Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

New Paradigm for Host and Viral Gene Regulation by MERS Coronavirus nsp1

Project Number
5R01AI114657-05

Contact PI/Project Leader
MAKINO, SHINJI

Awardee Organization
UNIVERSITY OF TEXAS MED BR GALVESTON

Description

Abstract Text

DESCRIPTION (provided by applicant): Middle East respiratory syndrome coronavirus (MCoV) emerged in Saudi Arabia in 2012 and has been disseminated into other countries in the Middle East, North Africa and Europe. Although MERS is most probably a zoonosis, MCoV can spread person-to-person. MCoV infection causes fever, cough and pneumonia leading to respiratory failure, and the reported case fatality is ~50%. Little is known about the mechanisms of MCoV's high virulence and pathogenesis. Coronaviruses (CoVs) carry a single-stranded, positive-sense RNA genome of ~30 kb. Immediately after infection, the translation of the viral genome produces two large polyproteins that are processed into 15 or 16 mature nonstructural proteins (nsp1-nsp16), most of which are involved in viral RNA synthesis, while some have other biological functions. Nsp1 protein of various CoVs inhibits host gene expression. Viral proteins that inhibit host gene expression are often major virulence factors, and, hence, CoV nsp1 proteins most probably play a critical role in CoV pathogenesis. Indeed, mouse hepatitis virus nsp1 is a major virulence factor, and SARS-CoV (SCoV) nsp1 inhibits the production of type I interferon and interferon-stimulated genes in infected cells. Nsp1 proteins of different CoVs use divergent strategies to exert host gene expression suppression; by binding to the 40S ribosomal subunit, SCoV nsp1 inhibits mRNA translation and induces endonucleolytic mRNA cleavage, while nsp1 of transmissible gastroenteritis virus does not induce mRNA cleavage, yet suppresses translation without binding to the 40S ribosomal subunits. Our data that MCoV nsp1 inhibited translation of host mRNAs and promoted mRNA cleavage without binding to the 40S subunits and other experimental results led us to hypothesize that MCoV nsp1 suppresses host gene expression by using mechanisms that have not been described in any viral proteins. This application aims to delineate the mechanisms of MCoV nsp1-induced translation inhibition and mRNA cleavage. We will also clarify the strategy that allows robust viral gene expression in MCoV-infected cells under conditions of nsp1- induced translation inhibition. The proposed studies will provide a foundation for understanding the modulation of host gene expression by MCoV and expand our knowledge of viral pathogenicity at the molecular level.

Public Health Relevance Statement

PUBLIC HEALTH RELEVANCE: Middle East respiratory syndrome coronavirus (MCoV) emerged in Saudi Arabia in 2012 and has been disseminated into other countries in the Middle East, North Africa and Europe. Because MCoV can spread person-to-person, it is an area of international public health concern. To understand MCoV pathogenicity at the molecular level, we will study how nsp1 protein, one of MCoV proteins, inhibits host gene expression and exerts robust viral gene expression in infected cells, where nsp1 efficiently suppresses host gene expression.

NIH Spending Category

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

Project Terms

5' Untranslated Regions Acute Kidney Failure Animals Area Binding Biological Process Camels Case Fatality Rates Case Study Cell Nucleus Cells Chiroptera Chronic Complex Coronavirus Coughing Country

Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

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UNIVERSITY OF TEXAS MED BR GALVESTON

Read More

Details

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Not Applicable

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UNIVERSITY OF TEXAS MED BR GALVESTON

City
GALVESTON

Country
UNITED STATES (US)

Department Type
MICROBIOLOGY/IMMUN/VIROL(

Organization Type
SCHOOLS OF MEDICINE

State Code
TX

Congressional District
14

Other Information

FOA
PA-13-302

Study Section
Virology - A Study Section[VIRA]

Fiscal Year
2019

Award Notice Date
12-April-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
800771149

CFDA Code
855

Project Start Date
01-May-2015

Project End Date
30-April-2021

Budget Start Date
01-May-2019

Budget End Date
30-April-2021

Project Funding Information for 2019

Total Funding
$387,500

Direct Costs
$250,000

Indirect Costs
$137,500

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$387,500

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category

Thank you for your feedback!

Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

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Awardee Organization
UNIVERSITY OF TEXAS MED BR GALVESTON

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

Sub Projects

No Sub Projects information available for 5R01AI114657-05

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Simila Publi
Characterization of the Molecular Interactions That Govern the Packaging of Viral RNA Segments into Rift Valley Fever Phlebovirus Particles.			
Journal of virology 2021 06 24; 95 (14) e0042921	Tercero, Breanna; Narayanan, Krishna; Terasaki, Kaori; Makino, Shinji	2021	
Mechanisms of Coronavirus Nsp1-Mediated Control of Host and Viral Gene Expression.			
Cells 2021 02 02; 10 (2)	Nakagawa, Keisuke; Makino, Shinji	2021	
An Infectious cDNA Clone of SARS-CoV-2.			
Cell host & microbe 2020 05 13; 27 (5) 841-848.e3	Xie, Xuping; Muruato, View All	2020	iCite 44.63
Reverse genetics approaches for the development of bunyavirus vaccines.			
Current opinion in virology 2020 10; 44 16-25	Tercero, Breanna; Makino, Shinji	2020	iCite 1.04
Severe Acute Respiratory Syndrome Coronavirus 2 from Patient with Coronavirus Disease, United States.			
Emerging infectious diseases 2020 06; 26 (6) 1266-1273	Harcourt, Jennifer: View All	2020	iCite 56.15
A nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19.			

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Back to Search Results

Description

Details

Sub-Projects

Publications

Patents

Outcomes

Clinical Studies

News and More

History

Similar Projects

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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 5R01AI114657-05

Clinical Studies

No Clinical Studies information available for 5R01AI114657-05

News and More

Related News Releases

No news release information available for 5R01AI114657-05

History

No Historical information available for 5R01AI114657-05

Similar Projects

No Similar Projects information available for 5R01AI114657-05