quality of the response was significantly altered, and the magnitude of the response was increased in asthmatics. Further, the response persisted longer in asthmatics versus controls. Thus, in patients with asthma, the ability to sense RhinoVirus and the ensuing immune response is inherently altered.

Interrogation of the Effects of Rhinovirus on Th2 Promoting Pathways in Allergic Asthma

Rachana Agrawal, PhD1, Peter W. Heymann, MD2, Thomas A. E. Platts-Mills, MD, PhD, FAAAAI FRS1, Judith A. Woodfolk, MBChB, PhD, FAAAAI2; 1Division of Asthma, Allergy & Immunology, University of Virginia Health System, Charlottesville, VA, 2University of Virginia Asthma and Allergic Diseases Center and the Department of Pediatrics Division of Respiratory Medicine, Charlottesville, VA.

RATIONALE: The cellular mechanisms involved in rhinovirus (RV) induced asthma exacerbations in allergic subjects remain unclear. Basophils and dendritic cells (DCs) are key players in promoting Th2-driven inflammation in allergic asthma. We recently reported increased IgE responsiveness in circulating basophils of allergic asthmatics following RV exposure. Thus, we aimed to explore how RV infection impacts Th2-associated pathways in basophils and DCs.

METHODS: Allergic asthmatics (n = 9) were challenged intranasally with human rhinovirus 16. Flow cytometry was employed to capture global changes and extensively immunophenotype circulating basophils, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in fresh whole blood obtained pre-inoculation (day 0), and during acute (day 4) and convalescent (day 21) phases post-inoculation. The multi-dimensional data analysis software, viSNE, was used to generate cell clusters of similar phenotypes.

RESULTS: During the acute phase, viSNE analysis revealed enhanced expression of activation markers on mDCs and pDCs, including HLA-DR and CD86, in conjunction with unconventional markers on mDCs including CD63 and prostaglandin D2 receptor (CRTH2). Furthermore, expression of intracellular Syk increased both in mDCs and pDCs, with little change in FcεRIα. By contrast, basophils displayed increased expression of FcεRIα, Syk and CD63, and levels of FcεRIα and CD63 remained elevated at day 21. At baseline, asthmatics segregated into IL-4hi (n = 6) and IL-4lo (n = 3) subgroups based on the percentage of IL-4+ basophils, mDCs and pDCs. Paradoxically, IL-4lo asthmatics developed more severe respiratory symptoms than the IL-4hi group.

CONCLUSIONS: Collectively these findings highlight complex cellular changes induced by RV infection in allergic asthmatics that do not fit a simple Th2 amplification model.