Evolution and Emergence of Invasive Serotype M1T1 Group a Streptotococci

MJ Walker[1] *, A Hollands[1,2], PG Maamary[1], JN Cole[1,2], RK Aziz[3,4], DR Johnson[5], MA Pence[2], AM Timmer[2], SR Osvath[6], L Turnbull[6], AJ Cork[1], ML Sanderson-Smith[1], JK Kirk[1], JD McArthur[1], WL Taylor[4], CB Whitchurch[6], EL Kaplan[5], M Kotb[4,7], and V. Nizet[2]

[1]University of Wollongong, Australia; [2]University of California San Diego, USA; [3]Cairo University, Egypt; [4]University of Tennessee Health Science Center, USA; [5]University of Minnesota, USA; [6]University of Technology Sydney, Australia; [7]University of Cincinnati, USA

The globally disseminated M1T1 clone of group A *Streptococcus* (GAS) is linked with the rare but life-threatening syndromes of necrotizing fasciitis and toxic shock syndrome. Mutations in the GAS control of virulence regulatory sensor kinase (*covRS*) operon are associated with severe invasive disease, abolishing expression of a broad-spectrum cysteine protease (SpeB). Loss of SpeB allows the recruitment and activation of host plasminogen on the bacterial surface, which facilitates invasive spread. Bacteriophage-encoded GAS DNase (Sda1), which mediates the pathogen's escape from neutrophil extracellular traps (NETs) serves as a selective force for *covRS* mutation. In comparison to wild-type, GAS M1T1 *covR/S* mutant bacteria exhibit decreased binding to extracellular matrix components and epithelial cell monolayers, diminished biofilm formation, and a reduced capacity to colonise the skin surface. Impaired colonization suggests *covR/S* mutant M1T1 GAS strains are not rapidly spread amongst the human population. Interrogation of a bank of 10 isogenic M1T1 GAS virulence gene mutants suggests that the capacity to switch to the SpeB-negative *covR/S* mutant phenotype is reliant on a quorum of neutrophil resistance genes working in concert. With access to a comprehensive WHO collection of M1 GAS isolates, we have reconstructed the evolutionary series of events leading to the emergence of M1T1 GAS. While much is understood regarding the capacity of pathogens to cause disease, much less is known of the specific evolutionary events selecting for their emergence. Our data maps the genetic events and selective pressures that have driven the rise of the hyperinvasive M1T1 GAS clone.