Medical Countermeasures for Biothreat Agents: Need for Inhalation Challenge Models

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The list of biothreat agents is often debated as the criteria for qualifying a pathogenic microorganism or toxin in the Select Agent and Toxin List (SATL) is diverse. Common factors to prioritize these agents in terms of their threat potentials, is their ability to cause symptoms through inhalation route, infectious dose or toxicity, availability of therapeutics/prophylaxis, and stability in the environment. For instance the category A, B, and C priority pathogen list of National Institute of Allergy and Infectious Diseases (NIAID) includes most of the highly infectious viral agents in the category A group. The current SATL is jointly regulated by the US Department of Health and Human Services (HHS) and the US Department of Agriculture and contains approximately 80 microbial agents and toxins [1]. Biological Weapons and Toxins Convention of 1972 sought a prohibition on the use of micro organisms and toxins in warfare. This was followed by creation of regulations on possession and transfer of these agents in the shadow of biosecurity concerns. Casadevall and Relman [1] expressed concern, that many microbiologists and research groups share about the potential detrimental effect of the law enforcements pertaining to select agents on the research for developing countermeasures against such microorganisms. The authors argue that ‘regulations that inhibit research with certain microorganisms could reduce preparedness against future nefarious or natural outbreaks with that agent and could conceivably interfere with the development of therapies against other conditions that rely on products from such organisms’.

Research pertaining to medical countermeasures against select agents can potentially reduce the threats by the creation of diagnostics, vaccines and new therapies. In case a pathogenic microbe is deliberately used to cause harm to human population, the envisaged mode of delivery is aerosol which is likely to cause extensive damage to the target population. This warrants evaluation of currently available vaccines against the selected agents by inhalation challenge and development of newer prophylactic agents with effective protection through this envisaged route of exposure. This entails a need for development of animal models (preferably non-human primates) for infection or intoxication with select agents through inhalation route. Various animal models have been used for testing the protective activities of vaccines against infection with pathogenic microbes, including mice, rats, guinea pigs, hamsters, rabbits, and nonhuman primates. However, traditionally vaccine studies on animal challenge models rely on intramuscular (i.m.), intraperitoneal (i.p.), subcutaneous (s.c.), intradermal (i.d.), and intranasal (i.n.) route of exposure, leaving a void of data for its possible utility in pre-exposure prophylaxis of population at risk of cowardly uses of biological and toxin warfare (BTW) agents in the form of aerosol. A few groups exclusively working towards countermeasures for select agents in BTW or bioterrorism scenario have started realizing this emergent need and initial investigations were expectedly directed towards protection against inhalational anthrax using known vaccine candidates [2,3]. The reason for this was partly due to the fact that although naturally acquired pulmonary anthrax is very unusual, the mortality of pulmonary anthrax is almost 100% if not treated very early [4]. The potential of B. anthracis spores as a biological weapon or as bioterrorism agent has increased the need for an effective vaccine to protect humans against inhalational anthrax. Notably, the most common human form of anthrax is cutaneous anthrax with a mortality rate of nearly 20% if untreated; gastrointestinal anthrax generally leading to fatal systemic disease if untreated [5]. Similarly, pneumatic tularemia caused by inhalation of the type A strains of Francisella tularensis is associated with high morbidity and mortality in humans and attenuated live vaccine strain (LVS) which were tested for inhalation challenge in Fischer 344 rat which was proposed as a model for studying pneumatic tularemia and evaluating potential vaccine candidates [6]. Brucella melitensis is a highly infectious pathogen that can infect animals and humans and is an etiologic agent for brucellosis. Brucella species are considered potential biothreat agents due to their high infectivity, the persistent nature of human disease, and its easy dissemination by aerosols to cause disease. Rhesus macaque (RM) has been demonstrated as an animal model for inhalational brucellosis to evaluate the efficacy of novel vaccines against B. melitensis [7].

Despite these efforts to mitigate threat from clandestine uses of biological agents, the research activities on prophylaxis against BTW agents has been dismal. The problem is confounded by the lack of commercial interest from pharmaceutical and biotech industries and inhalation challenge is never a criterion for evaluating efficacy of vaccine candidates if aerosol is not the natural route of infection. The situation is still bleaker for toxins of warfare or bioterrorism significance, as natural exposure through inhalational route is hardly of any magnitude to draw attention of funding agencies in this direction. Protective effect of two recombinant ricin subunit vaccines in the New Zealand white rabbit subjected to a lethal aerosolized ricin challenge has been recently reported [8]. However, similar studies for other select toxins are scanty, despite their potential to cause extensive damage to both human and animal population through inhalation route of exposure. Hence, development of appropriate animal models for inhalational infection or intoxication and evaluation of the efficacy of vaccine candidates for aerosol challenge is of paramount importance for the development of effective countermeasures against biothreat agents.

References

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