THE HOST-PATHOGEN INTERACTION

We study microbial pathogenesis by the use of a mass spectrometry-based data-driven approach to uniquely probe proteome dynamics, including posttranslational modifications (PTMs), during the host-pathogen interaction. This systems approach is used to uncover new infection biology and to formulate testable hypotheses. Recently, we used this platform to study and characterize a novel virulence factor, named S protein, in the bacterium Group A Streptococcus (GAS; *S. pyogenes*). GAS is a β-hemolytic, Gram-positive bacterium and a human specific pathogen. GAS produces over 700 million infections localized to the pharynx ("strep throat") and skin (e.g. impetigo), and is also associated with more severe and life-threatening invasive diseases such as necrotizing fasciitis, sepsis, and pneumonia, toxin mediated syndromes such as scarlet fever and streptococcal toxic shock syndrome (STSS), and post-infectious immunologically-mediated syndromes including glomerulonephritis and rheumatic heart disease (RHD). For the first time, we have shown that S protein governs the coating of the GAS cell surface with lysed RBC membranes which functions through a molecular mimicry mechanism to promote GAS pathogenicity and immune evasion *in vitro* and *in vivo*. This property finally links a hallmark phenotype of GAS in the clinical laboratory, "β-hemolysis" due to lysis of RBC on blood agar media, to a mechanistic role in GAS pathogenesis. We have published this work (***Weirzbicki and Campeau et al., Cell Reports 2019***) and its importance has been highlighted in multiple independent reviews: Smithsonian, EurekAlert, ScienceDaily, Contagionlive, Drugtargetreview, Intelligentliving, ID-HUB, PlumX.

Another project within the contexts of host-pathogen interactions is the study of a largely unexplored molecular space –the peptidome (i.e. endogenous peptides/microproteins). A comprehensive understanding of bacterial pathogenesis not only requires a detailed knowledge of the genome and proteome, but also the peptidome elaborated during the progression of infection. Here, we have built upon our exciting preliminary observations describing the identification of endogenous microproteins and peptides detected in cell-free supernatants of the major human pathogen community-associated (CA) MRSA cultures. Within this group we identified two novel microproteins originating from an unannotated locus in the CA-MRSA genome. We found that these microproteins, termed *S. aureus* microprotein 1 (SAM1) and *S. aureus* microprotein 2 (SAM2), are highly conserved among Staphylococci and are regulated by the classical accessory gene regulatory system. We have started to characterize these factors, showing that SAM1 appears to act as a canonical cytolysin. Intriguingly, SAM2 possesses unique bioactivity, the perturbation of keratin networks that promotes an *in vivo* switch from a localized *S. aureus* skin infection to an invasive dissemination to the underlying tissues. The central hypothesis of this work is that SAMs significantly contribute to CA-MRSA's ability to cause disease in a host. **We have been awarded an NIH R01 (2020-2025 funding period) for this project.**

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