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





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-1B and IL-6. These cytokines have been implicated as playing a role in asthma pathogenesis.
- Question: How does inflammasome activation relate to risk of childhood wheeze?
- We hypothesized that increased inducible inflammasome activation in PBMCs is associated with early childhood wheezing.

METHODS

Experimental Design



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



Peripheral Blood Mononuclear Cells stimulated ex vivo with LPS or Staph aureus (SAC). Supernatant collected at 24hrs.



Cytokine quantification (IL-6 and IL-1B) 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.

<u>Analysis</u>

- 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-1B) with P<0.05 (one-way ANOVA) was considered significant

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

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

RESULTS

Rhinovirus (RV) wheeze during the first 3yrs of life.



during the first 3yrs of life. LPS induced IL-1B was NOT associated.

RESULTS

- inflammasome activation as demonstrated by increased IL-1B 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.

- (CREW)

American Family Children's Hospital



Department of Pediatrics UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE AND PUBLIC HEALTH

• Staph aureus (SAC) stimulation resulted in significantly increased proinflammatory cytokine (IL-6, IL-1B) levels in children who wheezed in the first 3 years of life (P=0.02 and 0.01 respectively, data not shown).

> This association is seen in RV-related wheeze (Figure 1 and 2) but NOT in RSV-related wheeze (data not shown) during the first 3yrs of life.

The association with SAC induced IL-6 and IL-1B is **NOT** significant in Year 1 of life but is significant in Years 2 (P=0.002) and 3 (P=0.03) of life. Aerosensitization showed no effect on outcomes

(data not shown). • LPS stimulation resulted in significant increased IL-6

levels (but not IL-1B) in RV-associated wheeze during the first 3yrs of life

CONCLUSIONS

• Early childhood wheeze (first 3yrs of life) was associated with a higher level of inducible

<u>Acknowledgements</u> **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 5UG30D023282