6 Nov 2023,
BT 304
Lecture 37

Lymphocytes (small intestine)

- Largely effector/memory phenotype
- Conventional T cells
  - CD4+ and CD8+
  - Transient residents

- Regulatory T cells - promote oral tolerance; prevent unwanted inflammation
  - Tr1 - secrete IL-10
  - Th3 - secrete TGFβ (enables class switching to IgA)
  - nTreg - high levels of Foxp3

- Intraepithelial lymphocytes (IEL) - markers are those of chronically activated T cells - primarily CD8+
  - CD8αβ+TCRαβ+ (dominant population)

- Dendritic cells (CD103+ DCs) "train/educate" T cells to home to gut

Features of mucosal B lymphocytes

- During their resting stages B cells can traffic through mucosal lymphoid follicles.
- As plasmablasts they can migrate to the lamina propria.
- They tend to become committed to IgA production. However, IgM and IgG are also produced.
- There is some evidence that mucosal epithelial cells can condition mucosal DCs to present Ag directly to mucosal B cells to produce immunoglobulins.

IgA has multiple properties that are adapted for host defense in the GI tract

- IgA relatively resistant to proteolysis (IgA2 > IgA1)
- Poor activator of complement
- Inhibits
  - Bacterial adhesion
  - Macromolecule absorption
  - Inflammatory effects of other immunoglobulins
- Neutralizes viruses, toxins
- Enhances nonspecific defense mechanisms
  - Lactoperoxidase
  - Lactoferrin
- Mediates antibody dependent cytotoxicity

IgA type immunoglobulin

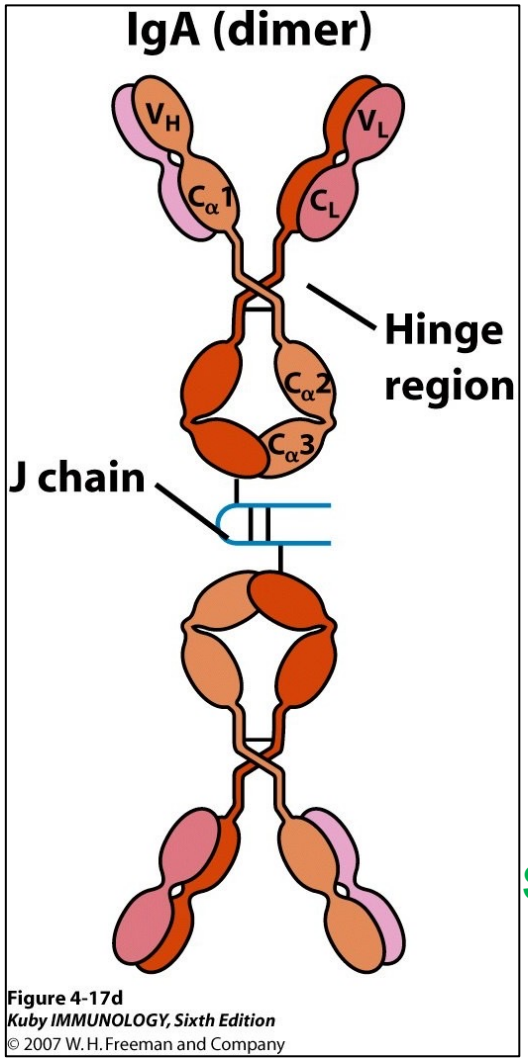


Figure 4-17d
Kuby IMMUNOLOGY, Sixth Edition

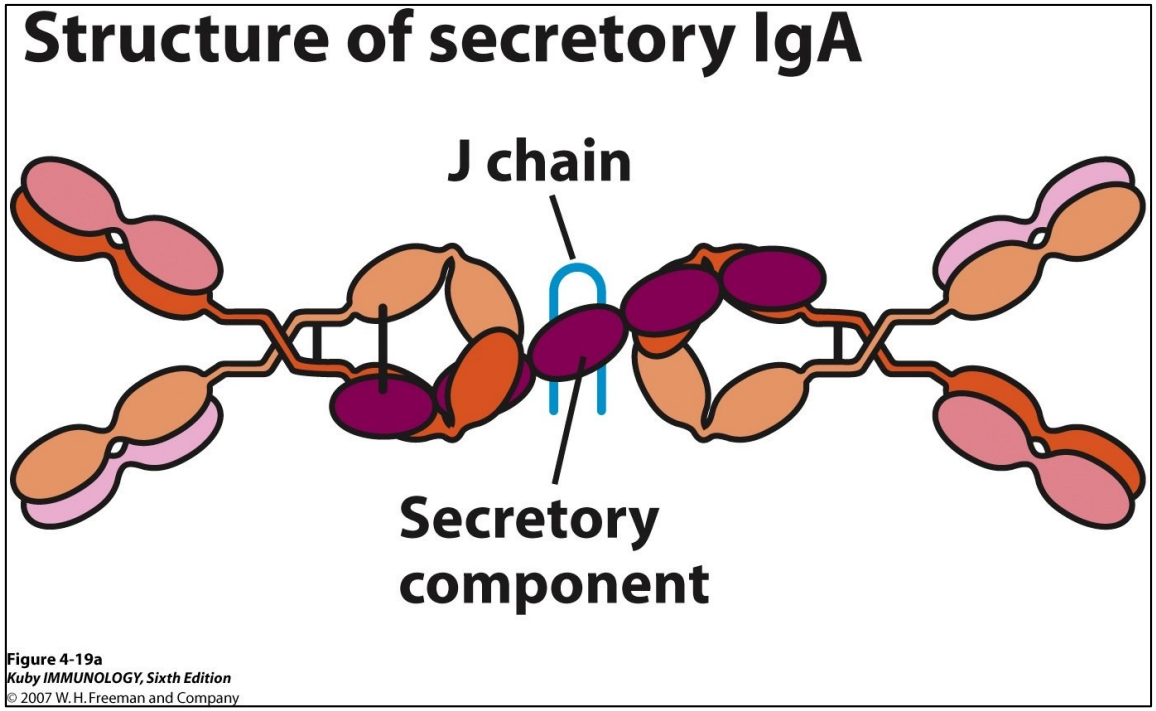


Figure 4-19a
Kuby IMMUNOLOGY, Sixth Edition

Serum - monomer **Secretions - dimer predominates**

Formation of secretory IgA

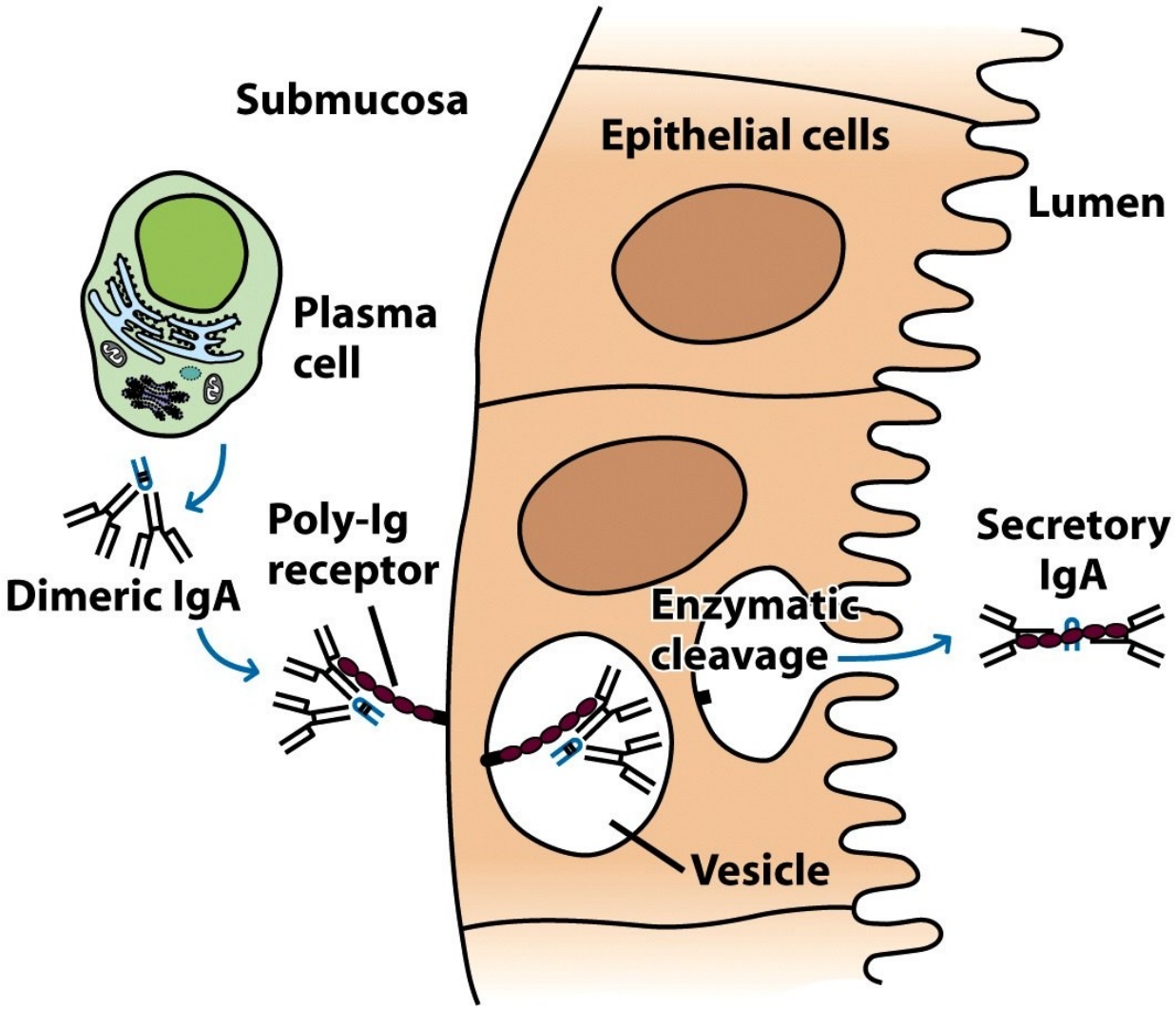
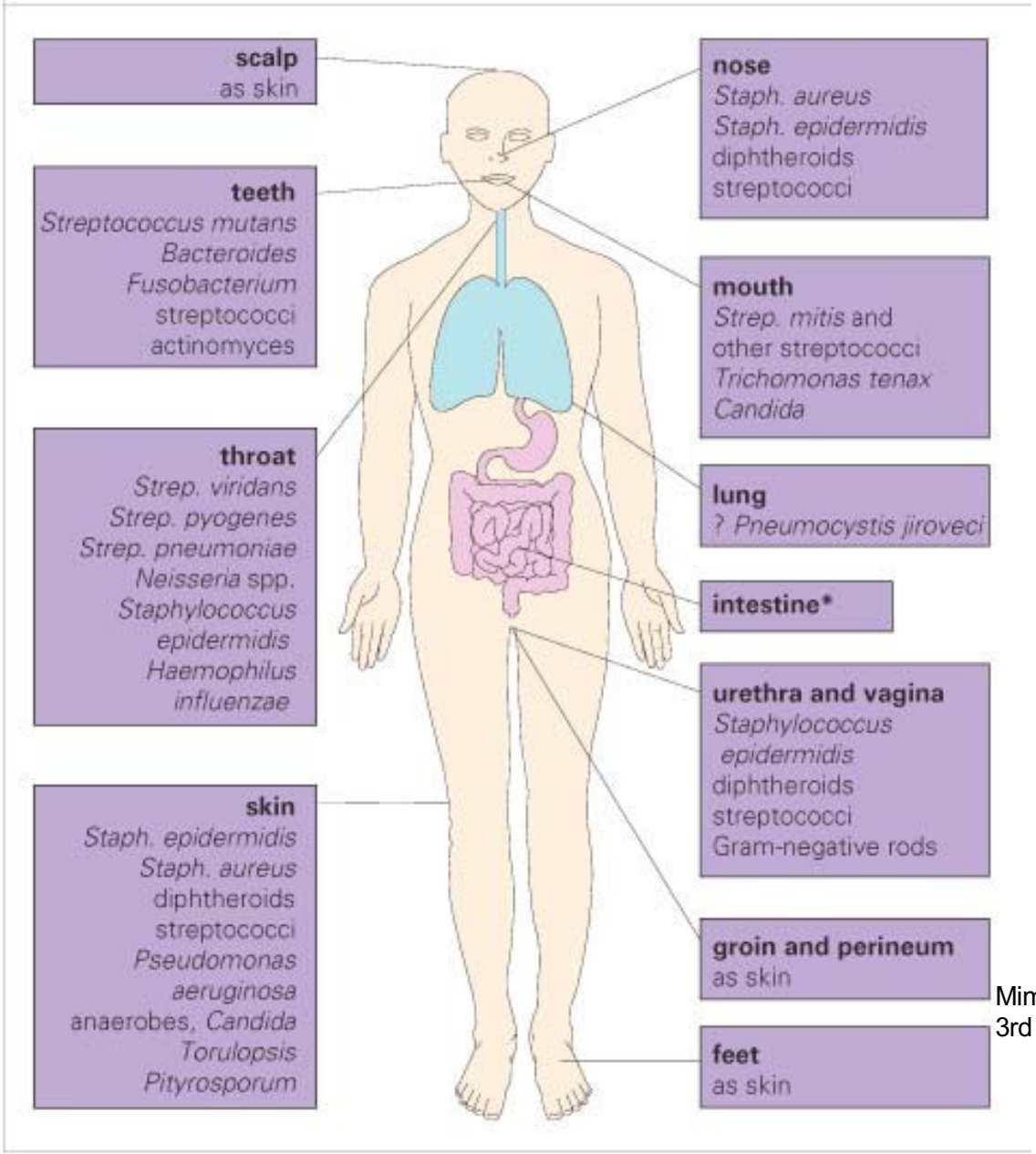
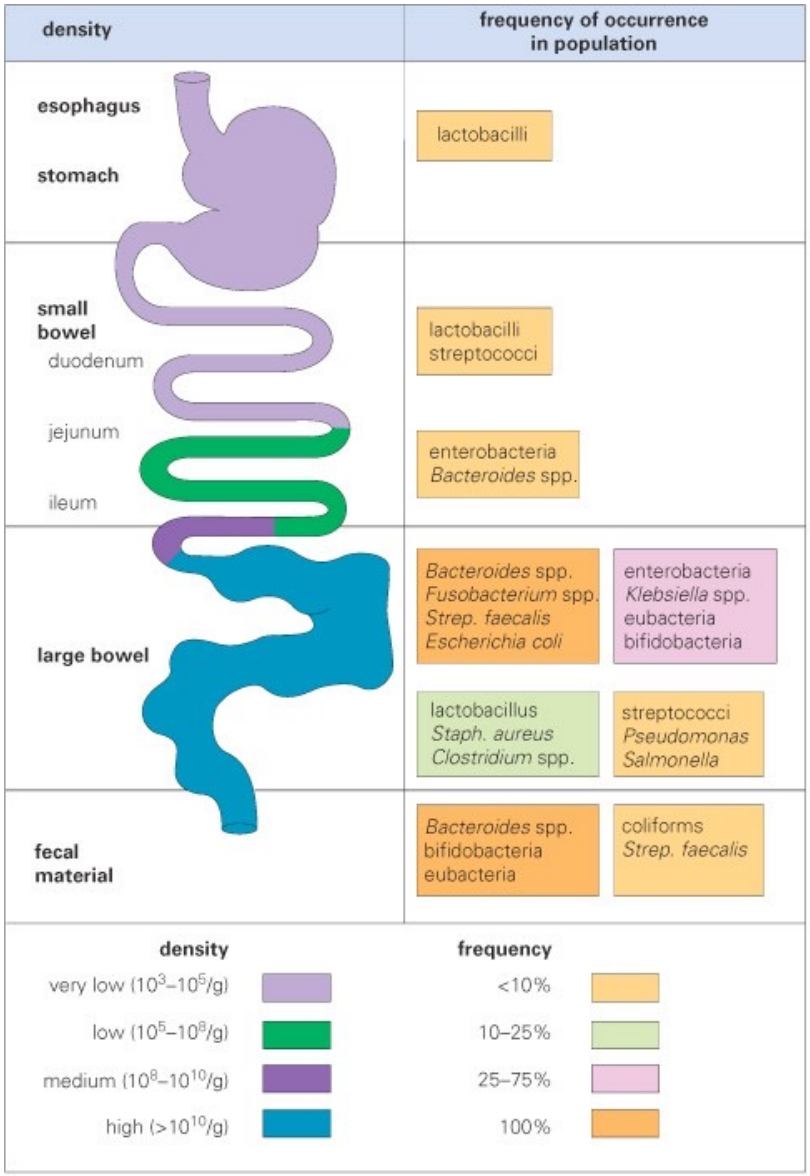


Figure 4-19b
Kuby IMMUNOLOGY, Sixth Edition

Normal flora and their location



Mims et al. Medical Microbiology 3rd ed. Elsevier.



The longitudinal distribution, frequency of occurrence and densities of the bacteria making up the normal flora of the human gastrointestinal tract.

Commensal bacteria (Latin = “at the table together”)

- Prevent colonization by more pathogenic species
- Produce metabolites that are used by the host
- Colonization of the gut begins immediately after birth
  - 10^{13}-10^{14} microorganisms
  - 400 to 500 different species
  - Majority are obligate anaerobes
- Negative effects on normal bacterial flora may explain the rise of immune disorders (allergies and IBD)

Beneficial effects of indigenous GI microflora

- Formation of anatomical structures (Peyer's patches)
- Expansion of germinal center reactions involving B and T cells
- Increased IgA production by intestinal B cells
- Expansion of IEL populations
- Bacterial antagonism
- Maintain GI tract peristalsis and intestinal mucosal integrity
- Convert dietary precarcinogens and carcinogens to noncarcinogens
- Synthesis of vitamin K and vitamin B complexes
- However, translocating bacteria can cause infections in debilitated patients

Why does the immune system ignore commensals?

- Mesenteric lymph nodes form a barrier that prevents commensals from reaching the systemic compartment of the host immune system and from eliciting a damaging immune response.

- DCs present Ag directly to B cells resulting in IgA production that prevents the bacteria from straying beyond the gut mucosa.

Macpherson & Uhr. Science 303:1662-1665, 2004.

Why does the immune system ignore commensals?

- Sequestration of indigenous microflora by surface epithelia
- Regulation of magnitude and duration of TLR signaling
- Proinflammatory bacteria may be controlled by anti-inflammatory effects of commensals
- Blocking of NF kappa B (transcription regulator) activation

Why does the immune system ignore commensals?

- Commensal bacteria may use type III or type IV secretion systems - might be able to deliver bacterial effector molecules to host cells which modify the outcome of infection with pathogenic bacteria.

Why does the immune system ignore commensals?

- Treg cells - tolerance, primarily local but probably systemic as well
- IL-10-producing dendritic cells
- Inhibition of the generation of Th1 cells

Commensals as therapeutics

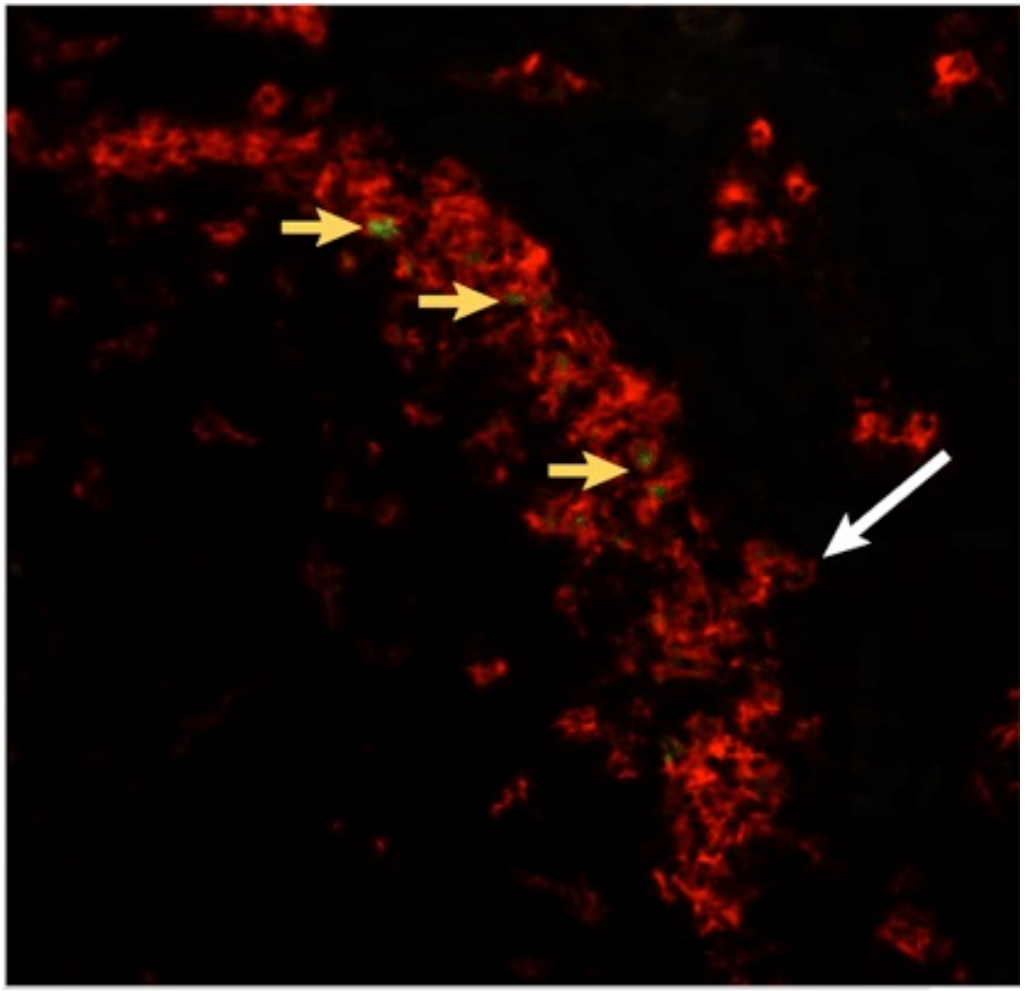
- Probiotics - dietary supplements containing potentially beneficial bacteria (primarily Lactobacillus sp, Bifidobacterium sp) and yeasts (*Saccharomyces boulardii*)
- Bacterial products

Target Disorders

Probiotic Microbes: A Report from the Academy of Microbiology based on a colloquium convened November 5- 7, 2005, in Baltimore, Maryland

- Diarrhea
- Pouchitis
- Irritable bowel syndrome (IBD)
- Bladder cancer
- Urogenital infections
- *Clostridium difficile* infection
- Atopic Eczema

Pathogenic microbes can cross the epithelial barrier



Nature Reviews Immunology 1:59-67, 2001

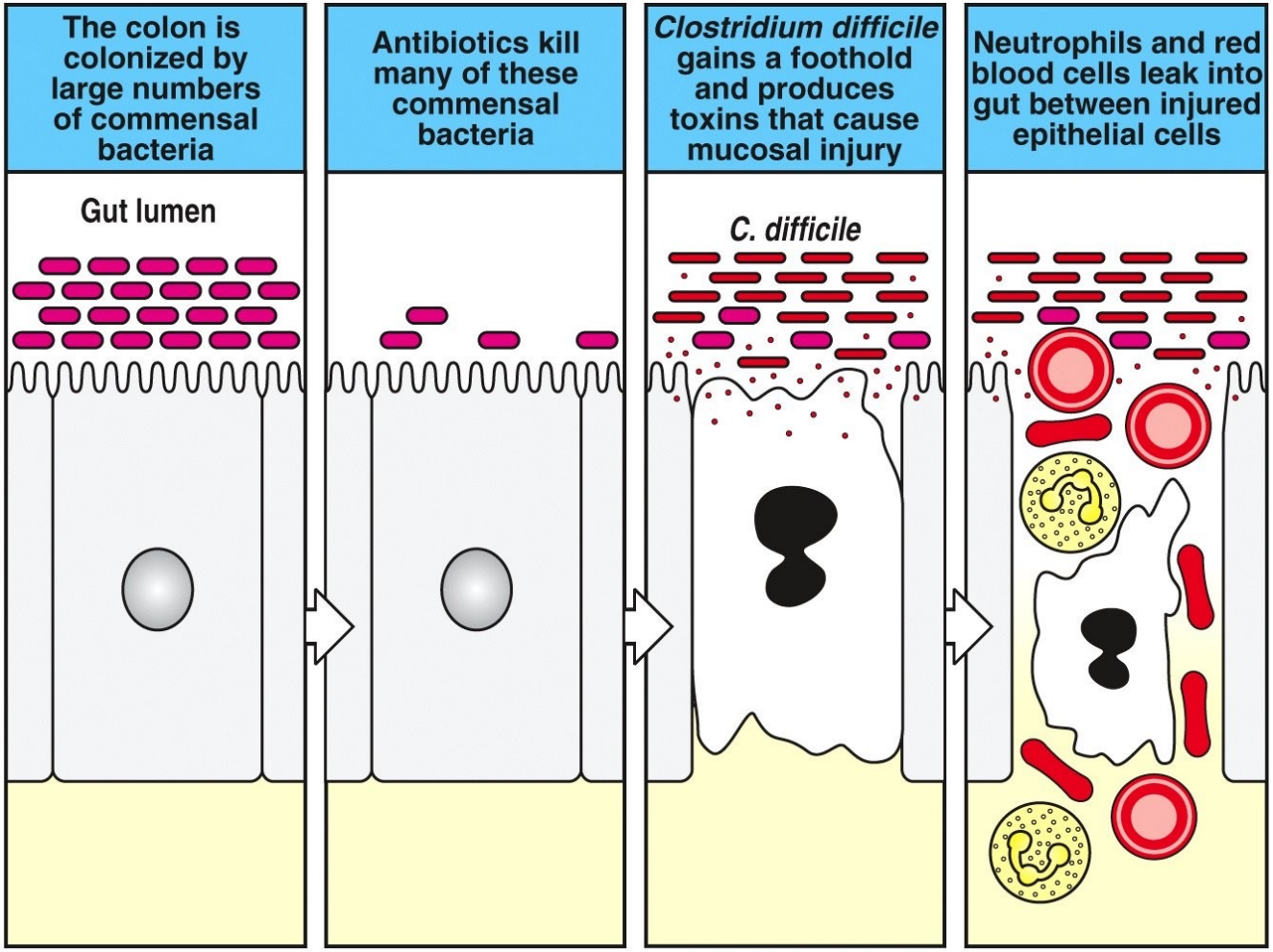


Figure 10-25 Immunobiology, 6/e. (© Garland Science 2005)

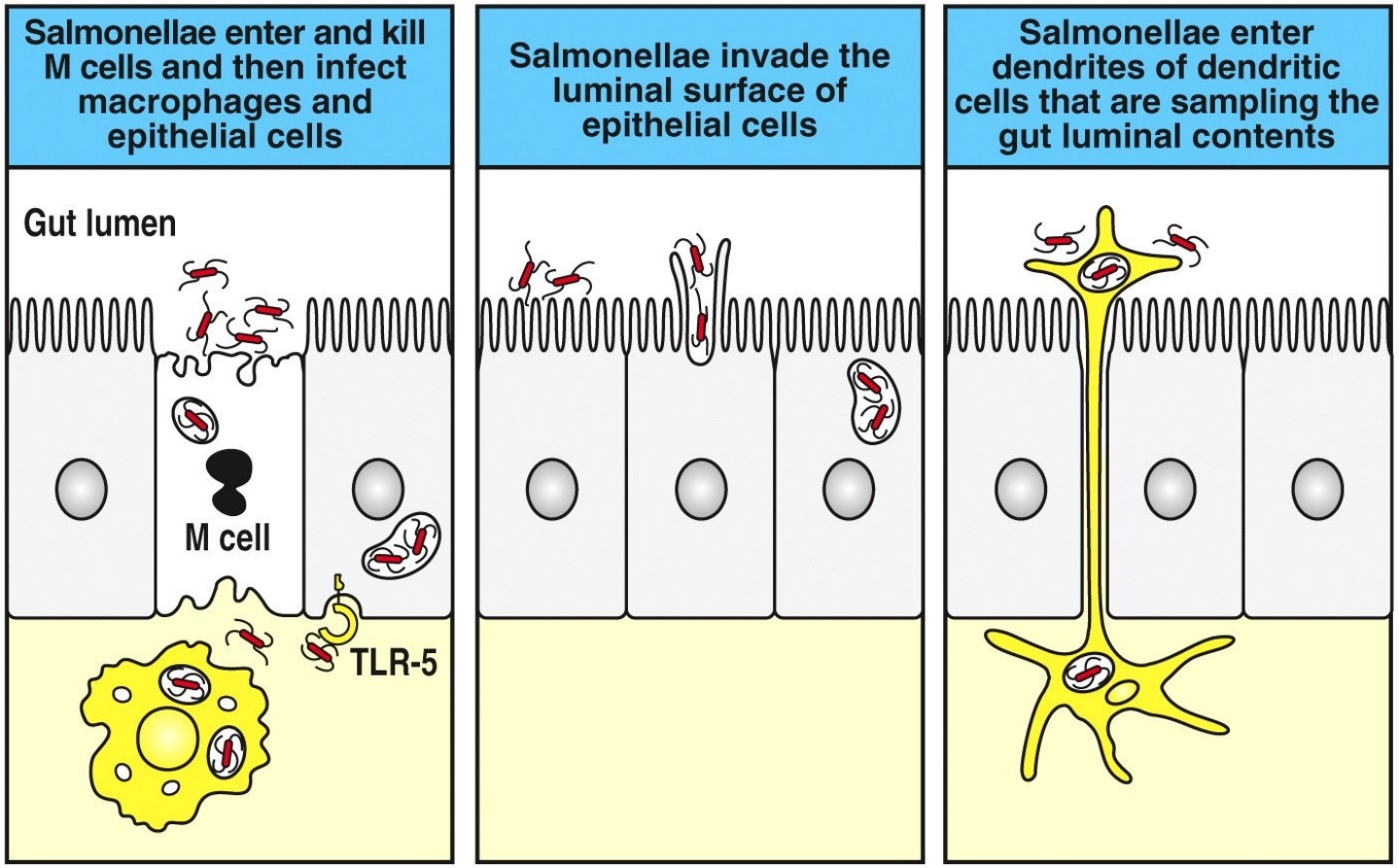


Figure 10-26 Immunobiology, 6/e. (© Garland Science 2005)

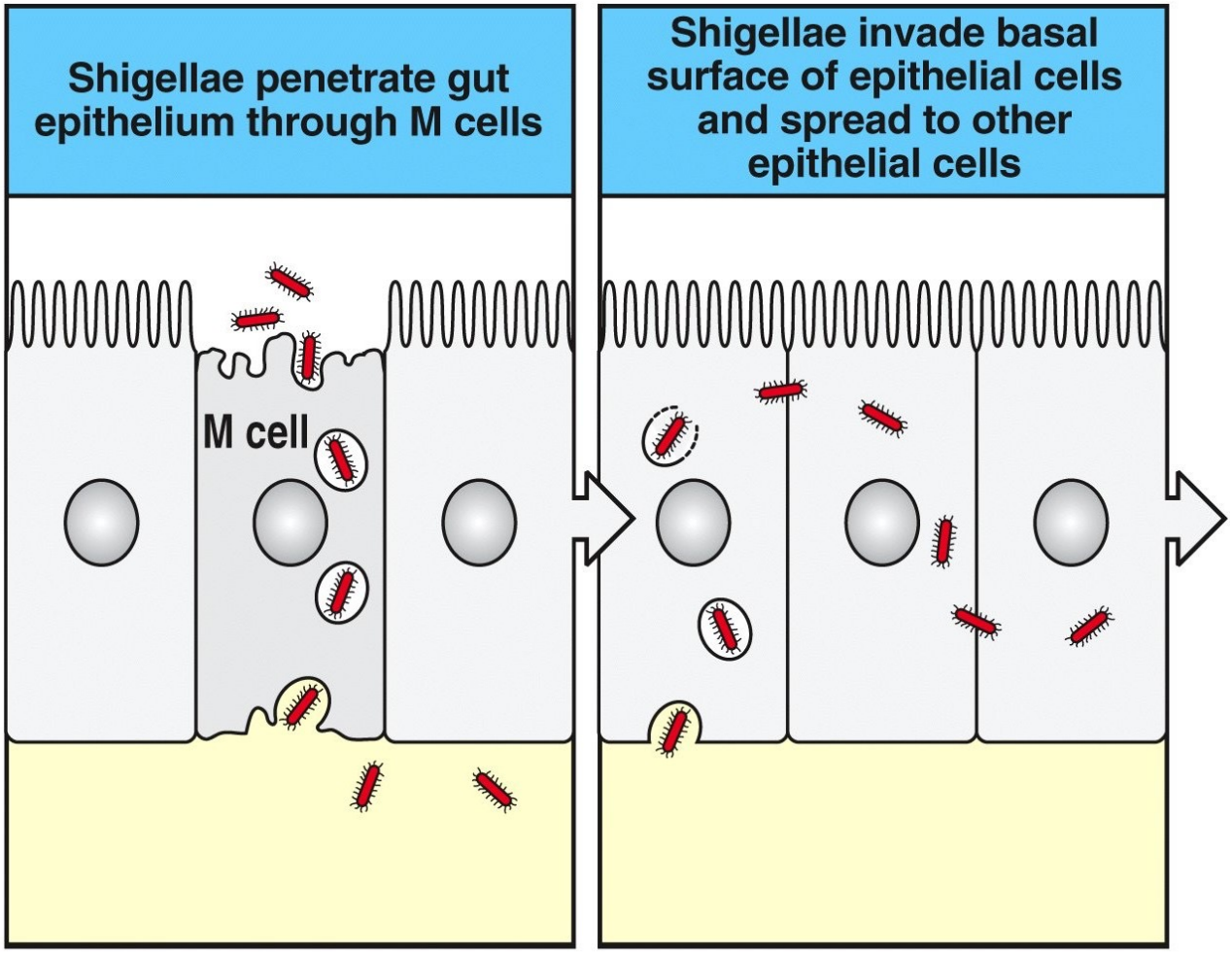


Figure 10-27 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

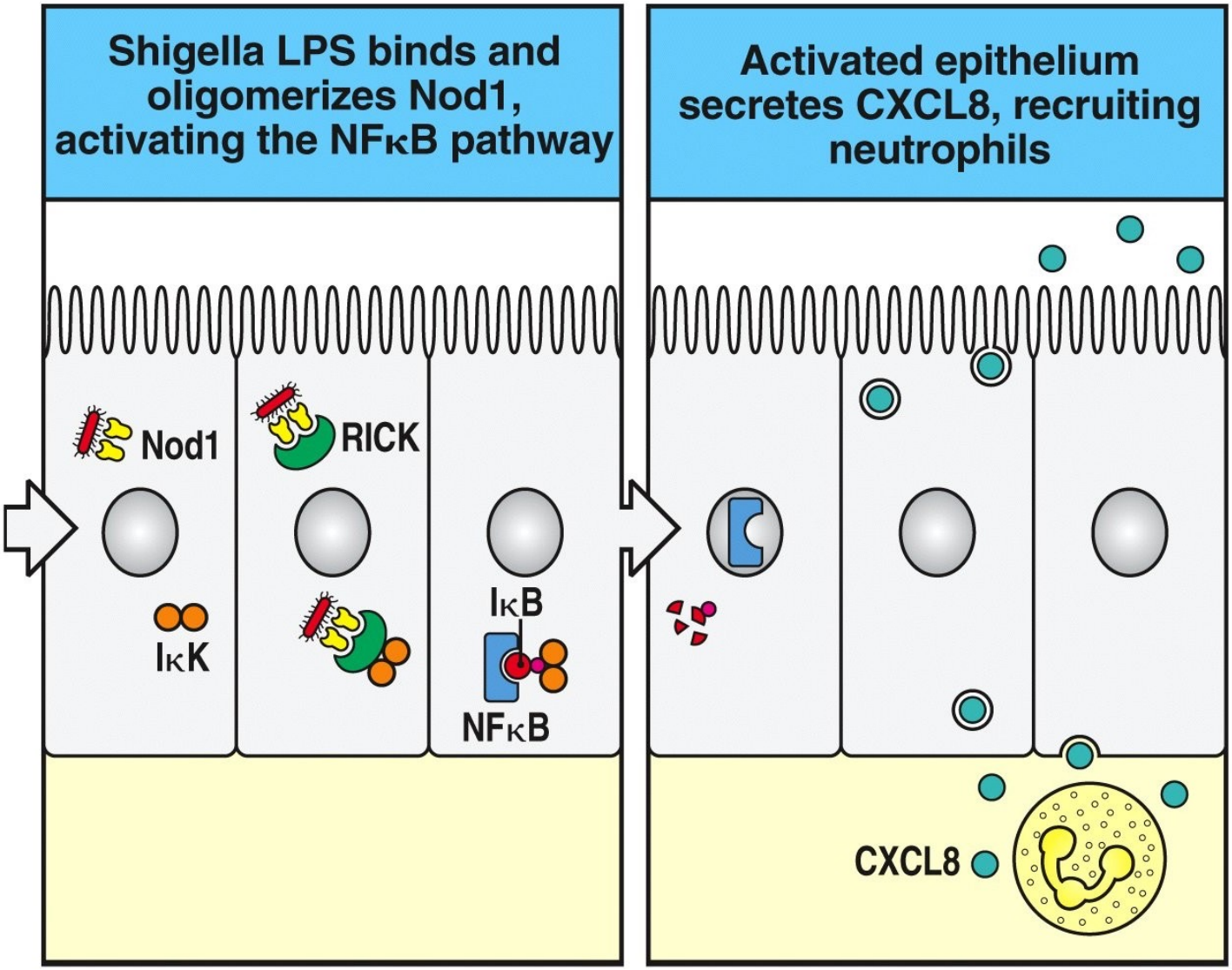
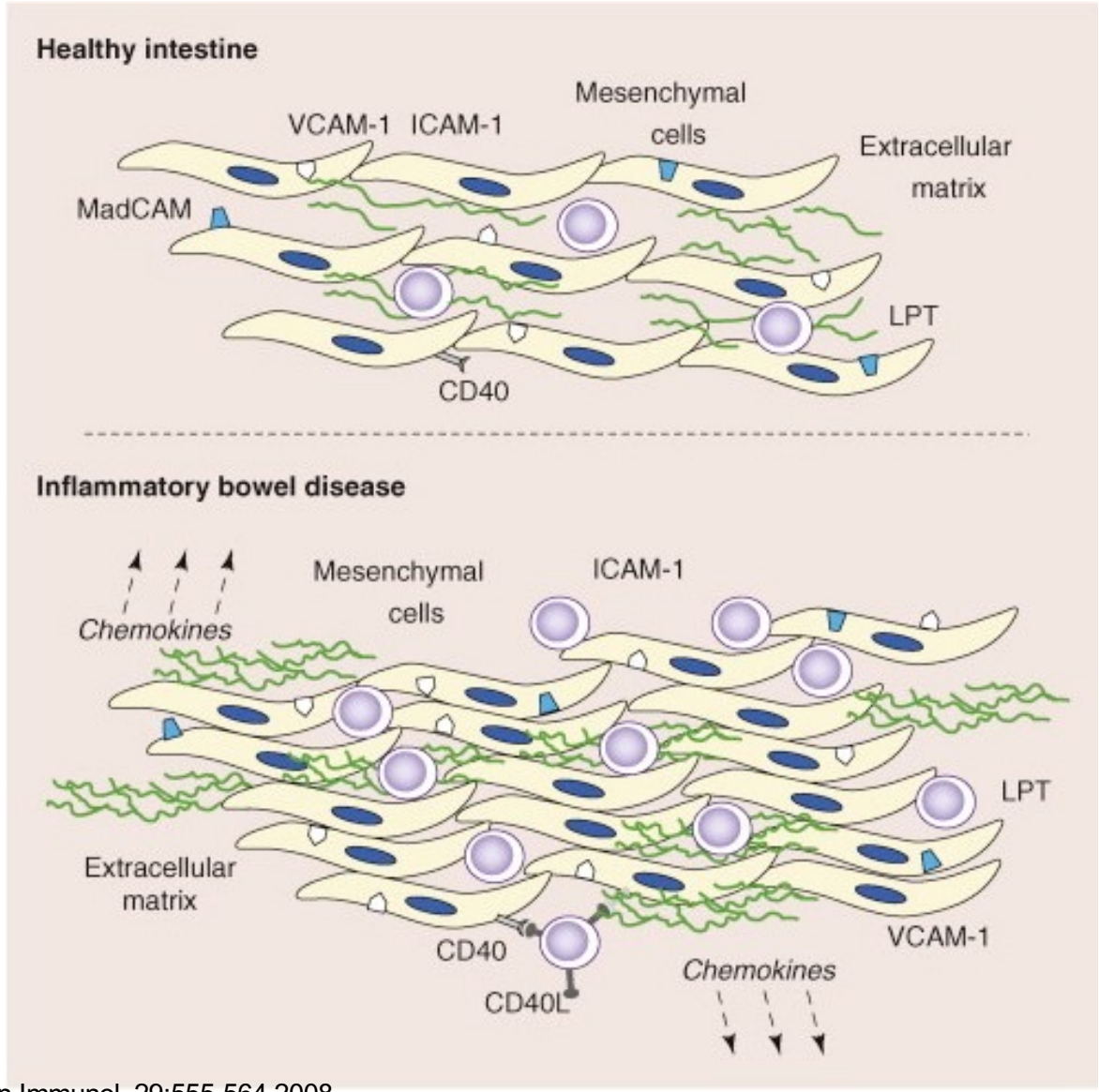


Figure 10-27 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)



Danese, Trends in Immunol. 29:555-564,2008

7 Nov 2023,
BT 304
Lecture 38

Crohn's Disease

- Chronic inflammatory disease with epithelial cell damage. PMNs are present.
- Occurs primarily in Western developed countries.
- May involve any part of the GI tract - damage can be discontinuous.
- Granuloma formation, aphthous ulcers - suggests infectious agent involvement although none has been identified.
- Question: autoimmune disease?
- Th1 T cell-mediated response
  - Production of IFN gamma, TNF-alpha by T cells
  - Production of IL-12, IL-18 by mø
  - Increase in GM-CSF production
- Enhanced IL-12 production and Th1 activation may be due to failure of NOD2 to inhibit TLR2 signaling.

Distinctive features of the mucosal immune system	
Anatomical features	Intimate interactions between mucosal epithelia and lymphoid tissues
	Discrete compartments of diffuse lymphoid tissue and more organized structures such as Peyer's patches, isolated lymphoid follicles, and tonsils
	Specialized antigen-uptake mechanisms provided by M cells in Peyer's patches, adenoids, and tonsils
Effector mechanisms	Activated effector T cells predominate even in the absence of infection
	Plasma cells are in the tissues where antibodies are needed
Immunoregulatory environment	Dominant and active downregulation of inflammatory immune responses to food and other innocuous environmental antigens
	Inhibitory macrophages and tolerance-inducing dendritic cells

Figure 10.17 The Immune System, 3ed. (© Garland Science 2009)