



Compositions and Methods for Inactivating or Suppressing Inflammatory Cells

Principal Investigators

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Introduction:

Kupffer cells, the resident macrophages of the liver, are strategically positioned in the sinusoidal lumen and play an important role in the removal of altered self or foreign substances from the blood. Phagocytosis usually generates reactive oxygen species (ROS), which is lethal to many microbial pathogens. Interestingly, Kupffer cells and other macrophages do not kill *Plasmodium* sporozoites, the causative agents of malaria. Therefore, *Plasmodium* sporozoites must possess a means of suppressing macrophage activation, possibly by inducing intracellular signaling events. A thorough understanding of this process will help us comprehend how to suppress inflammatory responses in general, which is critical for the successful control of a variety of inflammation-associated disorders.

Description of the Project:

Dr. Frevert found that a major surface protein of malaria sporozoites, circumsporozoite protein (CSP), suppresses or deactivates phagocytic cells. Using both sporozoites and recombinant CSP, Dr. Frevert demonstrated that *Plasmodium* sporozoites use CSP to adhere to Kupffer cells by interacting with two molecules on the Kupffer cell surface: syndecans, a family of transmembrane proteoglycans, and LRP-1, the low density lipoprotein receptor-related protein. Sporozoite contact leads to a series of signal transduction events in Kupffer cells, resulting in the blockage of phagocytosis and ROS production.

Applications:

1. It provides a method of reducing the activity or function of an inflammatory cell by administering to a subject an effective amount of purified CSP, or fragments, homologs, and mimics of CSP, in order to treat, or prevent, inflammatory diseases, including cirrhosis and fibrosis of liver, pain, fever, asthma, bronchitis, vascular disease, nephritic syndrome, and myocardial ischemia.
2. It provides a method of treating an immune disease by inducing antigen-specific tolerance via administration of the antigen in conjunction with CSP, or fragments, homologs, and mimics of CSP. Non-limiting examples of antigens for which tolerance of the immune system is desirable include transplant antigens, allergens, and autoantigens.
3. It provides a method of formulating CSP, or fragments and homologs of CSP, into a pharmaceutical composition with a pharmaceutically acceptable carrier for treating inflammatory conditions such as those mentioned above. In addition, this invention provides for identification of small molecule mimics of CSP, or fragments and homologs of CSP, for use as an agent that suppresses inflammatory cells.

Patent Status:

A patent application has been filed in the United States.