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Molecular basis for improved anthrax vaccines

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Abstract

The current vaccine for anthrax has been licensed since 1970 and was developed based on the outcome of human trials conducted in the 1950s. This vaccine, known as anthrax vaccine adsorbed (AVA), consists of a culture filtrate from an attenuated strain of *Bacillus anthracis* adsorbed to aluminum salts as an adjuvant. This vaccine is considered safe and effective, but is difficult to produce and is associated with complaints about reactogenicity among users of the vaccine. Much of the work in the past decade on generating a second generation vaccine is based on the observation that antibodies to protective antigen (PA) are crucial in the protection against exposure to virulent anthrax spores. Antibodies to PA are thought to prevent binding to its cellular receptor and subsequent binding of lethal factor (LF) and edema factor (EF), which are required events for the action of the two toxins: lethal toxin (LeTx) and edema toxin (EdTx). The bacterial capsule as well as the two toxins are virulence factors of *B. anthracis*. The levels of antibodies to PA must exceed a certain minimal threshold in order to induce and maintain protective immunity. Immunity can be generated by vaccination with purified PA, as well as spores and DNA plasmids that express PA. Although antibodies to PA address the toxemia component of anthrax disease, antibodies to additional virulence factors, including the capsule or somatic antigens in the spore, may be critical in development of complete, sterilizing immunity to anthrax exposure. The next generation anthrax vaccines will be derived from the thorough understanding of the interaction of virulence factors with human and animal hosts and the role the immune response plays in providing protective immunity.

Keywords: Anthrax; *Bacillus anthracis*; Vaccine; Protective antigen; Lethal toxin; Edema toxin; Ames strain; Sterne strain; Lethal factor; Edema factor; Protective immunity; Recombinant PA; Monoclonal antibody; Genetic immunization; Adjuvants; Epitopes

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1. Introduction

It is clear that the coincidence of the anthrax incidents in the fall of 2001 in the wake of the attacks on the World Trade Center accentuates the vulnerability of the United States and the rest of the world to organized assaults with biological weapons. A heightened interest in anthrax pathogenesis, immunity, and vaccine development has ensued as a consequence of these events. The relatively small-scale dissemination of anthrax spores in a few paper envelopes that may have exposed as many as 30,000 people to anthrax spores, resulting in 11 cases of inhalational anthrax and 5 deaths [1,2] could only indicate that a more organized attack focused on delivering spores by aerosolization could result in proportionately larger number of deaths and social and political chaos. Although technology for large-scale aerosolization of anthrax spores is not known to have been fully developed, these technologies have been part of biological weapons programs in Iraq [3] and the former Soviet Union [4]. An effective mass aerosol release of *Bacillus anthracis* would have a potentially devastating impact on an urban population, perhaps resulting in hundreds of thousands infected from the release of 50 kg of purified anthrax spores [4,5].

The available vaccine for anthrax relies on technology that dates back to the early sixties. At the time of the attacks in the fall of 2001, the only US-licensed human vaccine was not available because the manufacturer (BioPort Corporation) had not received FDA certification of its new manufacturing process. It is also likely that the antiquated anthrax vaccine does work: that is, it elicits protective immunity with a great degree of safety. However, the factors that drive the development of replacement vaccines, in the current environment, will be a combination of improved safety and efficacy, as well as speed of development. Achieving more rapid onset of immunity with an accelerated dosing schedule is also an objective, especially for the military. The development of safer and more effective vaccines relies more and more heavily on detailed knowledge of pathogenesis, interaction of the agent with the host and the host immune system, and detailed knowledge of the factors that account for protective immunity in humans. The latter is especially challenging, since no human efficacy trials can be done with the biological agents, and licensure of the vaccine by the FDA and other regulatory bodies must depend on the overwhelming bulk of human immunogenicity data that correlate to data from controlled challenge studies in susceptible