NIH Award from the National Institute of Allergy and Infectious Diseases

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- **Project:** Maturation of IL-1beta and IL-18 in novel macrophage aggresomes
- **Start Date:** June 5, 2009
- **Total Award Amount:** $5,687

**How the results of this project will benefit society:**
Interleukin (IL)-12 and IL-18 are key mediators promoting inflammatory reactions. Excessive production of IL-12 and IL-18 directly are responsible for the symptoms of some of the most common diseases of industrialized nations, including arthritis, asthma, inflammatory bowel disease, ulcerative colitis, atherosclerosis, peridontitis, type 2 Diabetes, lung fibrosis, multiple sclerosis, Alzheimer’s disease, and stroke. Currently there are no effective treatments available, causing patients’ life-long symptoms and a huge economical and financial impact on our social and medical systems.

**The problem the project is trying to solve:**
Localized inflammatory responses are important mechanisms to limit pathogen infections and to promote wound healing. However, excessive and uncontrolled production of IL-12 and IL-18 and resulting inappropriate inflammation is linked to tissue destruction and the debilitating symptoms of the growing number of inflammatory diseases. The molecular mechanisms that control inflammasome formation and activation are poorly understood, but have a high potential to provide the basis for novel strategies to interfere with IL-12 and IL-18 release for the treatment of inflammatory diseases.

**How this project will work:**
Our central hypothesis for the proposed study is that inflammasomes represent inducible, specialized cytosolic structures in macrophages, where inflammasome components are specifically recruited to activate caspase-1. Our hypothesis is based on preliminary imaging results from inflammasomes in macrophages, and in this study we propose to address the mechanism of inducible inflammasome formation and link it to the IL-12 and IL-18 release mechanism. Our hypothesis is based on our preliminary findings showing that (1) inflammasomes require inducible redistribution of inflammasome components; (2) inflammasomes are inducible formed in the cytosol of macrophages; (3) inflammasomes contain characteristic marker proteins that directly link it to specialized cellular ultrastructures.

We propose two specific aims: Specific aim #1 will establish inflammasomes as distinct structures in macrophages, while specific aim #2 will determine the impact on IL-12 and IL-18 maturation as a consequence of disrupting formation of these structures. At the completion of this study, we expect to provide the currently elusive mechanism by which inflammasomes assemble in response to infection and stress, which will open new avenues for inhibiting maturation of IL-12 and IL-18.

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