Inflammasome Activation To Staphylococcus aureus Is Associated With Increased Wheezing In Early Life

Eric Schauberger¹, Victoria Rajamanickam¹, Robert F Lemanske, Jr¹, James E Gern¹, Daniel J Jackson¹
University of Wisconsin – Madison, School of Medicine and Public Health, Departments of ¹Pediatrics and ²Statistics

BACKGROUND

• Aberrant immune responses to pathogenic airway bacteria in infancy have been associated with the development of asthma.
• The inflammasome is an intracellular pattern recognition receptor that detects microbial products as endogenous danger signals.
• Inflammasome activation results in the production of proinflammatory cytokines IL-1β and IL-6. These cytokines have been implicated as playing a role in asthma pathogenesis.
• Question: How does inflammasome activation in PBMCs relate to childhood asthma risk?
• We hypothesized that increased levels of proinflammatory cytokines IL-1β and IL-6 are associated with inflammasome activation in PBMCs in association with early childhood wheezing.

METHODS

Experimental Design

Blood collected from COAST children at 1yr of age (N=277)

Peripheral Blood Mononuclear Cells (PBMCs)

Cytokine quantification (IL-6 and IL-1β) by multiplex assay (Luminex)

COAST birth cohort

• Children at high-risk for the development of asthma were studied prospectively from birth in the Childhood Origins of Asthma (COAST) study; 259 were followed to age 6, and 217 to age 13.
• Number of wheeze episodes were quantified for the first 3yrs of life.
• Nasal samples were collected during respiratory illnesses and etiology was assessed by multiplex PCR. RSV and RV infections were specifically investigated.

Analysis

• All data were log transformed and visualized on a Violin plot (with median, q1,q3, min, max and interquartile ranges provided).
• Comparisons of cytokine values (IL-6 and IL-1β) were analyzed using one-way ANOVA with P<0.05 (one-way ANOVA) considered significant.

RESULTS

Bacterial-induced inflammasome activation may be differentially associated with wheezing illness during early childhood depending on viral etiology.

Figure 1: LPS and SAC induced IL-6 level is associated with Rhinovirus (RV) wheeze during the first 3yrs of life.

Figure 2: SAC induced IL-1β is associated with RV wheeze during the first 3yrs of life. LPS induced IL-1β was NOT associated.

CONCLUSIONS

• Early childhood wheeze (first 3yrs of life) was associated with a higher level of inducible inflammasome activation as demonstrated by increased IL-1β and IL-6.
• This association is strongest in childhood wheeze occurring in years 2 and 3 of life.
• Rhinovirus-related wheeze was associated with increased inflammasome activation. No association was seen with RSV.
• The inducible activation is stronger with SAC than LPS consistent with a different mechanism or greater potency of stimulation.
• Limitations include:
  • These are associations and no causal relationship established.
  • We did not measure inflammasome activity directly but cytokine products.

Acknowledgements

• COAST Families
• Amy Dresen (and the rest of the Gern Lab)
• Christopher Tisler
• Funded by: P01 HL070831, U10 HL064305, R01 HL061879 (COAST); HHS/NIH grant 5UG3OD023282 (CREW)