The Host Immune Response to *Salmonella ssp.* Enteritidis-induced Gastroenteritis

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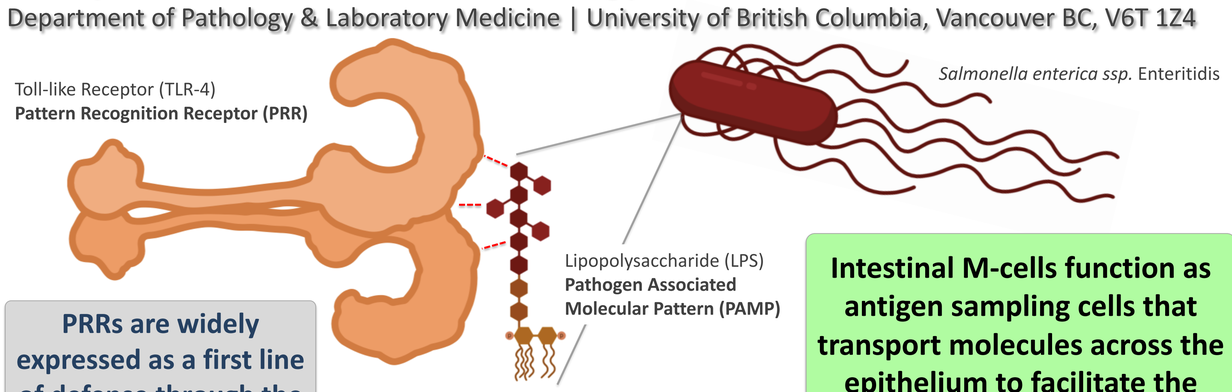
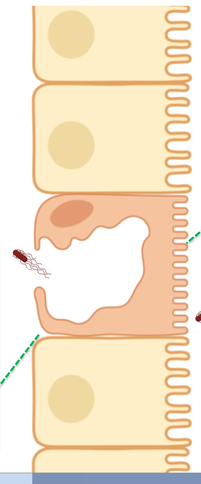


PRRs are widely expressed as a first line of defense through the surveillance of PAMPs

TLR-4 activates upon interaction with LPS

Intestinal M-cells function as antigen sampling cells that transport molecules across the epithelium to facilitate the host immune response



Salmonella exploits and invades specialized Microfold (M-cells) cells of the intestinal mucosa

Inflammatory molecules like INF-γ are key drivers of the immune response

Reactive oxygen species (ROS) are produced by neutrophils and NK cells for direct pathogen lysis

Components of the complement cascade act as chemokines and direct bacterial killing molecules

Possessing a diverse intestinal microbiome can provide protection from new infection with *Salmonella*

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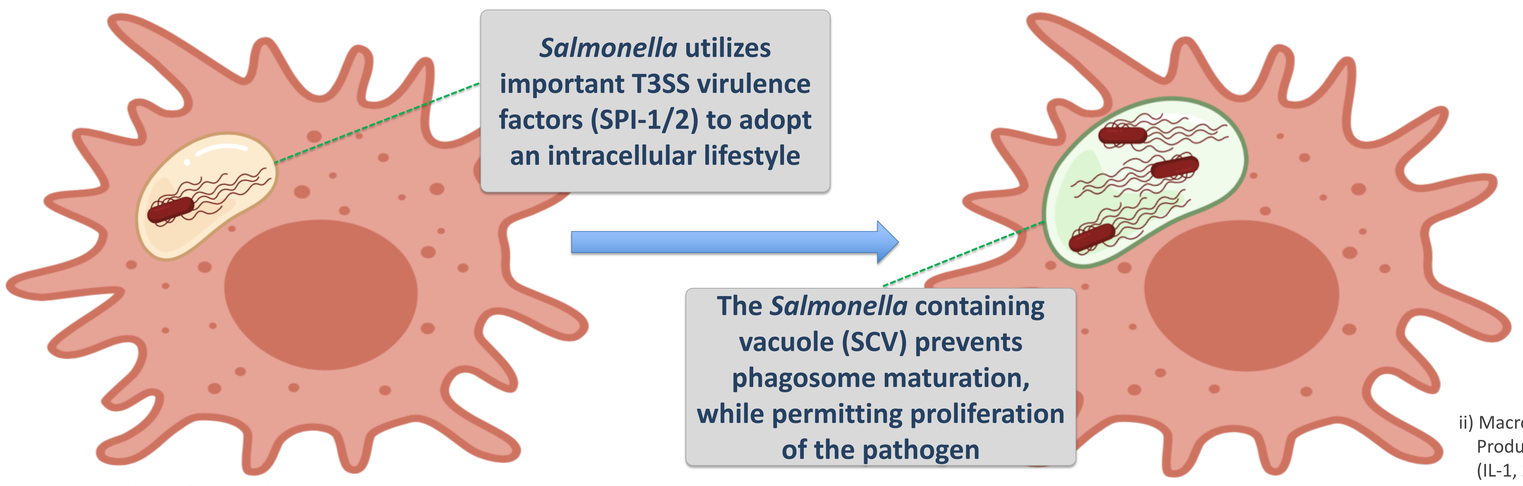
Primary (Innate) Immune Response

- Harsh acidity of the stomach (pH < 3)
- M-cells probe intestinal contents for foreign antigens
- Activation of complement via TLR4, resulting in:
  1) Direct lysis of the bacteria
  2) Marked for destruction by macrophages or NK cells
- Production of antimicrobial peptides (lipocalin-2) and ROS for direct killing or inhibition of the pathogen
- Production of inflammatory cytokines (INF-γ, IL-2, IL-6) and chemokines to recruit neutrophils, macrophages, followed by cells of the Adaptive Immune System

Salmonella Immune Evasion Strategy

- Production of acid shock proteins and efflux pumps
- Exploitation and invasion of host M-cells
- *Salmonella* works to decrease macrophage recruitment through the modulation of intestinal epithelial cells, via miR-128 and Macrophage Colony Stimulating Factor
- Modification of outer LPS molecules via PhoP/Q + PrmA, for decreased interaction with lipocalin-2 and ROS
- Once adapted to an intracellular niche, the *Salmonella*-containing vacuole (SCV) allows evasion from many aspects of the Innate and Adaptive Immune Responses



Adapted from (1) Hurley *et al.* 2014. *Front Immunol.* Fig 3
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Adaptive Immune Response

- B + T lymphocytes are activated by MHC-2 on macrophage or dendritic antigen presenting cells (APCs)
- Helper CD4+ T cells help to exaggerate the innate response through inflammatory cytokine signaling
- Cytotoxic CD8+ T cells can identify and destroy infected host epithelial cells through interaction with MHC-1

Salmonella Immune Evasion Strategy

- Replicating within macrophages, *Salmonella* inhibits APC presentation to B + T lymphocytes through MHC-2
- The SCV is achieved through Type-3 secretory systems present on *Salmonella* Pathogenicity Islands (SPI-1 + 2)
- Modification of outer LPS molecules can contribute to persistent immune evasion (continuous shedding)

Immunological Memory

- B cells are activated by antigen-specific T cells, allowing the formation of antibody-secreting plasma cells
- A subset of these will become memory B + T cells, which provide **<u>an improved and accelerated response</u>** to secondary infection with *Salmonella ssp.* Enteritidis

Damage to Host Tissues

- Prolonged exposure to ROS and inflammatory cytokines can negatively impact mucosal structure + function
  - Blunting of intestinal microvilli projections
  - Reduced nutrient absorption
- Dehydration and electrolyte imbalances from fluid loss

References: 1) Hurley *et al.* 2014. Front Immunol. (5):481. 2) Pham and McSorley. 2015. Future Microbiol. (10):101. 3) Zhang *et al.* 2014. *J Infect Dis. 209(12):2000.*