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Modulation of Human Cells by Virulent Francisella tularensis

Project Number
1ZIAAI001097-12

Contact PI/Project Leader
BOSIO, CATHARINE

Awardee Organization
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Description

Abstract Text

Francisella tularensis (FT), the causative agent for **tularemia**, can infect humans by a number of routes, including vector-borne transmission. However, it is inhalation of the bacterium, and the resulting pneumonic **tularemia**, that represents the most dangerous form of disease. This is due to the short incubation time (3-5 days), non-specific symptoms, and a high mortality rate (greater than 80%) in untreated individuals. Furthermore, FT has been weaponized by both the United States and the former Soviet Union making it a viable candidate for use as a biological weapon. Despite over 80 years of research on FT around the world, very little is understood about the dynamic interaction of this bacterium with the host, especially following aerosol infection. My laboratory has established that, similarly to murine cells, human dendritic cells and macrophages are acutely susceptible to infection with FT, but fail to produce pro-inflammatory cytokines or undergo maturation. Further, virulent FT actively interferes with the ability of human DC and macrophages to respond to secondary stimuli. Understanding the mechanism by which FT actively suppresses DC and macrophage function is a central directive of my laboratory. We are tackling this directive in two different ways. Specific Aim 1: We are analyzing the role Francisella lipids play in mediating anti-inflammatory responses. Structures present on the surface of bacteria are the first components encountered by the host cell. Thus, it is possible that, in the context of FT infections, these structures contribute to the early, rapid suppression of human dendritic cells. Bacterial lipids represent one such structure. We have recently identified one of the active lipid species present in FT that inhibit inflammation. We have tested a synthetic version of this lipid and confirmed that it also impairs inflammatory responses. We have identified one of the receptors utilized by both the intact bacterium and purified lipid as well as a host signaling molecule required to promote immunosuppressive responses. Importantly, we have also demonstrated that FT lipids can limit pathogenic inflammatory responses driven by other infectious agents in vitro, including Dengue virus. We have screened FT lipids (including synthetic liposomes) for off target effects in vivo following delivery via multiple routes and have also found that they potently dampen inflammation driven by unrelated bacterial infection in vivo. We have filed a patent application for use of FT lipids as novel anti-inflammatory therapeutics. We are currently identifying the other lipids present in FT that contribute to suppression of inflammation and additional mechanisms by which they interfere with functions in human cell. We have generated a lipid mutant and identified a requirement for a specific species of FT lipid in evasion, but not suppression, of pro-inflammatory responses in human cells. Additionally, we are examining the contribution of host lipid synthesis pathways following infection with F. tularensis. Specific Aim 2: We are exploring the role of carbohydrates associated with the outer surface of FT in directing immunosuppressive programs in human cells. The major outer surface carbohydrate structure of FT is the O-Antigen (O-Ag) capsule. Typically, capsules are thought to simply cover up proteins present on the bacterial surface that could stimulate an inflammatory response. However, our data demonstrates that FT capsule directly inhibits pro-inflammatory responses in human cells. Further, we have demonstrated that capsule influences specific metabolic pathways in the host the modulate cell health and inflammatory responses. Utilizing mutants with specific defects in capsule synthesis along with purified FT capsule, we are currently identifying the specific receptors and host signaling pathways modulated by capsule to initiate an anti-inflammatory program inhuman cells.

Public Health Relevance Statement

Data not available.

NIH Spending Category

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

Project Terms

Acellular Vaccines Acute Aerosols Anti-Inflammatory Agents Bacteria Bacterial Infections Carbohydrates Cells Dangerousness Data Defect Dendritic Cells Dengue Virus Development Disease Francisella Francisella tularensis Goals Health Human Immune response Immune system Immunosuppression Impairment In Vitro Individual Infection Infectious Agent Inflammation Inflammatory Inflammatory Response Inhalation Invaded Laboratories Legal patent Lipid Synthesis Pathway Lipids Liposomes Mediating Membrane Metabolic Metabolic Pathway Metabolism Microbe Mus Natural Immunity

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Name
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Email not available

Other PIs

Not Applicable

Program Official

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Name
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

City

Country

Department Type
Unavailable

Organization Type
Unavailable

State Code

Congressional District

Other Information

FOA

Study Section

Fiscal Year
2020

Award Notice Date

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number

CFDA Code

Project Start Date

Project End Date

Budget Start Date

Budget End Date

Project Funding Information for 2020

Total Funding
$1,021,978

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,021,978

NIH Categorical Spending

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,021,978	Biodefense; Emerging Infectious Diseases; Infectious Diseases; Orphan Drug; Rare Diseases; Vector-Borne Diseases;

Sub Projects

No Sub Projects information available for 1ZIAAI001097-12

Publications

No Publications available for 1ZIAAI001097-12

Patents

No Patents information available for 1ZIAAI001097-12

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