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Recent Developments in Anti-dotes Against Anthrax

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Abstract: The etiologic agent of disease anthrax, *Bacillus anthracis*, causes recurrent outbreaks among the livestock and intermittent infections in humans across the world. Controlling animal infections by vaccination can minimize the incidence of disease in humans. Prevention of anthrax in occupationally exposed personnel is achieved through vaccination with either live spores or precipitates of culture supernatants from attenuated strains of *B. anthracis*. However, anthrax vaccination of the large human population is impractical as well as inappropriate. Broad-range antibiotics like amoxicillin, ciprofloxacin, clindamycin, streptomycin, and penicillin G are recommended for the treatment of human anthrax infections, but the threat of antibiotic resistant strains always remains. Moreover, in the absence of any specific symptom (s) during early infection, the diagnosis of anthrax is delayed causing elevated levels of anthrax toxin component which could be fatal. For these reasons, there is a need to develop new antimicrobial agents against virulent *B. anthracis* to effectively combat this fatal pathogen. Over the last two decades, extensive studies have been carried out to develop specific inhibitors against virulence factors of *B. anthracis* such as capsule, protective antigen, lethal factor and edema factor. Research has also been focused in developing inhibitors of anthrax toxin receptors (including the use of receptor decoys) and host furin endoproteases which are required for activation of toxin. This review highlights the recent progress made in developing the diverse countermeasures for anthrax infections targeting *B. anthracis* virulence factors and their counterparts in host.

Keywords: Anthrax toxin receptors, anthrolysin O, *Bacillus anthracis*, capsule, edema factor, furin endoproteases, immunoglobulin, inhibitors, lethal factor, protective antigen, spore, vaccine.

ANTHRAX

Anthrax is a zoonotic disease caused by endospore forming Gram-positive bacterium, *Bacillus anthracis*. Anthrax epidemics among animals caused huge economic loss in the past century [1]. *B. anthracis* causes three types of anthrax infection in humans namely, cutaneous, inhalational and gastro-intestinal. Major outbreaks of anthrax (especially cutaneous) continue to be reported across the globe [2-7]. Humans are exposed to *B. anthracis* spores through soil, contaminated meat and animal products like wool, hide etc. The inhaled or ingested spores are phagocytosed by macrophages and sense the optimum growth conditions followed by their germination into the vegetative cells. Bacteria then multiply and enter the blood stream causing systemic infection [8]. *B. anthracis* has also been used as a biological warfare agent, more recently in 2001 in the United States [9]. Potential misuse of *B. anthracis* virulent strains as biological warfare agent is an imminent danger in future.

B. anthracis bears two large extra-chromosomal plasmids, pXO1 (181.6 Kbp) and pXO2 (96 Kbp). Plasmid pXO1 encodes for anthrax toxin activator (AtxA), the central regulator of pathogenesis that regulates the expression of major virulence factors i.e. toxin genes (*cya, lef, pagA*) and anti-phagocytic capsule (*capBCDAE* operon). AtxA expression and activity is found to be regulated by temperature and CO_2, respectively. AtxA enhances the transcriptional levels of tripartite toxin genes present in the pathogenic islands of pXO1 plasmid [10, 11]. Moreover, AtxA also triggers the transcriptional activators of *cap* operon which are anthrax capsule activator A (AcpA) and anthrax capsule activator B (AcpB) present in pXO2 plasmid [12]. The capsule is a homo-polymer of D-glutamic acid residues which inhibits phagocytosis and enables bacterial dissemination during the course of anthrax pathogenesis [13, 14].

B. anthracis secretes two toxin proteins with enzymatic activity [lethal factor (LF, 89KDa), edema factor (EF, 92KDa)] and a receptor binding protein [protective antigen (PA, 83KDa)] into the extra-cellular milieu. PA interacts with tumor endothelial marker 8 (TEM8) or capillary morphogenesis gene 2 (CMG2) receptors present on the host cell surface. PA cannot interact with LF or EF until cleaved by host endoproteases. Furin endoprotease cleaves the RKKR (^{164}Arg-Lys-Lys-Arg^{167}) amino acid sequence in the domain I of PA [15-17]. This cleavage has tremendous impact on the interaction ability of PA. It has been reported that amino acid residues F202, L203, P205 and I207 on PA domain I get exposed upon cleavage that leads to interaction

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