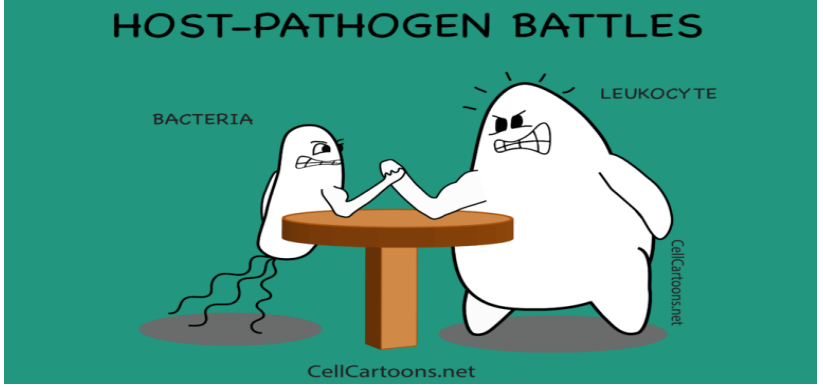
Immunological Perspective: *Helicobacter pylori* Infection

Prof. Dr. Batool Hassan AL-Ghurabi

Introduction



- *H. pylori* is one of the most common infections in humans.
- There is a hypothesis suggesting the role of immune response in the pathogenesis of infection.
- The immune response against the infection is ineffective, causing persistent microorganisms and inflammation.

Immunology at a glance

- There are two major groups of immunity—innate and adaptive immune responses.

- Innate immunity responses which do not require the previous contact with immune triggers (Ag).

- The response is rapid but not specific and has no memory.

- Acts as the first line of defense against harmful substances.

Immunology At A Glance

- Activation of the innate immune response may eliminate the substance and trigger inflammation by releasing mediators such as cytokines, reactive oxygen species, and nitric oxide.
- Elimination may be carried on by cell-dependent mechanisms, such as phagocytosis and cytotoxicity.

Immunology at a glance

- **Adaptive immunity** is an immune response against previously contacted Ag.
- This immune system is specific and has immunologic memory.
- Activation of adaptive immunity is related to innate immunity.
- For example, antigen-presenting cells (macrophages and dendritic cells), as a part of the innate immune system, trigger activation and differentiation of T-helper (Th) cells, which part of the adaptive immune response .

Immune response to *H. pylori* infection

- Many diseases, including infection due to *H. pylori*, involve dysregulation of the immune system.
- Infection is both active, marked by neutrophilic accumulation, and chronic, marked by lymphocytic deposition.
- Anti-*H. pylori* antibodies are also detected after initial infection, marked by the high levels of immunoglobulin (Ig) M, IgG, and IgA in gastric mucosa of infected patients.

Immune response toward *H. pylori* infection

- The infiltration of macrophages and neutrophils in the stomach is observed in the first 2 days after infection.
- By day 10 after infection, the numbers of macrophages and neutrophils are decreased to baseline levels.
- The adaptive immune response is started to appear in the 3rd week, marked by infiltration of T lymphocytes in lymph nodes and elevated expression of TNF-α and IFN-γ.

Immune response toward *H. pylori* infection

- The levels of IgM and IgA anti-*H. pylori* in patients are 40- to 50-fold higher compared to non-infected subjects.
- However, the presence of *H. pylori* in the stomach for a long period of time supports the ineffective immune response.
- The presence of this microorganism causes a persistent and chronic infection.

- ***H. pylori* infection** also activates humoral and cellular immunity as the parts of the adaptive immune system.
- ***Bacteria*** which have been ingested by antigen-presenting cells activate the adaptive immune response.

- Macrophages and neutrophils may also eliminate *H. pylori* through nitric oxide dependent phagocytosis or ROS production.
- They release cytokines such as IL-12, IL-10, and IL-23 which in turn stimulate naïve Th cells.
- In the other way, dendritic cells present *H. pylori* antigen to naïve Th cells. Naïve Th cells then differentiate into Th1 or Th2.

- However, Th1 is more prominent compared to Th2 cells.
- Th1 then produces IFNγ, TNFα, and IL-2.
- Elevation of pro-inflammatory cytokines, such as IL-1β, TNFα, IL-8, and IL-6, is observed.
- The release of cytokines promotes inflammation in the stomach and leads to gastritis.
- The role of B lymphocyte in this infection is indeterminate.

- Studies reported that antibodies against *H. pylori* are produced but they might be counterproductive.
- They are easily degraded and unstable in structure.
- Other literature states that the presence of IgA anti-*H. pylori* gives a protective effect against infection and gastric malignancy.

Mechanism of immune evasion of *H. pylori*

- The **outer membrane proteins** in *H. pylori* are found to be **less immunogenic** compared to proteins from other pathogens; therefore, the immune response elicited by the innate immune system is less powerful.
- *H. pylori*'s lipopolysaccharide has lower endotoxic activity than in other bacteria.
- The presence of arginase enzyme in *bacteria* decrease L-arginine, the substrate for NO level. So low NO level will impair phagocytosis by macrophage and prevent *H. pylori* elimination.

- *H. pylori* are also capable of producing urea by the urease enzyme. Ammonia is neutralize gastric acid and sustain the survival of *H. pylori*.
- Bacteria modulates its surface molecules including flagellin to avoid recognition by toll-like receptors on antigen-presenting cells.

- **The molecules are recognized as self molecules and thus do not trigger the immune response**.
- Even after being phagocytized, *H. pylori* may survive from killing by the help of cag PAI and VacA. Both delay phagosome formation inside macrophages.

- Chronic exposure of **dendritic cells** to *H. pylori* decreases the ability of dendritic cells to induce Th1 response and support the persistence of infection.
- Antigen form *H. pylori* may also bind dendritic cell and blocked Th1 cell recruitment.

- *H. pylori* promote the expansion of the **T-reg cell** and their recruitment to the site of infection.
- Treg suppresses the activity of T cells (Th1). This lead to increase Th2 activity, and increased level of TGF-β and IL-10

- **Host factor--Defects in cytokine coding genes** are involved in the persistence of *H. pylori* infection.
- Defects in gene coding IL-1 and TNF are associated with decreased cytokines production and increased risk for gastric cancer.

Vaccination and immune response toward *H. pylori*

- The trend of antibiotic resistance in *H. pylori* is increasing recently.
- Besides, reinfection may occur even after the complete eradication of the previous infection.
- This induction the development of a vaccine against *H. pylori*. Much effort has been devoted to the development of a vaccine as an alternative treatment for *H. pylori* infection.

Vaccination and immune response toward *H. pylori*

- The **first** report on *H. pylori* vaccine development was submitted in **2011** by **Moss** et al., They conducted trials in **mice** and showed promising results.

Vaccination and immune response toward *H. pylori*

- The utilization of the vaccine seems promising, but this option still needs further development, especially in humans, considering the immune evasion ability of *H. pylori*.