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Abstract

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Grant Number:	1R29AI040694-01
PI Name:	SWANSON, MICHELE S.
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PI Title:	ASSISTANT PROFESSOR
Project Title:	EVASION OF MACROPHAGE LYSOSOMES BY L PNEUMOPHILA

Abstract: (Adapted from the applicant's abstract) After uptake by macrophages, membrane-bounded Legionella pneumophila evade fusion with lysosomes, associated with endoplasmic reticulum, and replicate to high numbers. Thus, L.pneumophila shares with Mycobacterial, Toxoplasma, Chlamydia and associate HIV the capacity to subvert a host cell that is central to both humoral and cell-mediated immunity. Therefore, knowledge of the host and bacterial factors that govern the intracellular fate of L.pneumopila will likely suggest novel therapeutic approaches to a variety of human diseases. The goal of this work is to understand how L.pneumophila phagosomes avoid fusion with lysosomes. L. pneumophila factors that are required for intracellular survival will be identified by genetic and molecular analysis of two previously characterized mutants that are degraded in the lysosomes. The loci identified by these mutants will be isolated by genetic complementation of their intracellular growth defects. The cloned genes will be used to determine the number of complementation groups identified by the mutants, to construct non-polar null alleles, and to determine the predicted amino acid sequence of each locus. Bacterial factors required for evasion of lysosomes will also be sought by a complementary gain-of - function strategy. Macrophages derived from A/J mouse bone marrow cells deliver L. pneumophila to lysosomes, and the bacterial are killed. An L. pneumophila genomic L. pneumophila molecular, and biochemical characterization of the L. pneumophila factors required for evasion of he lysosomes should elucidate the cellular mechanisms that govern the fate of phagosomes. To gain insight to the strategy used by L. pneumophila to subvert the endocytic pathway, the composition of bacterial phagosomes at different stages of maturation will be compared to the phagosomes that follow the more conventional pathway. To determine whether biogenesis of the L. pneumophila phagosome occurs by vesicle-mediated recycling of membrane components, the fate of labeled plasma membrane proteins and phospholipid bilayers will be followed microscopically. This study will serve as a foundation for future analysis of the interactions between host and bacterial that determine the fate of phagosomes in macrophages.

Thesaurus Terms:
Legionella, bacterial genetics, host organism interaction, lysosome, phagocytosis

bacterial cytopathogenic effect, bacterial protein, endocytosis, gene complementation, macrophage, membrane protein, mutant, vesicle /vacuole
electron microscopy, fluorescence microscopy, immunoperoxidase, laboratory mouse, southern blotting, tissue /cell culture, transfection

Institution:	UNIVERSITY OF MICHIGAN AT ANN ARBOR ANN ARBOR, MI 48109
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