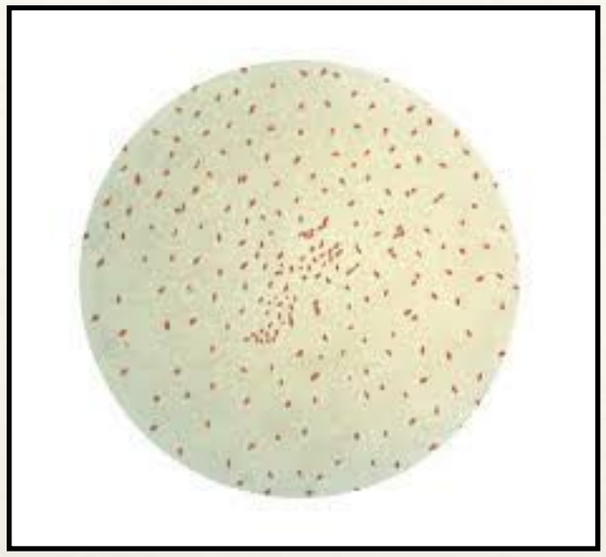


The Immune response: *Case 4: Bortedella pertussis*

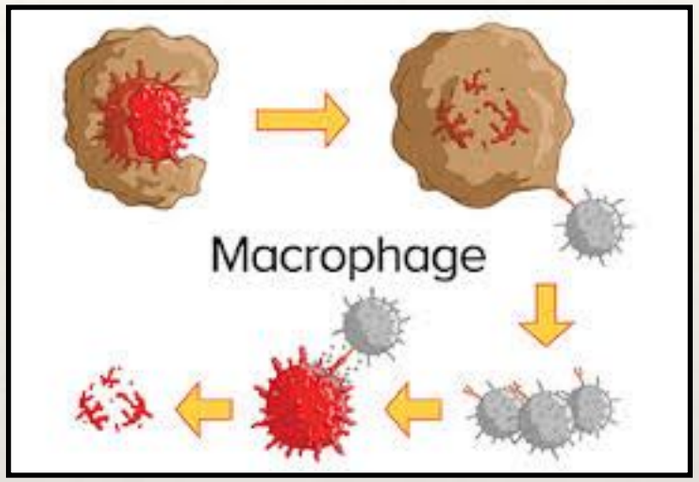
By: Kunye Hu

A Summary

- Host response
- Host damage
- Bacterial evasion
- Outcome

The innate immune response

- First to respond to an infection
- Immune cells involved: Dendritic cells, macrophages, neutrophils, natural killer cells, and antimicrobial peptides
- Acidic compartments of the macrophages kill engulfed bacteria
- Includes epithelial barrier of the respiratory tract: mucociliary clearance and secretion of antimicrobial peptides such as lysozymes, lactoferrin, defensins, and secretory leukoproteinase inhibitor

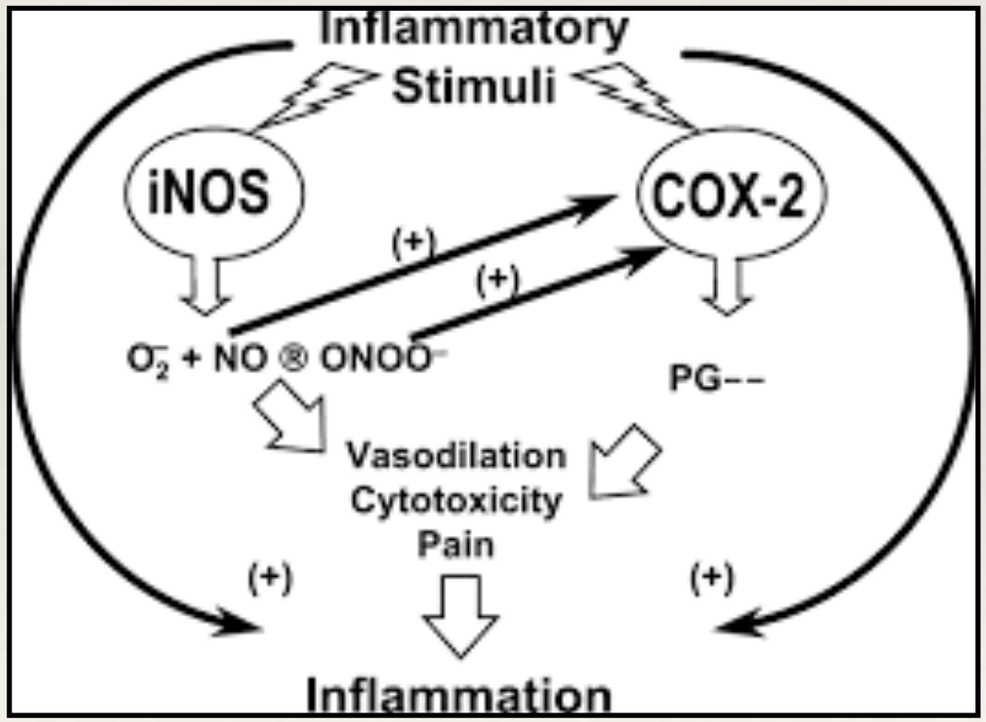


Innate Immune Response - Inflammation

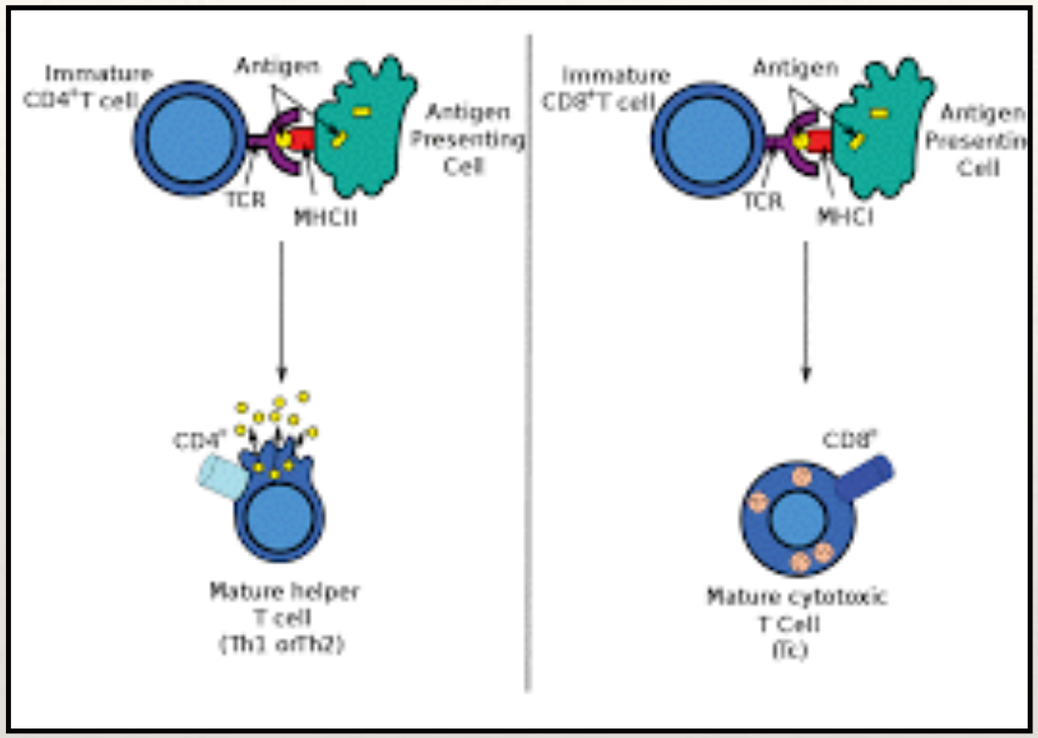
- Mature DCs to secrete inflammatory cytokines IL-12 and IFN-γ - induces T-cells , also triggers IL-10 production

- IL-10 promotes regulatory T-cells to inhibit the immune system from excessive immune responses in the respiratory airways

- Inflammatory cytokines : IFN-γ induces macrophages to produce nitric oxide (NO) to destroy the phagocytosed bacteria



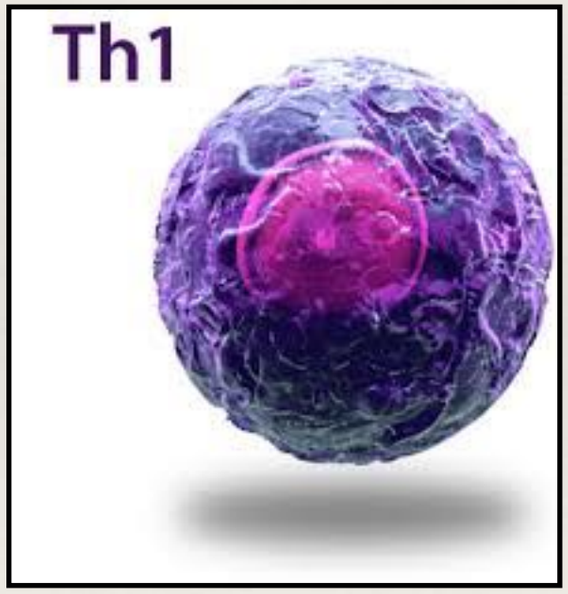
Innate Immune Response APC'S



- Dendritic cells (DCs)- act as antigen-presenting cells (APC's)
- Produced cytokines promote differentiation of naïve T-cells,
- Both the innate and adaptive cellular immune responses activated
- Immature DCs are activated via Toll-Like Receptor (TLR)-4 signalling cascade, which detect pathogen-associated molecular patterns (PAMPs) and virulence factors such as lipopolysaccharide (LPS)

Cellular Immune Response

- CD4+ Th1 T-cells at work 3 weeks post-infection
- virulence factors such as FHA and CyaA act as antigens to promote response
- Naïve T-cells detect inflammatory cytokines secreted by innate immune cells & mature to Th1 cells
- Th1 cells secrete IFN-γ,: opsonize antibody production and further activate macrophages and neutrophils for phagocytosis



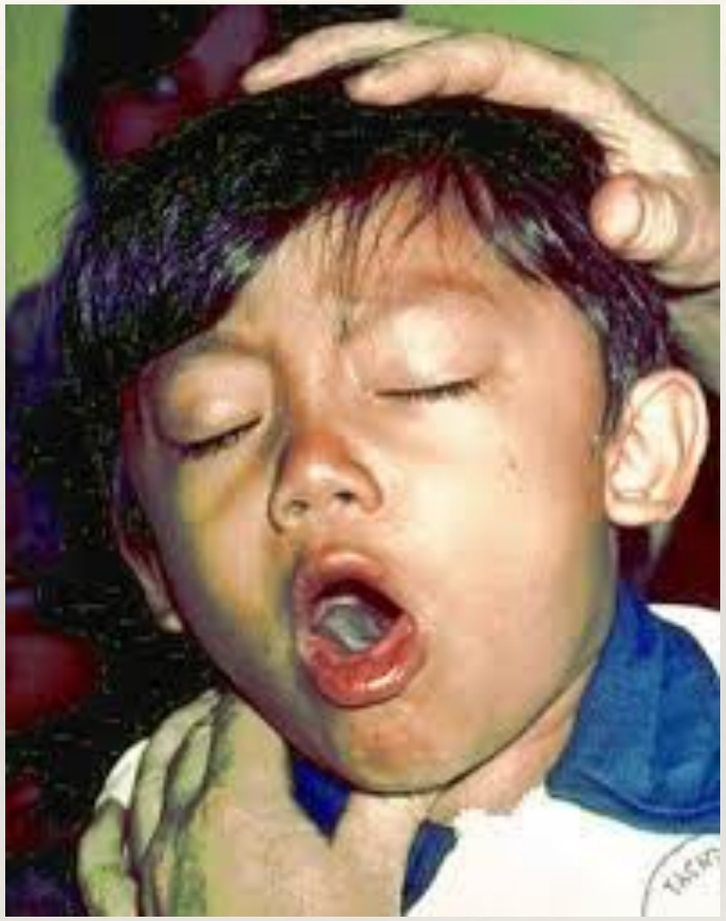
Humoral Immune Response

- IgA and IgG **antibodies**: neutralize bacterial toxins and inhibit extracellular bacteria from binding to respiratory tract & enhance bacterial uptake by macrophages and neutrophils
- Responses are enhanced by Th2 cells, which are also activated via virulence factors
- Th2 cells secrete IL-4, IL-5, and IL-6, which help antibodies fight against the infection
- Pertussis toxin enhances antibody activity against antigens, via stimulation of cytokine IL-1 production by macrophages

Host damage

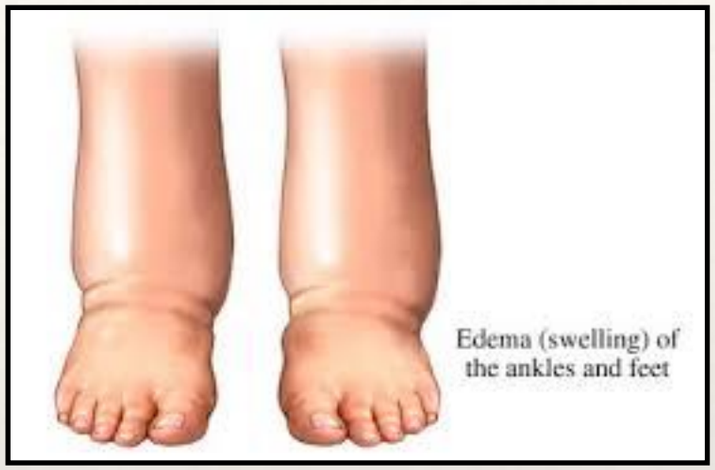
what damage ensues to the host from the immune response?

- B. pertussis attaches to the cilia on the epithelial cell in respiratory tract and produce toxins
- Tracheal toxin stimulates the release of IL-1 and may also cause a fever - inhibiting ciliary beating which can kill cells in respiratory tract
- Bacterial toxins released cause immunomodulation: damage to host cells and potential secondary infections, like pneumonia



Host Damage-Inflammation

- Driven by Th1 and Th17, inflammation can damage host tissues and prevent pulmonary secretion clearing
- Redness, heat, pain, and swelling due to inflammation may cause irritation of the upper respiratory tract
- Inflammation increases fluid in the lungs to increase leukocyte mobility
- Vasodilation and increased vascular permeability can cause edema
- Release of prostaglandin E2 (PGE2) can cause fever
- Lethal toxin can cause subsequent necrosis at infection sites



Host Damage- Other Cell Damage

- Pertussis toxin can cause an increase in cAMP -—> metabolic changes in the host cell induces immunosuppression and could cause secondary infection or lymphocytosis
- Neutrophils, macrophages, and dendritic cells may overproduce nitric oxide (NO) ——>combines with ROS and can degrade cells

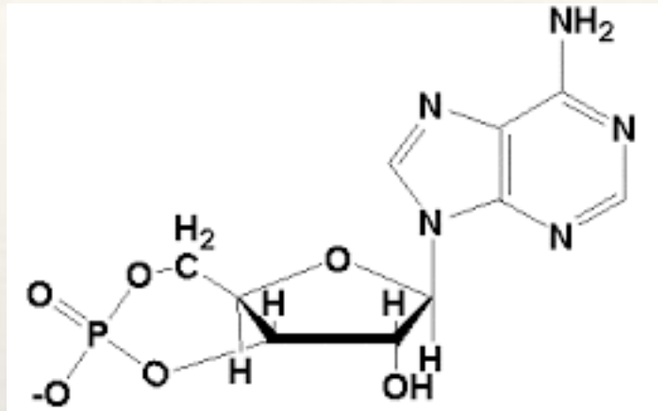
Bacterial evasion

how does the bacteria attempt to evade these host response elements?

- Filamentous haemagglutinin (Fha) promote both macrophage and neutrophil phagocytosis
- Once inside, pathogen uses adenylate cyclase toxin (ACT) to suppress of intracellular killing by increasing cAMP levels in the cell
- Rise in cellular cAMP prevents neutrophils from making extracellular traps and prevents oxidative burst
- ACT can suppress the secretion of proinflammatory cytokines like IL-12 and TNF-a
- ACT can induce innate immune cells to undergo apoptosis and cell cycle arrest, while hindering their actions of phagocytosis, chemotaxis and superoxide generation

Bacterial evasion

- Fha used to suppress the inflammatory response of innate immune cell
- Pertussis Toxin (PT) enhances Fha-mediated adhesion to facilitate bacterial uptake by innate immune cells for immune evasion
- PT further increases production of cAMP
- PT inactivates Gi protein to inhibit chemokine signalling pathways —> impaired macrophage, neutrophil and other lymphocyte movement to the sites of infection
- Inactivation of Gi also results in decreased phagocytic properties and oxidative burst
- PT delays the adaptive immune response by inhibiting phagocytosis by APC's



Cyclic adenosine monophosphate (cAMP)

Bacterial Invasion

- Three Secretion System (TTSS) also inhibits NFkB activation and blocks defensin expression by innate immune cells
- Bps polysaccharide on the LPS surface can engage in complement resistance
- BrkA protein reduces the amount of C3 and C4 present on bacterial cell surface to decrease frequency of MAC formation
- Bacterial binding to C1 esterase inhibitor further inhibits complement activity

Outcome

is the bacteria completely removed, does the patient recover fully and is there immunity to future infections from this particular bacteria?

- B.pertussis is completely removed from the body by approximately 3 weeks post- infection
- Patient may experience symptoms for up to 2-3 months
- Potential long-term complications: weight loss, rib fractures, pneumonia, apnea, encephalopathy, and death
- Unclear whether host immune response leads to acquired immunity:
- Some immunity occurs, lasting anywhere from 2 to 30 but does not protect against other species of Bordetella

Outcome- Vaccines?

- Both acellular and cellular vaccines have been developed to confer immunity against B.pertussis,
- No vaccine to date is 100% effective
- Booster vaccines may be useful