Development of a Novel cAMP–Inhibitor that Restores Epithelial and/or Endothelial Barrier Integrity in Human Cells Infected by Pathogenic Bacteria

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Technology description

Researchers at UC San Diego have developed a strategy to block the pathogenic effects of Anthrax Edema Toxin (ET) and Cholera Toxin (CT) which represent key virulence factors for the respective pathogens,Bacillus anthracisandVibrio cholerae. These toxins disrupt vascular endothelial (ET) and intestinal epithelial (CT) barrier integrity by blocking transport of adhesion proteins such as cadherins and signaling molecules to cell-cell junctions. As discussed above, ET and CT both act to dramatically elevate cAMP levels in the cell, but by distinct mechanisms. Two well-known cAMP binding proteins mediate the effects of cAMP in host cells: protein kinase A (PKA) and EPAC, a guanine nucleotide exchange factor for the small GTPase Rap1. Our invention uses a small molecule inhibitor (ESI09) of Rap1 to protect against the barrier disruptive effects of ET and CT, and to fortify endothelial and epithelial integrity in a wide variety of medical conditions in which barrier dysfunction is an important pathophysiologic feature.

Pathogenic bacteria have evolved elaborate and clever ways to enter our cells and breach the protection offered by our innate immune system. To initiate disease, many bacterial toxins target a specific cell, usually by binding to a receptor and thereby gaining access to the cytoplasm to promote pathogenesis.

Interestingly, a set of toxins produced by diverse bacterial species act by distinct mechanisms to dramatically increase the intracellular concentration of cAMP. This striking evolutionary convergence suggests that overproduction of this second messenger represents a successful strategy to promote growth and dissemination of infectious agents, as well as disease symptoms. The organisms that produce these toxins that disrupt cAMP include:Bacillus anthracis(B.a. and Anthrax edema toxin- ET, LT),Bordetella pertussis(CyaA), andVibrio cholerae(Ctx) will be the focus of this study.

Current therapies to alleviate symptoms of cholera and anthrax are less than adequate and demonstrate that there is an urgent need for updated strategies and therapies for the treatment of these pathogenic diseases.

Related Materials

Annabel Guichard, Prashant Jain, Mahtab Moayeri, Ruth Schwartz, Stephen Chin, Lin Zhu, Beatriz Cruz-Moreno, Janet Z. Liu, Bernice Aguilar, Andrew Hollands, Stephen H. Leppla, Victor Nizet, Ethan Bier.

Anthrax edema toxin disrupts distinct steps in Rab11-dependent junctional transport. 2017. PLoS Pathog

Application area

The inhibitor, ES109 is a potential therapeutic for the treatment of the diseases caused by anthrax, cholera or pertussis toxins and can restore, preserve, or both, epithelial and endothelial barrier integrity.

Advantages

The current inhibitor provides an alternative strategy for the treatment of diseases caused by anthrax, cholera or pertussis toxins.

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