Coughing up a Cure for Whooping Cough with Pertussis Toxin

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Introduction

The CDC reported 32,971 cases of pertussis, or whooping cough, in 2014. This respiratory infection mainly affects unvaccinated infants and toddlers, and symptoms include paroxysmal coughing with whooping, vomiting, and pulmonary complications which can lead to death. Pertussis toxin (PT), produced by the pathogenic bacteria Bordetella pertussis, causes whooping cough, by inactivating the Go protein that inactivates adenyl cyclase, leading to an increased intracellular concentration of cAMP. Increased concentrations of cAMP can interfere with normal cell signaling, disrupting specific cellular functions. PT is a critical virulence factor for B. pertussis that also has potential to create human immunity against pertussis. The Cedarburg SMART Team (Students Modeling A Research Topic) modeled PT using 3-D printing technology to study structure-function relationships. Effective vaccines contain chemically-inactivated PT. However, whole cell pertussis vaccine may cause severe side effects, while acellular pertussis vaccine is not as potent. Non-toxic derivatives of pertussis toxin may be engineered, improving the potency of the acellular vaccine without harmful side effects.

Pertussis is a leading cause of respiratory disease in infants and young adults throughout the USA.

- Humans are the only carriers of pertussis; infection rates can be high.
- Pertussis vaccine given to infants older than three months.
- Infants can be allergic or sensitive to the whole cell pertussis vaccine.
- Most of the U.S. population is vaccinated, so unvaccinated students are unlikely to contract the disease due to herd immunity.
- Multiple outbreaks are observed every three to five years.

Photolabeling experiments provide evidence that Pertussis toxin is an ADP-ribosylating protein.

Figure A: Three proteins, egg albumin (EA), diphtheria toxin A (DTA), and a portion of pertussis toxin (C180) are separated by gel electrophoresis. C180 is a recombinant peptide, containing the first 180 residues of the S1 subunit of PT. PT shows the same separation pattern when irradiated with UV light (+) as when it is not subjected to UV light (-).

Figure B: Photolabeling results show that UV irradiation induced efficient transfer of radiolabel from NAD to C180, which is a single subunit catalytic domain that binds the toxin to respiratory cells and is responsible for intracellular trafficking of PT. The binding domain of PT (circled in pink) is responsible for binding PT to the respiratory cells and for intracellular trafficking of PT.

The binding domain (B) and catalytic domain (A) dissociate in the ER and the catalytic domain (A) unfolds and then refolds in the cytosol.

- B. pertussis infects the respiratory system in people, but the disease is systemic.
- B. pertussis targets cells in the upper respiratory tract.
- Only B. pertussis produces pertussis toxin (PT).

The binding domain of PT (circled in pink) is responsible for binding PT to the respiratory cells and for intracellular trafficking of PT.

Conclusion

- B. pertussis is still a threat to health even with current vaccines. Historically, outbreaks of pertussis occur every 3-5 years.
- B. pertussis only infects ciliated respiratory cells in humans. While whole cell vaccines are potent, they are associated with greater reactivity.
- Whole cell vaccines contain the entire, but inactivated, B. pertussis cell. Whole cell vaccines are potent, they are associated with greater reactivity.

Whole Cell vs. Acellular Vaccine

Potency and Reactivity

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<th>Product</th>
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Four vaccines (listed in the table as μg per dose) are the only acellular vaccines approved for use in humans in the U.S.

Proteins found in B. pertussis, including PT, comprise acellular pertussis vaccines. Whole cell vaccines contain the entire, but inactivated, B. pertussis cell. Whole cell vaccines are potent, they are associated with greater reactivity.

References
