Causes of whooping cough

Abstract

Introduction

The genus *Bordetella* contains species of bacteria which are related serologically each displaying similar characteristics such as morphology, size and staining reactions (Website 1). The *Bordetella* genus is responsible for respiratory infections that are common in both people and animals (journal 1); *Bordetella pertussis* was first isolated in pure culture in 1906 and was long considered the sole causing factor of whooping cough. However, further studies revealed that mild forms of whooping cough could be caused by *Bordetella parapertussis* and on occasions *Bordetella bronchiseptica* (website 1). Whooping cough is a highly contagious respiratory illness that affects humans caused by the gram negative bacterial pathogen *Bordetella pertussis* . This particular pathogen is a strict human pathogen with no evidence of an impact on animals or the environment (journal 1). The disease can be characterised by bronchopneumonia, paroxysmal coughing and the distinctive ‘ whooping’ intake of air. Pertussis is more prevelant in developing countries where essential medical care is often not available and disease (journal 2)

Species Associated with *Bordetella*

Bacteria that belong to the genus *Bordetella* are of importance to both paediatric and veterinary medicine due to their ability to colonise and multiply on the ciliated epithelial cells of the respiratory tract (journal 4)

Nine species have been identified within the *Bordetella* genus to date, only three additional members, *B. bronchiseptica , B. parapertussis* and *b. homlessi (journal 3). B. pertussis* and *B. parapertussis* are extremely closely related according to their genomes; *B. bronchiseptica,* which by DNA-DNA and DNA-rRNA hybridisation are also closely related to the two previous species. A more recent addition to the genus includes *B. avium* (formerly known as *Alceligenes faecalis*) (website 1) which is described as a bird pathogen causes turkey coryza and other respiratory infections in fowl (journal 2). Another late addition includes *B. hinzii* (formerly known as *A. faecalis* type II), which can lead to respiratory disease in poultry and is very rarely found in humans (website 1). *B. trematum* has recently been proposed for a novel species isolated from human wounds and ear infections; although none of the new species identified were associated with respiratory infections, they are phylogenetically similar to other members of the genus (journal 2).

Transmission

Infection typically begins with the bacterium entering the airways of the host via airborne droplets derived from the cough of an infected individual. The pathogen proceeds down the respiratory tract and adhering to ciliated epithelial cells of the trachea and nasopharnyx in the host. Once attachment has occurred, the pathogen proceeds to replicate and colonise any adjacent areas. As part of *Bordetella* 's extensive range of virulence factors, it secretes toxins that damage the epithelial cells, which results in the loss of ciliated cells; this process induces the characteristic coughing (journal 2).

Virulence Factors

The main objective of any pathogenic bacterium is to colonise and replicate by exploiting its environment to the fullest extent. This can be achieved by the bacterium controlling and producing specific factors that enable it to infect the host (journal 2). Many of the virulence factors characterised in the *bordetellae* are common across the three species (*B. pertussis, B parapertussis* and *B. bronchiseptica*). These include adhesions such as filamentous hemagglutinin (FHA), pertactin tracheal colonisation factor and fimbriae, and toxins including adenylate cyclasehemolysin, dermonecrotic and tracheal cytotoxin. Other virulence factors are expressed by just one of the species, such as the pertussis toxin and serum resistant protein secreted by *B. pertussis* or a type III secretion system expressed by the species *B. bronchiseptica* (Journal 5)

Bvg Regulation

The majority of virulence factors displaced by this genus are controlled by BvgAS regulatory locus, a two-component regulatory system. BvgA is a 23 kDa (journal 9) DNA binding response regulator (journal 8). BvgS is a 135 kDa (journal 9) transmembrane sensor protein kinase (journal 8). This system assists the transition of *B. pertussis* between its virulent phase of Bvg $^{+}$ and its Bvg $^{-}$ phase which is avirulent (JOURNAL 10). For both *B. bronchiseptica* and *B. pertussis,* in order for sufficient respiratory tract colonisation the Bvg $^{+}$ phase is necessary (journal 8), this phase can be demonstrated when bacteria is grown on a rich media at 37°C (journal 11)

BvgAS undergoes a series of phosphorelay signal transduction events in response to an environmental stimulus that leads to differential transcriptions of target genes. This regulatory system has a distinct intermediate phase, Bvg ^{1} that can be achieved with the growth of bacteria in that conditions are between Bvg $^{+}$ and Bvg $^{-}$ phases (journal 11). BvgS undergoes autophosphorylation when there is an absence of modulators, after several steps the phosphate group is transferred to the amino terminal domain of the second component. The phosphorylation activates BvgA and binds to promoter regions located on *B. pertussis* virulence activated genes (Journal 12).

Filamentous Haemagglutinin

Many virulence factors of *Bordetella pertussis* are well characterised and any mutations in these factors causes significant reduction or complete loss of virulence. The bacteria adhere to ciliated cells of the epithelium in the upper section of the respiratory tract. The filamentous haemagglutinin (FHA) is the major adhesion present across *B. pertussis, B. parapertussis* and *B. bronchiseptica* (journal 6). This particular virulence factor is crucial in order for *B. pertussis* to attach the pathogen to the host cell. FHA is a 220-kDA surface associated protein that is secreted to the extracellular environment to assist the adherence to ciliated epithelial cells, therefore initiating the pathogenic cycle (Journal 2). However, in recent studies using the closely related species *Bordetella bronchiseptica* it has shown that other adhesions are just as important in initiating an infection; any deletion of any of the four adhesions (FHA, Pertactin, fimbriae, Brk A) results in the decreased ability of *B. bronchiseptica* to bind to host cells (Book 1)

Pertactin

Pertactin can also be known as aliases p. 69 and OMP 68 due to its electrophoretic mobility in SDS-Page, pertactin is a 60-kDa outer membrane protein which assists bacterial adherence. Similar molecules are produced by other members of the same genus; *B. parapertussis* produces p. 70 and p. 68 in *B. bronchiseptica* (Journal 2). In a comparison of the prn gene sequences of *B. bronchiseptica, B. pertussis* and *B. parapertussis* , the precursors were found to be homologous (journal 6).

The mechanism in which pertactin promotes the adherence to the ciliated epithelial cells is unknown and no receptor has been found, It has been demonstrated by a number of groups that pertactin can be described as an immunoprotective antigen (Journal 2).

Adenylate cyclase toxin/haemolysin

Adenylate cyclase toxin, a 177 kDa polypeptide (book 1) is a highly toxic potent repeats in toxin (RTX) family and is a substrate of T1SS. This particular toxin consists of two functional molecules; adenylate cyclase domain which binds calmodulin and catalyses unregulated conversion of ATP to cAMP, and an RTX haemolytic domain which is responsible for the binding to target cells and translocating adenylate domain into the cytosol (journal 7). Evidence suggests that the increasing levels of cAMP produced can lead to a decrease in phagocytosis as well as inhibition of chemotaxis; this therefore affects a major part of the innate immune response book 1).

ACT has the potential to play a role in adhesion by modifying a carbohydrate binding domain of FHA leading to an increased ability to bind to host cells.

However, the main function of ACT appears to be its ability to inhibit the function of neutrophils (book 1).

Pertussis Toxin (PT) – Type IV Secretion

Pertussis toxin is a member of the AB_5 toxin family, indicating it consists of five different subunits (book 2), with two copies of the subunit 2 together with single copies of S 2, 3 and 5 forming a pentameric ring. This mediates host cell receptor binding and the translocation of the S 1 subunit (ADP ribosyltransferase) (BOOK 4), it is considered the most complex bacterial toxin. Pertussis toxin is essential for bacterial virulence; it interferes with the mechanism used by host cells to remain in communication with the rest of the host's body. Other affects include weight loss, elevated igE production, and increased sensitivity to histamine, serotonin and cold. While the pertussis toxin alters the behaviour of both human and animal cells, its ability to inhibit activation of the immune system in response to infection best explains its role in human whooping cough (book 2).

A full understanding of Type IV secretion is yet to be achieved; however, it does provide a good example of the ability of bacteria to adapt groups of proteins to its new needs (book 4).

Epidemiology

In terms of epidemiological quantities, there are two fundamental aspects: the transmission rate and the length of the infectious period; these values determine the basic reproductive rate R_0 (journal 13). The mucous membranes of the human respiratory tract are the natural habitat for

Bordetella bacteria, although *B. pertussis* can survive outside the body for up to a few days and can be transmitted via contaminated items. Majority of infectors occur through direct contact with an infected individual (website 1).

Prior to the 20 th century was considered a terrible childhood disease, in 2008 it still occurs for approximately 195, 000 deaths worldwide. Of these fatal cases 95% occurred in developing countries. Outbreaks have been found to be linked with incomplete or reduced immunisation of individuals.

The vaccine formerly used was known as DTP and included antibodies diphtheria toxin (D), tetanus toxin (T) and pertussis (P); however, this vaccine has been replaced with a safer DTaP vaccine, reducing the side effects (website 2).

Discussion

Although many advances have been made, much remains to be discovered as to how the adhesions and toxins produced by the *Bordetella* species establish and maintain infection and development of disease. in host cell organisms.

http://www. ncbi. nlm. nih. gov/books/NBK7813/WEBSITE 1

http://www. who. int/immunization/topics/pertussis/en/index. htmlWEBSITE 2

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BOOK 4 BACTERIAL MECHANISMS