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Structural Basis for Henipavirus Matrix Protein Nucleo-Cytoplasmic Trafficking

Project Number
1R21AI144880-01

Contact PI/Project Leader
BASLER, CHRISTOPHER F

Awardee Organization
GEORGIA STATE UNIVERSITY

Description

Abstract Text

Nipah virus (NiV) and Hendra virus (HeV) are related, highly pathogenic, zoonotic paramyxoviruses that use **bats** from the Pteropus genus as reservoir hosts. First identified in an outbreak in Malaysia, near annual NiV outbreaks in Bangladesh and India are now known to occur. Since 2001, the case fatality rate in Bangladesh and India has been 75% and there is also evidence of human-to-human transmission of NiV. These facts demonstrate the potential public health impact of such infection. Of the nine main proteins produced by NiV and HeV, the matrix protein (M) is of note because of several unique properties and intermolecular interactions. M directs the assembly and budding of new viral particles and impairs innate antiviral signaling that leads to type I interferon (IFN) responses. Interestingly, despite M assembly and anti-IFN functions occurring in the cytoplasm, M traffics to the nucleus and data suggests that nuclear trafficking is important for budding. Two classical nuclear localization signals (cNLSs) have been reported in NiV M, one monopartite (monoNLS) and one bipartite (bpNLS). However, the bpNLS is reported to be more important, with K258 within the bpNLS deemed critical for nuclear import and K258 ubiquitination required for nuclear-cytoplasmic trafficking. K258R mutants still enter the nucleus but are retained in the nucleolus whereas K258A mutants fail to go to the nucleus. Both mutants are defective for budding suggesting either a critical role for nuclear import or for ubiquitination in budding. Interestingly, suppression of IFN also requires K258 that lies in the proposed bpNLS, raising the possibility that nuclear trafficking and IFN suppressing functions of M might be co-regulated. However, the recently published X-ray crystal structure of the HeV M raises questions as to the current model of M nuclear import. The bpNLS is within an alpha-helix, however there are no bpNLSs that exist as an alpha-helix in the protein data bank (PDB). Moreover, mutations to the bpNLS that disrupt nuclear import are likely to introduce other defects in the protein as this region is reported to be a hot spot for ubiquitination. In contrast, our Preliminary data demonstrates that when the monopartite and bipartite NLS regions are separately fused with GST, only the monoNLS binds to importin-α (IMPα). We have also been able to generate a co-crystal between the monoNLS and IMPα. These data suggest the likelihood that M nuclear import is mediated through interaction of the monoNLS with IMPα. Given the critical role for nucleocytoplasmic trafficking of M for its budding function and the overlap of the regulatory lysine K258 with a reported nuclear import signal, understanding the precise mechanisms of trafficking will be important to fully appreciate M function and henipavirus biology. To clarify the mechanisms of M trafficking we will use structural and biophysical approaches to define the interactions between the NiV and HeV M monopartite and bipartite NLS peptides and IMPα and to characterize the interaction between the full-length NiV M and IMPα:IMPβ. Based on these data, we will then test the functional significance of M-IMPα interactions through the use of cell-based assays of M function and wild-type or mutated NiV and HeV M proteins.

Public Health Relevance Statement

Pathogenic Nipah virus and Hendra virus cause intermittent deadly outbreaks among human populations. High fatality rates coupled with concerns about for misuse in the form of bioterrorism, underscore the importance of our proposed studies on these viruses to global health. The current studies focus on a key viral protein, the matrix protein, that is required for virus propagation, however, the proposed studies will define how matrix protein contributes to virus replication and to identify new antiviral drug targets, thereby addressing important scientific and medical needs.

NIH Spending Category

Biodefense | Emerging Infectious Diseases | Infectious Diseases | Rare Diseases

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Defect Disease Outbreaks Drug Targeting Emerging Communicable Diseases Encephalitis Equus caballus Exhibits Family Family suidae Fatality rate Felis catus Genus Pteropus Hendra Virus Henipavirus Hot Spot Human Impairment India Infection Interferon Type I Interferons Length

Read More

Details

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Department Type
MISCELLANEOUS

Organization Type
ORGANIZED RESEARCH UNITS

State Code
GA

Congressional District
05

Other Information

FOA
PA-18-489

Study Section
Virology - A Study Section[VIRA]

Fiscal Year
2019

Award Notice Date
06-February-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
837322494

CFDA Code
855

Project Start Date
06-February-2019

Project End Date
31-January-2021

Budget Start Date
06-February-2019

Budget End Date
31-January-2020

Project Funding Information for 2019

Total Funding
$178,341

Direct Costs
$129,823

Indirect Costs
$48,518

Year	Funding IC	
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$178,341

Thank you for your feedback!

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Diseases; Infectious Diseases; Rare Diseases;

Sub Projects

No Sub Projects information available for 1R21AI144880-01

Publications

No Publications available for 1R21AI144880-01

Patents

No Patents information available for 1R21AI144880-01

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 1R21AI144880-01

Clinical Studies

No Clinical Studies information available for 1R21AI144880-01

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Related News Releases

No news release information available for 1R21AI144880-01

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No Historical information available for 1R21AI144880-01

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Structural Basis for Henipavirus Matrix Protein Nucleo-Cytoplasmic Trafficking

Project Number	Contact PI/Project Leader	Awardee Organization
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