PALADINS: PROTECTIVE APPROACHES LEVERAGING AD-APTIVE AND IN-NATE SYSTEMS

Humoral And Cellular Immune Correlates Of Protection For Live, Attenuated Tularemia Vaccines In The Outbred New Zealand White Rabbit.

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Background: Tularemia is an endemic disease but also a potential bioweapon. The causative agent is Francisella tularensis, a facultative intracellular gram-negative non-motile coccobacillus. As few as 15 cfu of F. tularensis can cause disease when inhaled. Licensed vaccines that can protect the warfighter against this threat are urgently needed. We have previously demonstrated that New Zealand White rabbits develop severe bronchopneumonia and sepsis within 4-6 days after inhalation of small particle aerosols containing SCHU S4, a virulent strain of F. tularensis. Live, attenuated recombinant derivatives of SCHU S4 protected rabbits against aerosol challenge with virulent SCHU S4, particularly when vaccination was via the aerosol route for both the prime and boost.

Objective: Evaluate the immune response to live vaccine candidates to develop immune correlates in the rabbit that can predict survival against aerosol challenge with SCHU S4.
Methods: Rabbits were vaccinated by inhalation of live vaccine candidates (S4ΔguaBA, S4ΔaroD, LVS) in small particle aerosols, given in 2 doses 14 days apart. At various times, blood samples were collected to analyze the host response to infection. Plasma was assessed for antibody against F. tularensis antigens and in functional assays (opsonization). RNA isolated from white blood cells was analyzed by transcriptomics to evaluate potential markers of cellular immune responses.

Results: Assessment of plasma antibody identified potential correlates of protection. Antibody to F. tularensis endotoxin correlated with protection in rabbits vaccinated with S4ΔguaBA or LVS. For S4ΔaroD, the ratio of antibody responses to GroEL and Tul4 predicted survival against SCHU S4 challenge in rabbits. Increased opsonization of LVS was noted using antibody from vaccinated rabbits. RNA from PBMC of rabbits vaccinated with S4ΔguaBA found increased expression of IFNg, TNFα, and TGFβ in rabbits that survived subsequent challenge. In S4ΔaroD-vaccinated rabbits, CXCL10 correlated strongly with survival. The fever response to prime vaccination was also identified as a potential physiological correlate; however, it was the lack of fever that correlated with survival.

Conclusions & Impact: we have identified several potential correlates that predict survival of vaccinated rabbits after aerosol challenge with virulent SCHU S4. The correlates identified so far are specific to individual vaccine candidates, but we continue to evaluate additional humoral and cellular elements to identify potential ‘universal’ correlates for all tularemia vaccines.

Impact to the DTRA mission and warfighter: We have previously demonstrated that live, attenuated recombinant tularemia are efficacious in the rabbit model. These vaccines could protect the warfighter against aerosol exposure to F. tularensis. Here, we have identified correlates that could be used to bridge between animal and human immune responses so that vaccine studies which demonstrate protection in animals against aerosol challenge would give confidence that the warfighter would be protected.

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