COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Targeting Toll-like Receptor 7 (TLR7) For Intervention During Pneumonic Plague

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Yersinia pestis is the causative agent of plague, a flea borne invasive disease that occurs naturally throughout the globe, with high rates of morbidity and mortality. It is a tier 1 select agent, with significant potential for use as a genetically modified weapon of mass destruction. Plague is rapidly progressing due to two major secreted immune modulatory virulence factors: the type III secretion system (T3SS) effector proteins (Yops) and an iron-binding siderophore yersiniabactin (Ybt). We previously identified roles for several inflammatory mediators in promoting the progression of pneumonic plague: Toll-like receptor 7 (TLR7), myeloid differentiation protein factor 88 (MyD88), and type I interferon (IFN). While MyD88 and type I IFN are fundamentally critical for fighting many infections that make them unsafe targets of immunotherapy, TLR7 inhibitors have been developed and shown to be effective in reducing the progression of infectious diseases including those caused by RNA viruses of importance to human health. Therefore, in this work, we sought to explore the potential for TLR7 to serve as a target for therapeutic intervention during pneumonic plague in a murine model. We identified critical host pathogen interactions and a dominant role for Ybt in driving TLR7-dependent pathology. Furthermore, we characterized inflammatory transcriptome in order to define IFN-dependent and -independent responses activated by TLR7 and the associated biomarkers in the lungs and blood that signify progressing disease. Overall these data will be useful in developing TLR7-targeted host treatments that may be broadly protective against bacterial and viral infection.