Microbiome and shaping of the Immune Response

Jan 31, 2017
Identify the lymphoid organ indicated by the green arrows.
M cell (microfold cell) in the surface of the Peyer’s patch is the cell specialized to uptake Ag from the gut
M cells do not have microvilli, but have a flat smooth surface. They have a deep pocket under them containing B cells, T cells and APC’s, including DCs. They endocytose Ags from the gut and transport them across the cell to deliver them to the area of the immune cells. Leads to activation of B cells—become plasma cells and release Abs into the gut.
M-cells (microfold cells) at the surface of Peyer’s patches are important for antigen uptake from gut 

see Fig 1.20 p22 of Janeway

Dome: has dendritic cells
PP DC’s extend processes through M cells to explore lumen

Lelouard et al, Gastroenterology (2012)
DC’s & M cells in Peyer’s patches
PP DC’s extended processes take up microspheres

M-cell= red
DC= green
Microsphere= yellow

~20 min

Lelouard et al, Gastroenterology (2012)
DC’s & M cells in Peyer’s patches
The GI Immune system

• Lamina propria, mesenteric LN, int ep cells
• Assist in immune cell migration and house cells
  – DC process Ags of lumen and tissues, I
  – Neutrophils & mϕ respond to tissue damage & translocated bacteria- orchestrate response
  – B-cell make Abs, IgA
  – When activated- immune cells produce pro-inflammatory cytokines (Il-6, IL-1B, TNFa) and anti-inflammatory mediators (Il-10, Il-4)
• Il-17 and Il-23 are pro-inflammatory mediators of mucosal immune function
• Chemokines- CCL6, CCL14, CCL15 chemotactic for T cells, Neutrophils & mϕ

Peyer’s Patch Dendritic Cells Sample antigens by Extending Dendrites through M Cell-Specific Transcellular Pores

Lelouard, Fallet, Bovis, Meresse and Gorvel
Gastroenterology 2011
Role of Gut microbiome

- Prokaryotic bacteria, viruses, yeast and helminthes
- Population affects host immune system and physiology
Bacteria

Described species: 4,000

Estimated total species: 1,000,000

The Convention on Biological Diversity
http://www.biodiv.org/convention/default.shtml
The Nobel Prize in Physiology or Medicine 2005

"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"

Barry J. Marshall
Australia
b. 1951

J. Robin Warren
Australia
b. 1937
Duodenal Ulcer (DU)  
Gastric Ulcer (GU)
Prevalence and Incidence of Peptic Ulcer

Prevalence Rate: 1 in 54 or 5 million people in USA

Incidence extrapolations for USA for Peptic Ulcer: 7 per minute

Lifetime risk for Peptic Ulcer: 1 in 10 Americans over lifetime

Probably most common chronic disease of humans. Human populations throughout the world affected. Incidence increases with age and occurs earlier and at increased rates in the developing world and lower socioeconomic groups. Up to 90% of some populations affected.

.... en 1987!

"...certain patterns of relationships were more common in 'ulcer' families. Thus the mothers of ulcer patients tended to have psychogenic symptoms, and to be striving, obsessional, and dominant in the home; fathers tended to be steady, unassertive, and passive."

"The description of these families...emphasizes the conflict in duodenal ulcer patients between dependence engendered by a powerful mother and demands of adult roles."

"The variations in peptic ulcer in different geographical, historical, and social contexts are unequivocal evidence of the influence of ways of life in this disease. The specific elements that contribute to the variations probably include diet, alcohol, cigarette smoking, emotional strain, personality, and genotype... This does not exclude the possibility that a major single causal effect awaits discovery."
*Lancet* (i): 1273

*Lancet* (i): 1311-1314
« I preferred to believe my eyes, not the medical textbooks of the medical fraternity »

R. Warren (2002)
Koch's Postulates

I. The organism, a germ, should always be **found microscopically** in the bodies of animals having the disease and in that disease only; it should occur in such numbers and be distributed in such a manner as to explain the lesions of the disease.

II. The germ should be obtained from the diseased animal and **grown outside the body**.

III. The inoculation of these germs, grown in pure cultures, freed by successive transplantations from the smallest particle of matter taken from the original animal, **should produce the same disease in a susceptible animal**.

IV. The germs should be found in the diseased areas so produced in the animal.

Attempt to fulfil Koch's postulates for pyloric Campylobacter.

A volunteer with histologically normal gastric mucosa received pyloric campylobacter by mouth. A mild illness developed, which lasted 14 days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day. The syndrome of acute pyloric campylobacter gastritis is described. It is proposed that this disorder may progress to a chronic infection which predisposes to peptic ulceration.

PATHOGENIC PROPERTIES OF *HELCOBACTER PYLORI*

- Adheres to gastric epithelium
- Lives within mucous gel layer overlying gastric epithelium
- Penetrates intercellular junctions
- Invades gastric glands and canaliculi of parietal cells
- Produces cytotoxins that may play role in pathogenicity
- Induces epithelial cytolysis and disrupts intercellular junctions
- Increases permeability of mucous layer to hydrogen ions and pepsin
- Enables gastric acid and pepsin to create ulcer craters
- Evades host immune defenses
- Damages tissue
- Secretes urease to produce ammonia, which protects it from gastric acid
Helicobacter pylori
— the bacterium causing peptic ulcer disease

Infection
*Helicobacter pylori* infects the lower part of the stomach, antrum.

[Diagram of the stomach with labeled parts: Corpus, Duodenum, Pylorus, Antrum, Helicobacter pylori]
Inflammation

*Helicobacter pylori* causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.
Ulcer
Gastric inflammation may lead to duodenal or gastric ulcer. Severe complications include bleeding ulcer and perforated ulcer.

Duodenal ulcer
Increased acid secretion

Inflammation

Bleeding ulcer

Gastric ulcer

Inflammation

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