Systems Biology Research Symposium
Oral Presentation Session

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Disarming of Host Neutrophil Defenses by *Neisseria gonorrhoeae*

Alison Criss[1], Elizabeth Stohl[2], and H. Steven Seifert[2]

[1]Department of Microbiology, University of Virginia, Charlottesville, VA, USA, [2]Department of Microbiology-Immunology, Northwestern University, Chicago, IL, USA
Presenter's email address: akc2r@virginia.edu

The Gram-negative bacterium *Neisseria gonorrhoeae* (Gc) is the causative agent of the sexually transmitted infection gonorrhea, which affects millions of individuals worldwide every year. *In vitro* models of Gc interaction with host cells have been established and several Gc genomes have been sequenced and annotated; however, most of the virulence factors used by Gc for infection of their obligate human hosts remain enigmatic. Identifying these bacterial factors and their host cell targets can provide new opportunities for therapeutic intervention, which are urgently needed given the high frequency of antibiotic resistance in gonorrhea and the lack of protective vaccines.

Our research examines the interactions between Gc and neutrophils, the main immune cell population recruited during acute infection. Although neutrophils are professional antimicrobial cells, gonorrheal neutrophil-rich secretions contain viable bacteria, indicating that Gc resist some bactericidal components of neutrophils. One major class of neutrophil antimicrobial products are the reactive oxygen species (ROS). Since Gc encounter neutrophils during infection, and since neutrophils produce ROS, we hypothesized that Gc exposed to ROS undergo transcriptional changes that protect the organism from neutrophils. In support of this hypothesis, we defined the transcriptional response of Gc to sublethal concentrations of hydrogen peroxide and found that two ROS-induced gene products, *recN* and *ngo1686*, protected Gc from neutrophil killing. However, further experiments showed that primary human neutrophils are relatively inefficient at killing Gc, the small fraction of Gc that are killed by neutrophils occurs non-oxidatively, and RecN and Ngo1686 protect Gc from non-oxidative neutrophil products. As a partial explanation for these observations, we found that exponentially-growing, metabolically active Gc failed to elicit any ROS production from neutrophils. Moreover, live Gc suppressed neutrophil ROS production that is induced by formylated peptides and *Staphylococcus aureus*. In contrast, dead or agar-grown Gc stimulated ROS production in neutrophils, indicating that the growth state of Gc modulates this aspect of neutrophil antimicrobial function. We plan to use the power of bacterial genetics and genomics to identify Gc gene products participating in bacterial defense from neutrophils, as well as genomic and proteomic approaches to characterize the non-oxidative products of neutrophils with anti-Gc activity. We predict that defining the molecular interactions between Gc and human neutrophils will establish new paradigms for how highly host-adapted pathogens subvert immune defenses to facilitate colonization, invasion, and transmission.

Key words: gonorrhea, neutrophil, transcriptome, innate immunity, reactive oxygen species