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Opinion Article

Role of Endocytic Pathways in Bacterial Infections

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DESCRIPTION

Many bacterial pathogens produce toxins that target intracellular molecules to alter or disrupt normal cell function. The endocytic pathways of mammalian cells either take up molecules from the plasma membrane and bring them back to the surface (as in early endosomes and recycling endosomes) or sort them for degradation (like in endosomes and lysosomes) composed of different membrane compartments. The clathrin-dependent pathway of endocytosis is the best endocytic pathway. It is found in all mammalian cells and is the primary pathway through which cells obtain nutrients. For example, it facilitates the uptake of iron by using transferrin and cholesterol by low-density lipoprotein. The main types of endocytosis are phagocytosis, pinocytosis and receptor-mediated endocytosis. An endocytosis is a process for the uptake of proteins into cells occurs in the bacterium *Gemmata obscuriglobus*, a member of the phylum Planktomyceae, a characteristic budding bacterium that lacks peptidoglycan. To enter cells, these toxins often use endocytic pathways, by using cellular machinery to mediate their internalization. As bacteria are becoming increasingly resistant to antibiotics, alternative ways are needed to treat or prevent diseases caused by bacterial toxins. Small molecules that target key proteins involved in endocytic transport pathways. Inhibitors offer an opportunity to develop these compounds as potential therapeutic. Pathogenic microorganisms and toxins have evolved various mechanisms to gain access to the host cell cytosol, thereby exerting toxic effects on the host. A common mechanism of cell entry requires to acidic endosomes that facilitate translocation across host membranes. To identify small molecule inhibitors that block this process, a library of 30,000 small molecules were screened for inhibitors of the lethal anthrax toxin. 4-bromobenzaldehyde N-(2,6-dimethylphenyl) semicarbazone, the most active compound identified which inhibits lethal toxin poisoning and several other acid-dependent bacterial toxins which block the entry of viruses into mammalian cells. Some compounds used to slow lysosomal targeting and degradation of epidermal growth factor receptor, indicating that it targets host membrane.

The success of a wide range of microbial pathogens depends on their ability to enter the host cell cytosol or to transport proteins into the cytosol. Bacterial toxins that act intracellularly have evolved to exploit multiple host-mediated entry mechanisms. These toxins have become ideal tools for studying endocytosis and vesicular trafficking. Indeed, the use of bacterial toxins has contributed to important discoveries such as membrane recycling, clathrin-independent endocytosis, and retrograde transport. Compounds have been identified that inhibit entry of ricin, Shiga toxin, and Pseudomonas aeruginosa Exotoxin-A (ExoA) into host cells. These small molecules exhibit multiple mechanisms of action, including blocking retrograde transport of toxins at the early endosomal Trans-Golgi Network (TGN) junction, morphologically disrupting the Golgi apparatus, and inhibiting the toxin's active site. Small molecules that interfere with toxin binding, entry, transport, and host responses not only serve as probes for interrupting eukaryotic pathways, but also act as potential therapeutics for infections and genetic diseases. One of the examples that produce bacterial toxins is *Bacillus anthracis.*

Bacillus anthracis is a causative agent of anthrax, secretes a binary toxin that enters host cells and disrupts physiological processes. Lethal Factors (LF) cleaves Mitogen-Activated Protein Kinase Kinases (MAPKK) and Nlrp1b is Zn^{2+} dependent, recapitulating many anthrax diseases upon injection in experimental animals. Cellular entry of LF is dependent on cell-binding and translocation subunits known as protective antigens. PA is an 83 kDa protein that is cleaved by host proteases into 63 kDa and 20 kDa fragments that allow oligomerization of the toxin into prepores. Poly Amide (PA) oligomers can then bind up to four LF monomers to form holotoxin complexes. Two cytotoxin receptors, TEM8 and CMG2 mediate toxin binding and endocytic uptake. Acidification of the lumen of late endosomes triggers a confirmational change in the prepore, leading to insertion into the endosomal membrane and translocation of her LF to the cytosol. Alternatively, LF is localized within intraluminal vesicles and transported to late endosomes through multivesicular bodies and ALIX-dependent process. The vesicle membrane then fuses with the restricting endosomal membrane, thereby delivering LF to the cytosol.

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