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

Inability To Synthesize Anthrose Leads To Pathophysiological Changes In Bacillus Anthracis.

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Background: Anthrax is a deadly zoonosis impacting humans, livestock, and wildlife caused by Bacillus anthracis, a spore-forming bacterium known to persist for long periods (years to decades) in certain soils. The disease has near global distribution and occurs annually, with varying outbreak intensity driven by local climatic conditions and host population dynamics. Bacillus anthracis is thought to be a slowly evolving pathogen. Mutations have caused differences in spore surface oligosaccharides that generate novel antigenic spore surfaces. Anthrose negative strains have been involved with high profile public health anthrax incidents in the last two decades and have been circulating in West Africa since the mid-1940s (if not longer). Loss of unique sugar components could weaken immune responses to spores and change the pathophysiology of strains that can no longer synthesize the exosporium decorating sugar, anthrose.

Purpose: Validate protective efficacy of Sterne vaccine against anthrose negative bacteria causing anthrax.
Objective: Understand the virulence, pathogenicity, and cell physiological impacts of anthrose on anthrax infections.
Rationale: By understanding the effects of anthrose negativity on virulence factor expression and pathogenicity in animal models we can design a comprehensive next-generation anthrax vaccine.
Relationship to other areas of study: Host-pathogen interactions, pathogen detection, and vaccinology.

Methods: Genome sequencing and whole genome SNP analysis for genome characterization was used to identify B. anthracis strains of interest. Complementation vectors were used to return anthrose negative strains to anthrose positivity to analyze toxin secretion. Anthrose was knocked out in B. anthracis (Sterne) to assess the role anthrose plays in vegetative growth. Luminescent promoter fusion strains were produced to allow dynamic expression analysis of important pathogenesis related genes in anthrose negative strains. Virulence of the fully virulent strains was assessed by LD50 studies in guinea pigs.
Preliminary results: Anthrose negative strains are from diverse B. anthracis lineages and are linked to high profile export related anthrax outbreaks. Anthrose in vegetatively growing B. anthracis is likely an important metabolic mediator whose absence can result in high levels of bacterial chaining and increased secretion of toxins under glucose limiting conditions. Lack of anthrose on the spore surface leads to decreased exosporium nap density and changes the reactivity of the spore. LD50 studies show the virulence of anthrose negative strains in the guinea pig model compared to the Ames strain.

Preliminary conclusions: Anthrose can act as an intracellular, extracellular, and intercellular signal that can modify physiology of the spore and vegetatively growing cell. Loss of the spore surface sugar can change the immunoreactivity of the spore and impact toxin secretion of the vegetative bacteria. In low glucose environments, such as the interstitial space, toxin secretion can be enhanced in the absence of anthrose, while in high glucose environments, like blood, toxin secretion could be decreased.

Impact to the DTRA mission and warfighter: Emergent anthrose negative anthrax presents a challenge to currently available vaccines. Next-generation vaccines will be developed and tested with these specific threat agents in mind, adding comprehensive deterrents to the defensive arsenal.