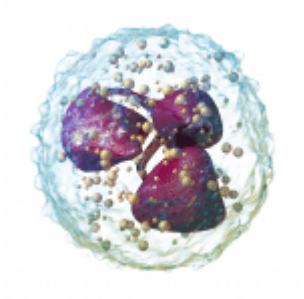
Neutrophilic aid – extracellular traps to enhance macrophage directed bacterial killing



Through several interesting and complex mechanisms, cells of our immune system communicate and cooperate in order to identify, capture and in layman's terms, destroy pathogenic bacteria.

Staphylococcus aureus is a pathogenic bacteria of particular significance due to the existence of significantly antibiotic-resistant forms which remain the leading cause of *hospital-acquired infections, infectious heart disease, and pus-forming skin and soft tissue infections*.

In ways almost imitating a spider trapping its' prey in the web, it has been reported that neutrophils and macrophages can cooperate in order to capture and destroy bacteria. Recently, researchers at the Vanderbilt Institute for Infection, Immunology, and Inflammation, have identified a novel antibacterial mechanism which could open the door to new therapeutics to combat *Staphylococcus aureus* infection as well as other bacterial infection.

In order to combat infection, neutrophils and macrophages produce, in conjunction with their phagocytic abilities, antimicrobial peptides (AMPs), reactive oxygen species (ROS),

and other enzymes in order to combat infection. The generation of NET (NETosis) is a recently discovered form of neutrophil directed antibacterial strategy seen to be a form of apoptosis. This programmed cell death leads to the release of neutrophil DNA which creates this “trap,” comprising additional antimicrobial peptides. Neutrophils, which form the first line of defense/response to infection, migrate to sites of infection and possess the ability to lyse and subsequently release their cellular content (comprising DNA and protein), leading to the formation of neutrophil extracellular traps (NETs). Monteith, et al., have discovered that NETs enhance the killing power of macrophages. Macrophages are essential for our innate immune response to *S. aureus* infection as well as other bacterial infection. *Following phagocytosis, macrophages generate ROS and reactive nitrogen species, mobilize transition metals, and acidify the phagosome to activate hydrolytic enzymes in an effort to intoxicate pathogens*.

It has been reported that *neutrophils can synergistically enhance the antibacterial function of macrophages*, as macrophages cannot successfully eradicate internilised infection in isolation. As most research investigating host-pathogen interactions studies involving *S. aureus* involved isolated immune cells or whole blood lacking mature macrophages, it was important for the researchers to investigate and describe how neutrophils and macrophages combat *S. aureus* infection. Essentially elucidating effective innate immune response to *S. aureus* and to provide insight into novel antibacterial strategies.

Monteith, et al., investigated NETosis in animal and *in vitro* model systems. They reported no significant increase in bacterial killing by neutrophils in isolation in the presence of increased NETosis. However, in the presence of macrophages, NET formation enhanced macrophage antibacterial activity by increasing phagocytosis of *S. aureus* which were inhibited by

the NETs and the presence of antimicrobial peptides.

The authors reported an increase in the killing of other bacterial pathogens namely, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa,* by means of this mechanism, suggesting *that neutrophil/NET-macrophage cooperation may represent a broadly applied immune defense mechanism*.

Interesting research with many more questions of NETosis left to be answered. Such questions include: *how and when neutrophils opt for this form of cell death* and how individual differences (genetic variation or due to disease state) in NETosis affect infection.

In their own words:

"*Our results demonstrate that NET formation acts as a conduit to broadly enhance antimicrobial activity in the presence of macrophages (Mφs) in response to bacterial pathogens," the authors concluded. "NET formation increases the antibacterial activity of Mφs by facilitating their phagocytosis of bacteria and by transferring biologically active neutrophil-specific AMPs to Mφs … These results demonstrate that achieving maximal bactericidal activity through NET formation requires macrophages and that accelerated and more robust suicidal NETosis makes neutrophils adept at increasing antibacterial activity…*"

Journal Article: Monteith, et al., 2021. Neutrophil extracellular traps enhance macrophage killing of bacterial pathogens. **Science Advances.**

Summary by Stefan Botha