Structure and functional dynamics of virus-host protein interactions

Project Number	Contact PI/Project Leader	Awardee Organization
5R01GM127723-02	CHO, JAE HYUN	TEXAS A&M AGRILIFE RESEARCH

Description

Abstract Text

The 1918 influenza A virus (IAV), also known as the Spanish flu, caused the worst influenza **pandemic** in human history. Nonstructural protein 1 (NS1) is a multifunctional virulence factor associated with the suppression of anti- viral immune responses and thereby has been identified as one of the molecular determinants of high pathogenicity of the 1918 IAV. NS1 of the 1918 IAV (1918 NS1) contains a proline-rich motif (PRM) that mediates binding with host CrkII with high affinity and selectivity. The 1918 NS1:CrkII interaction plays critical roles in the suppression of host anti-viral immune responses and the enhancement of viral replication. Moreover, NS1s of many avian/swine IAVs contain the CrkII-binding PRM. Given the zoonotic potential of IAVs, there is a critical need to determine the molecular mechanisms by which the interaction of 1918 NS1 and cellular CrkII is regulated. The long-term goal of our research program is to elucidate the molecular mechanisms underlying virus-host protein interactions. Our objectives in this proposal are to determine the structural mechanisms of the 1918 NS1:CrkII interaction, and to determine the molecular and cellular mechanisms whereby the 1918 NS1:CrkII complex induces PI3K activation, resulting in enhanced viral replication. Our central hypothesis is that the 1918 NS1:CrkII complex is structurally dynamic, which is functionally important for the interaction with the p85 regulatory subunit of PI3K. To test this hypothesis, we will determine the structure of the 1918 NS1:CrkII complex and elucidate how the complex interacts with p85 to activate the PI3K signaling pathway. Our rationale for these studies is that the mechanistic understanding of the interactions of 1918 NS1 with CrkII and p85 would help identify previously undiscovered target sites to develop for potential inhibitors against the 1918 NS1. Through a synergistic approach combining small-angle X-ray scattering, NMR spectroscopy, molecular dynamics simulation, and cell-based assays, we will pursue the following specific aims. Aim 1. To determine the structural mechanism of the 1918 NS1:CrkII interaction using a battery of biophysical experiments. Hijacking and relocation of CrkII into the nucleus is a distinctive feature of the 1918 **pandemic** IAV NS1. To understand this process, we will reveal structural and energetic mechanisms by which the affinity and lifetime (1/koff) of the 1918 NS1:CrkII complex are modulated. Aim 2. To determine the molecular mechanism underlying NS1-induced PI3K activation. The 1918 NS1:CrkII interaction markedly enhances NS1-induced PI3K activation; however, its molecular mechanism is unknown. We will seek to comprehensively determine the molecular mechanisms by which the 1918 NS1:CrkII complex interacts with the p85 subunit of PI3K, reveal its functional role in PI3K activation, and identify hotspot NS1 residues that interact with both CrkII and p85 . This study is expected to have a positive impact on the development of anti-viral agents targeting NS1-host protein interactions.

Public Health Relevance Statement

Project Narrative The proposed research is relevant to public health because the discovery of the structural and energetic mechanisms by which a viral virulence factor hijacks cellular signaling proteins is ultimately expected to increase understanding of the pathogenicity of influenza viruses and help the development of therapeutics for future influenza pandemics. Thus, the proposed research is relevant to the part of NIH's mission that pertains to developing fundamental knowledge that will advance understanding of human health and disease.

NIH Spending Category

Emerging Infectious Diseases Infectious Diseases Influenza Pneumonia & Influenza

Project Terms

Affinity Antiviral Agents Binding Binding Sites Biological Assay Biophysics Birds Cell Nucleus Cells Competitive Binding Complex Data Development Disease Epidemic Future Goals Health Human Immune response In Vitro Infection Influenza A virus Integration Host Factors Kinetics Knowledge Mediating Mission Molecular Molecular Conformation N-terminal NMR Spectroscopy Nonstructural Protein Pathogenicity Phosphotransferases Play Process Proline Proteins Public Health Recording of previous events Research Resolution Roentgen Rays

Signaling Protein Site Spanish flu Structural Models Structure Testing

Read More

Details

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BIOCHEMISTRY

Organization Type
SCHOOLS OF ARTS AND SCIENCES

State Code
TX

Congressional District
17

Other Information

FOA
PA-18-484

Study Section
Macromolecular Structure and Function B Study Section[MSFB]

Fiscal Year
2019

Award Notice Date
22-August-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

DUNS Number
847205713

CFDA Code
859

Project Start Date
20-September-2018

Project End Date
31-August-2023

Budget Start Date
01-September-2019

Budget End Date
31-August-2020

Project Funding Information for 2019

Total Funding
$315,177

Direct Costs
$244,362

Indirect Costs
$70,815

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES	$315,177

NIH Categorical Spending

Click here for more information on NIH Categorical Spending

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES	$315,177	Emerging Infectious Diseases; Infectious Diseases; Influenza; Pneumonia & Influenza;

Sub Projects

No Sub Projects information available for 5R01GM127723-02

Publications

Export

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite
Molecular Basis of the Ternary Interaction between NS1 of the 1918 Influenza A Virus, PI3K, and CRK.					
Viruses 2020 03 20; 12 (3)	Dubrow, Alyssa; Lin, Sirong; Savage, Nowlan; Shen, Qingliang; Cho, Jae-Hyun	2020			iCite 0.49
Entropy Hotspots for the Binding of Intrinsically Disordered Ligands to a Receptor Domain.					
Biophysical journal 2020 05 19; 118 (10) 2502-2512	Shi, Jie; Shen, Qingliang; Cho, Jae-Hyun; Hwang, Wonmuk	2020			iCite 0.35
Molecular recognition of a host protein by NS1 of pandemic and seasonal influenza A viruses					

Thank you for your feedback!

Journal (Link to PubMed abstract)	Authors	Publication Year	Similar Publications	CitedBy	iCite RCR
Proceedings of the National Academy of Sciences of the United States of America 2020 03 24; 117 (12) 6550-6558	Cho, Jae-Hyun; Zhao, Baoyu; Shi, Jie; Savage, Nowlan; Shen, Qingliang; Byrnes, James; Yang, Lin; Hwang, Wonmuk; Li, Pingwei	2020			0.74

The structure and conformational plasticity of the nonstructural protein 1 of the 1918 influenza A virus.

Biochemical and biophysical research communications 2019 10 08; 518 (1) 178-182	Shen, Qingliang; Cho, Jae-Hyun	2019			0.41

Patents

No Patents information available for 5R01GM127723-02

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 5R01GM127723-02

Clinical Studies

No Clinical Studies information available for 5R01GM127723-02

News and More

Related News Releases

No news release information available for 5R01GM127723-02

History

No Historical information available for 5R01GM127723-02

Similar Projects

No Similar Projects information available for 5R01GM127723-02

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