Unfolded protein response in Influenza virus infection and inflammation

Project Number
1R01HL141364-01A1

Contact PI/Project Leader
ANATHY, VIKAS

Awardee Organization
UNIVERSITY OF VERMONT & ST AGRIC COLLEGE

Description

Abstract Text

PROJECT SUMMARY After infection the demand for influenza (IAV) protein synthesis and processing, including formation of disulfide bonds in cysteines of IAV-proteins in the endoplasmic reticulum (ER) of lung epithelial cells induces ER stress. ER stress in turn induces an ER based unfolded protein response (UPR). Viruses activate and sustain UPR for their replication, however, chronic UPR results in pro-inflammatory response and induction of apoptosis. It is not clear whether specific UPR components are seized by IAV for propagation and they also contribute to massive increases in IAV-induced pro-inflammatory responses and injury to the lung. Our novel preliminary results suggest that IAV infection activates the latent transcription factor, ATF6α. ATF6α is known to bind to specific DNA elements of UPR related genes and upregulates their transcription. Computational analysis of IAV-induced cytokine/chemokine-promoters showed the presence of conserved ATF6α binding elements in the promoter regions of cytokines and chemokines. We next observed that deletion/inhibition of ATF6α decreases inflammation, cytokines/chemokines, IAV burden and airway hyperresponsiveness (AHR) in mice. Furthermore, we found that IAV infection increases specifically a PDI- PDIA3 in HBE cells and in mice infected with IAV. Lung epithelial specific ablation of PDIA3 significantly decreased disulfide bridges in IAV-proteins, cytokines/chemokines, IAV burden, and AHR responses in the lung. These results suggested a prominent role for ATF6α and PDIA3 during IAV infection and immunopathology. Our overarching hypothesis is that the IAV-induced activation of ATF6α and PDIA3 supports overt epithelial pro- inflammatory responses, disulfide bonds in IAV proteins and in pro-inflammatory cytokines to increase IAV propagation and lung immunopathology. We have designed two specific aims to test our hypothesis. In Specific Aim #1 we will determine the functional role of IAV-induced UPR-activated transcription factor ATF6α in regulating expression of cytokines/chemokines, subsequent induction of immunopathology and development of long lasting effects on lung health. The specific Aim #2 seeks to dissect the critical requirement of IAV-induced PDIA3 in disulfide mediated processing of IAV-proteins (HA & NA), pro-inflammatory cytokines/chemokines subsequent induction of immunopathology. In both aims we will use transgenic mouse models, cell culture and sensitive redox assays and biochemical assays. Most importantly we will assess the efficacy of specific inhibitors of ATF6α (Ceapin-A7) and PDIA3 (PACMA31) in easing IAV-induced UPR, decreasing subsequent pro- inflammatory responses, and ultimately resulting in resolution of IAV-induced immunopathology. These studies will shed light on the importance of the IAV-induced lung epithelial UPR in IAV propagation and overt pro- inflammatory responses and offers insight into new and highly needed treatment modalities for IAV infection and severe respiratory distress beyond supportive care.

Public Health Relevance Statement

PROJECT NARRATIVE In this proposal specifically we will examine the critical relationship between the stress caused by influenza virus in the endoplasmic reticulum (ER), activation of specific pathways resulting in influenza infection and overt cytokine/chemokine response from airway epithelial cells of the lung. The importance of these processes will be determined by deleting the proteins or enzymes that relay ER stress and ultimately cause damage to the lung; and we will take advantage of lung epithelial specific gene knock out mice, two specific inhibitors Ceapin-A7 and

PACMA31 to prove our hypothesis that specific components of ER stress pathway are involved in supporting IAV propagation, epithelial apoptosis, overt-pro-inflammatory response and subsequent development of lung injury. This project will likely yield alternative treatment strategies for influenza infection that potentially circumvent antigenic shifts and drifts, which results in development of resistance to existing therapies.

NIH Spending Category

Biodefense Emerging Infectious Diseases Genetics Infectious Diseases Influenza Lung Pneumonia & Influenza

Project Terms

ATF6 gene Ablation Apoptosis Binding Biochemical Biological Assay CCL20 gene CXCL1 gene Cell Culture Techniques Cells Chronic Clinical Computer Analysis Cysteine DNA Development Disulfides Elements Endoplasmic Reticulum Enzymes Epithelial Epithelial Cells Future Genes Genetic Transcription Goals Health Hemagglutinin Human IL8 gene Induction of Apoptosis Infection Inflammation Inflammatory Inflammatory Response Influenza Influenza A virus Influenza Hemagglutinin Injury Interleukin-6 Knockout Mice Light Lung Mechanics Mediating Messenger RNA Modality Modeling Molecular Mus

Details

No information available for 1R01HL141364-01A1

Sub Projects

No Sub Projects information available for 1R01HL141364-01A1

Publications

No Publications available for 1R01HL141364-01A1

Patents

No Patents information available for 1R01HL141364-01A1

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 conten

Thank you for your feedback!

No Outcomes available for 1R01HL141364-01A1

Clinical Studies

No Clinical Studies information available for 1R01HL141364-01A1

News and More

Related News Releases

No news release information available for 1R01HL141364-01A1

History

No Historical information available for 1R01HL141364-01A1

Similar Projects

No Similar Projects information available for 1R01HL141364-01A1

Thank you for your feedback!