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Influenza A Inhibits TH17 Host Defense Against Bacterial Pneumonia

Project Number
5R01HL107380-08

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Awardee Organization
UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Description

Abstract Text

SUMMARY Pneumonia, caused by bacterial and/or viral etiology, is the leading cause of death in children worldwide. Preceding viral illness, linked to influenza infection, is a primary risk factor associated with secondary bacterial pneumonia. Influenza infection is an annual, seasonal cause of morbidity and mortality throughout the world. Severe influenza pneumonia is often exacerbated by bacterial infection resulting in poor patient outcomes in those with preexisting lung morbidity and in previously healthy individuals. The **pandemic** potential of influenza viruses heightens the importance of understanding disease pathogenesis. Further, secondary bacterial pneumonia with Staphylococcus aureus is increasing in prevalence, while antibiotic resistance continues to propagate. The focus of this application is upon understanding the influenza-induced mechanisms of susceptibility to bacterial super-infection, the leading cause of death during **pandemic** outbreaks. During the previous funding period, our laboratory has identified suppression of bacterial-induced Type 17 immune responses by preceding influenza as a critical susceptibility mechanism. We have published extensively in the area of elucidating aberrant host defense pathways in this context. In this renewal application, we will build upon our ongoing work with three highly novel Aims derived from the original focus. We hypothesize that S. aureus-induced Type 17 innate immune activation is negatively regulated by influenza-induced STAT2 signaling and the Asc inflammasome. Further, we propose that exogenous antimicrobial peptide (AMP) therapy presents a novel therapeutic strategy in influenza, bacterial super-infection. In Aim 1 we will determine the mechanism(s) by which STAT2 signaling impairs anti-bacterial host defense against S. aureus during influenza super-infection. Aim 2 will focus on the mechanism(s) by which Asc inflammasome knockout mice are protected from exacerbation of secondary S. aureus infection. In Aim 3 we will investigate the mechanism of AMP production and evaluate the therapeutic potential of exogenous AMPs during influenza, S. aureus super- infection. The proposed studies will further our understanding of how influenza impairs subsequent immunity against S. aureus (Aim 1), how the immune response to S. aureus is initiated in the lung (Aim 2), and test novel therapeutic approaches for controlling post-influenza secondary bacterial pneumonia (Aim 3). Our overriding goal is to understand the critical mechanism(s) of susceptibility to influenza, S. aureus super- infection and provide novel treatment targets in a pre-clinical model of disease.

Public Health Relevance Statement

NARRATIVE The influenza virus infects millions globally each year and in some cases is complicated with bacterial super-infection, which can result in severe illness and/or death. This study addresses the mechanisms by which influenza makes the lung more susceptible to later bacterial infection. This proposal defines the molecular pathways by which influenza leads to suppressed Staphylococcus aureus host defense and attempts to identify novel therapeutic targets to improve patient outcomes.

NIH Spending Category

Thank you for your feedback!

Emerging Infectious Diseases Infectious Diseases Influenza Lung Pneumonia Pneumonia & Influenza Women's Health

Project Terms

Address Anti-Bacterial Agents Antibiotic Resistance Area Attenuated Bacterial Infections Bacterial Pneumonia Bone Marrow Cause of Death Cessation of life Child Chimera organism Data Disease Disease Outbreaks Disease model Epithelial Cells Epithelium Etiology Funding Goals Host Defense Human Immune response Immunity Impairment In Vitro Individual Infection Inflammasome Influenza Influenza A virus Interferon Type I Interferons Interleukin-1 beta Knockout Mice Laboratories Link Lung Mediating Mediator of activation protein Modeling Molecular Morbidity - disease rate

Details

No information available for 5R01HL107380-08

Sub Projects

No Sub Projects information available for 5R01HL107380-08

Publications

No Publications available for 5R01HL107380-08

Patents

No Patents information available for 5R01HL107380-08

Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

No Outcomes available for 5R01HL107380-08

Clinical Studies

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