BACKGROUND

- Acute respiratory distress syndrome (ARDS) remains a significant cause of morbidity and mortality in ICU patients. Oxidative stress and inflammation have significant role in pathogenesis of lung injury in ARDS.
- Extracellular superoxide dismutase (EC SOD) is an important enzymatic defense against superoxide.
- A R213G SNP in matrix binding region of EC-SOD results in release of EC-SOD into alveolar fluid without affecting enzyme activity.
- Carriers of R213G SNP have attenuates risk of exacerbations of COPD and allergic airway inflammation in asthma.
- We have demonstrated the protective effects of R213G SNP in bleomycin-induced lung fibrosis and LPS-induced lung injury.
- While the role of R213G SNP has been investigated in COPD and Asthma in human studies, and LPS- and bleomycin induced lung injury in animal studies, it's role in infectious pneumonia and sepsis remains unknown.

HYPOTHESIS

R213G variant results in re-distribution of EC-SOD to the alveolar compartment in response to Staphylococcus aureus infection, and is protective against S. aureus-induced acute lung injury and inflammation.

METHODS

*S. aureus pneumonia: C57BL/6 (WT) and R213G mice infected IT with 1x10^8 CFUs of methicillin-resistant S. Aureus (MRSA) strain. 24-hrs post-inoculation, lungs, spleen and bronchoalveolar fluid (BALF) was collected.

Protein analysis: EC-SOD protein expression measured in lung and BALF by Western blot.

Evaluation of lung injury: Total cell counts and differentials, total protein and albumin, measured in BALF.

Evaluation of inflammation: IL-1β, IL-6, CXCL-1 and TNF-α measured by ELISA in BALF and qPCR in lung homogenates.

Bacterial translocation: Spleens and lung homogenates plated on TSA agar and bacterial CFUs counted after 24hrs.

Statistical analysis: Data were analyzed by unpaired t-test or 2-way ANOVA with Bonferroni post-tests. Significance defined as p<0.05.
* p<=0.05, ** p<=0.01 ***p<=0.001 ****p<=0.0001

CONCLUSIONS

- R213G variant is protective against lung injury and inflammation in S. aureus pneumonia
- Neutrophils may play a significant role in mediating the severity of injury in this model.
- R213G variant is protective against bacterial translocation potentially due to preserved integrity of alveolar-capillary barrier or enhanced systemic clearance/killing of the bacteria
- Further studies will interrogate the mechanisms driving this protection and therapeutic implications

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