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Receptor recognition and cell entry of coronaviruses

Project Number
5R01AI089728-09

Contact PI/Project Leader
LI, FANG

Awardee Organization
UNIVERSITY OF MINNESOTA

Description

Abstract Text

Receptor recognition and cell entry by viruses are two initial and essential steps in viral infection cycles. They are important determinants of viral host ranges, tissue tropisms and pathogenesis, and are primary targets for human intervention. Coronaviruses (CoVs) pose serious health threats to humans and other animals. SARS-CoV and MERS-CoV have infected thousands of people with significant fatality, whereas porcine epidemic diarrhea CoV is currently causing ~100% fatality in piglets. A virus-surface spike protein guides CoV entry into host cells by binding to its host receptor via its S1 subunit and fusing viral and host membranes via its S2 subunit. S1 from different CoVs recognizes a variety of host receptors through one or both of its domains (S1-NTD and S1-CTD), and the S1/S2 boundary is cleaved by host proteases for activation of membrane fusion by S2. Our previous research has determined a number of crystal structures of CoV S1 domains by themselves or in complex with their respective receptor, and also shown how proteolysis regulates the cell entry of some CoVs. Our research has contributed critically to the current knowledge about the molecular mechanisms for CoV receptor recognition, cell entry, and cross-species transmission. In this competitive renewal of R01, we will continue to investigate how CoVs exploit host receptors and host proteases for cell entry. This proposal has three specific aims. Aim 1 examines receptor binding by CoV S1-NTDs. Specifically, we will investigate whether S1-NTDs from different CoV genera have the same structural fold and evolutionary origin as host galectins (galactose-binding lectins). We will also examine how CoV S1-NTDs recognize sugar receptors. These studies will reveal the evolutionary origins of CoV S1-NTDs, enhance understanding of sugar recognition by CoVs, and may facilitate future design of sugar analogues and subunit vaccines to inhibit CoV infections. Aim 2 focuses on receptor binding by CoV S1-CTDs. Specifically, we will analyze the interactions between the S1-CTDs of bat SARS-like CoVs (SL-CoVs) and the protein receptor homologues from humans and other animals, and elucidate how bat SL-CoVs transmitted to humans and other animals to cause the SARS epidemic through evolutionary changes in their S1-CTDs. These studies will provide critical information for understanding emergence potential of bat SL-CoVs and for facilitating epidemic monitoring and control. Aim 3 investigates cell entry by CoVs. Specifically, we will investigate what host proteases activate CoV entry and how the proteases motifs in CoV spikes have evolved to modulate CoV entry. These studies will reveal how host proteases regulate CoV entry to meet their specific need for host range, tissue tropism and pathogenesis, and may facilitate future design of protease inhibitors to block CoV entry. Overall, this proposal investigates the molecular and structural mechanisms for receptor recognition, cell entry, cross-species transmission, and tissue tropism of CoVs, which will lead to novel principles in virology. This research is also important for evaluating the emerging disease potentials of CoVs and for preventing, controlling and treating CoV infections in humans and other animals.

Public Health Relevance Statement

This research investigates the molecular and structural mechanisms for the receptor recognition and cell entry of coronaviruses. It explores novel principles governing viral evolution, receptor recognition, cell entry, host ranges, cross-species infections, and tissue tropisms. These studies are critical for evaluating the emerging disease potentials of coronaviruses and for preventing, controlling and treating the spread of coronaviruses in humans or other animals.

NIH Spending Category

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

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Cleaved cell Complex Coronavirus Coronavirus Infections
Coronavirus spike protein Crystallization Development Diarrhea Disease
Disease Outbreaks Electrons Epidemic Evolution Family Family suidae
Funding Future Galactose Binding Lectin Goals Grant Health
Homologous Gene Human Infection Intervention Intestines Knowledge
Mammals Membrane Membrane Fusion Microscopic Modeling

Read More

Details

Contact PI/ Project Leader

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Not Applicable

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UNITED STATES (US)

Department Type
PHARMACOLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
MN

Congressional District
05

Other Information

FOA
PA-13-302

Study Section
Virology - A Study Section[VIRA]

Fiscal Year
2019

Award Notice Date
24-May-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
555917996

CFDA Code
855

Project Start Date
07-June-2016

Project End Date
31-May-2021

Budget Start Date
01-June-2019

Budget End Date
31-May-2020

Project Funding Information for 2019

Total Funding
$455,796

Direct Costs
$338,184

Indirect Costs
$117,612

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$455,796

NIH Categorical Spending

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UNIVERSITY OF MINNESOTA

Infectious Diseases; Infectious Diseases; Lung; Pneumonia; Pneumonia & Influenza;

Sub Projects

No Sub Projects information available for 5R01AI089728-09

Publications

No Publications available for 5R01AI089728-09

Patents

No Patents information available for 5R01AI089728-09

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 5R01AI089728-09

Clinical Studies

No Clinical Studies information available for 5R01AI089728-09

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Related News Releases

No news release information available for 5R01AI089728-09

History

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No Similar Projects information available for 5R01AI089728-09

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