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Rickettsia-host interface and multiple paths to invasion

Project Number
5R01AI126853-04

Contact PI/Project Leader
AZAD, ABDU F

Awardee Organization
UNIVERSITY OF MARYLAND BALTIMORE

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Description

Abstract Text

The global impact of rickettsial infections is illustrated by the resurgence of long-known pathogens, as well as the emergence of newly recognized pathogens. Infections with Rickettsia rickettsii (Rocky Mountain Spotted Fever) continue with severe consequences in South and Central America. The resurgence of R. conorii (Mediterranean Spotted Fever) in Europe, the Middle East and Africa, as well as a recent worldwide rise in murine typhus (R. typhi), highlights the threats of rickettsial diseases. Despite the public health importance of pathogenic Rickettsia spp.,, our limited knowledge of ricketsial biology has been an impediment to progress towards more effective intervention modalities. Our phylogenomics analyses have highlighted considerable variation across Rickettsia genomes, providing a framework to link particular genotypes with their associated **disease** phenotypes. For several bona fide secretory proteins that have been characterized in universal rickettsial processes (i.e., host cell adhesion, invasion and intracellular growth and survival), a patchy genomic distribution indicates that the mechanisms underpinning these processes are inherently different across rickettsial groups. For instance, our recent work on R. typhi (Typhus Group) identified a novel invasin, RalF, which interacts with host Arf6 in a process dependent on host phosphoinositide PIP2. Curiously, RalF genes are absent from species of Spotted Fever Group (SFG). Conversely, two well-characterized surface proteins (Sca0 and Sca2) of SFG pathogens are either absent (Sca0) or highly divergent (Sca2) in non-SFG rickettsial species. Thus, mechanisms of Rickettsia host cell invasion are more complex than previously appreciated, necessitating the need to employ a comparative approach for investigating the factors underpinning pathogenesis. Under this proposal, our work will focus on identifying the mammalian and invertebrate host cell targets of Sca3 and divergent Sca2 (d-Sca2) proteins from non-SFG species (Aim 1). Additionally, we will investigate the manner by which non- SFG species trigger phosphoinositide (PIP) metabolism to facilitate membrane ruffling and rickettsial endocytosis, with identified host proteins and PIPs present on the early endosome further explored as docking sites for rickettsial phospholipases that mediate phagosome escape (Aim 2). The successful outcome of this work will provide important clues on how divergent Rickettsia species utilize different molecules to achieve the universal rickettsial process of host cytoplasmic infection via induction of phagocytosis. We anticipate this knowledge to yield **disease**-specific therapeutic approaches to combat fatal rickettsioses.

Public Health Relevance Statement

Project Narrative Arthropod-borne Rickettsia species, including several highly pathogenic species are responsible for significant morbidity and mortality in the absence of timely intervention. Our overall objective is to investigate the roles of secreted proteins by non- Spotted Fever Group species during host cell infection. This information will lay the foundation for more efficacious vaccine and therapeutic interventions for rickettsial diseases.

NIH Spending Category

Biodefense Emerging Infectious Diseases Infectious Diseases Rare Diseases Vector-Borne Diseases

Project Terms

Actins Adherence Adhesions Africa Arthropods Bacterial Adhesins Biology Bioterrorism Boutonneuse Fever Cell Adhesion Cells Central America Complex Cytolysis Cytoplasm Cytoskeleton Data **Disease** Docking Drug Design Early Endosome **Emerging** Communicable Diseases Endemic Flea-Borne Typhus Endocytosis Endothelial Cells Epithelial Eukaryotic Cell Europe FMNL1 gene Family Fever Fleas Foundations Genes Genome Genomics Genotype Genus Felis Goals Growth Infection Insecta Integrins Intervention Invertebrates Knowledge Lead Ligands Link Mediating Membrane Membrane Proteins Metabolism Middle East Modality Molecular

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Awardee Organization
UNIVERSITY OF MARYLAND BALTIMORE

Organization

Name
UNIVERSITY OF MARYLAND BALTIMORE

City
BALTIMORE

Country
UNITED STATES (US)

Department Type
MICROBIOLOGY/IMMUN/VIROLOGY

Organization Type
SCHOOLS OF MEDICINE

State Code
MD

Congressional District
07

Other Information

FOA
PA-13-302

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

Fiscal Year
2019

Award Notice Date
17-May-2019

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number
188435911

CFDA Code
855

Project Start Date **15-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
$560,764

Direct Costs
$362,954

Indirect Costs
$197,810

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$560,764

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 ALLERGY AND INFECTIOUS DISEASES	$560,764	Biodefense; Emerging Infectious Diseases; Infectious Diseases; Rare Diseases; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 5R01AI126853-04

Publications

No Publications available for 5R01AI126853-04

Patents

No Patents information available for 5R01AI126853-04

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 5R01AI126853-04

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No Clinical Studies information available for 5R01AI126853-04

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No news release information available for 5R01AI126853-04

History

No Historical information available for 5R01AI126853-04

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No Similar Projects information available for 5R01AI126853-04

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