Layman's description

Severe infections have never been in the spotlight more than they are now during the COVID-19 crisis. However severe infections, such as sepsis and meningitis, have been a major cause of death and disability long before the year 2020. Sepsis, a severe reaction to infections that leads to life threatening organ failure, is the cause of one in five deaths worldwide, a number that is increasing as bacteria gain resistance to antibiotics. Bacterial meningitis, a devastating infection of the protective membranes in the brain, often leads to sepsis, death, and neurological disability in survivors. Often the pathogen itself is not the main cause of damage in these infections. Instead the body and immune system often react so strongly to the pathogen that they cause collateral damage to the patient's own organs.This thesis focuses on two parts of this so-called "host response" to the infection: the endothelium and neutrophils.

The endothelium is a tight layer of cells that lines all blood vessels in the body and keeps components of the blood from leaking out. The glycocalyx is a protective layer of sugars and proteins that helps the endothelium fulfil its function. This thesis work showed that glypicans, an often ignored component of the glycocalyx, are elevated in patients with sepsis before they develop organ dysfunction.

Neutrophils are the most abundant white blood cells in the body and the first to respond to an infection. They carry an arsenal of tools to kill bacteria, but these tools can often backfire and damage healthy cells. One such tool is called "neutrophil extracellular traps" or NETs, in which neutrophils send out a sticky web of DNA coated with antimicrobial proteins to trap bacteria.

The work in this thesis found NETs in the brains of patients with bacterial meningitis, and also in patients receiving a brain surgery procedure, known as a ventriculostomy, that has a high risk of developing bacterial meningitis. Bacteria can hide in these NETs to avoid being killed by the immune system. Using a drug called DNase to dissolve NETs in the brains of rats with bacterial meningitis enhanced normal neutrophil killing mechanisms, killing of most of the bacteria. The large sticky NETs may also clog the brain's waste disposal system, known as the glymphatic system, leading to dangerous fluid build-up in the brain. Lastly, a rat model of bacterial meningitis was optimized for testing drugs such as DNase in the future.

Take home message: This thesis work identified two new biomarkers in infections: glypicans and NETs. It also suggests that removing NETs using DNase might help clear the infection and reduce dangerous fluid build-up during bacterial meningitis. The therapeutic potential of DNase should be explored further in animal models and, eventually, in human trials.