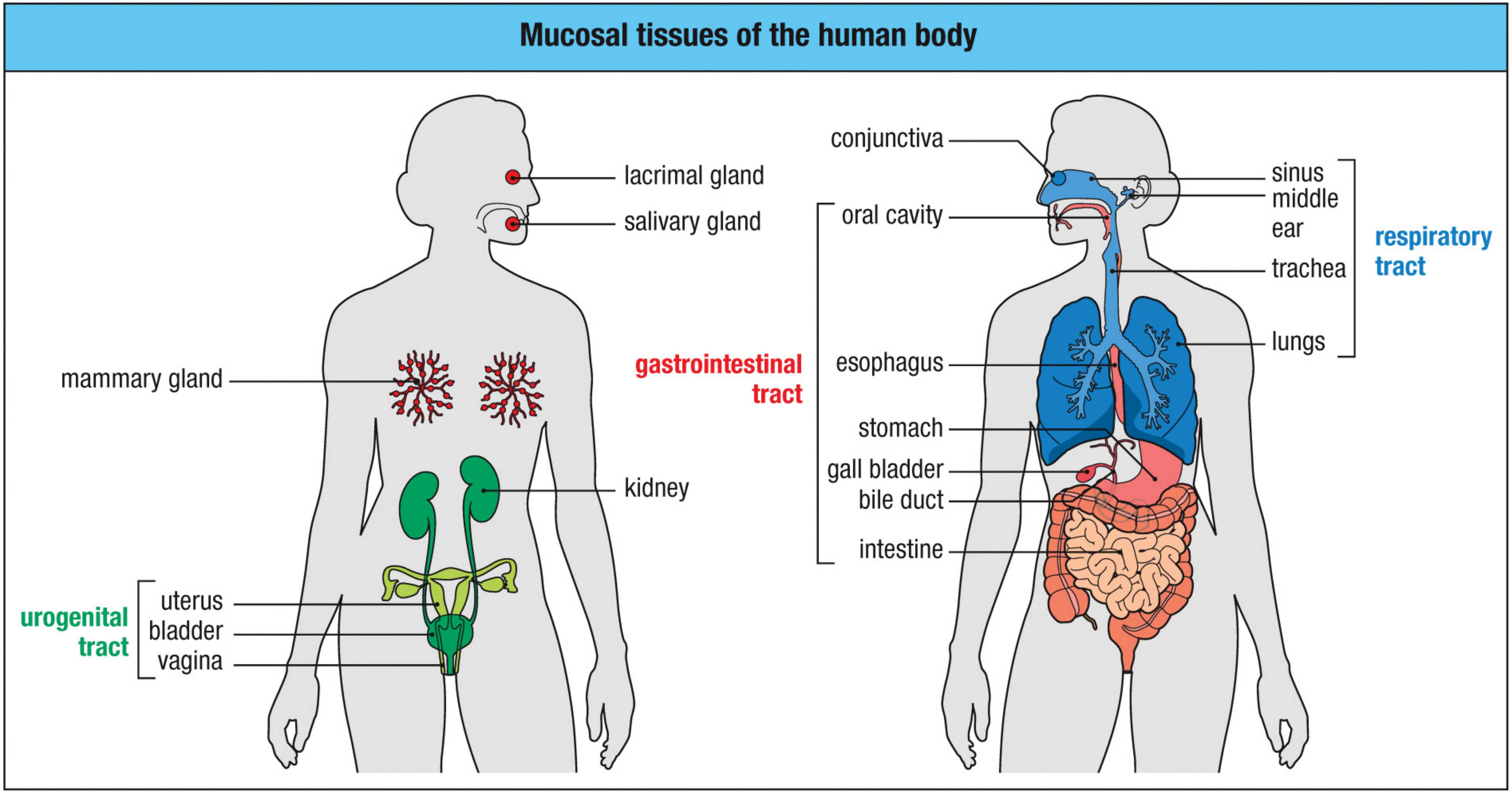
# Outline

- Mucosal immunity
  - anatomy of the mucosal immunity
  - cells and tissues of the mucosal immunity
  - mucosal immune response
    - Tolerance to food and commensal microorganisms
    - Pathogen defense

# Mucosal Immune System: The First Line of Defense



# Mucosal Tissues

Largest part of body’s immune tissues

Physical barriers that separate the body from external environment

Fragile and permeable

 entry point of pathogens

Exposure to foreign objects (food, microbiota)

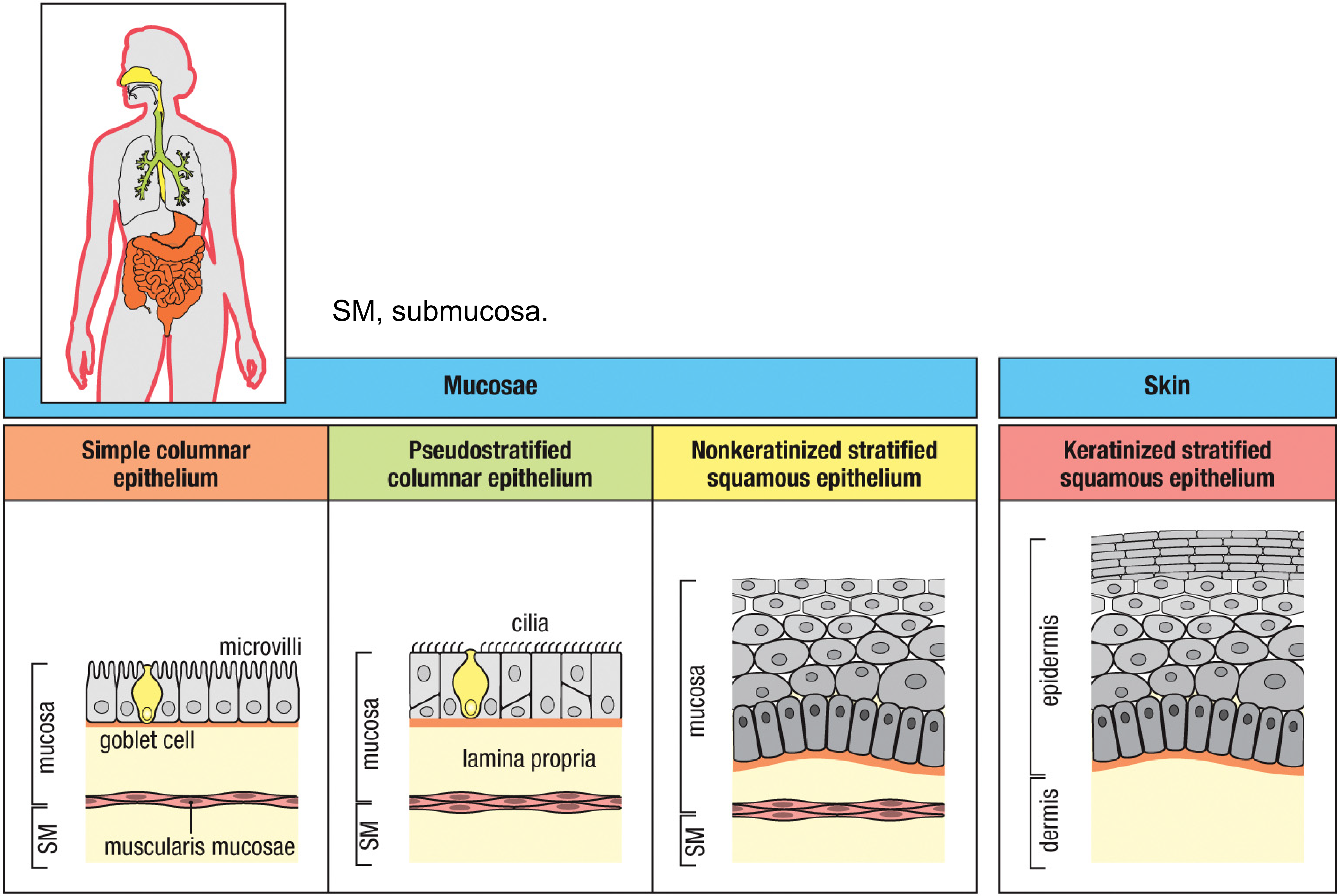
 distinguish from harmful and innocent antigens

# Barriers: The First Line of Defense

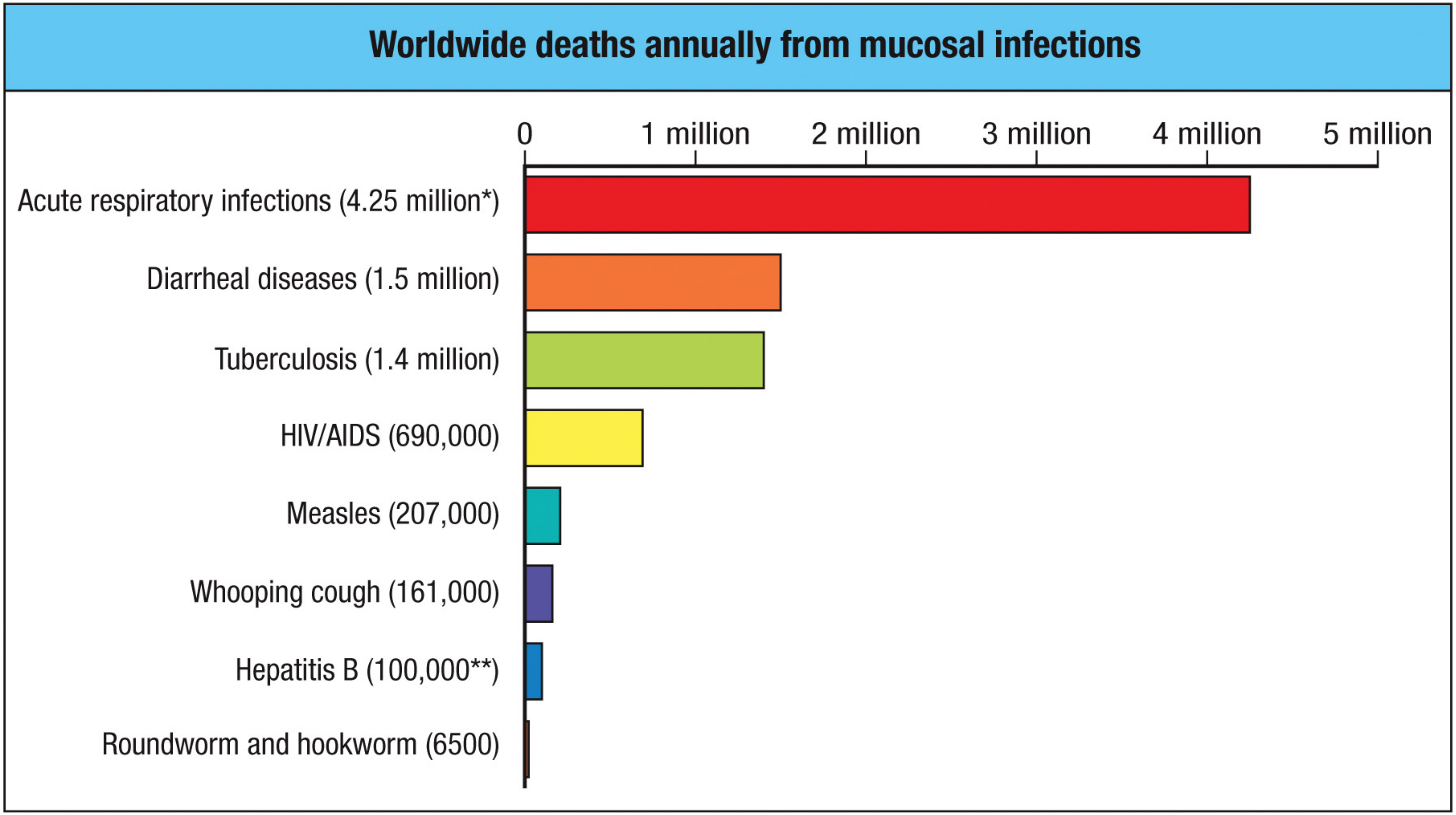
| | Skin | Gut | Lungs | Eyes/nose/oral cavity |
|---|---|---|---|---|
| | Stratified epithelium | Single cell layer of columnar epithelium | Upper airway: pseudostratified columnar epithelium<br>Lower airway: single cell layer of columnar epithelium | Pseudostratified columnar epithelium |
| Mechanical | Epithelial cells joined by tight junctions | | | |
| | Longitudinal flow of air or fluid | Longitudinal flow of air or fluid | Movement of mucus by cilia | Tears<br>Nasal cilia |
| Chemical | Fatty acids | Low pH<br>Enzymes (pepsin) | Pulmonary surfactant | Enzymes in tears and saliva (lysozyme) |
| | $\beta$-defensins<br>Lamellar bodies<br>Cathelicidin | $\alpha$-defensins (cryptdins)<br>RegIII (lecticidins)<br>Cathelicidin | $\alpha$-defensins<br>Cathelicidin | Histatins<br>$\beta$-defensins |
| Microbiological | Normal microbiota | | | |

# Types of Epithelium lining the Barrier Tissues

SM, submucosa.



# Mucosal Pathogens



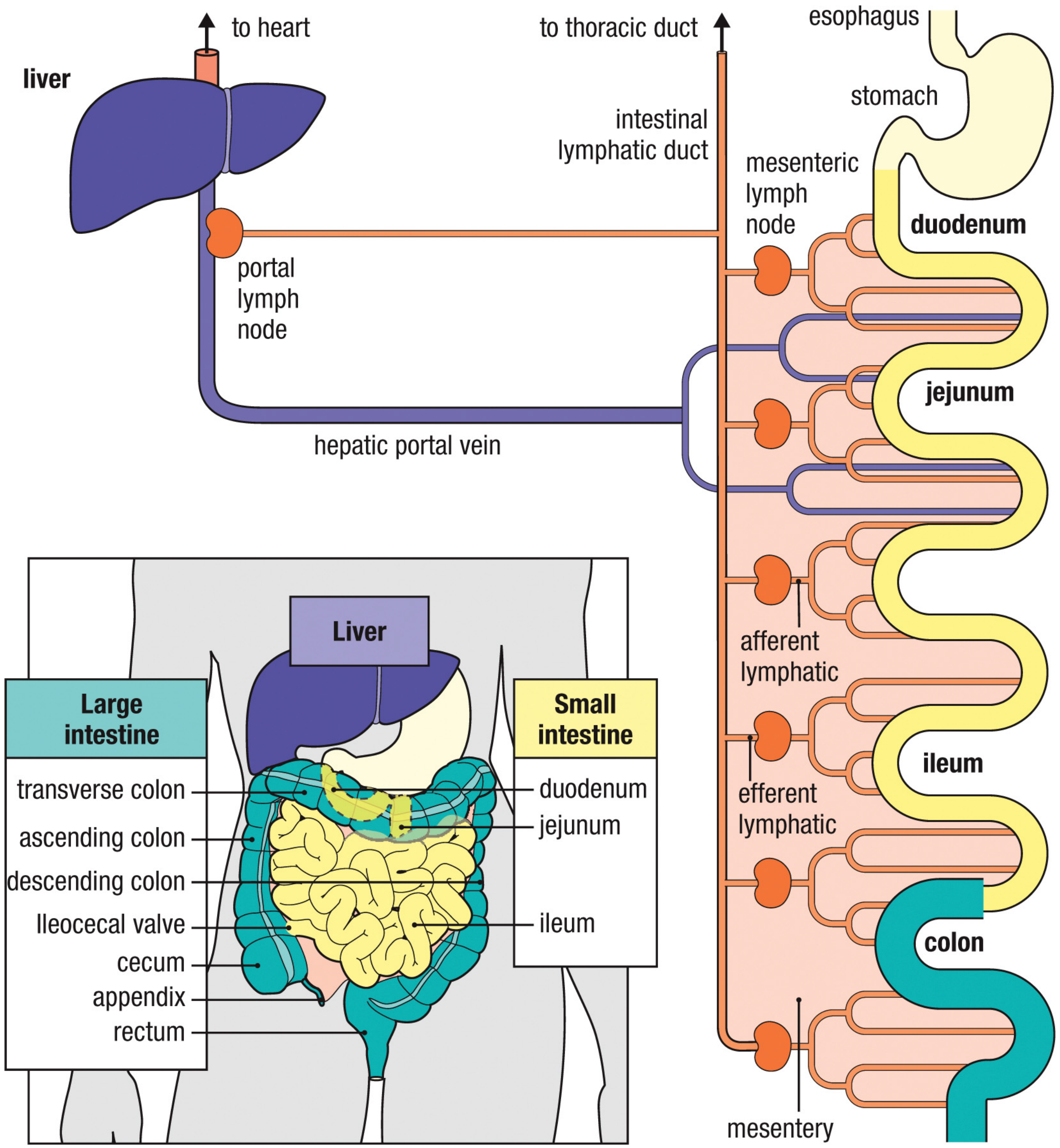

Microbiota v.s. Pathogen

# The Mucosal Immune System

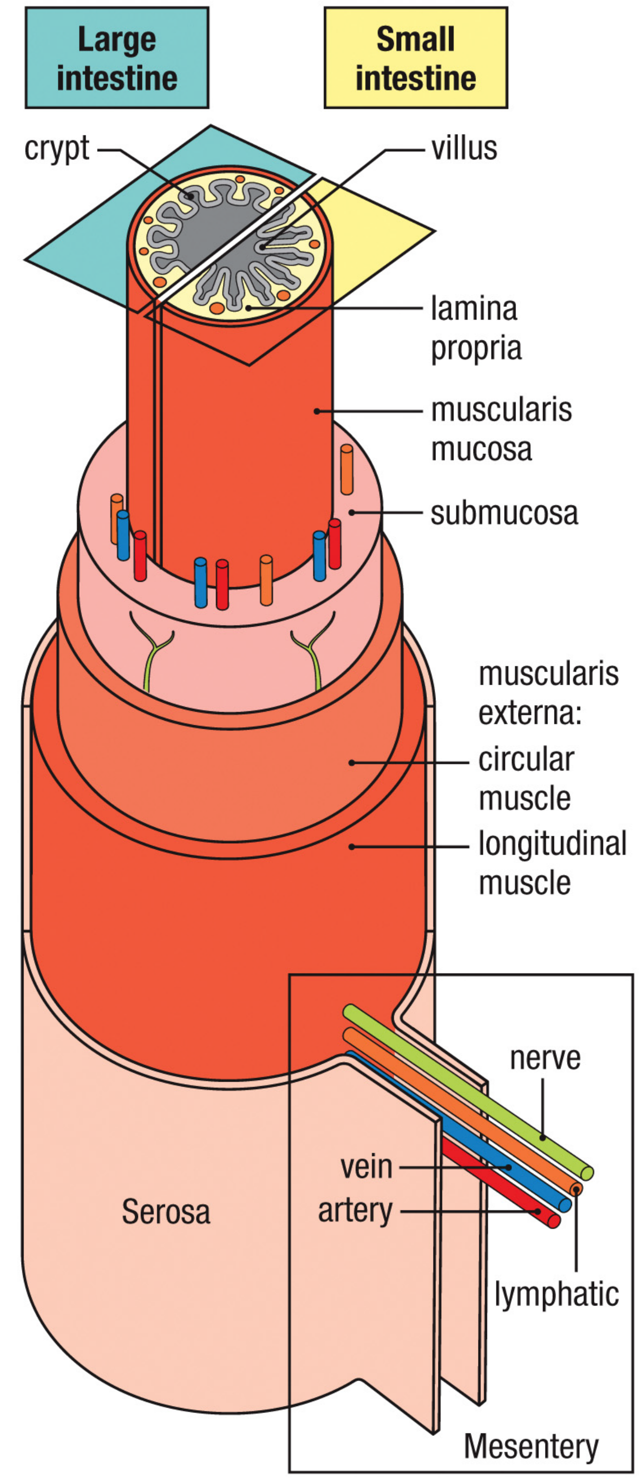
| Distinctive features of the mucosal immune system | |
|---|---|
| Anatomic features | Intimate interactions between mucosal polarized epithelia and lymphoid tissues |
| | Discrete compartments of diffuse lymphoid tissue and more organized structures such as Peyer's patches, isolated lymphoid follicles, and tonsils |
| | Specialized antigen-uptake mechanisms, e.g., M cells in Peyer's patches, adenoids, and tonsils |
| | Broad surface area in contact with environmental agents/microbes |
| Effector mechanisms | Activated/memory T cells predominate even in the absence of infection |
| | Multiple activated 'natural' effector/regulatory T cells present |
| | Production of mucins and mucus |
| | Secretory IgA antibodies |
| | Production of antimicrobial peptides (AMPs) |
| | Presence of distinctive microbiota |
| Immunoregulatory environment | Active down-regulation of immune responses (e.g., to food and other innocuous antigens) predominates at homeostasis |
| | Inhibitory macrophages and tolerance-inducing dendritic cells |
| | High number of FoxP3$^+$ $T_{reg}$ cells and FoxP3$^-$ $T_R1$ cells |

# Anatomy of the Gastrointestinal Tract

## Anatomy of the intestinal immune system




## Three-dimensional structure of intestines



# Outline

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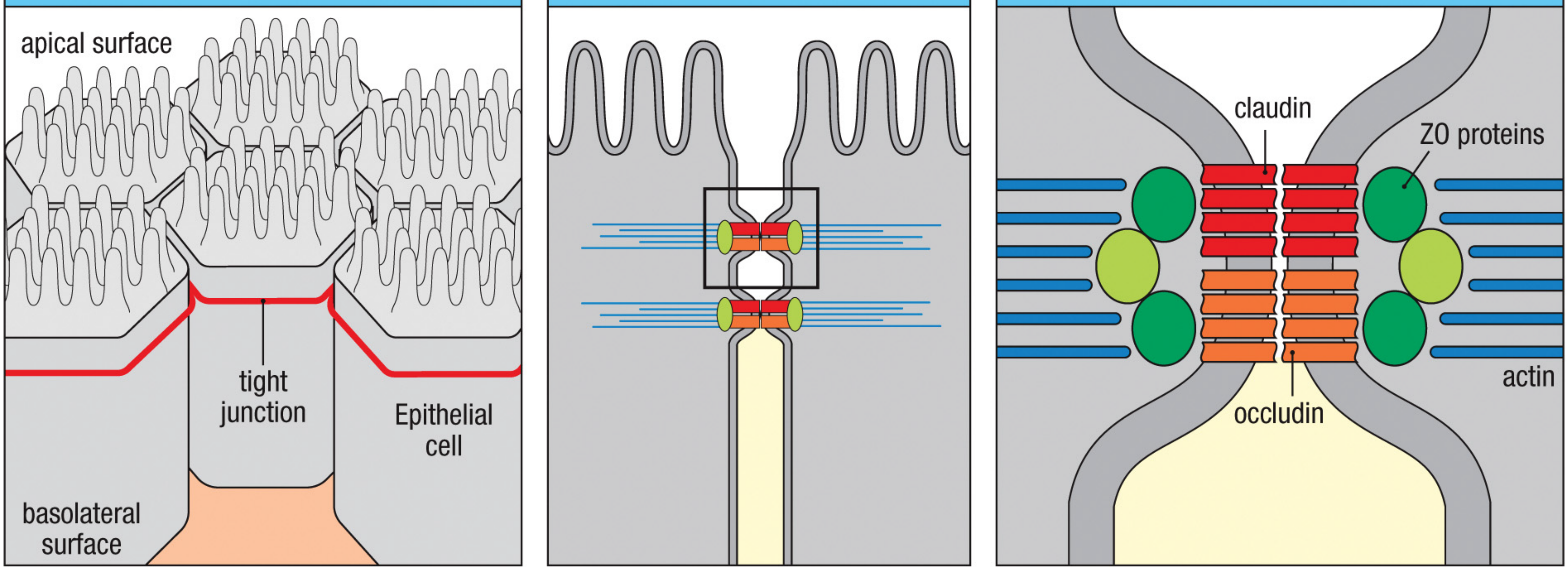
    - Pathogen defense

# Tight Junctions

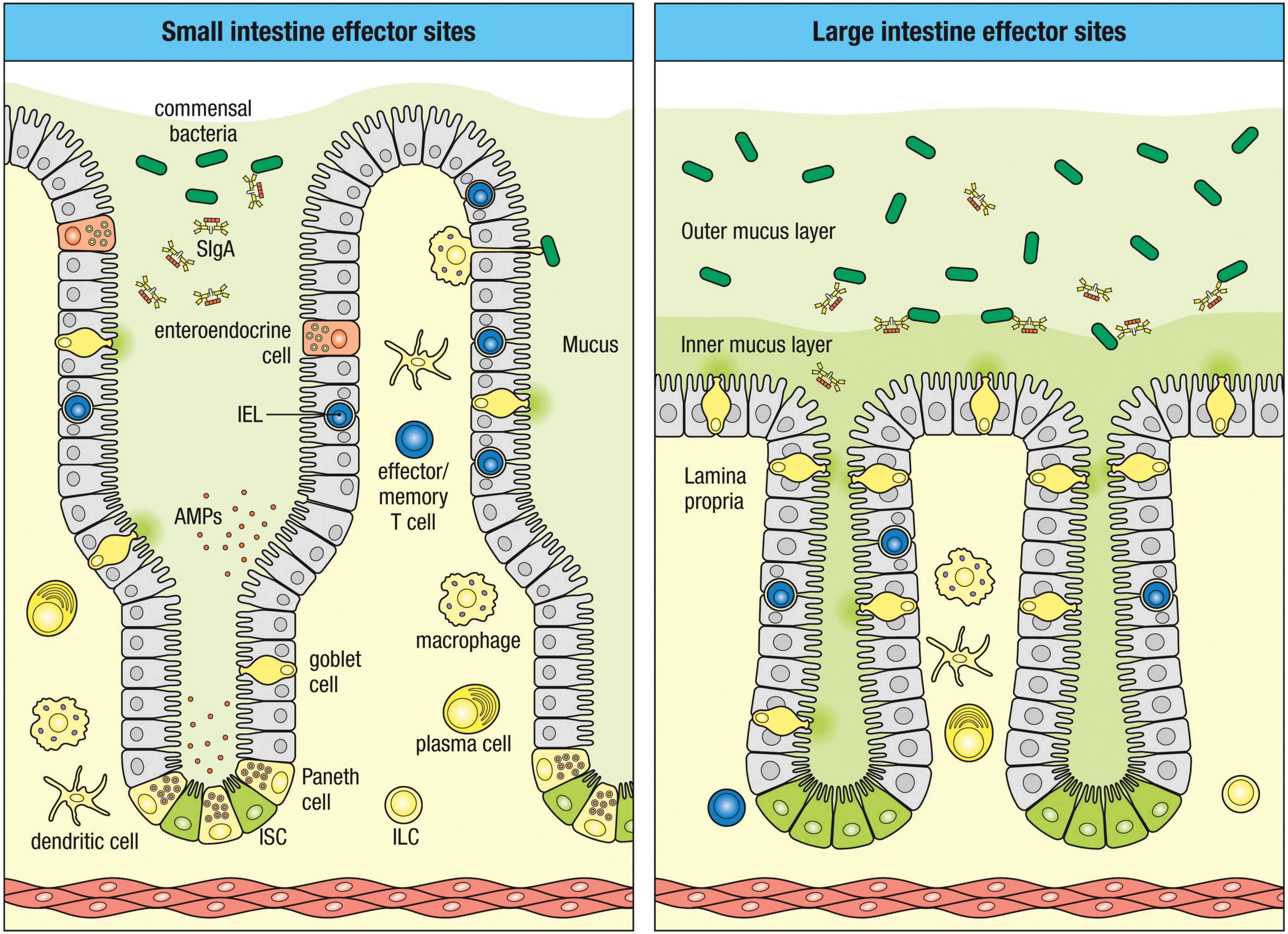
**Membranes of adjacent epithelial cells are tethered together near their apical surface to form a continuous intercellular barrier**

**Adhesion complexes create a seal preventing most molecules from passing through the intercellular space**

**The transmembrane proteins claudin and occludin associate with zonulin (ZO) proteins that interact with the actin cytoskeleton to regulate the permeability of tight junctions**



# Effector Sites of the Gut-Associated Lymphatic Tissue

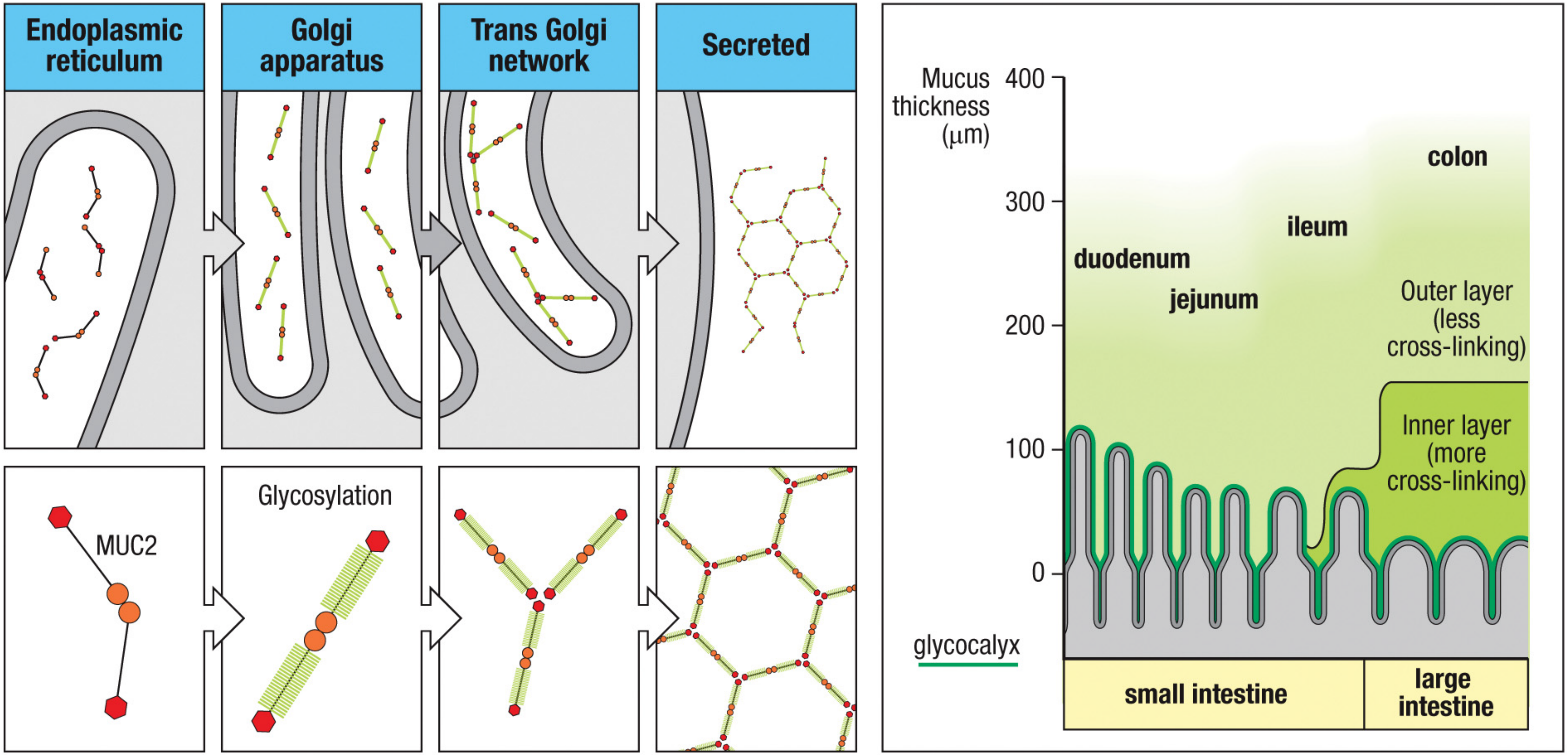



intraepithelial lymphocytes (IELs), antimicrobial peptides (AMPs), intestinal stem cell (ISC)

# Features of Intestinal Epithelial Cell Subsets

| Features of intestinal epithelial cell types | | | | |
|---|---|---|---|---|
| **Cell** | **Lineage** | **Cell markers** | **Tissue site(s)** | **Major functions** |
| Crypt base columnar (CBC) | Intestinal stem cell | LGR5 | Small intestine<br>Large intestine | Self-renewal<br>Production of all intestinal epithelial cell types |
| Absorptive enterocyte | Absorptive | Sucrose isomaltase<br>Lactase | Small intestine<br>Large intestine | Uptake of nutrients and fluids<br>Microbial and metabolic sensing<br>Transport of secretory immunoglobulins |
| Microfold (M) cell | Absorptive | RANK | Small intestine<br>Large intestine | Antigen uptake<br>Bacterial translocation |
| Goblet cell | Secretory | MUC2, Trefoil factor | Small intestine<br>Large intestine | Production of mucins<br>Antigen uptake |
| Paneth cell | Secretory | Lysozyme | Small intestine | Support for intestinal stem cells<br>Secretion of antimicrobial peptides (AMPs) |
| Tuft cell | Secretory | IL-25 | Small intestine<br>Large intestine | Sensing of helminthic odorants and succinate<br>Mobilization of type 2 ILCs via IL-25 and eicosanoid release |
| Enteroendocrine cell | Secretory | Chromogranin A | Small intestine<br>Large intestine | Respond to multiple nutrient and microbial-secreted products to release hormones and neurotransmitters |

# Mucins and Mucus

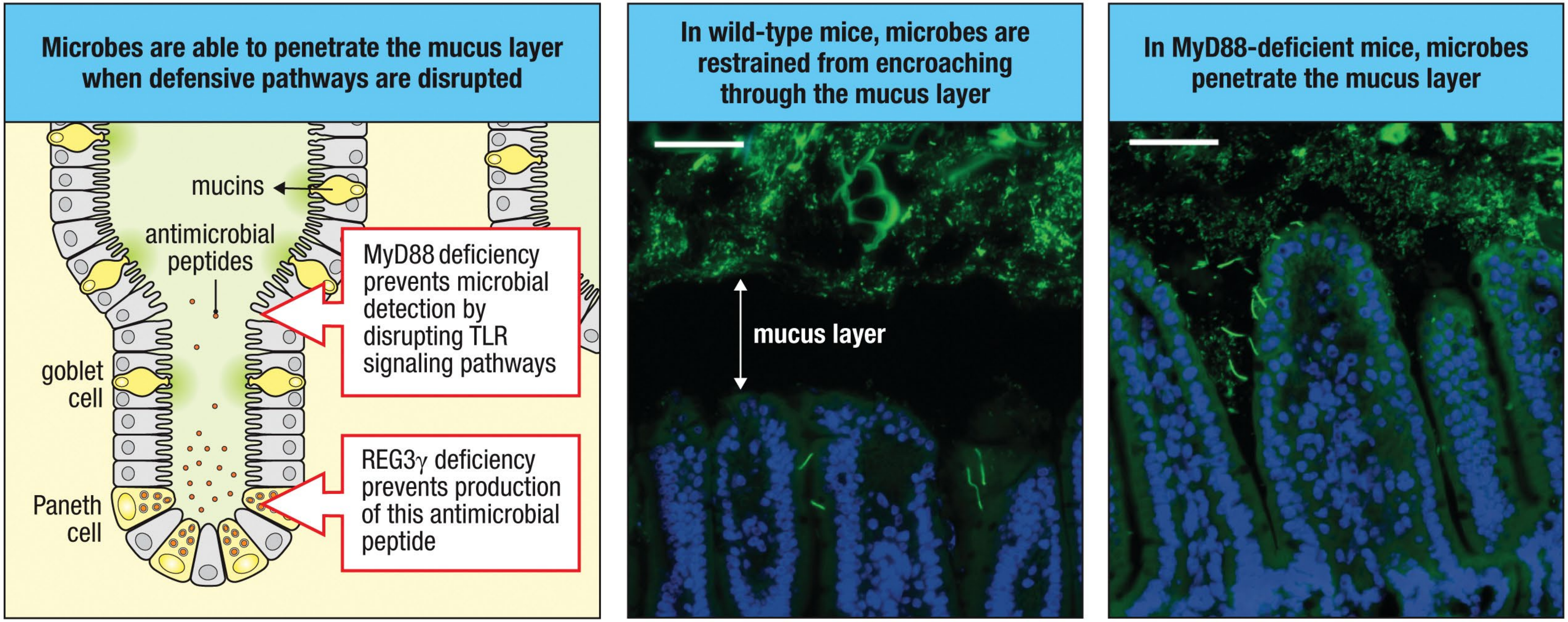



The thickness and structure of mucus are different along the length of the intestines, correlating somewhat with the density of the commensal microbiota from which the epithelium is protected.

# Antimicrobial Proteins

| Antimicrobial proteins produced in the intestinal mucosa | | | |
|---|---|---|---|
| **Family (examples)** | **Mechanism of action** | **Cellular source** | **Microbial targets** |
| α-Defensins (humans)<br>Cryptidins (mice) | Cell membrane disruption | Paneth cells<br>Neutrophils<br>Macrophages | Gram+ and Gram– bacteria, fungi, protozoa, viruses |
| β-Defensins<br>(e.g., BD1, BD2, BD3) | Cell membrane disruption | Enterocytes | Gram+ and Gram– bacteria, fungi, protozoa, viruses |
| Calprotectin<br>(S100A8–S100A9) | Metal chelation | Enterocytes<br>Neutrophils | Gram+ and Gram– bacteria, fungi, viruses |
| C-type lectins<br>(e.g., REG3β, REG3γ) | Cell membrane disruption | Paneth cells<br>Enterocytes | Gram+ and Gram– bacteria |
| Lysozyme | Cleavage of bacterial cell wall peptidoglycan | Paneth cells | Gram+ > Gram– bacteria |
| Phospholipase $A_2$ | Cleavage of bacterial cell membrane phospholipids | Paneth cells<br>Macrophages | Gram+ bacteria |

# Microbial Signals Activate the Production of Antimicrobial Peptides

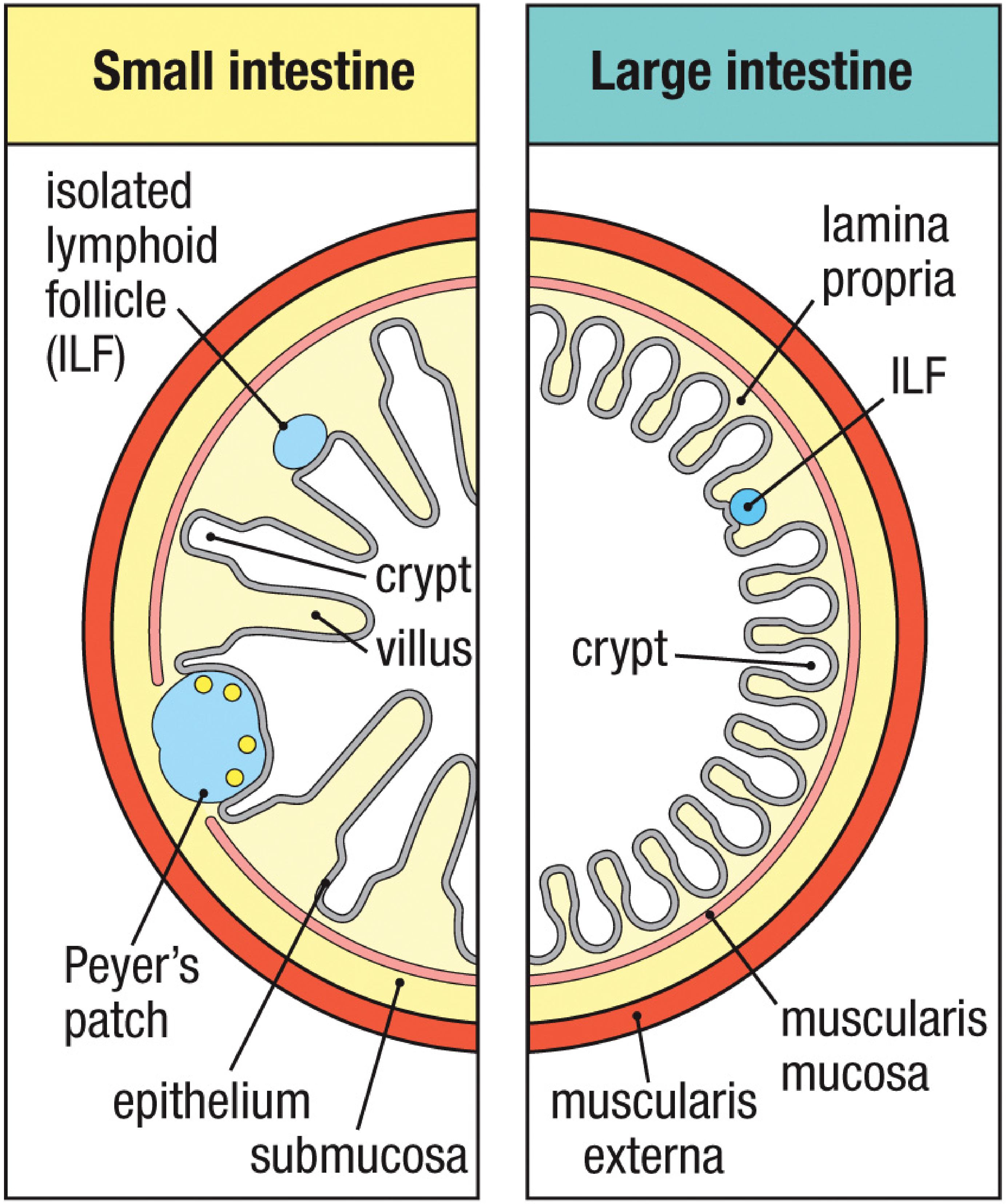



(both) Vaishnava S., et al.: *Science* 2011, 334:255–258. ©AAAS.

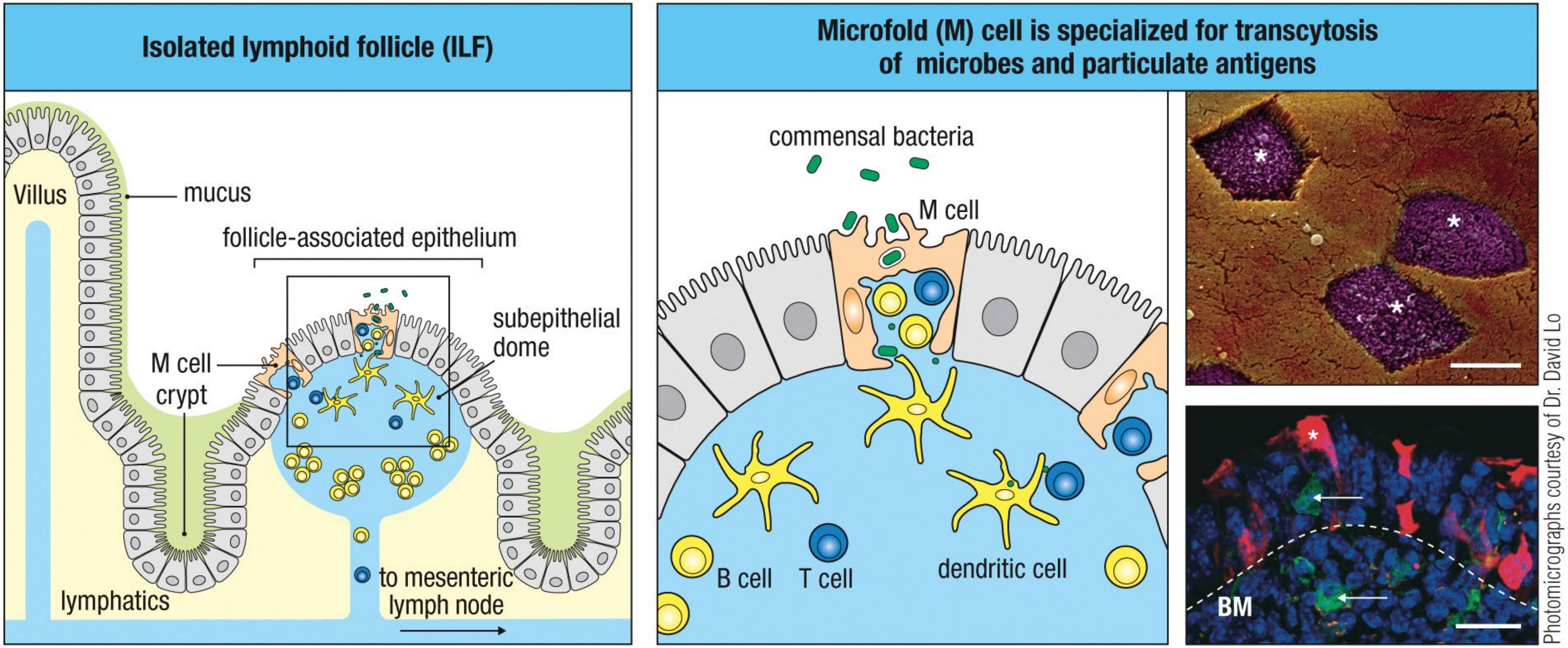
Highest concentration of antimicrobial peptides (AMPs) is in the crypts and at the crypt openings

antimicrobial C-type lectin REG3γ targets Gram-positive bacteria

# Architecture of the Small and Large Intestinal Mucosae

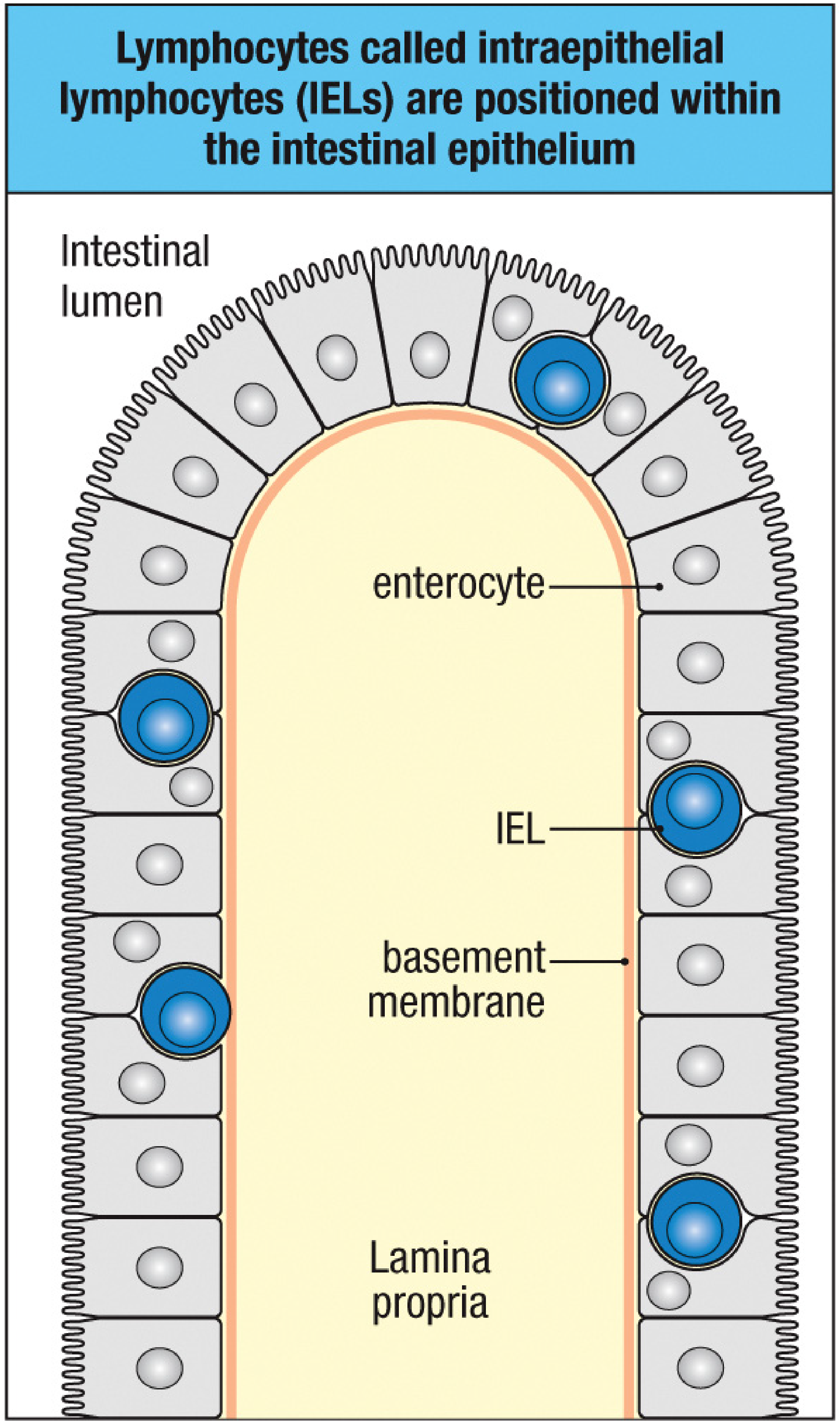


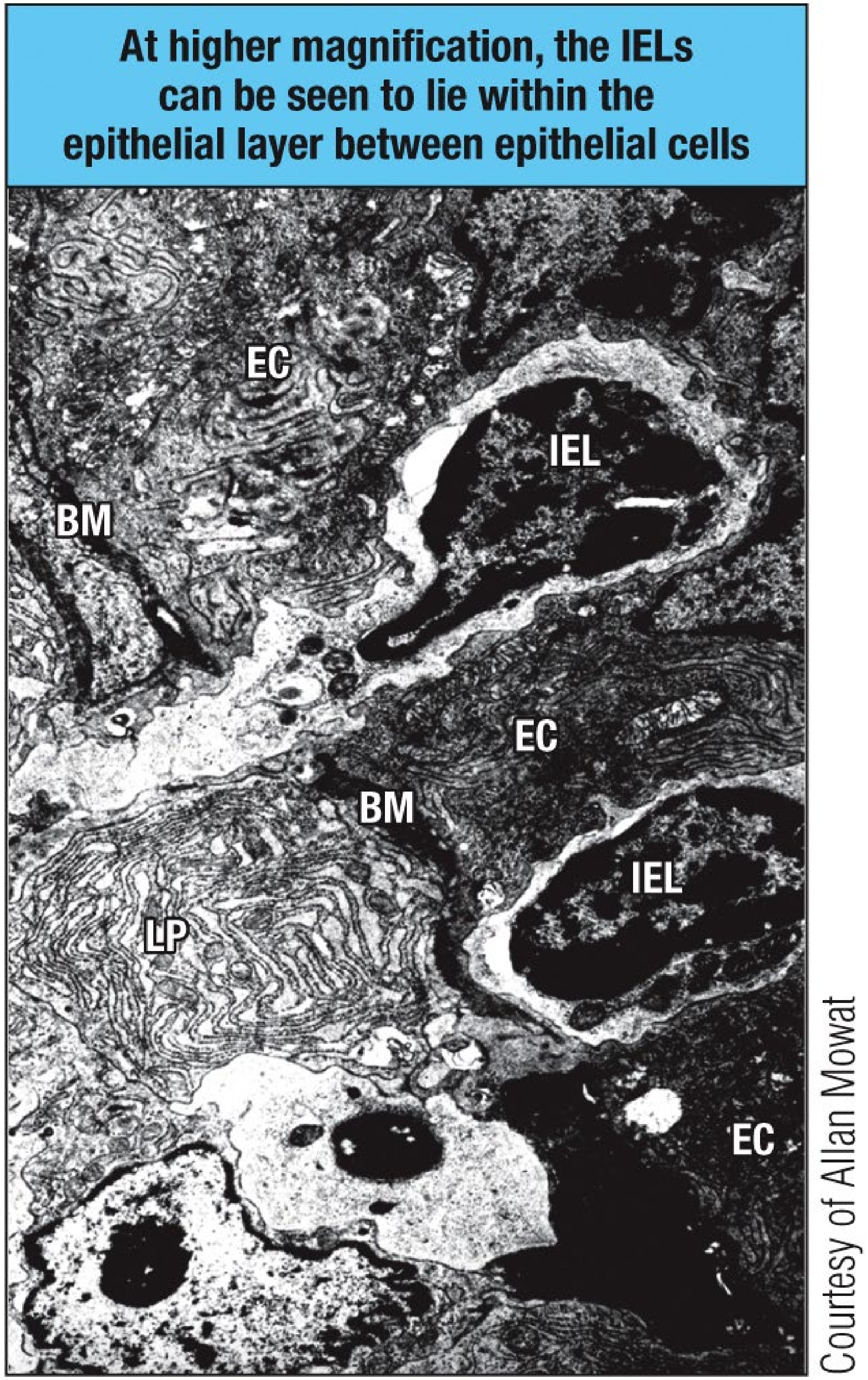
# Isolated Lymphoid Follicle




M cells identified by expression of peptidoglycan recognition protein-S (PGRP-S; red, example highlighted by asterisk) interacting with processes extended across the basement membrane (BM; indicated by dotted line) by CX3CR1-expressing myeloid cells (green; arrows).

# Intraepithelial Lymphocytes

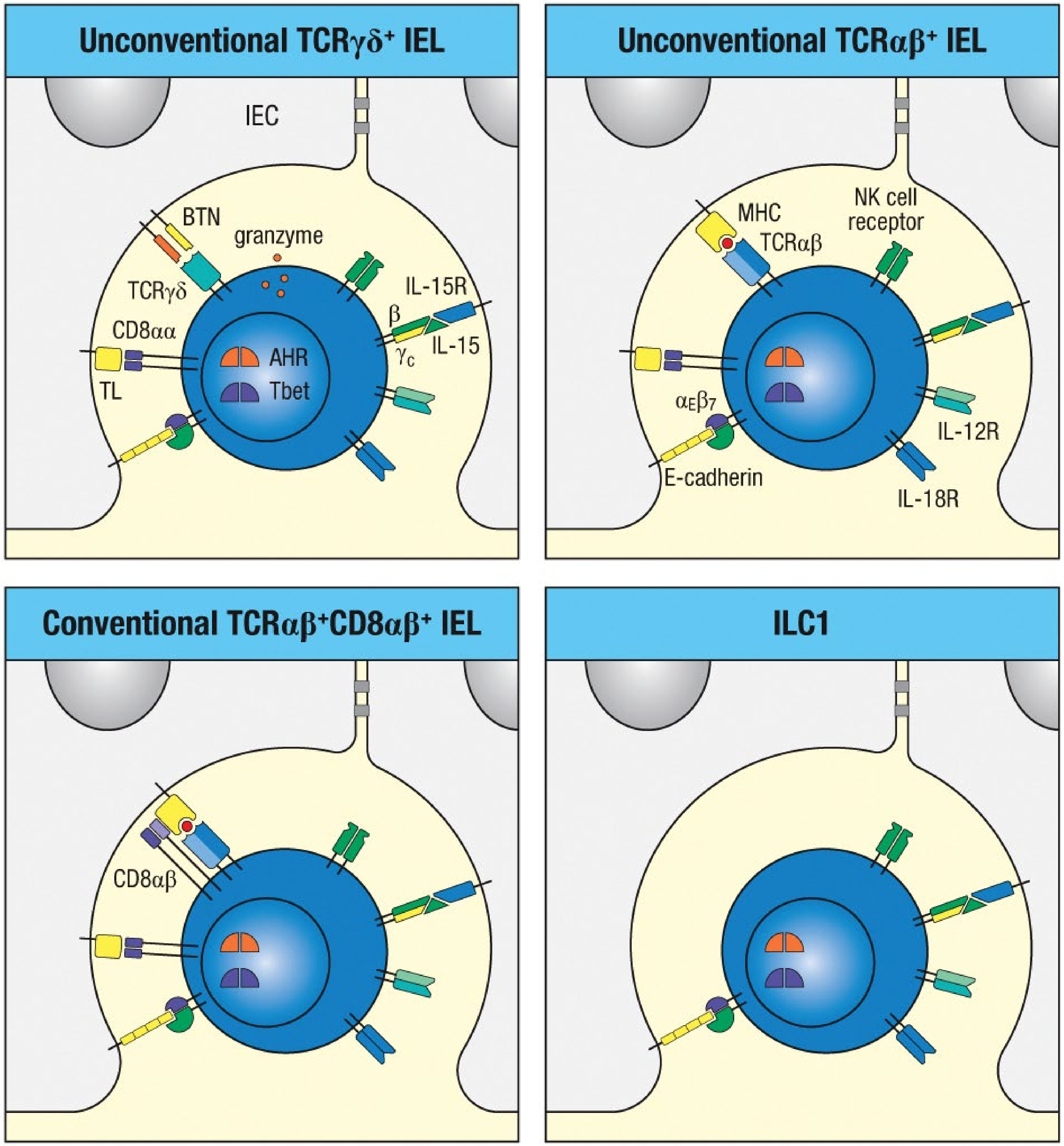


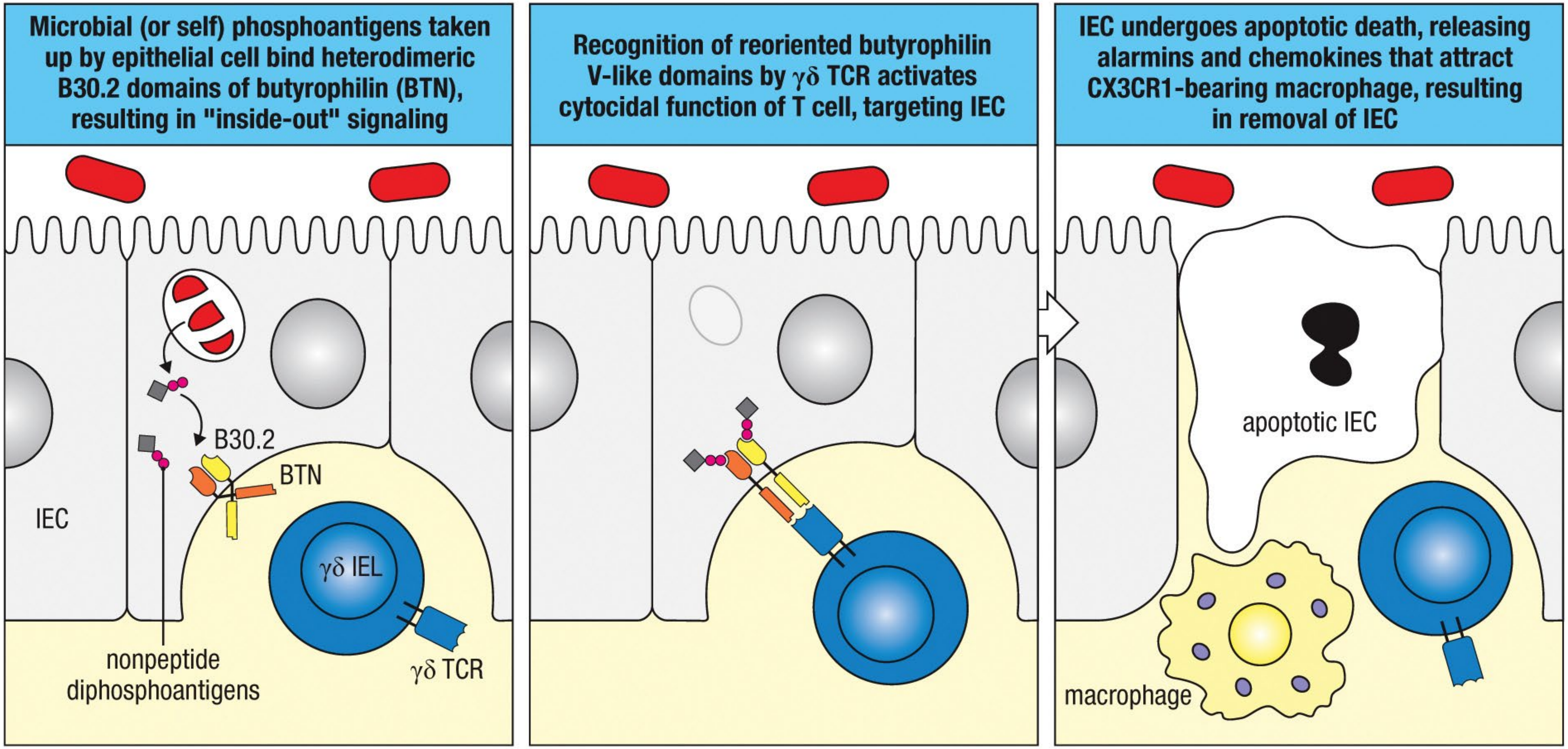
# Types of Intraepithelial Lymphocytes

| Characteristics of intraepithelial lymphocytes | | | | |
|---|---|---|---|---|
| **IEL subset** | **Co-receptor expression** | **TCR repertoire** | **NK receptors** | **Antigenic ligands** |
| Unconventional TCR$\gamma\delta$ nIEL | $CD4^-CD8^-$<br>$CD8\alpha\alpha$ | TCRV$\gamma$7 > TCRV$\gamma$4 (mouse)<br>TCRV$\gamma$1 (human) | NKG2 family<br>CD94<br>LY49 family (mouse)<br>KIR family (human) | BTNLs (mouse, ? human)<br>MULT1, H60a, Qa-1 (mouse)<br>CD1, MICA, MICB, ULBP (human) |
| Unconventional TCR$\alpha\beta$ nIEL | $CD4^-CD8^-$<br>$CD8\alpha\alpha$ | Oligoclonal | NKG2 family<br>CD94<br>LY49 family (mouse)<br>KIR family (human) | MHC I, MHC II (mouse, human)<br>Non-classical MHC I (mouse)<br>MICA, MICB, ULBP (human) |
| Conventional TCR$\alpha\beta$ pIEL | $CD8^+CD8\alpha\alpha$<br>$CD4^+CD8\alpha\alpha$ | Diverse | None | Peptide:MHC I<br>Peptide:MHC II |
| ILC1 | $CD4^-CD8^-$ | None | NKG2 family<br>CD94<br>LY49 family (mouse)<br>KIR family (human) | MULT1, H60a, Qa-1 (mouse)<br>MICA, MICB, ULBP (human) |

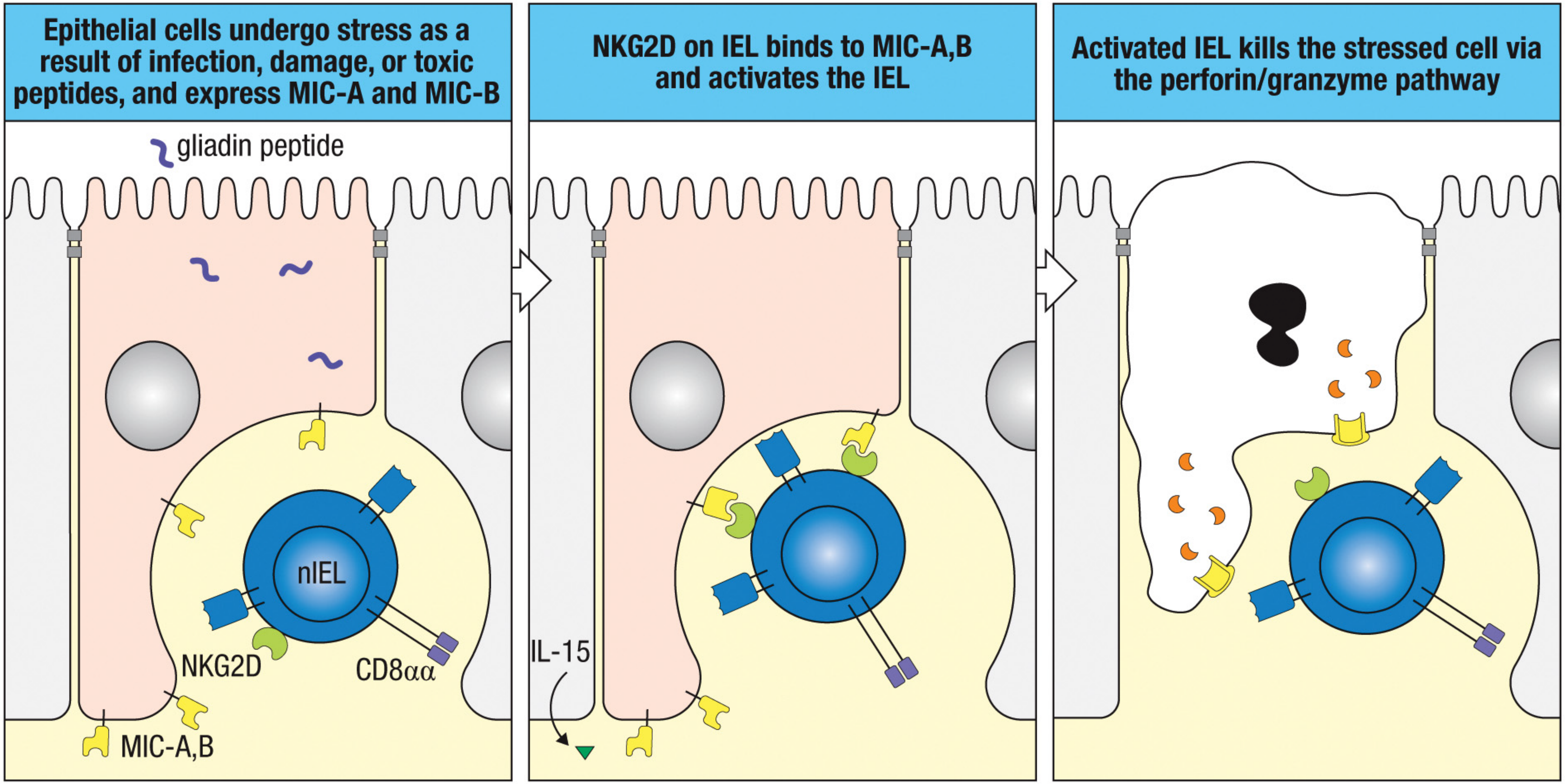
# Types of Intraepithelial Lymphocytes



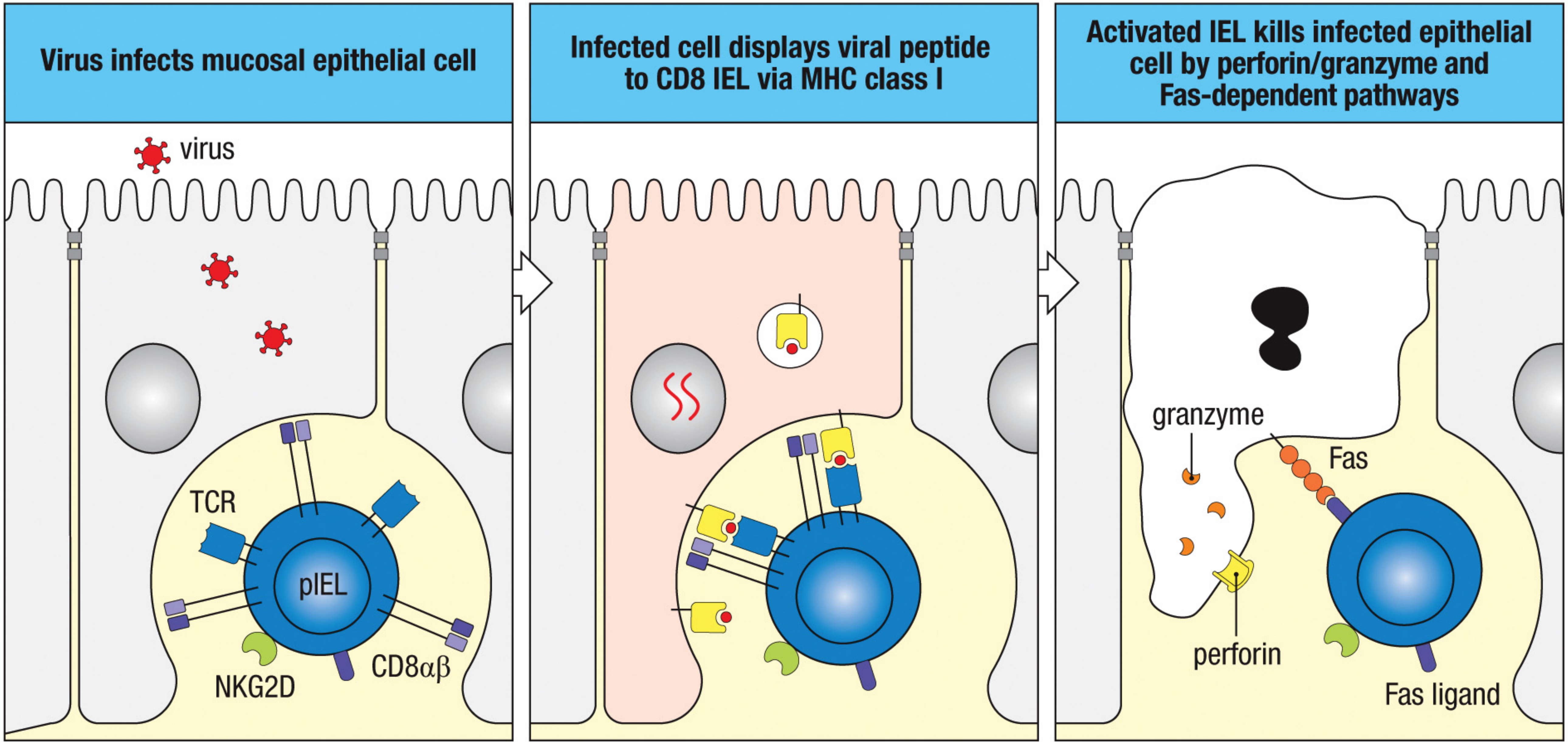
# Function of Intraepithelial Lymphocytes



# Function of Intraepithelial Lymphocytes



# Function of Intraepithelial Lymphocytes

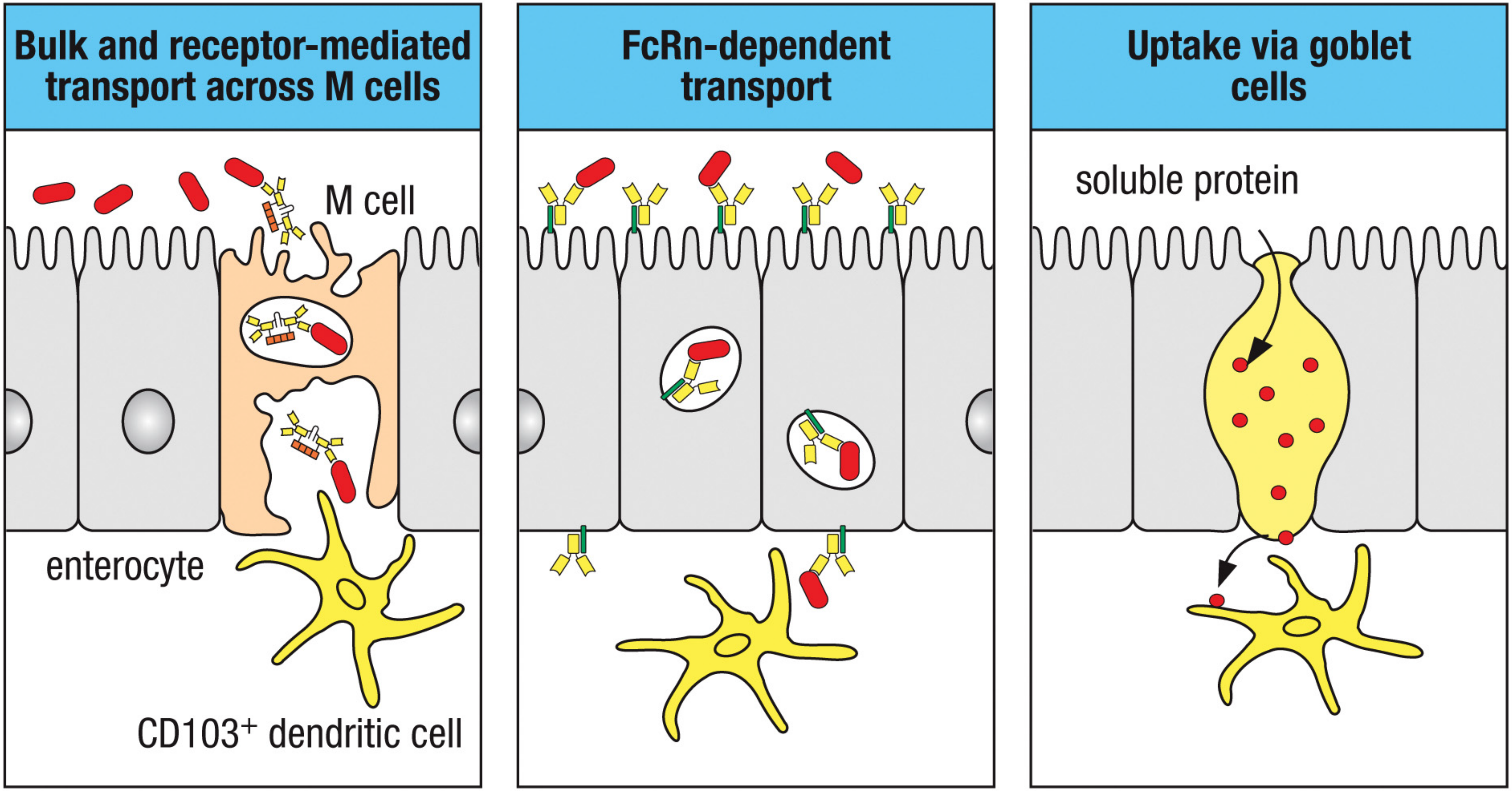


# Antigen Presentation

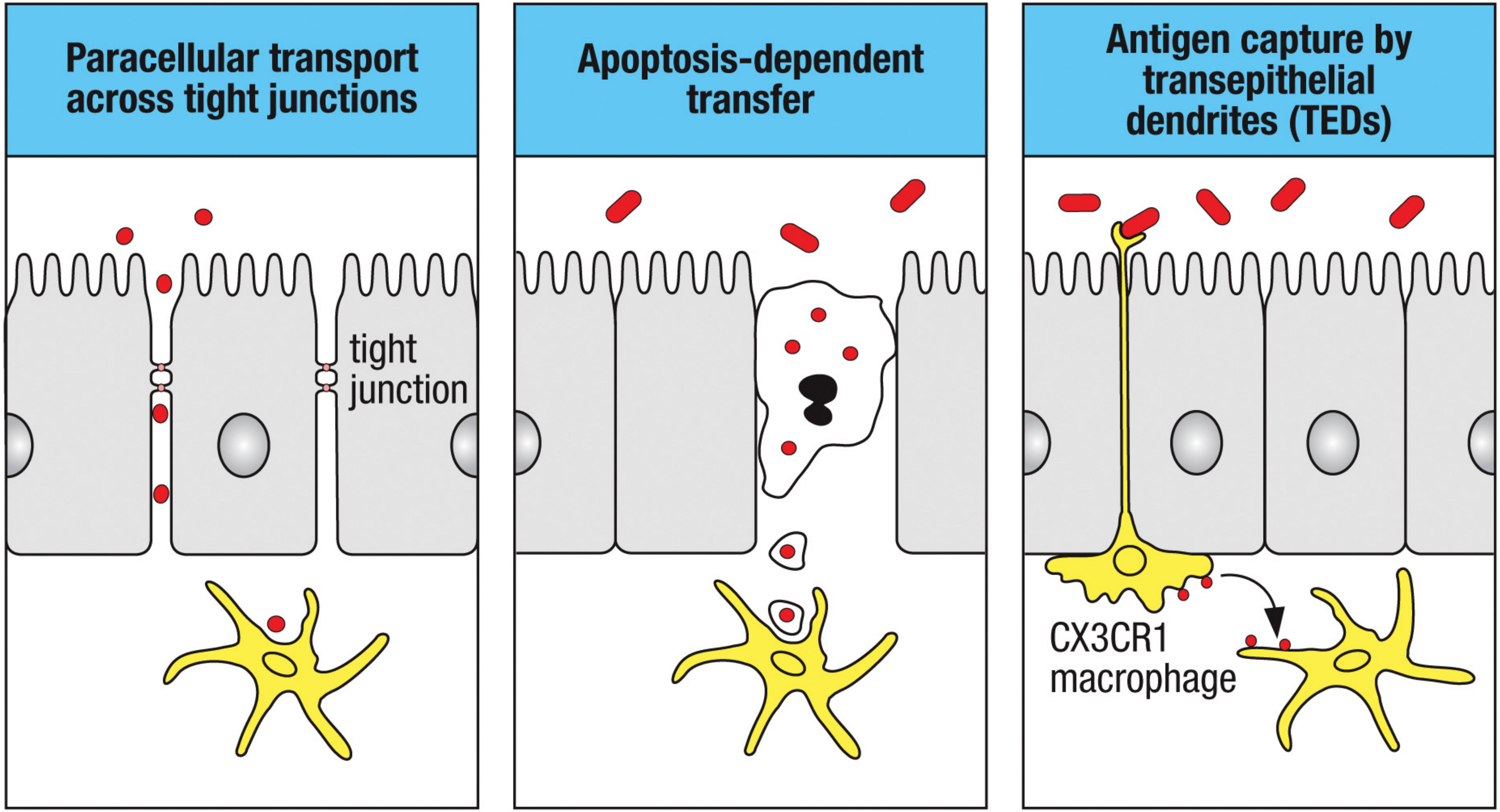
| Characteristics of major mononuclear phagocytes in the intestines | | | |
|---|---|---|---|
| **Intestinal mononuclear phagocyte** | **Tissue-resident macrophage** | **Conventional dendritic cell 1 (cDC1)** | **Conventional dendritic cell 2 (cDC2)** |
| Common surface markers | MHC class II<br>CD11c<br>CCR2 | MHC class II<br>CD11c<br>CCR2 | MHC class II<br>CD11c<br>CCR2 |
| Unique surface markers | CX3CR1<br>Fcγ RI (CD64)<br>$\alpha_v\beta_8$ | XCR1 | SIRPα |
| Key inducing cytokines | CSF1 (M-CSF) | FLT3L | FLT3L |
| TLRs | TLR-$4^{lo}$, various | TLR-$3^{+}$, various | TLR-$3^{-}$, various |
| Cytokines produced | TGF-β (activation)<br>(IL-10) | IL-12 | IL-6, IL-23, TGF-β |
| Prevalence | Abundant | Frequent | Abundant |
| Major functions | “Silent” bacterial uptake and destruction<br>Antigen transfer to migratory DCs<br>Efferocytosis<br>Transepithelial antigen sampling | Antigen presentation to naive CD8 T cells | Antigen presentation to naive CD4 T cells |

# Acquisition of Antigens

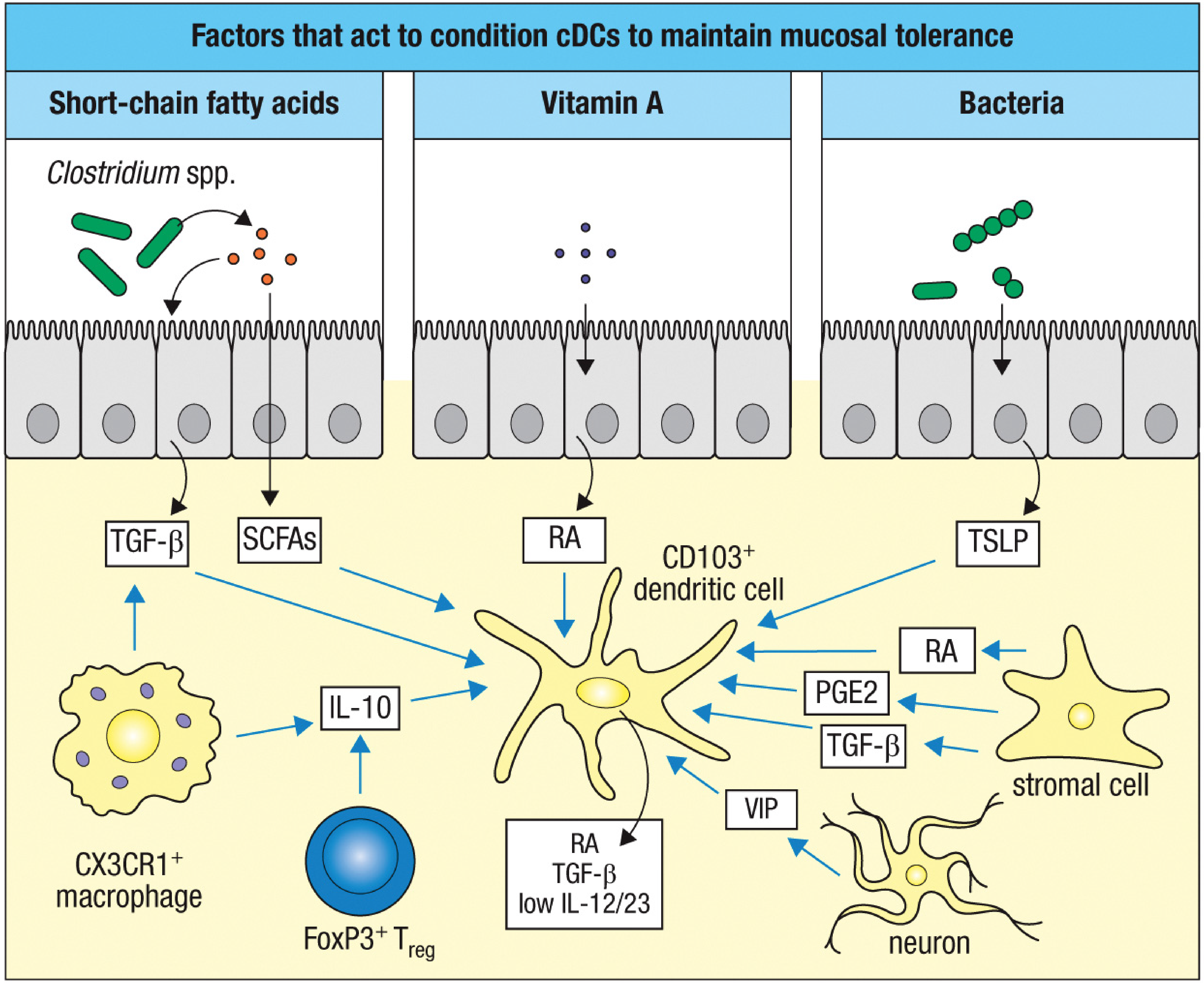
neonatal Fc receptor (FcRn)



# Acquisition of Antigens



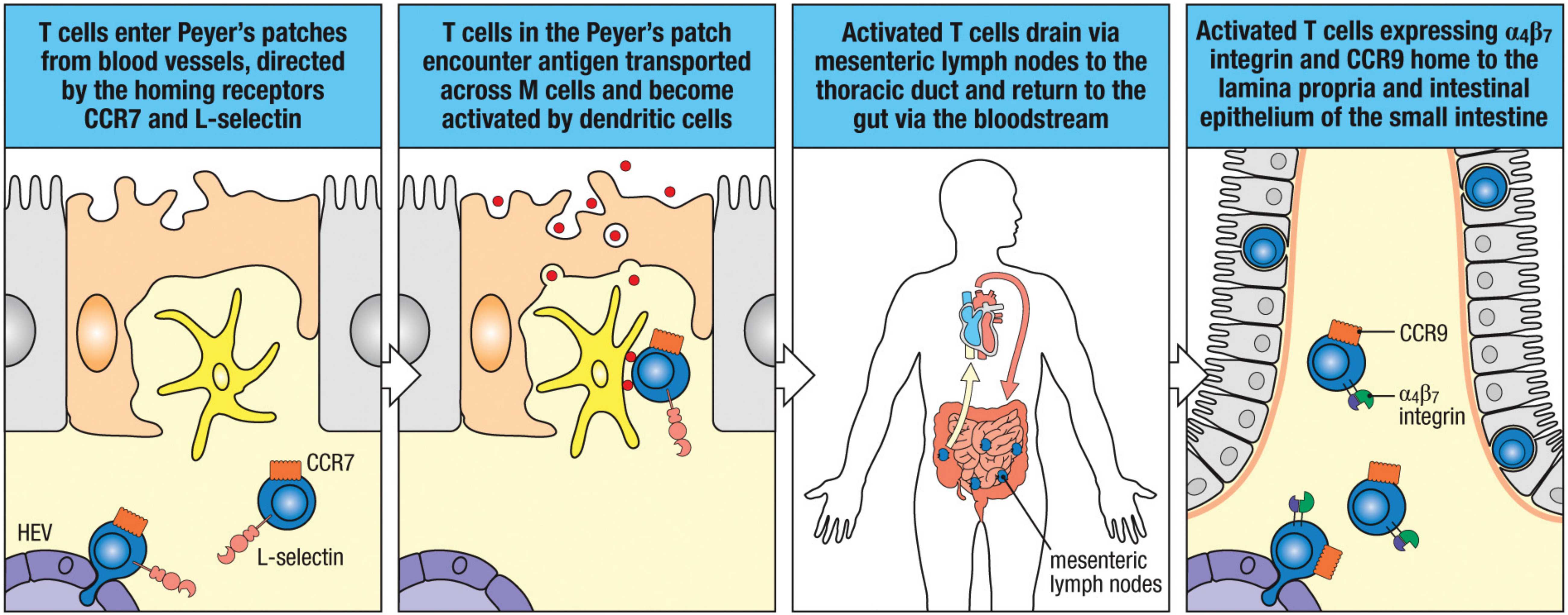
# Immune Tolerance



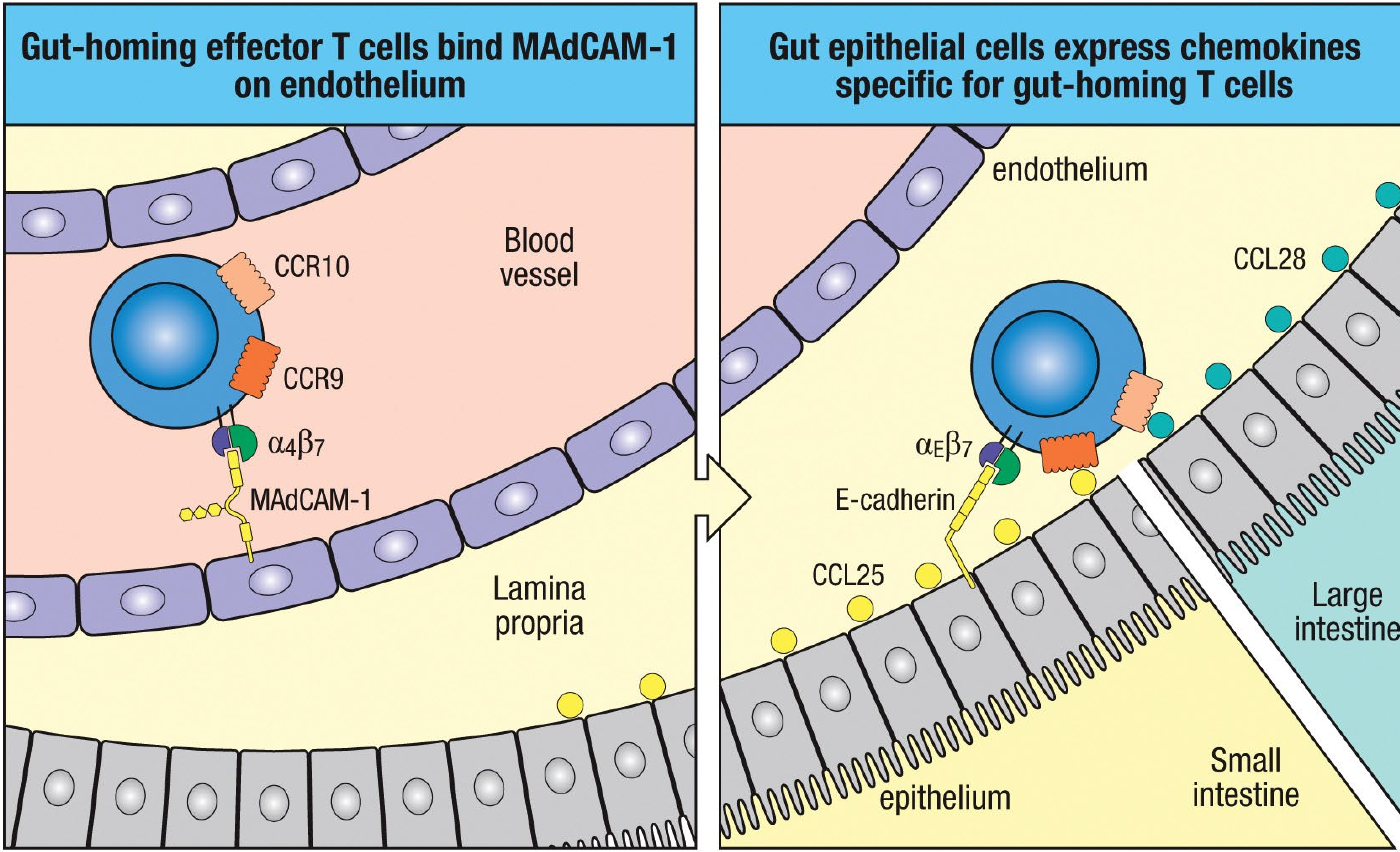
# Immune Tolerance

| | $T_{reg}$ cells are highly enriched in the intestinal mucosa | | | |
|---|---|---|---|---|
| | $CD4^+FoxP3^-$ | | $CD4^+FoxP3^+$ | |
| | $IL\text{-}10^-$ | $IL\text{-}10^+$ | $IL\text{-}10^-$ | $IL\text{-}10^+$ |
| Mesenteric LNs | 80–90% | ~1% | 5–10% | ~1% |
| Small intestine | 70–80% | 5–10% | 5–10% | 5–10% |
| Large intestine | 60–70% | 3–5% | 10–15% | 15–20% |
| Large intestine, GF | 80–90% | ~1% | 5–10% | ~1% |

# Intestine-specific Homing of Lymphocytes

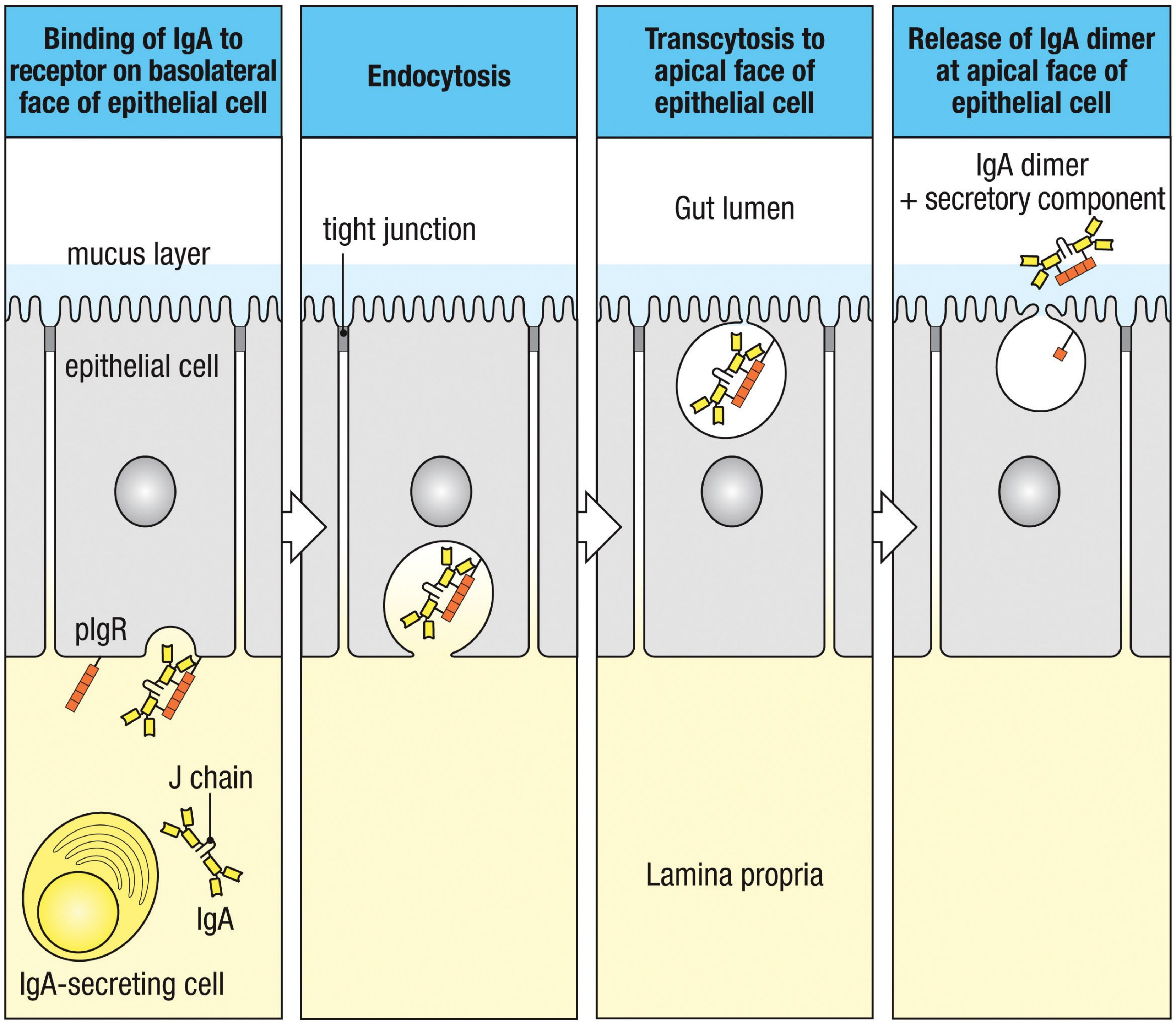


# Intestine-specific Homing of Lymphocytes



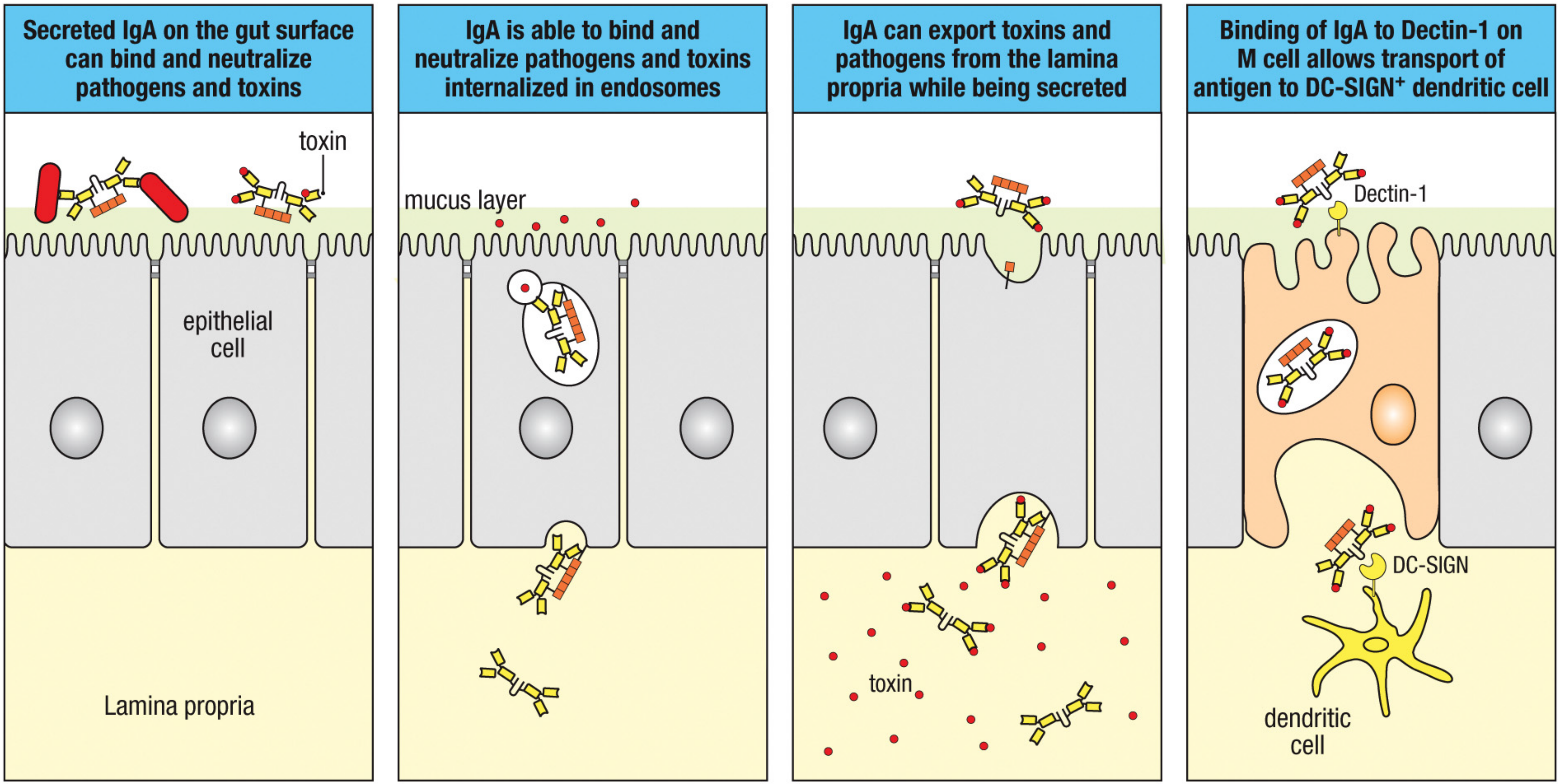
# IgA Mediates Mucosal Immunity

B cells activated in GALT receive TGF-beta—IgA
Recirculate and home to mucosal tissue



# IgA Neutralizes Microbes and Toxins

## IgA effector function is not inflammatory



# Question

- What are the two cells that facilitate sampling of the microbiota in the gut?
- What is physiological inflammation?

# Outline

- Mucosal immunity
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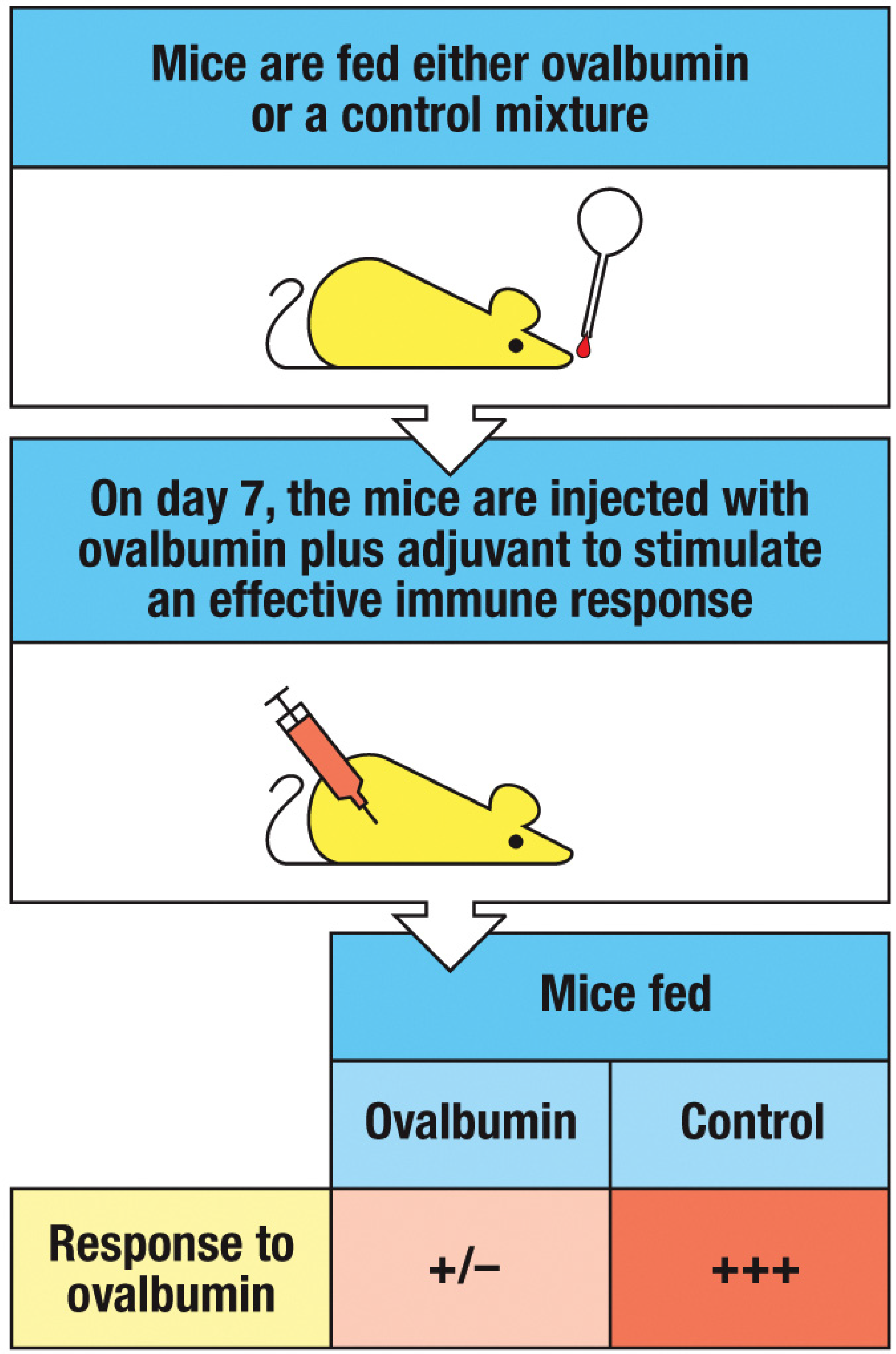
# Exposure to Food Proteins Induces Oral Tolerance

| | Protective immunity | Mucosal tolerance |
|---|---|---|
| Antigen | Invasive bacteria, viruses, toxins | Food proteins; commensal bacteria |
| Primary Ig production | Intestinal IgA and IgG<br>Specific Ab present in serum | Some local IgA<br>Low or no Ab in serum |
| Primary T-cell response | Local and systemic effector and memory T cells | $pT_{reg}$ cell induction; no local effector T-cell response |
| Response to antigen reexposure | Enhanced (memory) response | Low or no response or systemic response |

# Exposure to Food Proteins Induces Oral Tolerance



# Peanut Allergy





The Real-Life Science of *Game of Thrones'* Wildfire

Two Contestants on Australia's *The Bachelor* Have Fallen in Love With Each Other

Rihanna Posts Emotional Plea After Her Backup Dancer Is Reported Missing

This Is How Early Voting Became a Thing

Watch Uber's Self-Driving Trucks Make a Beer Run

Ricky Gervais Tells Jimmy Fallon Which of the Seven Dwarves He'd Be

HEALTH MEDICINE

## The Surprising Way to Treat Peanut Allergies

Alice Park @aliceparkny | Feb. 23, 2015

**In a breakthrough study, researchers show that it's not only possible to tamp down allergic reactions to peanuts, but by eating small amounts of them infants can avoid getting allergic in the first place**

More studies hint that it's possible to "train" the immune system to tolerate peanuts even if it doesn't want to by giving children with peanut allergies small amounts of peanuts over a period of time. But researchers now report that it may be possible to *prevent* peanut allergies altogether. In a study published Monday in the *New England Journal of Medicine*, researchers led by Gideon Lack, a professor of pediatric allergy at King's College London and Guy's and St. Thomas' Hospital, found that non-allergic young infants who ate small amounts of peanuts at an early age had a much lower rate of peanut allergy than those who avoided nuts altogether for five years.

**MORE** This 'Peanut Patch' Could Protect Against Peanut Allergies

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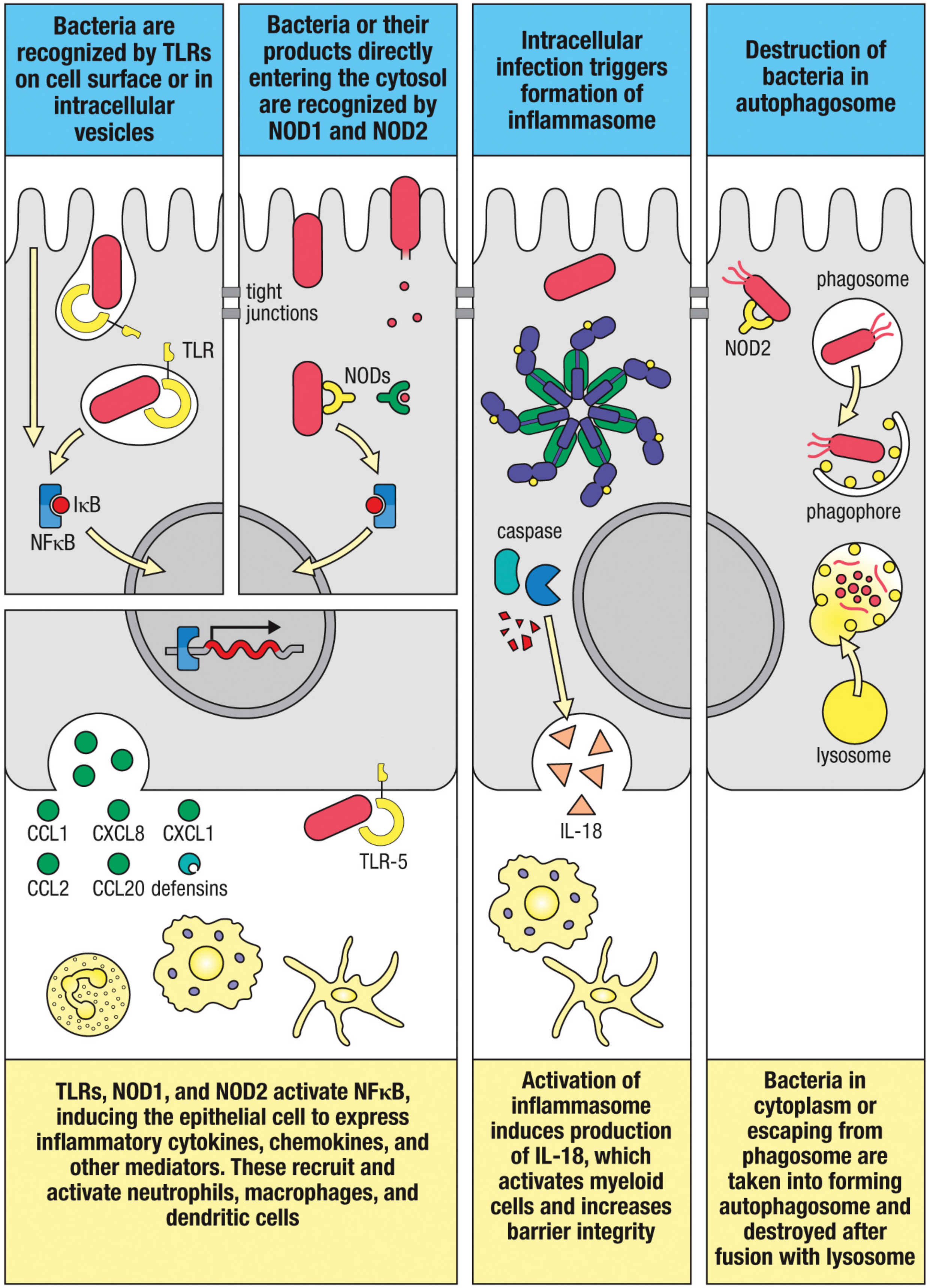
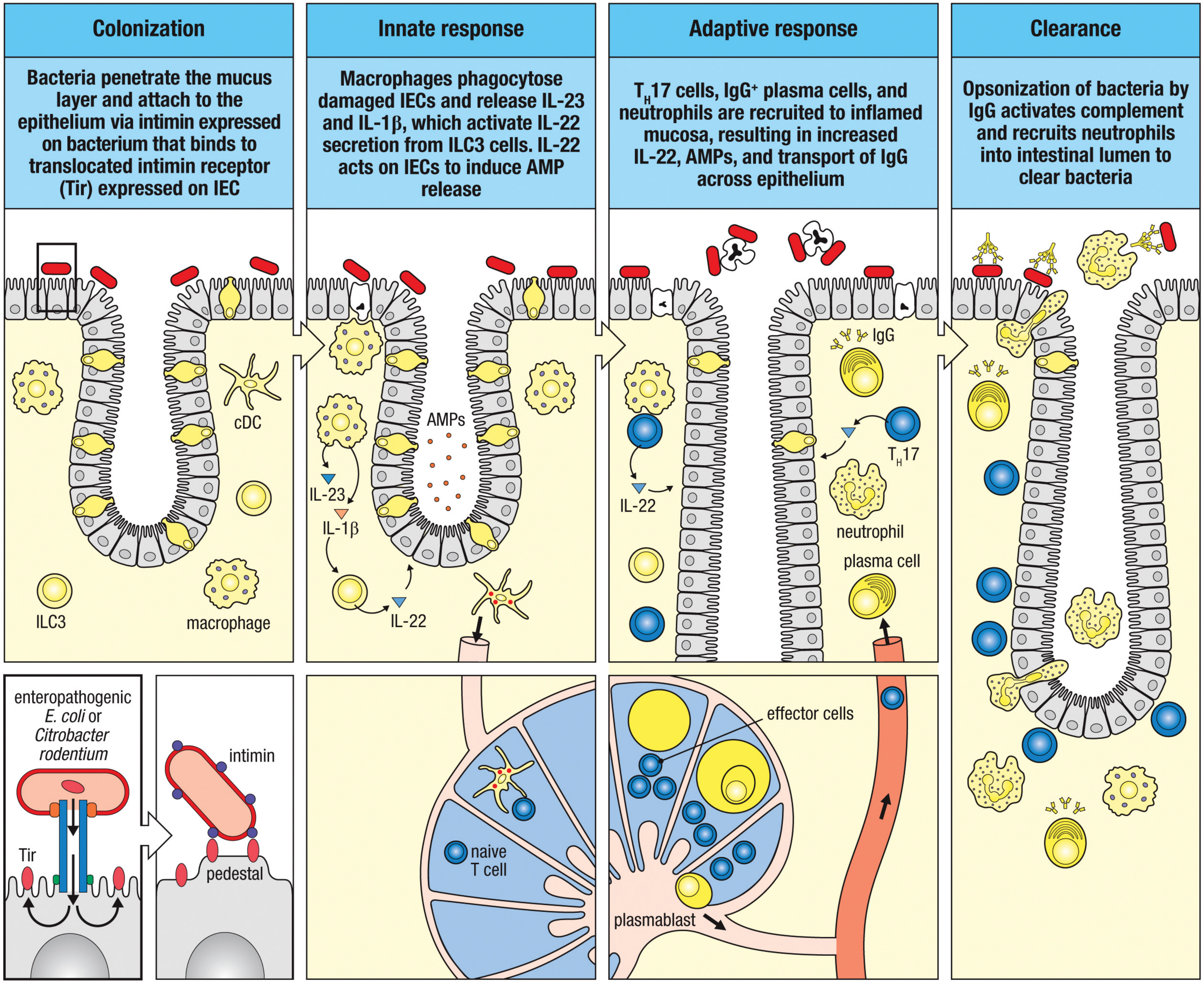
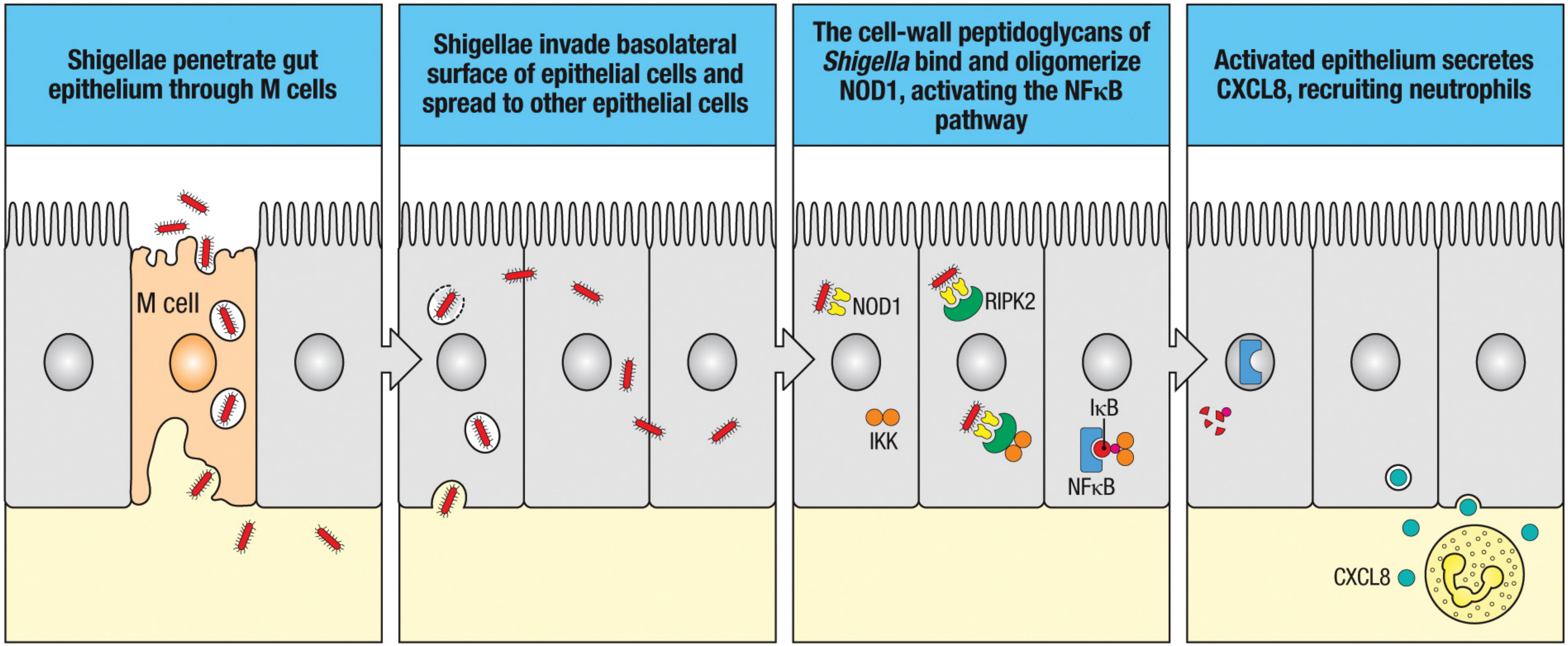
# Intestinal Epithelium in Innate Response



# Host Response to Attaching and Effacing Enteropathogenic Bacteria



# *Shigella flexneri* infection



# News of Salmonella- Jan 2016

https://www.cdc.gov/salmonella/outbreaks.html

List of Selected Outbreak Investigations Linked to Food, by Year

2018 | 2017 | 2016 | 2015 | 2014 | 2013 | 2012 | 2011 | 2010 | 2009 | 2008 | 2007 | 2006

- Chicken Salad – *Salmonella* Typhimurium
- Kratom – *Salmonella* I 4,[5],12:b:-
- Raw Sprouts [Español] – *Salmonella* Montevideo
- Frozen Shredded Coconut [Vietnamese [PDF – 3 pages]] [Español] – *Salmonella* I 4,[5],12:b:- and *Salmonella* Newport

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## Mexican Cucumbers Fuel Salmonella Poona Outbreak

BY DAN FLYNN | JANUARY 27, 2016

The Salmonella Poona outbreak first disclosed to the public last Sept. 4, and since found to be caused by imported Mexican cucumbers has now rolled into the new year with up to two additional deaths and 50 more cases in 16 states since the last report from the federal Centers for Disease Control and Prevention in Atlanta.

CDC Tuesday issued its first update on the deadly outbreak since last Nov. 19, saying 888 illnesses and six deaths are now associated with the Salmonella Poona outbreak in 39 states. The dangerous outbreak has sent 191 to local hospitals for care. And 106 illnesses have occurred since the recalled cucumbers should have no longer been available in grocery stores or restaurants.

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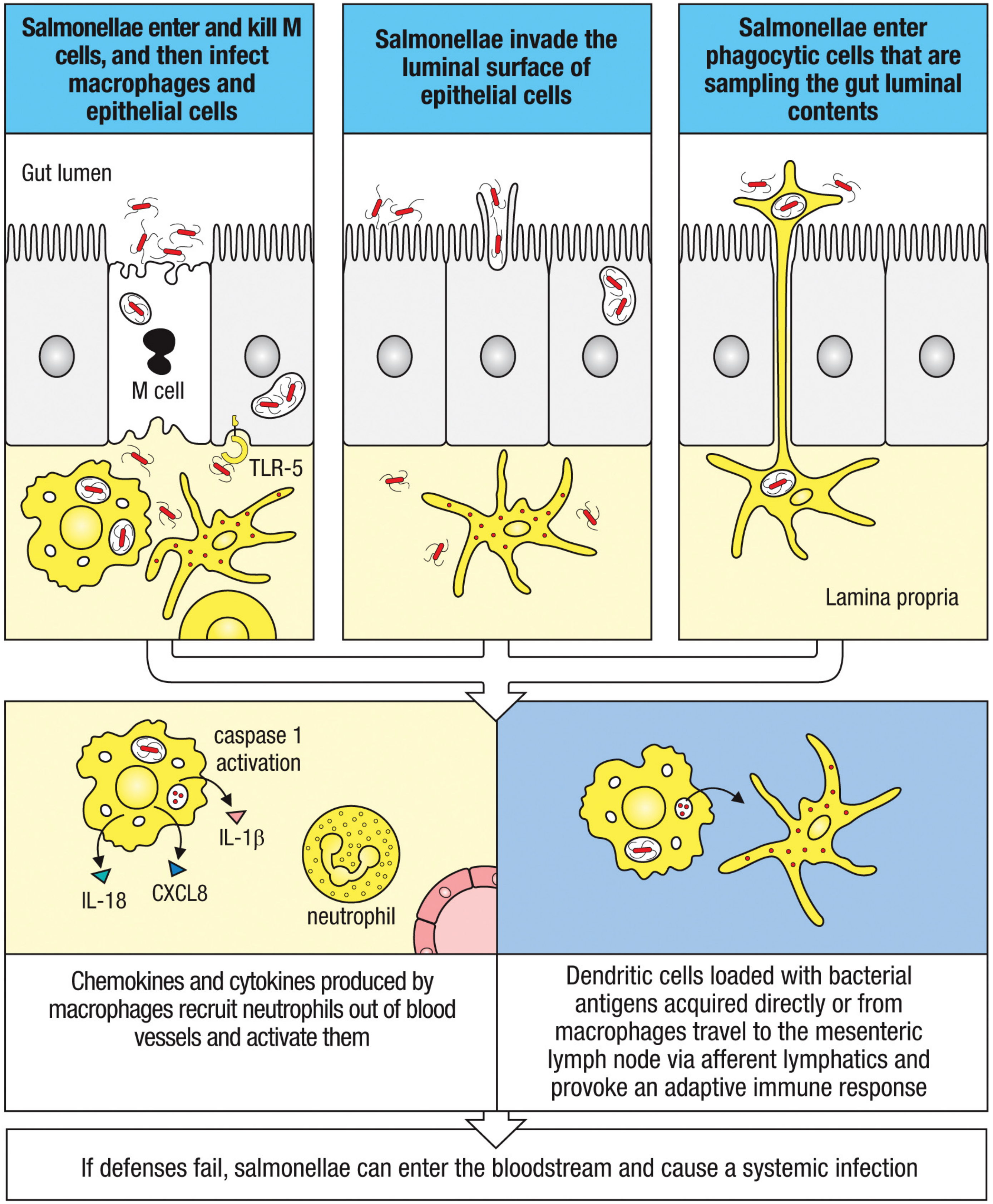
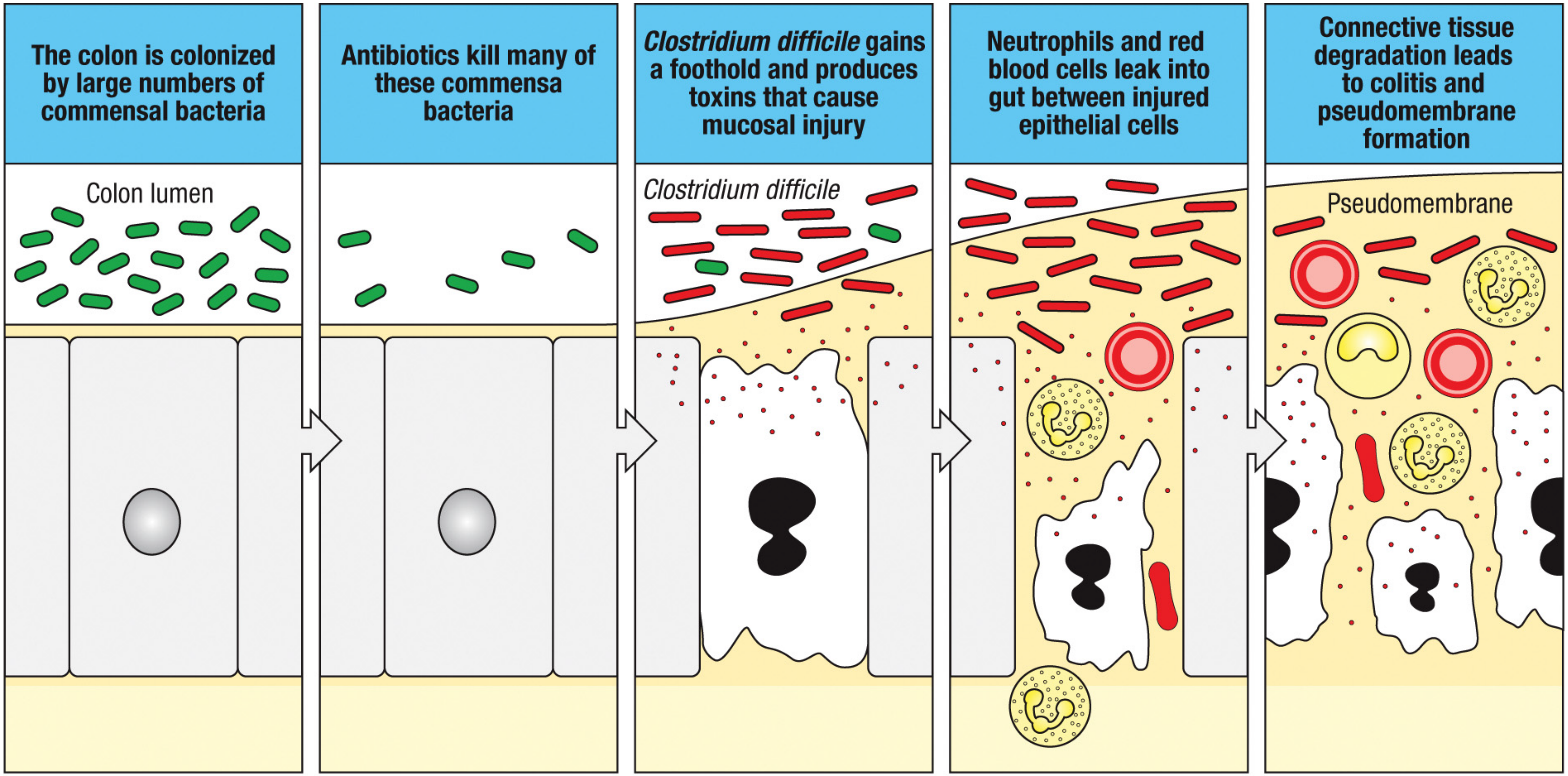
# Routes of Salmonella Entry

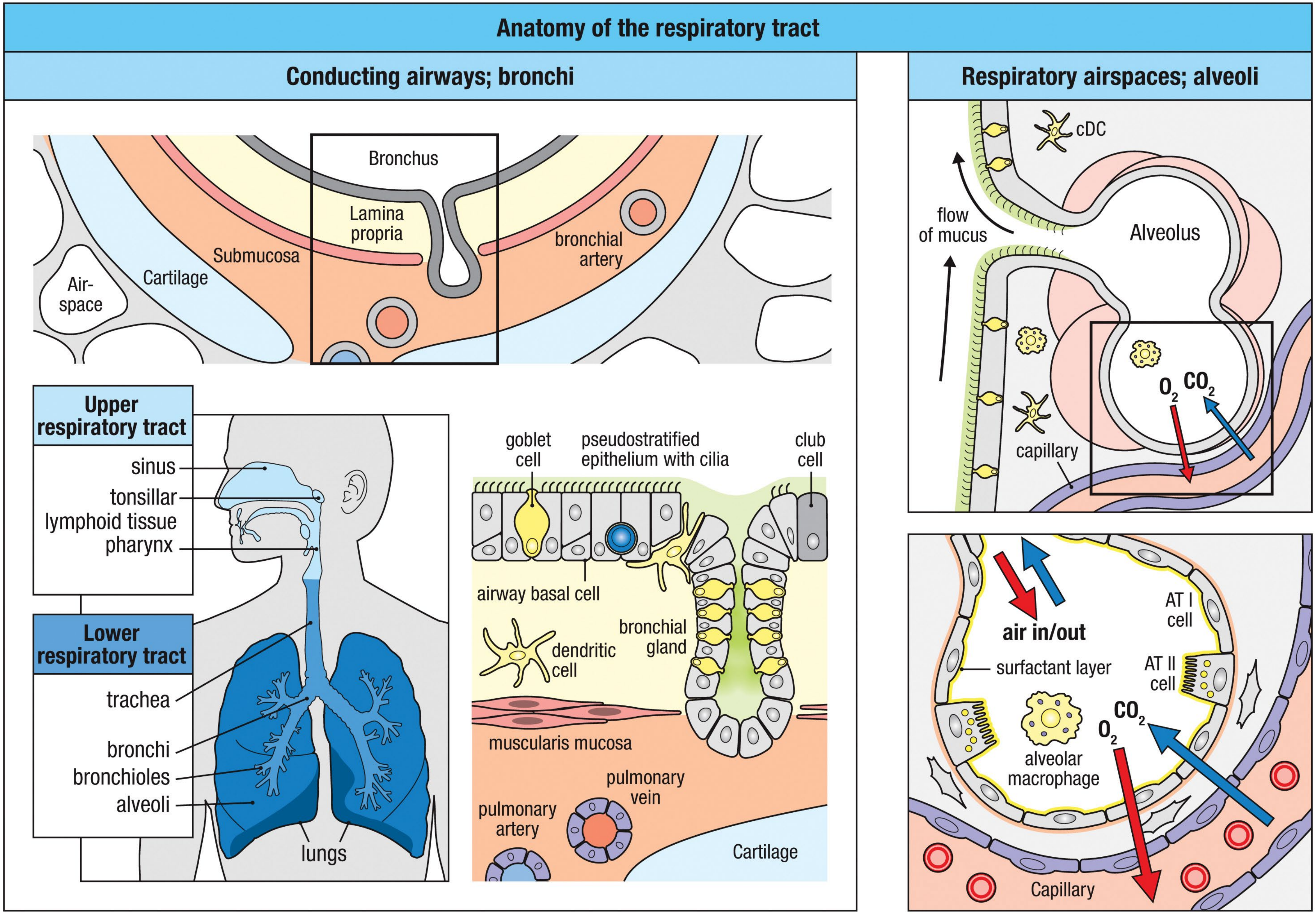


# Antibiotic Toxicity

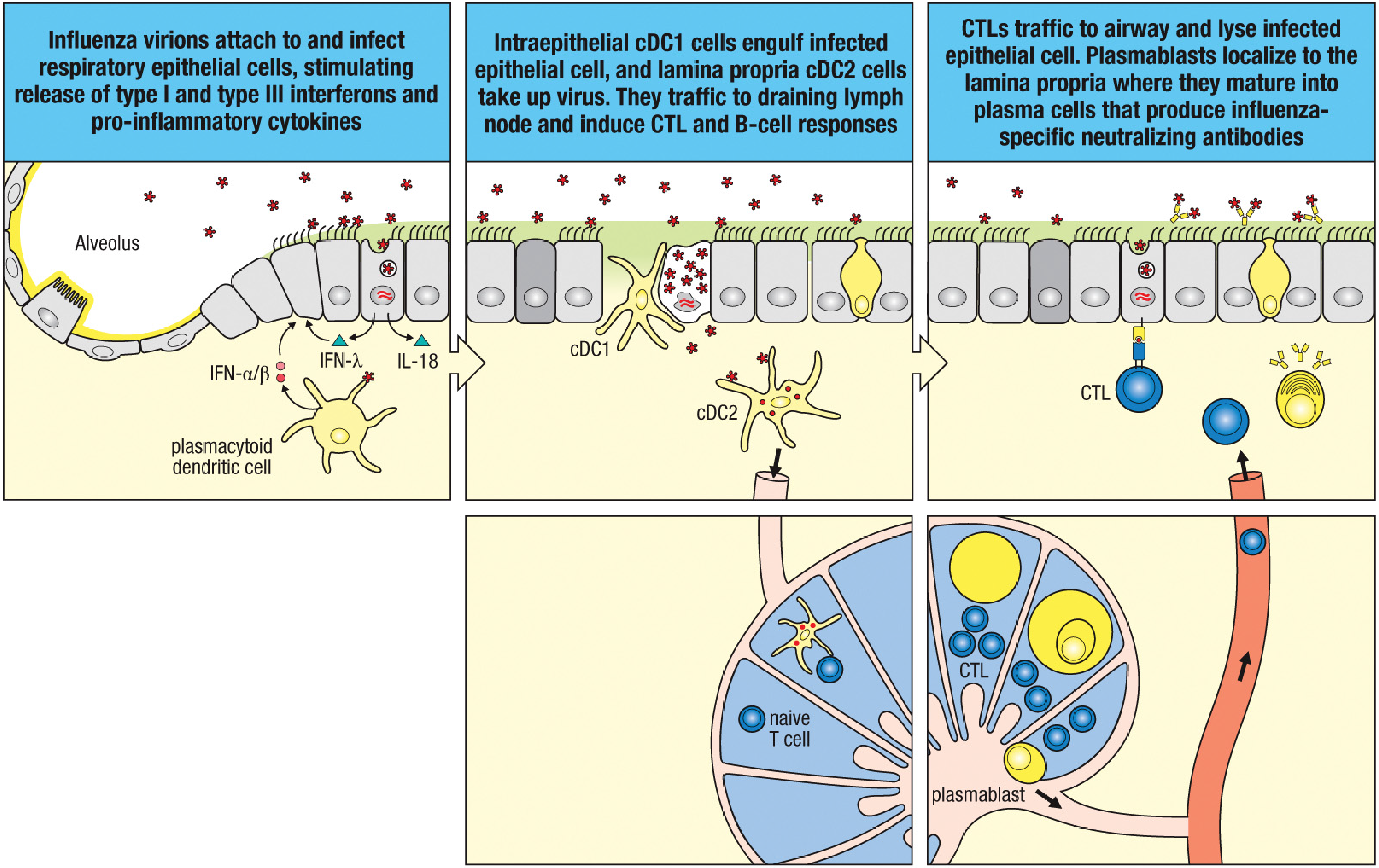
Microbiological barrier
Physiological barrier is compromised during inflammation



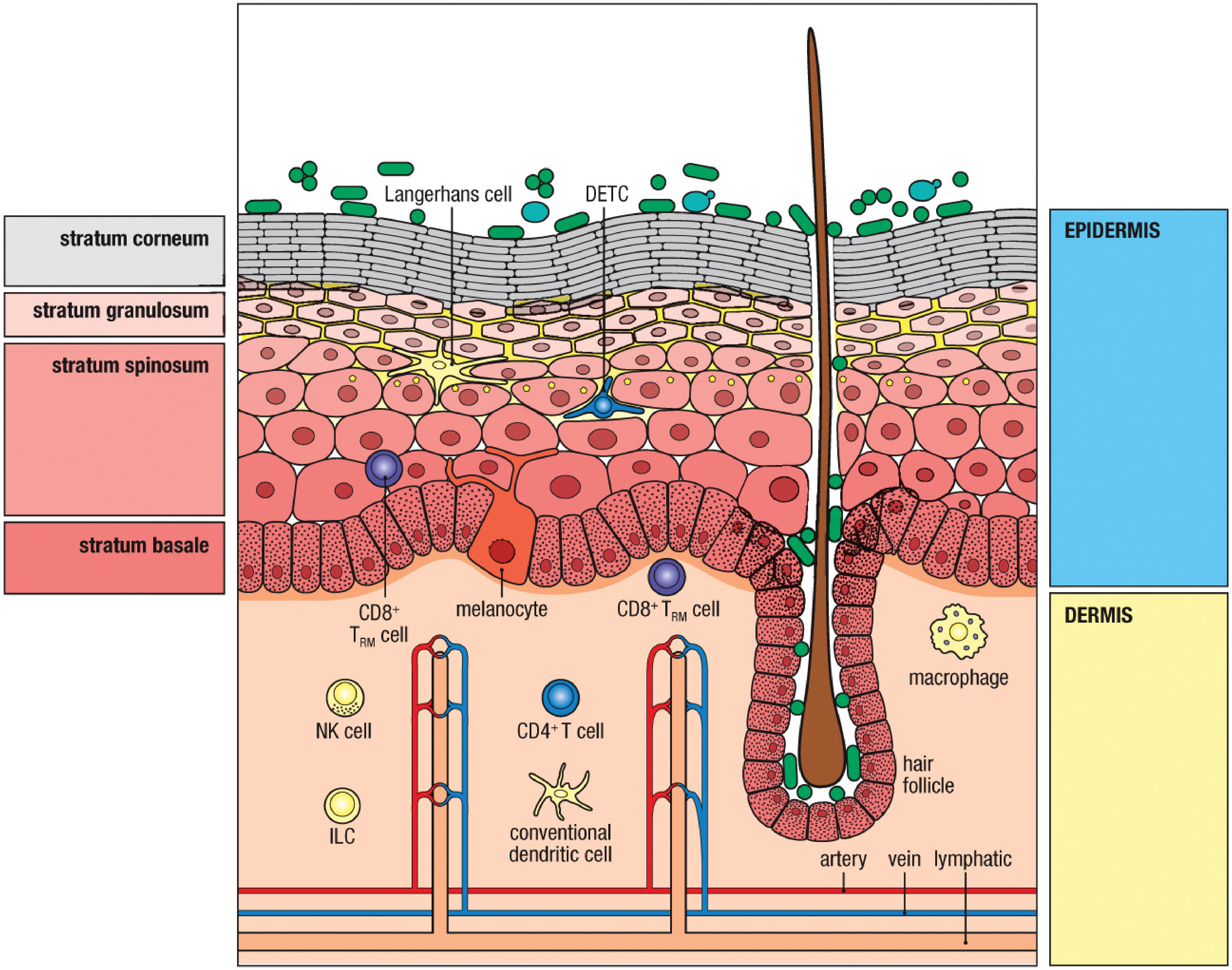
# Anatomy of the Respiratory Tract



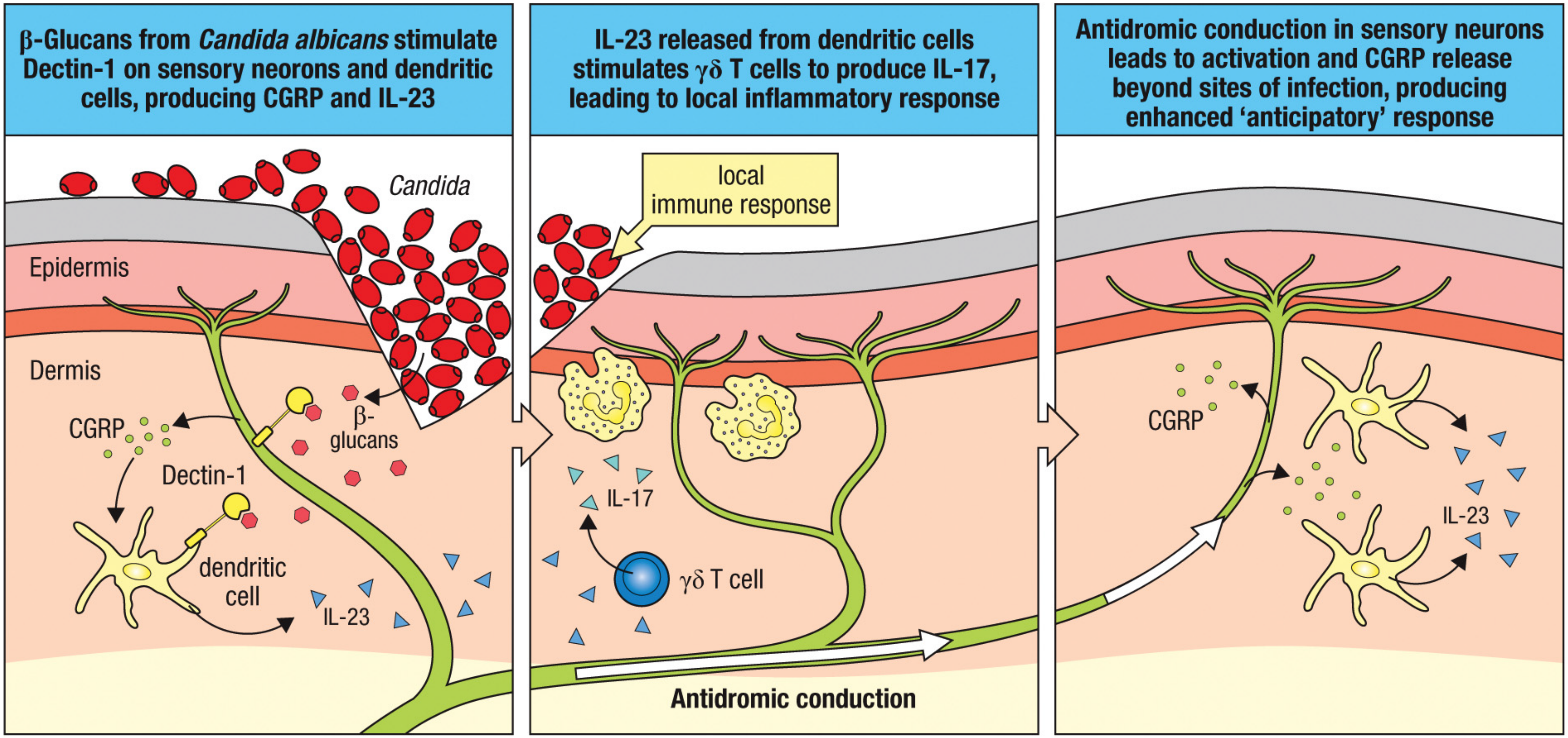
# The Immune Response to Respiratory Viruses



# Immune Components of Barrier Function in Skin



# Communication between Sensory Neurons and Dermal Dendritic Cells



# Question

- What determines the balance between tolerance and immunity in the gut?

# Fine Balance in Mucosal Immunity

- Tolerance
  - Food
  - Microbiota (Nutrition and barrier)
- Immunity
  - Invading Pathogens
  - Integrity of the physical barrier
- Coevolution of immunity and microbiota
  - Microbiota shapes immunity: development and allergy

# Question

- What is NOT true about mucosal immunity?

A) It contains largest part of body's immune tissues

B) It is the largest entry point of pathogens

C) It will attach all foreign objects

D) It contains both innate and adaptive immunity

E) Barrier integrity is a primary concern in diseases at mucosal surfaces

# Case Studies

- Celiac disease
- Crohn’s disease

# Celiac Disease (gluten sensitive enteropathy)

- Patient:
  - 12 month baby girl
  - Weight lose
  - Protuberant abdomen
  - Muscle wasting
  - No enlargement of lymph nodes
- Tests:
  - Serologic tests, antibodies to TTG
  - Biopsy of small intestine
- Treatment:
  - Gluten-free diet and recovered

# Internal Biopsy

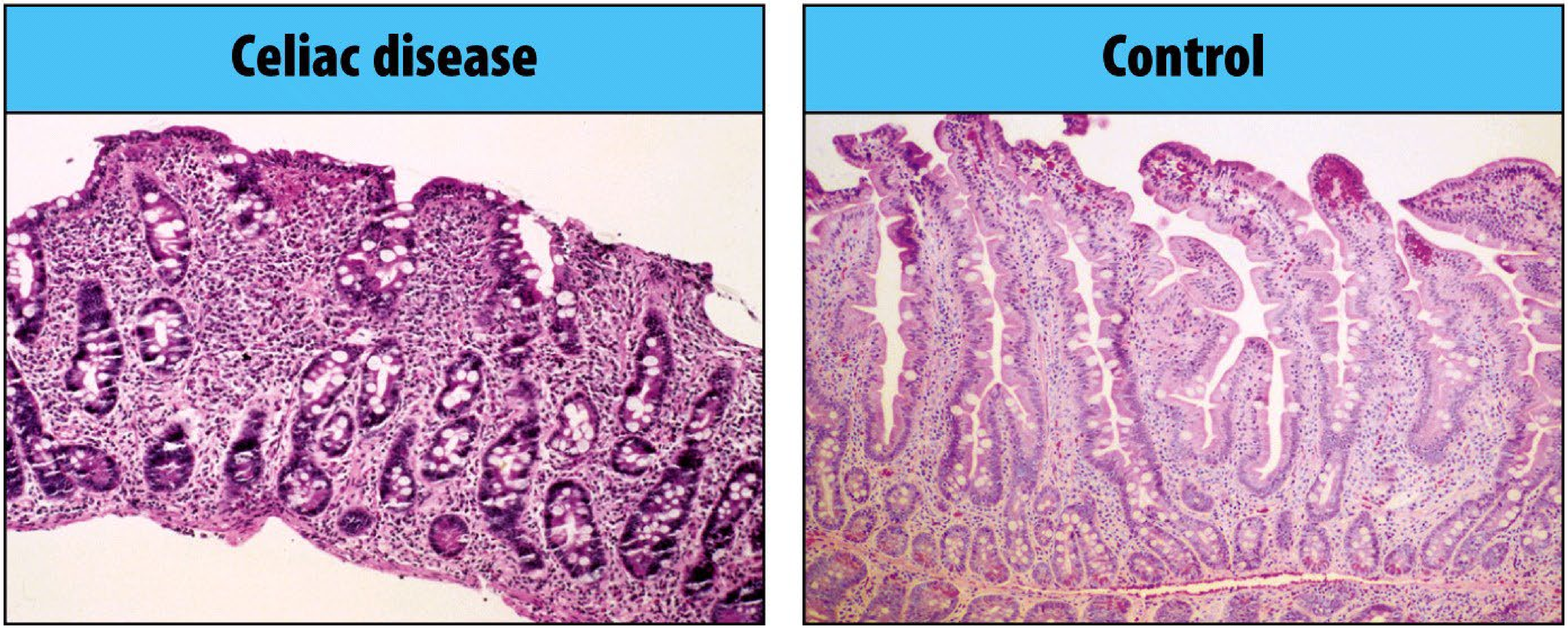



Figure 44.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

# Gliadin Antigen and HLA-DQ2

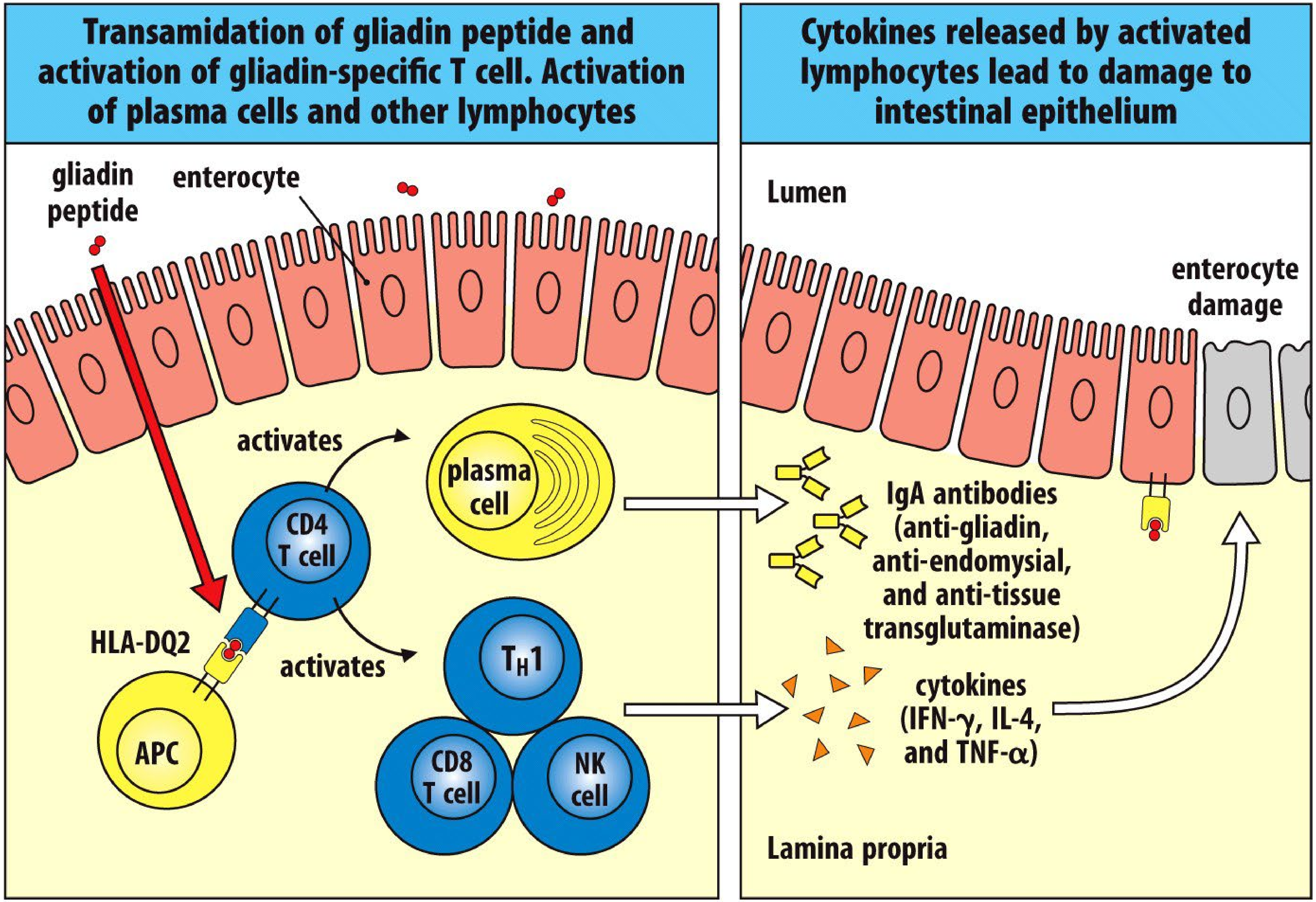



Figure 44.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

# What's Wrong with the Patient?

- Mounting of adaptive immunity to food antigen
- Dependent on HLA-DQ2/DQ8
- Helped with tissue transglutaminase
  - Antigen process
  - Generation of autoantibody
    - Unknown mechanism
- Avoid antigen will cure disease

# Crohn's Disease

- Patient:
  - Abdominal pain
  - Systemic inflammation
    - Toe swelling/Oral ulcers/Shin
  - Weight loss
- Tests:
  - Check for inflammation
  - Biopsy of small intestine
- Treatment:
  - Weekly injection of immune suppressive agents
  - Surgical removal of badly inflamed tissue

# Multiple Genetic Factors

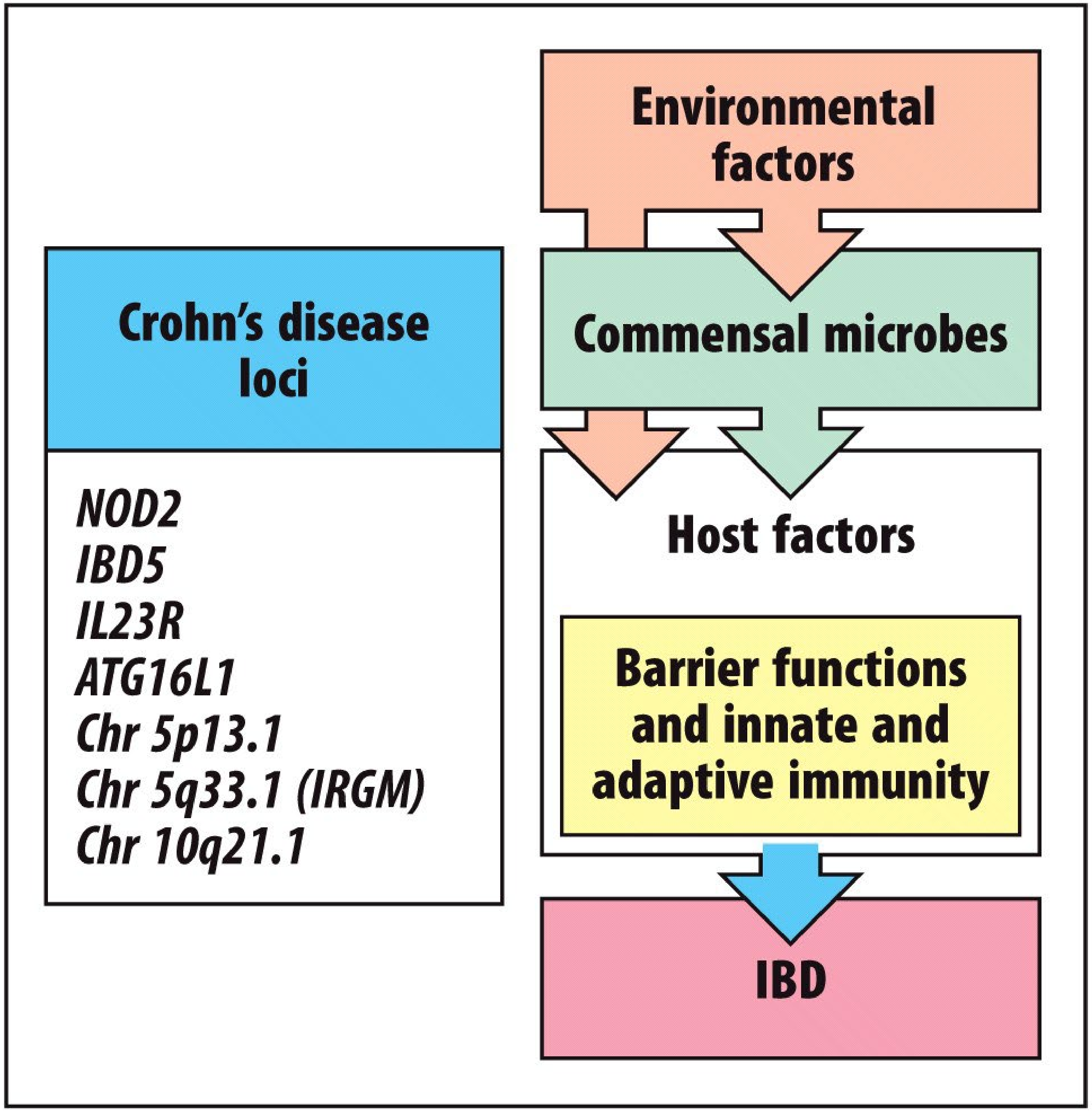



Figure 39.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

# What's Wrong with the Patient?

- Intolerance of microbiota leading to systemic inflammation