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Novel VP30-host Interactions that Negatively Regulate Ebola Virus Infection

Project Number
1R01AI143292-01A1

Contact PI/Project Leader
AMARASINGHE, GAYA K.Other PIs

Awardee Organization
WASHINGTON UNIVERSITY

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Description

Abstract Text

ABSTRACT The filoviruses, Ebola and Marburg viruses (EBOV and MARV), are emerging, negative-strand RNA viruses associated with outbreaks of severe viral hemorrhagic fever. The virulence and emerging nature of these zoonotic pathogens makes them a significant threat to human health, potential agents of bioterrorism, and NIAID category A priority pathogens. Currently, no approved anti-filovirus therapeutics are available. Importantly, there is a major gap in our understanding with regard to the role of host factors at critical stages in the viral replication cycle. The overall goal of this revised R01 application is to characterize EBOV VP30 (eVP30), a key viral protein that facilitates viral transcription, and its interactions with host factors. Our plan builds on recent successes in structurally and functionally characterizing how eVP30 interacts with the viral nucleoprotein (NP) to modulate EBOV RNA synthesis and on a joint (Amarasinghe, Basler, and Krogan groups) unbiased proteomics screen using EBOV proteins as bait that uncovered 193 high-confidence EBOV- human protein-protein interactions (PPIs), including one between eVP30 and the host ubiquitin ligase RBBP6. A crystal structure of this complex revealed that RBBP6 and the viral NP compete for the same VP30 binding surface. Comparison of NP and RBBP6 peptides that bind eVP30 revealed a common PPxPxY motif that is necessary for the interaction. Whereas knockdown of endogenous RBBP6 stimulated viral transcription and increased EBOV infectivity, overexpression of RBBP6 or its peptide severely inhibited EBOV transcription and infection. Interestingly, at least two additional eVP30 interactors from our dataset (hnRNP L and hnRNP UL1) also possess PPxPxY motifs. Based on these findings, we propose a multidisciplinary approach to (1) Determine the structure of eVP30 N-terminus and define its association with RNA and protein ligands in the absence and presence of NP; (2) Determine the mechanisms by which eVP30-interacting proteins RBBP6, hnRNP L, and hnRNP UL1 modulate eVP30 function and RNA synthesis; and (3) Test the hypothesis that eVP30 modulates the function of host factors RBBP6, hnRNP L, and hnRNP UL1. These studies will characterize unique host interactions that negatively regulate EBOV replication with the goals of defining how EBOV manipulates host pathways and identifying novel therapeutic targets.

Public Health Relevance Statement

PROJECT NARRATIVE Pathogenic Ebola and Marburg viruses cause rare but deadly outbreaks among human populations. The recent outbreak in West-Africa coupled with a rising potential for misuse in the form of bioterrorism, underscore the importance of our proposed studies on these viruses to global health. The current studies are important as they will identify novel host targets that are important for viral replication and define broad spectrum targets to develop therapy.

NIH Spending Category

Biodefense Emerging Infectious Diseases Genetics Infectious Diseases Rare Diseases

Project Terms

Address Affinity Africa Binding Biochemical Biochemistry Biological Assay Bioterrorism Category A pathogen Cell physiology Cells Collaborations Complex Coupled Crystallization Data Data Set Democratic Republic of the Congo Disease Outbreaks Ebola virus Equilibrium Family member Filovirus Frankfurt-Marburg Syndrome Virus Gene Expression Genes Genetic Transcription Genome Goals Growth Health Heterogeneous-Nuclear Ribonucleoprotein L Heterogeneous-Nuclear Ribonucleoproteins Human Infection Integration Host Factors Joints Ligands Mediating Messenger RNA Mutate National Institute of Allergy and Infectious Disease Nature Nucleoproteins Pathogenicity

Read More

Details

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Awardee Organization
WASHINGTON UNIVERSITY

WASHINGTON UNIVERSITY

City
SAINT LOUIS

Country
UNITED STATES (US)

PATHOLOGY

Organization Type
SCHOOLS OF MEDICINE

MO

Congressional District
01

Other Information

FOA
PA-18-484

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

Fiscal Year
2019

Award Notice Date
28-February-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
068552207

CFDA Code
855

Project Start Date **01-March-2019**

Project End Date **29-February-2024**

Budget Start Date **01-March-2019**

Budget End Date **29-February-2020**

Project Funding Information for 2019

Total Funding
$832,743

Direct Costs
$711,741

Indirect Costs
$121,002

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$832,743

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$832,743	Biodefense; Emerging Infectious Diseases; Genetics; Infectious Diseases; Rare Diseases;

Sub Projects

No Sub Projects information available for 1R01AI143292-01A1

Publications

No Publications available for 1R01AI143292-01A1

Patents

No Patents information available for 1R01AI143292-01A1

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 content below.

No Outcomes available for 1R01AI143292-01A1

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No news release information available for 1R01AI143292-01A1

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No Historical information available for 1R01AI143292-01A1

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