Anthrax toxin is a three-protein exotoxin secreted by virulent strains of the bacterium, *Bacillus anthracis*—the causative agent of anthrax. The toxin was first discovered by Harry Smith in 1954.[1] Anthrax toxin is composed of a cell-binding protein, known as protective antigen (PA), and two enzyme components, called edema factor (EF) and lethal factor (LF). These three protein components act together to impart their physiological effects. Assembled complexes containing the toxin components are endocytosed. In the endosome, the enzymatic components of the toxin translocate into the cytoplasm of a target cell. Once in the cytosol, the enzymatic components of the toxin disrupts various immune cell functions, namely cellular signaling and cell migration. The toxin may even induce cell lysis, as is observed for macrophage cells. Anthrax toxin allows the bacteria to evade the immune system, proliferate, and ultimately kill the host animal.[2] Research on anthrax toxin also provides insight into the generation of macromolecular assemblies, and on protein translocation, pore formation, endocytosis, and other biochemical processes.

Bacillus anthracis virulence factors

Anthrax is a disease caused by *Bacillus anthracis*, a spore-forming, Gram positive, rod-shaped bacterium (Fig. 1). The lethality of the disease is caused by the bacterium's two principal virulence factors: (i) the polyglutamic acid capsule, which is anti-phagocytic, and (ii) the tripartite protein toxin, called anthrax toxin. Anthrax toxin is a mixture of three protein components: (i) protective antigen (PA), (ii) edema factor (EF), and (iii) lethal factor (LF).

Anthrax toxin is an *A/B* toxin[Edit]

Each individual anthrax toxin protein is nontoxic. Toxic symptoms are not observed when these proteins are injected individually into laboratory animals. The co-injection of PA and EF causes edema, and the co-injection of PA and LF is lethal. The former combination is called edema toxin, and the latter combination is called lethal toxin. Thus the manifestation of physiological symptoms requires PA, in either case.

The PA requirement observed in animal-model experiments demonstrates a common paradigm for bacterial toxins, called the *A* / *B* paradigm. The *A* component is enzymatically active, and the *B* component is the cell binding component. Anthrax toxin is of the form A_2B, where the two

enzymes, EF and LF, are the *A* components and PA is the *B* component. Thus, PA acts as a Trojan Horse, which carries EF and LF through the plasma membrane into the cytosol, where they may then catalyze reactions that disrupt normal cellular physiology.

Anthrax toxin assembly and translocation

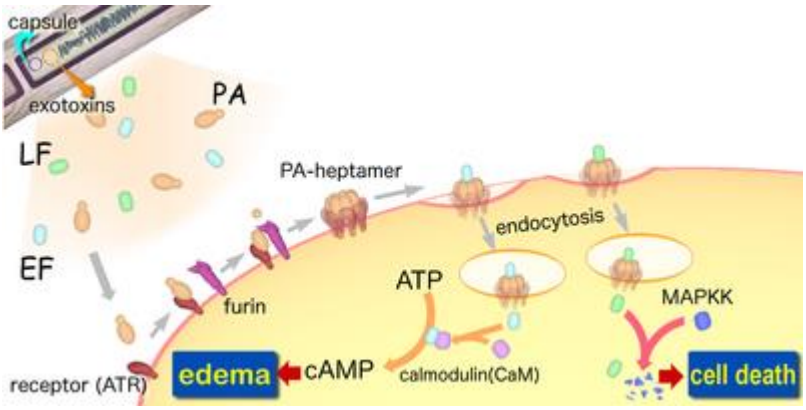

Diagram of the actions of the secreted anthrax toxins

Anthrax toxin protein components must assemble into holotoxin complexes to function. In order for LF and EF to function inside a target cell, they must localize to the cell and enter its cytoplasm. Through a series of steps, PA can translocate EF and LF into the cell (Fig. 2). This process starts when the 83-kDa form of PA, called PA83, binds to an anthrax toxin receptor. There are two known homologous receptors, which bind to PA83, called tumor endothelium marker-8 (TEM8) and capillary morphogenesis protein 2 (CMG2).[3] Then a 20 kDa fragment (PA20) is cleaved off PA83's amino terminus by membrane endoproteases from the furin family. When PA20 dissociates, the remaining receptor-bound portion of PA, called PA63, may assemble into either a heptameric[4] or octameric[5] ring-shaped oligomer. This ring-shaped oligomer is often referred to as the pre-pore (or pre-channel) form of PA, since later in the pathway it will become a translocase pore (or channel). The surface of the pre-pore oligomer, which was exposed upon release of the PA20 moiety, can then bind to LF and EF.[6] The heptameric and octameric forms of the PA oligomer may then bind with

up to three or four molecules of EF and/or LF, respectively.[5][7] The cell then endocytoses these assembled complexes and carries them to an acidic compartment in the cell. The low pH encountered in the endosome causes the PA63 pre-channel to convert into a cation-selective channel. EF and LF are driven through the channel by a pH gradient, allowing the enzyme factors to enter the cytosol