Abstract
Neutrophil defense mechanisms as a potential therapeutic target in sepsis
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Background: Neutrophils are important for the clearance of bacterial infections, but many of their defense mechanisms also can have destructive effects on the host tissue. The neutrophil protein Heparin Binding Protein (HBP) is detrimental to the vascular endothelial barrier and is associated with lung and kidney injury in sepsis. Neutrophils can release DNA and proteins to form neutrophil extracellular traps (NETs) that can have both beneficial and destructive effects.

Research Question: Two projects will be presented at this half-time review. The purpose of the first study is to determine how HBP is cleared from the circulation. The second is to determine the presence of neutrophil extracellular traps affects the course of bacterial meningitis.

Method: In the first project, HBP was injected intravenously into rats and its concentration over time in the blood and in various organs was measured by ELISA. The localization of HBP in the organ was determined by histology. In the second project, the presence of NETs was determined by immunofluorescence in cerebrospinal fluid during pneumococcal meningitis in human patients and in a rat model. DNase was administered to disrupt the NETs and bacterial counts were determined in the brain and various organs. Mechanisms of bacterial killing by neutrophils after DNase treatment were determined by measurement of myeloperoxidase activity and phagocytosis of bacteria.

Preliminary results: HBP was found to disappear from the circulation within five minutes and accumulated primarily in the liver. Disruption of NETs by DNase was found to reduce bacterial load in the brain and to prevent bacterial dissemination to the blood and other organs. DNase treatment resulted in increased myeloperoxidase activity and bacterial phagocytosis.

Significance: Understanding the kinetics of HBP in the blood could guide its use as a biomarker and potential therapeutic target in sepsis. DNase is an approved drug for use cystic fibrosis in humans (Pulmozyme). Its ability to enhance bacterial killing in pneumococcal meningitis could therefore be explored as a potential therapeutic.