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Visualization of Influenza Viral RNA Assembly

Project Number
5R01AI139063-02

Contact PI/Project Leader
LAKDAWALA, SEEMA S.

Awardee Organization
UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Description

Abstract Text

Influenza A viruses (IAV) pose a major public health threat through both seasonal epidemics and sporadic pandemics. The segmented nature of the viral genome promotes reassortment, a process where the genetic material between viruses is exchanged in a co-infected cell. In nature, reassortment leads to increased viral diversity and emergence of **pandemic** influenza viruses. For example, the 2009 influenza H1N1 ('swine flu') **pandemic** virus, emerged from reassortment of two circulating swine viruses. Prediction of future **pandemic** influenza viruses from circulating zoonotic virus populations is difficult because very little is known about the mechanism of reassortment within a single co-infected cell. To accurately define the process of reassortment, we must first understand the dynamics of intracellular viral RNA (vRNA) assembly. Influenza vRNA replicates in the nucleus and is transported to the plasma membrane for packaging, which requires one copy of all eight segments to assemble within a single virion to produce a fully infectious virus. In this proposal, we will build upon our previous data on influenza assembly and define 1) the assembly dynamics in physiologically relevant human and swine cell types, 2) the cellular proteins modulating vRNA transport, and 3) the location of reassortment within a co-infected cell. Our central hypothesis is that vRNA assembly occurs in a cell-type specific manner that correlates with IAV reassortment in different host species. The Specific Aims of this application will use a variety of sophisticated microscopy tools, including live cell imaging with a custom light-sheet microscope, to determine the assembly mechanism in various cell culture models. Aim 1 will utilize multicolor fluorescent in situ hybridization and live cell imaging techniques to explore the dynamics of influenza vRNA assembly in human and swine differentiated airway epithelial cells. Aim 2 will uncover the identity and roles of cellular cytoskeletal proteins and membranous organelles utilized during influenza vRNA assembly using biochemical approaches like proximity-dependent biotinylation. Aim 3 will combine imaging and genomic approaches to characterize the cellular location of vRNA intermingling during co-infection with two heterologous viruses in differentiated airway epithelial cells. The proposed work will address many outstanding questions in influenza biology regarding reassortment that have remained unanswered due to a lack of tools to track vRNA movement in live cells during a productive infection. In addition, these studies will identify novel host factors involved in vRNA packaging that can be pursued as potential therapeutic targets.

Public Health Relevance Statement

Influenza viruses cause seasonal epidemics and sporadic pandemics that create a substantial public health burden with over 200,000 hospitalizations and 3,000-45,000 deaths annually. The influenza viral genome is composed of eight RNA segments, all of which must be packaged into a single progeny virion for it to be infectious. The goal of this proposal is to determine how all eight segments are selectively packaged during viral infection and identify host factors involved in this process within differentiated human and swine airway cells. This research will lead to a greater understanding of influenza assembly and reassortment in physiologically relevant cell culture models. In addition, these studies have the potential to identify novel therapeutic targets for influenza infection.

NIH Spending Category

Biodefense **Biotechnology** **Emerging Infectious Diseases** **Genetics**
Infectious Diseases **Influenza** **Pneumonia & Influenza**

Project Terms

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Genetic Genetic Materials Genetic Processes Genomic approach Goals Hospitalization Human Imagery Imaging Techniques Infection Influenza Influenza A Virus, H1N1 Subtype Influenza A virus

Read More

Details

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UNITED STATES (US)

Department Type
GENETICS

Organization Type
SCHOOLS OF MEDICINE

State Code
PA

Congressional District
18

Other Information

FOA
PA-16-160

Study Section
Special Emphasis Panel[ZRG1-IDM-X(02)M]

Fiscal Year
2019

Award Notice Date
05-July-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
004514360

CFDA Code
855

Project Start Date
16-August-2018

Project End Date
31-July-2023

Budget Start Date
01-August-2019

Budget End Date
31-July-2020

Project Funding Information for 2019

Total Funding
$382,409

Direct Costs
$250,000

Indirect Costs
$132,409

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$382,409

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending

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Infectious Diseases; Influenza; Pneumonia & Influenza;

Sub Projects

No Sub Projects information available for 5R01AI139063-02

Publications

No Publications available for 5R01AI139063-02

Patents

No Patents information available for 5R01AI139063-02

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 5R01AI139063-02

Clinical Studies

No Clinical Studies information available for 5R01AI139063-02

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No news release information available for 5R01AI139063-02

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