Medical Countermeasures for Biothreat Agents: in vivo Studies and Animal Models

Syed Inteyaz Alam*
Defence Research and Development Establishment, Jhansi Road, Gwalior, India

Biothreat agents are prioritized in terms of their threat potentials by taking several factors into account, such as inhalation route of infection / intoxication, infectious dose or toxicity, stability in the environment, and availability of therapeutics / prophylaxis. Most of these factors are intrinsic features of the given pathogen or toxin and are not under our control to modulate. However, pre-exposure prophylaxis and post exposure therapeutics are the criteria that intensive research can handle and dislodge a particular organism from the Select Agent and Toxin List (SATL) [1]. Our ability to impart immunity to human population against an infectious agent and/or treat the disease, substantially mitigates a potential threat and renders the agent obnoxious from bioterrorism or warfare viewpoint. For instance, Clostridium tetani and its neurotoxin are equivalent to Clostridium botulinum at least in terms of the lethality of the neurotoxins but the former is not considered a potential select agent for the availability of prophylactic measures and immunization regimen. The problems associated with pre-exposure prophylaxis for threat agents is confounded by several factors including the long list of select agents and the uncertainty of use for a particular agent. For the agents of public health importance, we are aware of the endemecity of natural disease outbreaks, but it is difficult to predict which agent will be used in a bioterror or BW attack. Theoretically, a pre-exposure prophylaxis in bioterror scenario requires immunization against all the agents or least against those posing potential threat. Assuming that we have developed vaccines for each of the threat agents, the vaccination of even a vulnerable population for this wide array of pathogens is a magnanimous task. The situation becomes bleaker as the efficacy of most of the vaccines needs to be tested for inhalational route of exposure. Another problem associate pre-exposure medical countermeasures especially for bacterial agents, is the selection of candidate as subunit vaccine. The toxins become default candidates for toxigenic pathogens while for others, immunodominance is the first criteria to short list potential candidates, irrespective of stage of infection at which it is expressed or the role it plays in disease pathogenesis. We need to look for a vaccine that blocks colonization, rather than the one that recognizes effectors that is released by the pathogen after the infection has set in. Post-exposure therapeutics for infectious agents, although plagued with antibiotics resistance are better suited for bioterror scenario as they are likely to provide protection on a broad spectrum.

Understanding the host-pathogen interaction, especially under in vivo settings, is likely to provide newer targets for both pre-exposure prophylaxis and post-exposure therapeutics. Common pathways implicated in host-response to many pathogens or elucidation of new virulence determinants produced by infectious agents can be of great value in this regard. The recent work by Smith et al. [2] pertaining to identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis is an excellent example of the kind. It is important to note that the envisaged mode of delivery for biothreat agents is aerosol, which is likely to cause extensive damage to the target population and trigger an epidemic if the disease is contagious. This necessitates development of suitable animal models for infection or intoxication through inhalation route. Despite a few reports for vaccine efficacy testing using animal inhalation challenge models [3-5], the development of animal models for such studies and those mimicking the pathogenesis of a particular human agent has been dismal.

High throughput technologies of genomics, transcriptomics, and proteomics are of immense value for elucidation of host response to infectious and toxin agents and is together known as ‘infecomics’. The development of these global approaches allows a detailed study of the host–pathogen interaction with an ultimate goal to integrate all experimental data from the diverse omics approaches to generate a global view of host–pathogen interplay [6]. Such studies can be directed either for vaccine design that blocks colonization of pathogens or identification of common biological pathways and novel drug targets. For example, using proteomic approaches, we can systematically identify the host proteins that are involved in infection, opening new possibilities for preventing and perturbing infection and therefore provide new targets for treatment [7]. These approaches can look for both host-directed and pathogen-directed drug targets and include elucidation of host and pathogen response during disease to determine the mechanism of pathogenesis. For therapeutics with an expanded horizon, we would look for general mechanisms that are shared among pathogens. Unfortunately, initial efforts in this regard were largely based on high throughput data with various cell lines, depicted as originating from target organ, and a subsequent validation in the same in vivo milieu. These studies with isolated cell lines grown in largely defined synthetic medium hardly provide any resemblance to the perturbations by pathogen or toxin in actual host settings. The lack of research activity in this direction is partly due to the reason that reproducing actual disease conditions in animal models, especially through inhalation route requires containment facility (BSL3 or BSL4) and regulatory approvals that many research laboratories do not have or for various reasons, avoid getting into. As a result, the bulk of data pertaining to host-pathogen interaction has remained not more than academic curiosity, lacking the key events that take place in the host environment. The host pathogen interactions is a complex and dynamic process and the in vitro conditions are grossly different from the in vivo environment as the circulating blood brings a myriad of effectors and signaling molecule and the cells interact with and respond to their neighboring cells. Even the basal transcriptomic and proteomic profile of the cells do not go hand in hand with those in actual host environment. Further, the volume of data describing global changes in

*Corresponding author: Syed Inteyaz Alam, Defence Research and Development Establishment, Jhansi Road, Gwalior, India, E-mail: symteyaz@gmail.com

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cell lines in response to infection or toxin exposure are predominantly based on transcriptomic analysis which suffers several limitations when compared with proteomic approaches; lack of information pertaining to localization, post translational modifications, and protein-protein interaction being some of them. Among all the high throughput technologies, proteomics provides answers related to disease pathology that is closest to the phenotype. Perhaps the reason for the preference of research groups for transcriptomics stems from the associated cost; most of the laboratories with limited funding prefer doing RNA based studies despite their latent admiration for the proteomic technology. If we are looking for host effectors that are critical for pathogen entry, survival and replication inside the host, we need to use a model as close as actual disease conditions. Simulation of disease conditions caused by infectious agents in suitable animal model and elucidation of new therapeutic targets aided by high throughput ‘OMICS’ technologies can help a great deal in mitigating the shadows of bioterror in the prevailing scenario of bioterrorism.

References