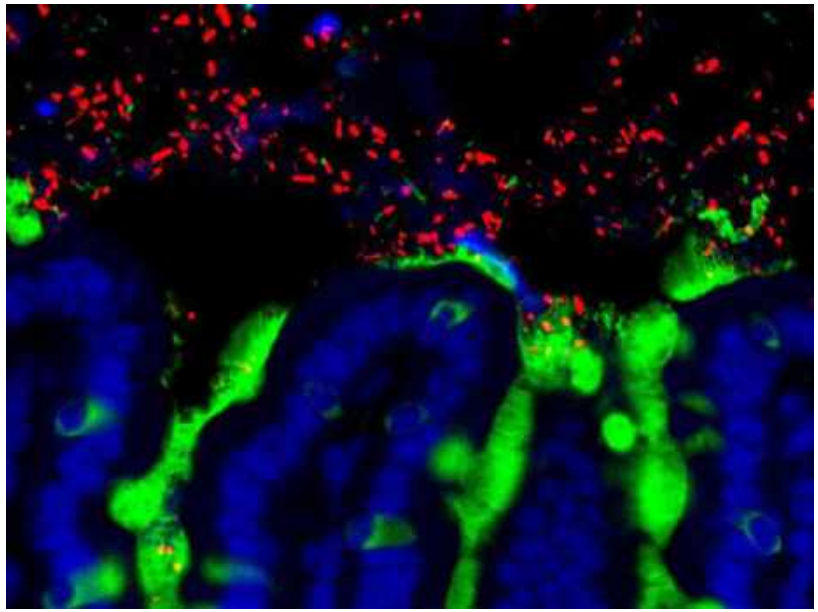
MUCOSAL IMMUNOLOGY



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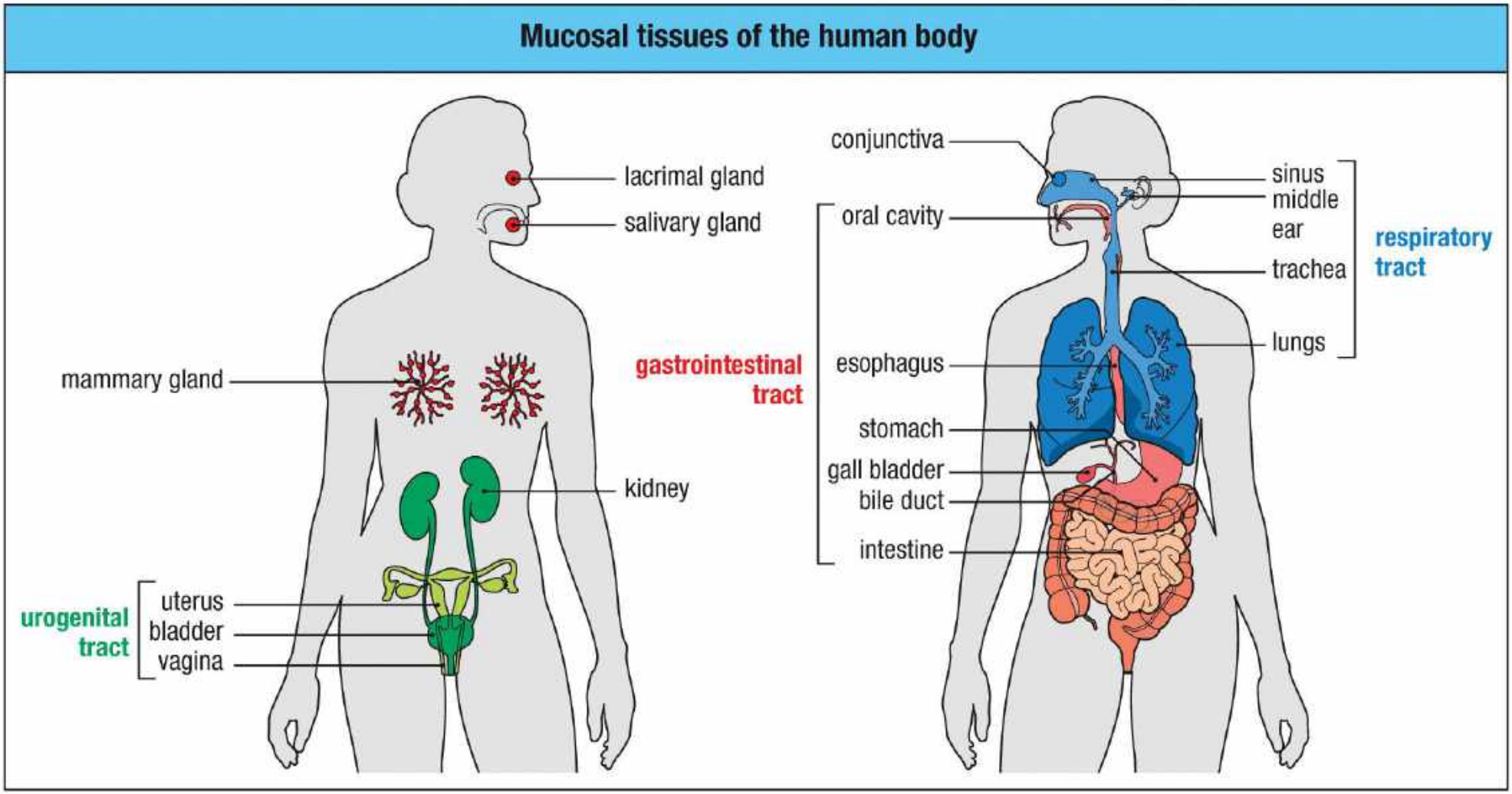
FOCIS Advanced Course in Basic and Clinical Immunology 2024

Estancia La Jolla, La Jolla, CA February 6, 2024



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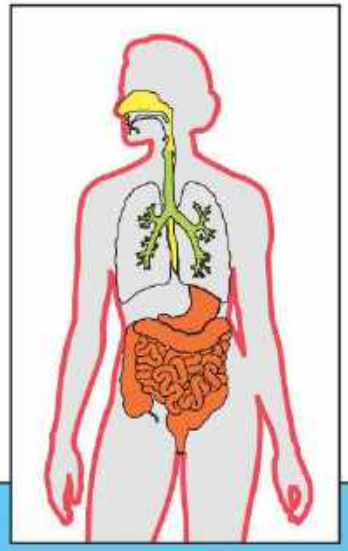
Mucosal surfaces are the major portals of entry for antigen

Largest area of contact of the immune system with the environment.

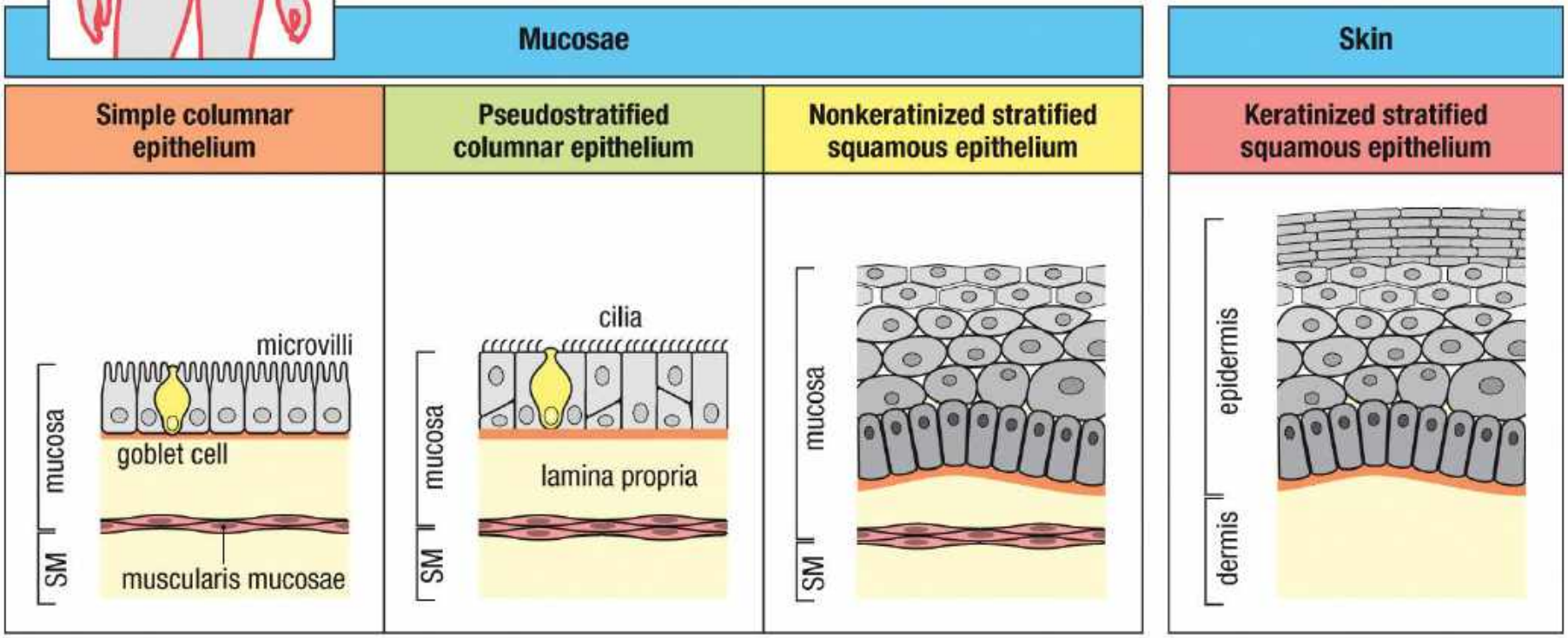
Largest accumulation of lymphoid tissue in the body:
6×10^{10} antibody forming cells in mucosal tissues vs 2.5×10^{10} in lymphoid organs.

The gut associated lymphoid tissue (GALT) contains more lymphocytes than all of the secondary lymphoid organs combined!

Secretory IgA is produced at a rate of 40-60 mg/kg/day.



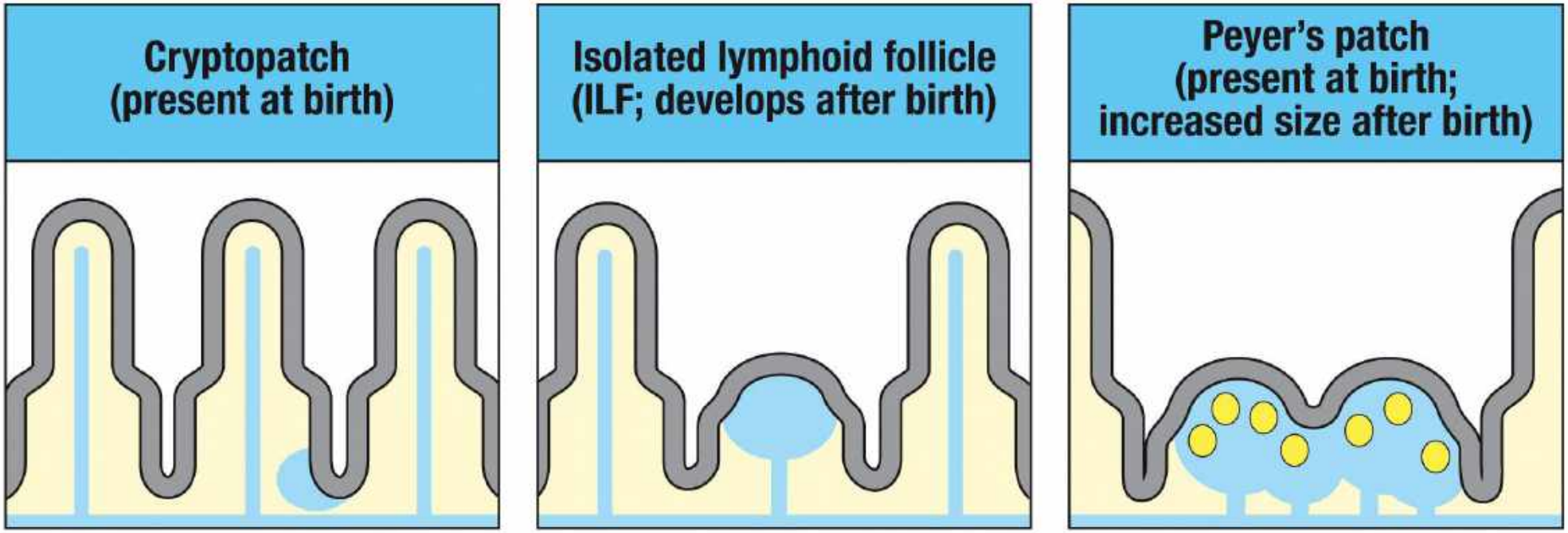
A variety of different types of epithelium line the barrier tissues



trachea, bronchi bronchioles

oral cavity, esophagus, rectum upper respiratory tract

Inductive sites of the GALT



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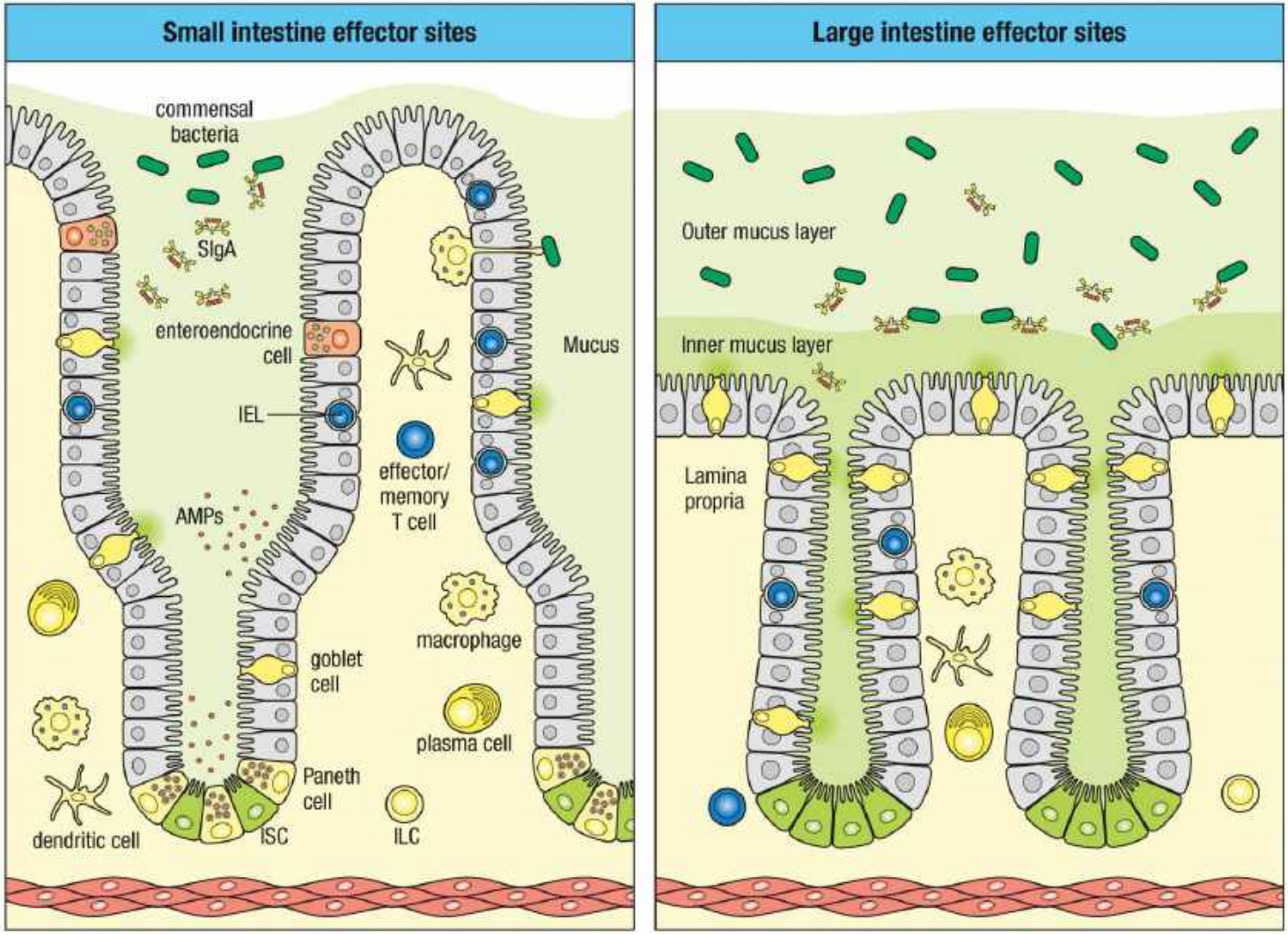
Effector sites of the GALT



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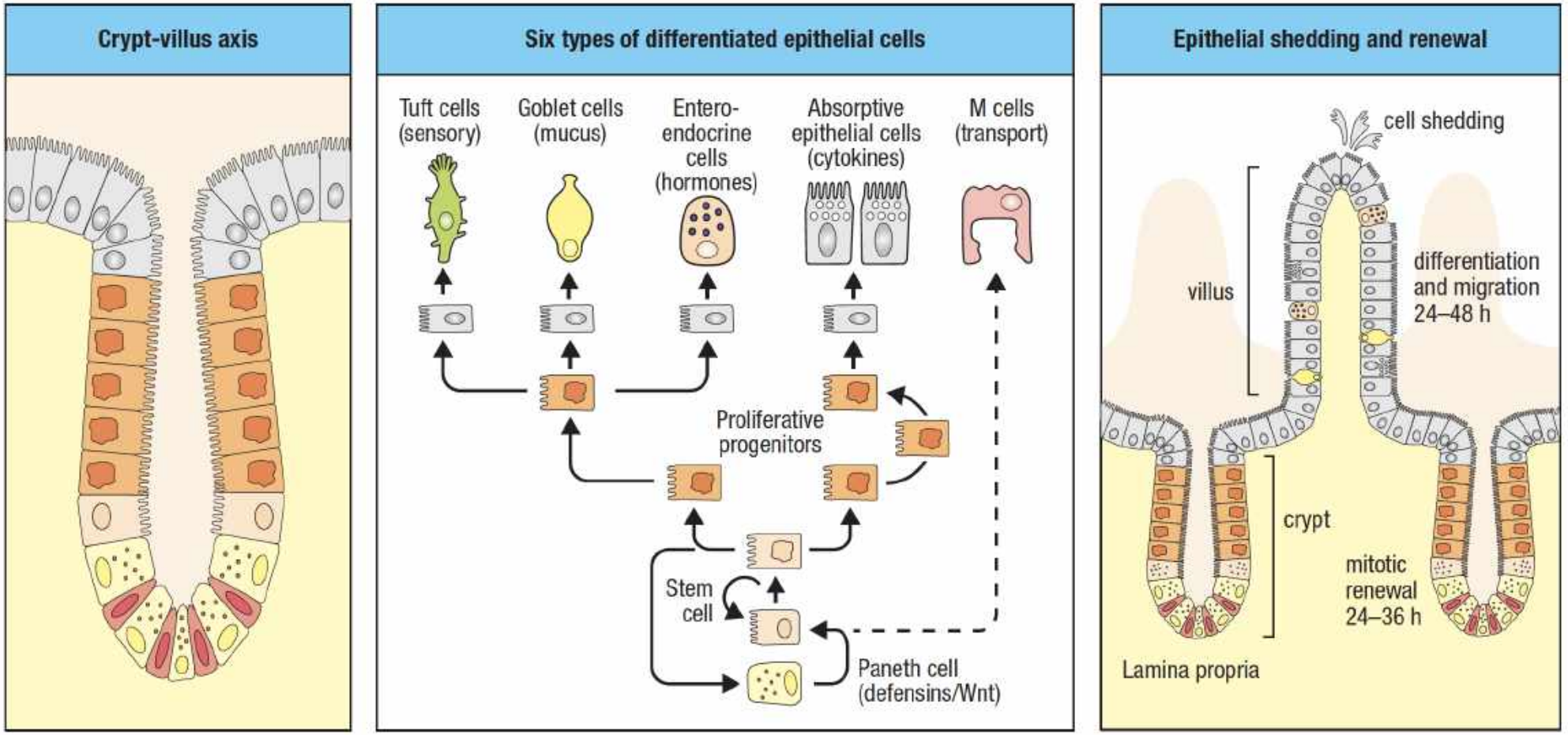
Intestinal epithelial cells arise from a common intestinal stem cell



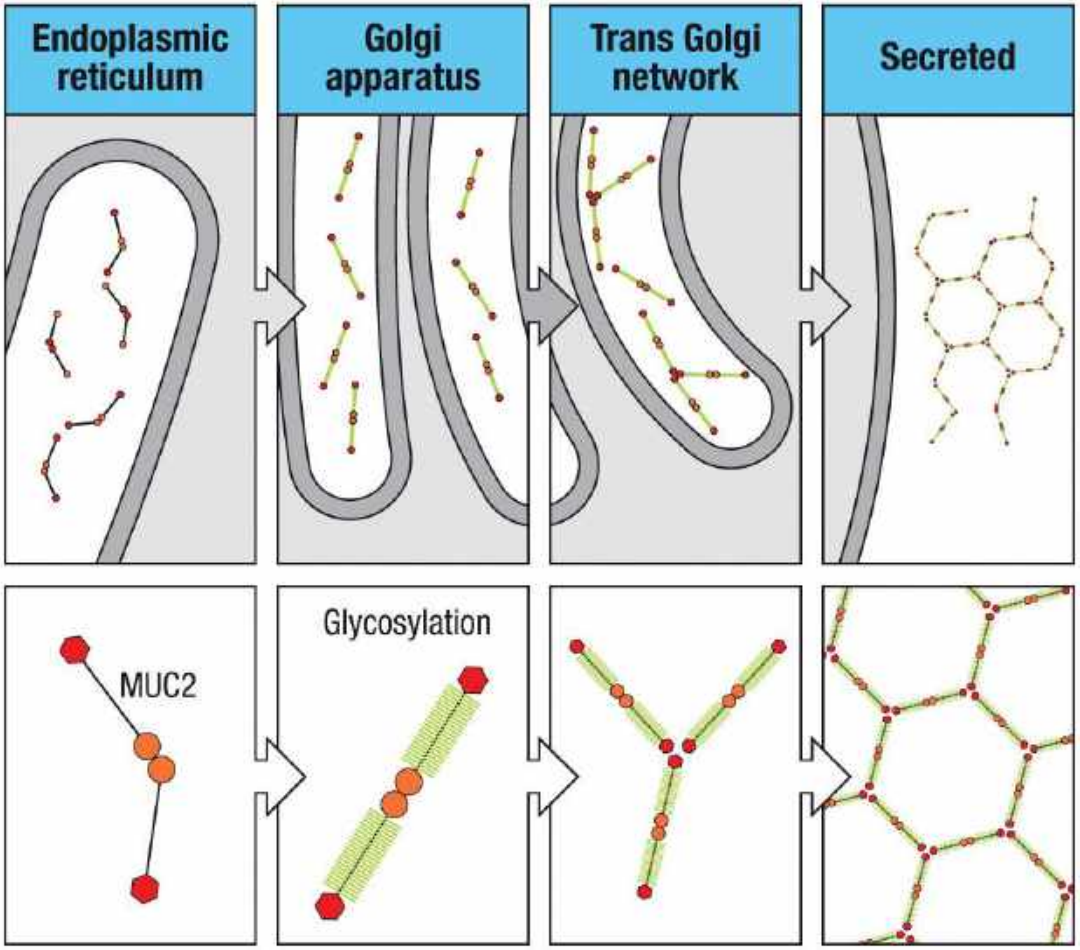
Principles of Mucosal Immunology, 2nd ed. (© CRC Press 2020)

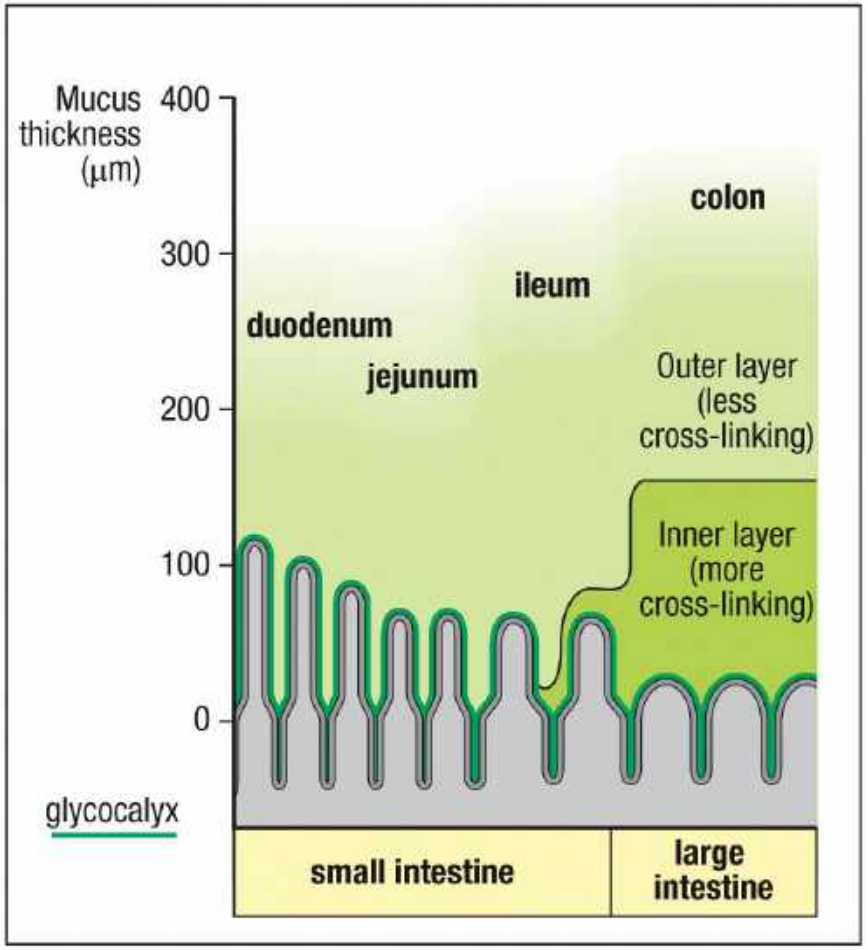
The epithelium is self-renewing. Cells migrate from crypt to tip in 2-6 days. Highest turnover in body.

Protective adaptations of the intestinal epithelial barrier

1. **Mucus**
2. **Anti-Microbial Peptides**
3. **Specialized enterocyte cell types**
4. **Intercellular tight junctions that restrict the passage of even very small (2kD) molecules between cells**
5. **Secretory IgA**

Structure and organization of mucins and mucus





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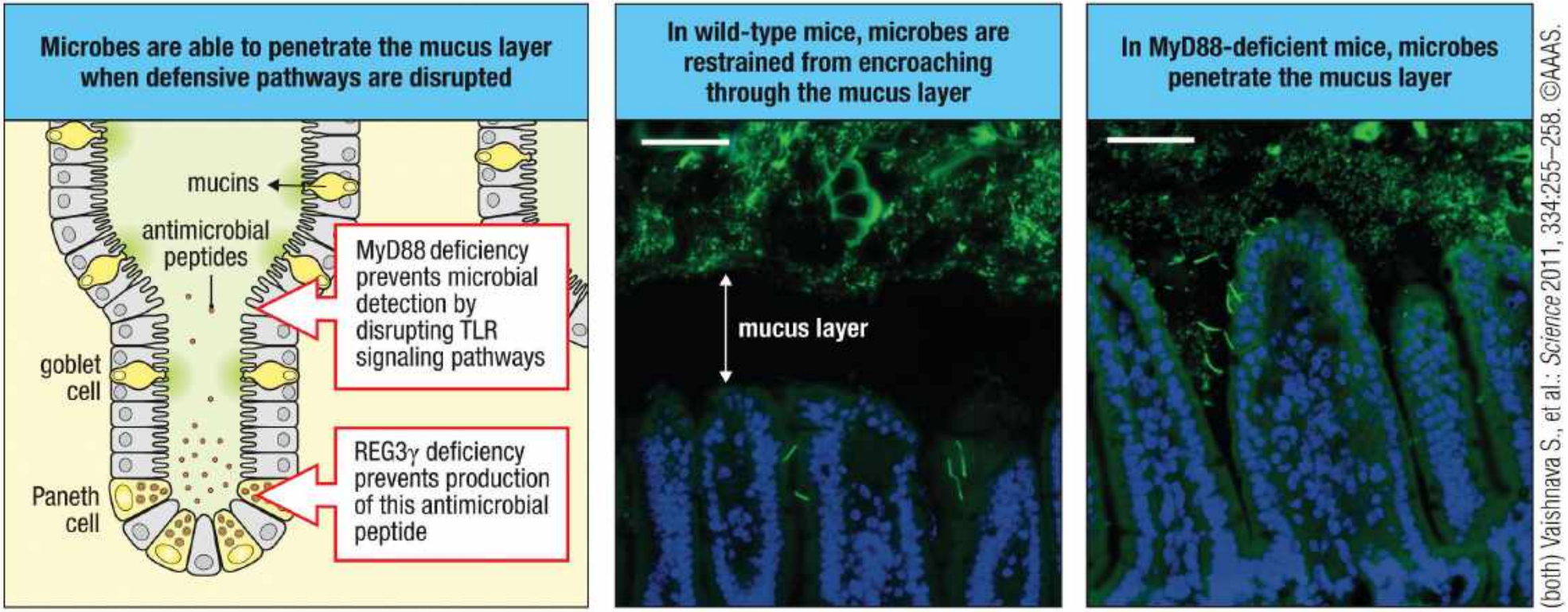
Mucins are glycoproteins with greater than 50% of their mass contributed by O-glycans. Two major types of mucins – transmembrane mucins are anchored to surface of mucosal epithelial cells and gel forming mucins (like MUC2) which are released.

Microbial signals activate the production of antimicrobial peptides the restrain bacterial encroachment of the intestinal epithelium



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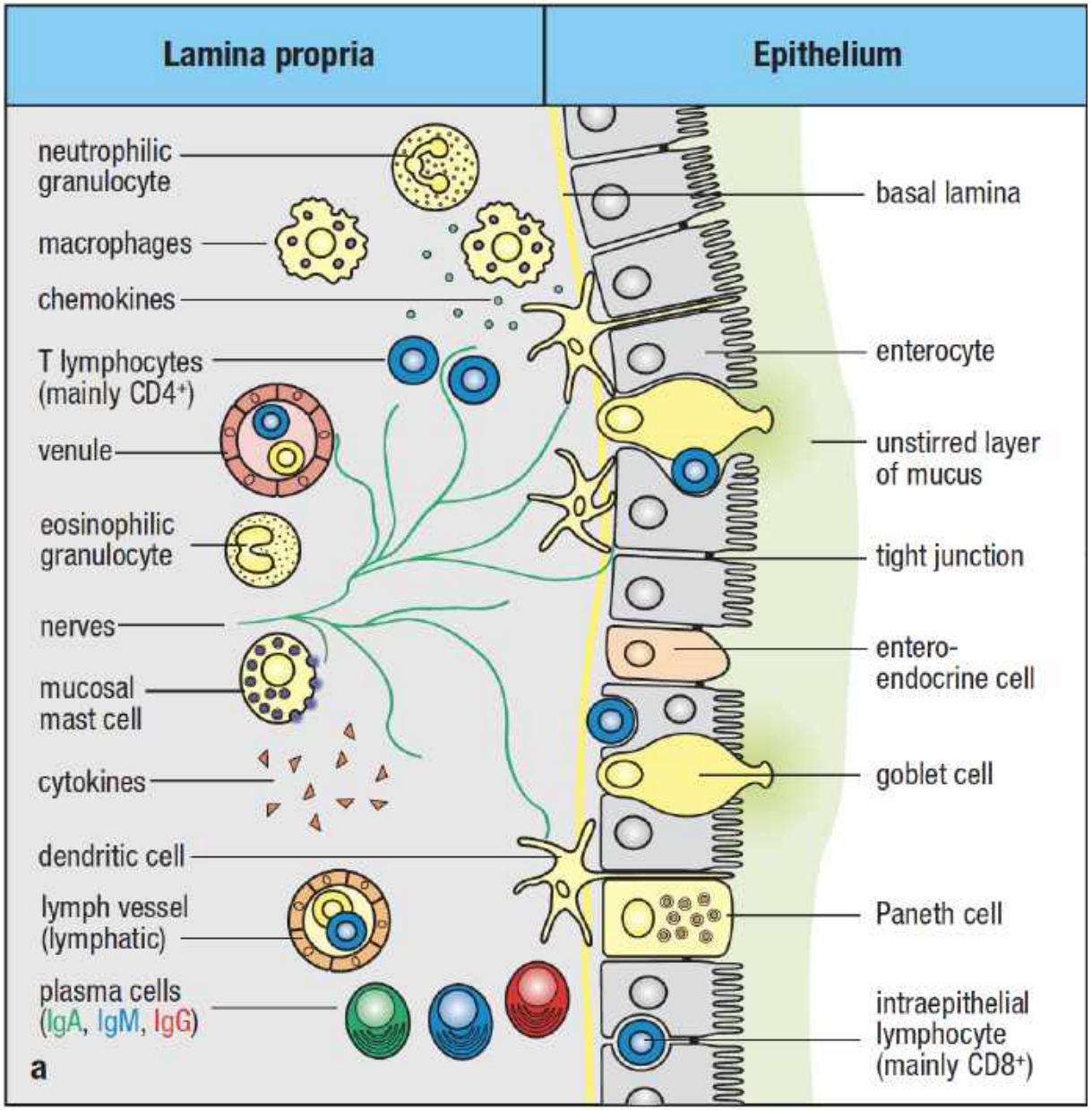
Specialized cell types in the gut epithelium and lamina propria



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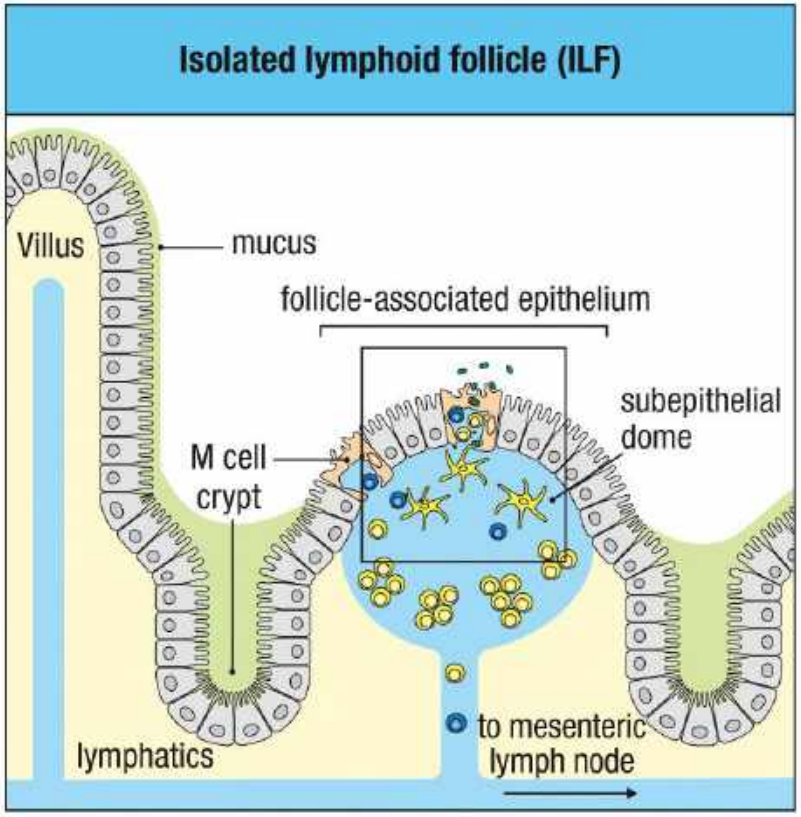
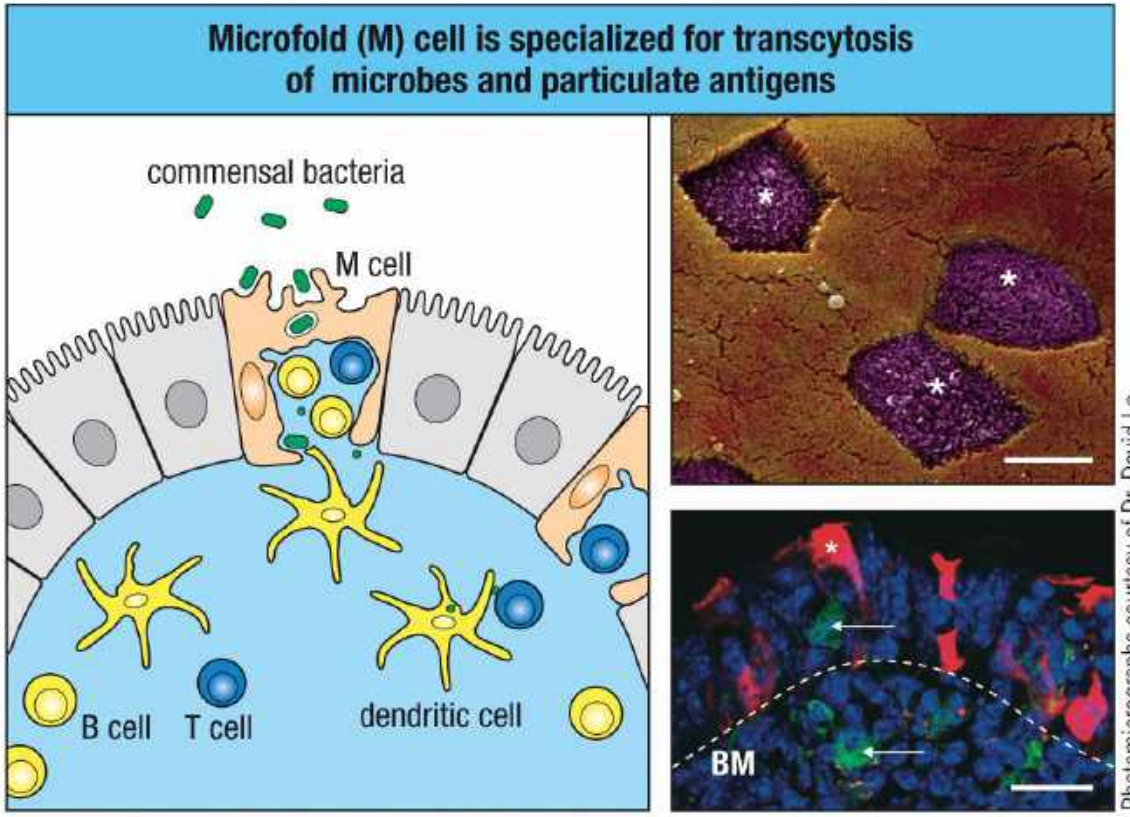
M cells are a specialized enterocyte cell type for uptake of particulate antigens





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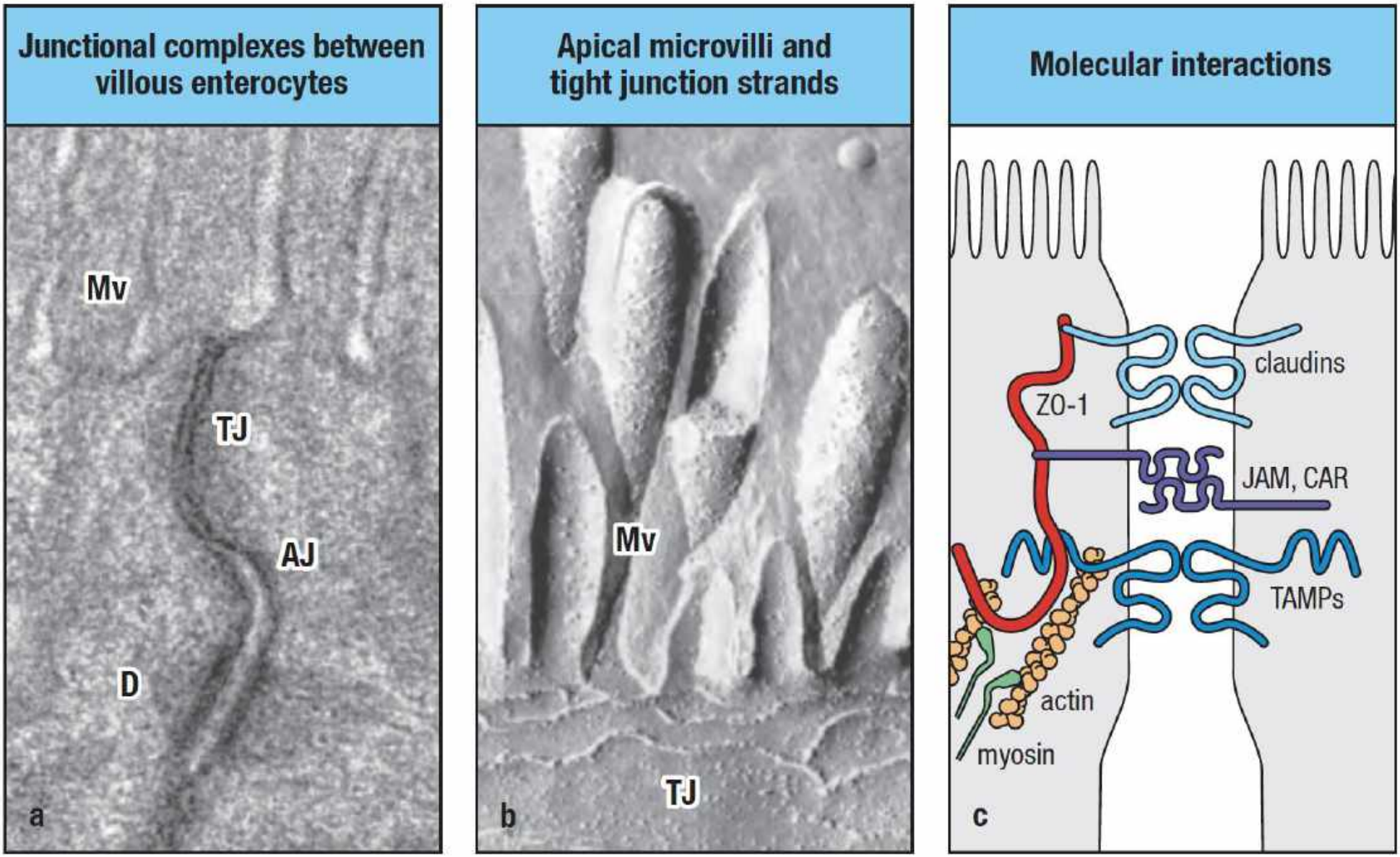
Intercellular junctional complexes between adjacent epithelial cells seal the apical surface



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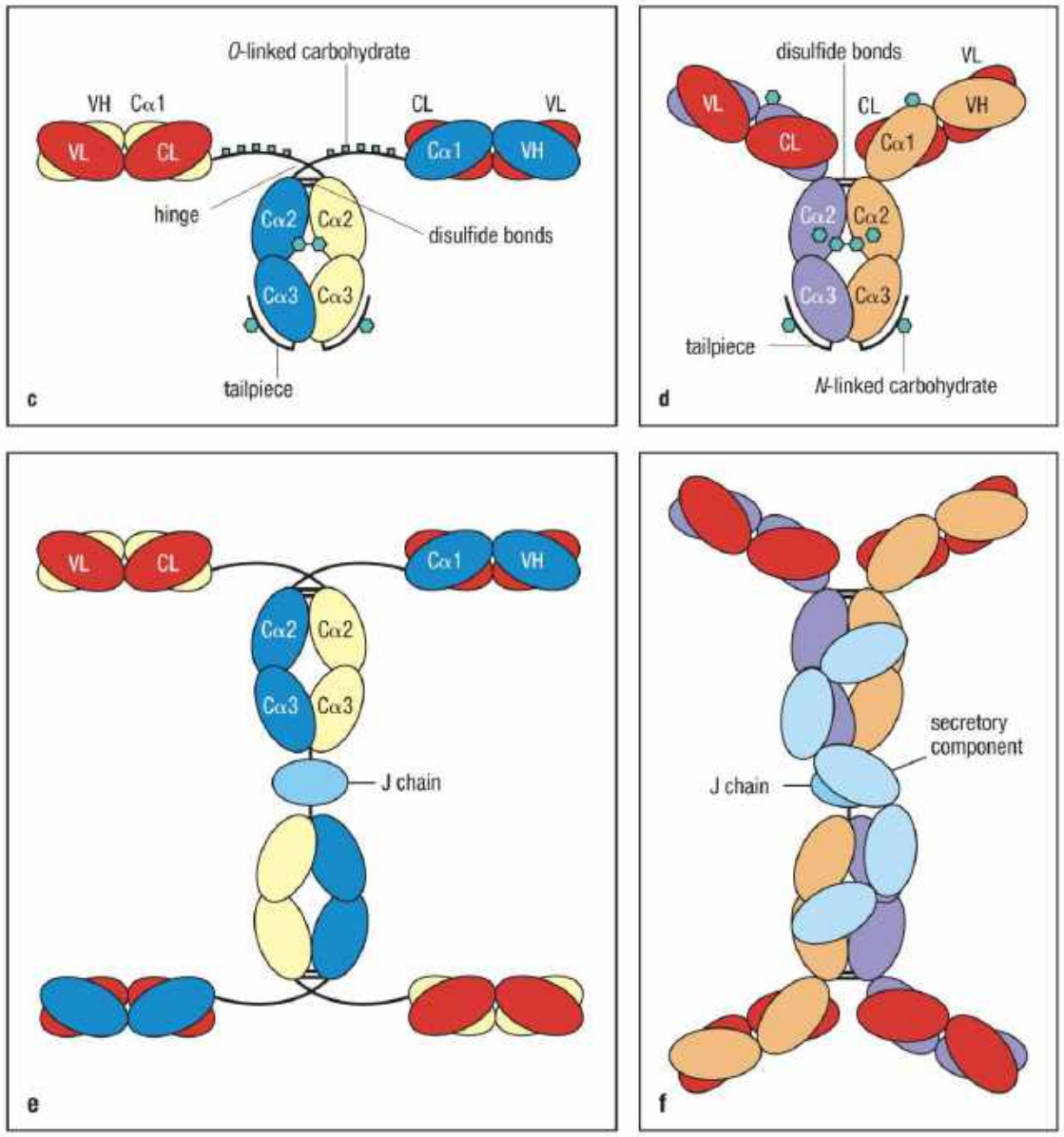
Structure of human IgA



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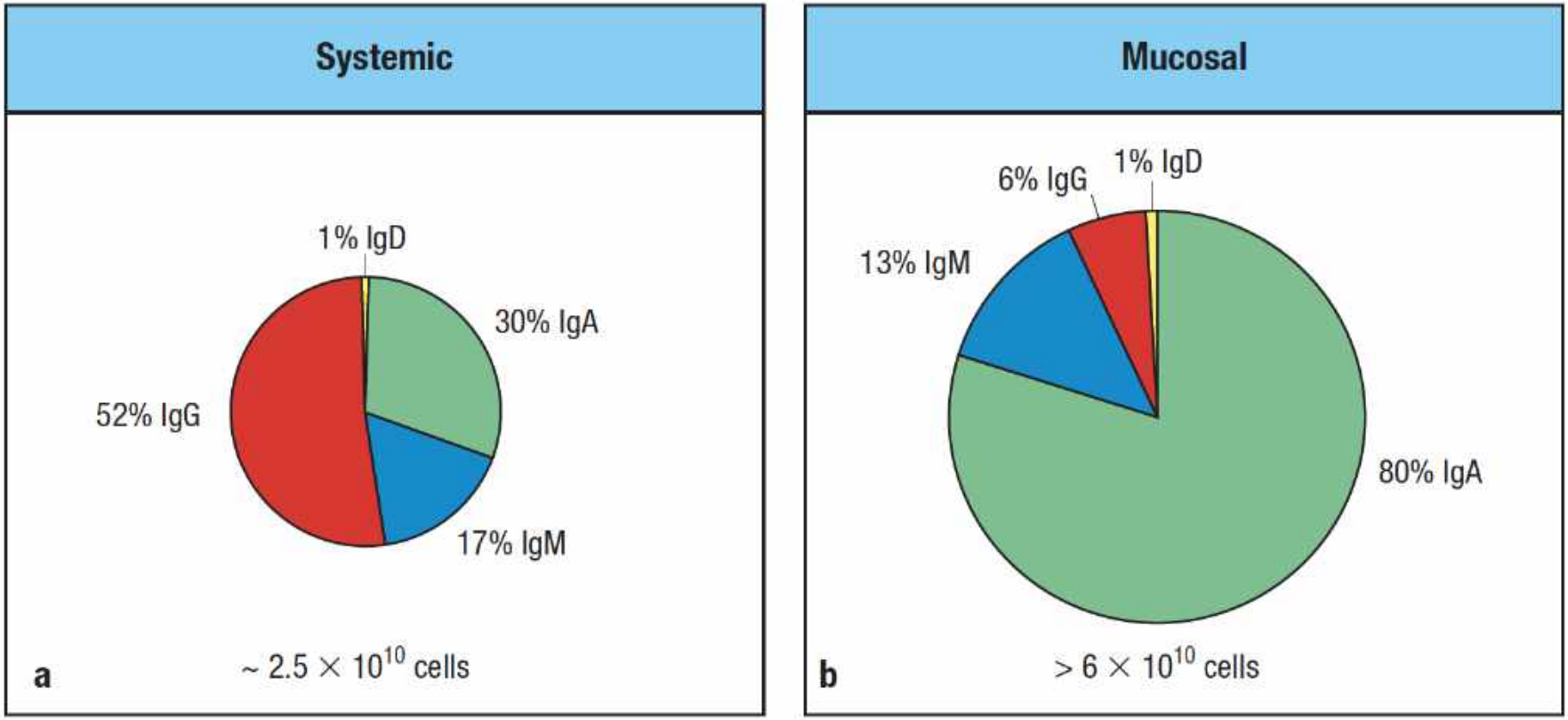
Comparative distribution of IgA-producing cells in systemic and mucosal compartments



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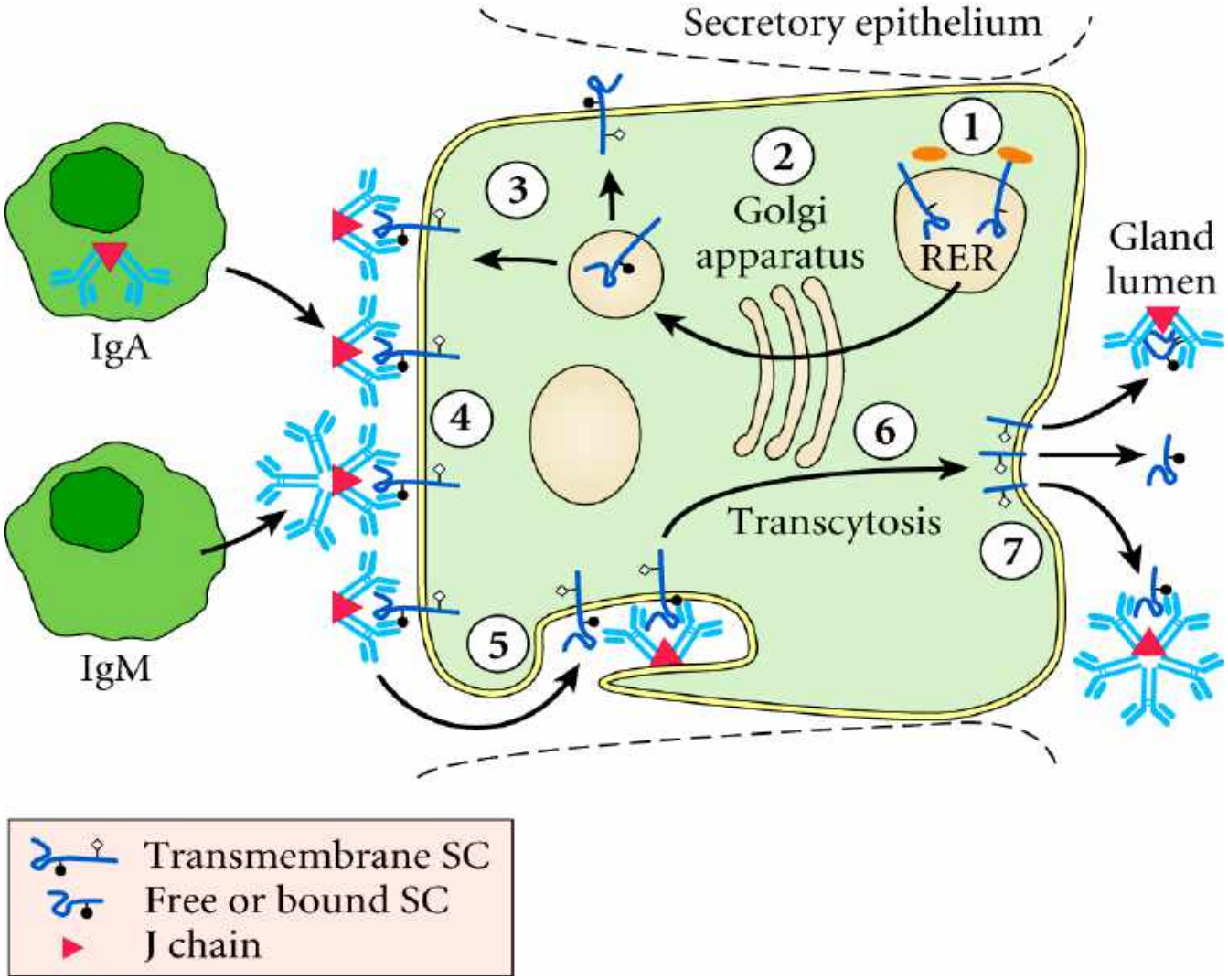
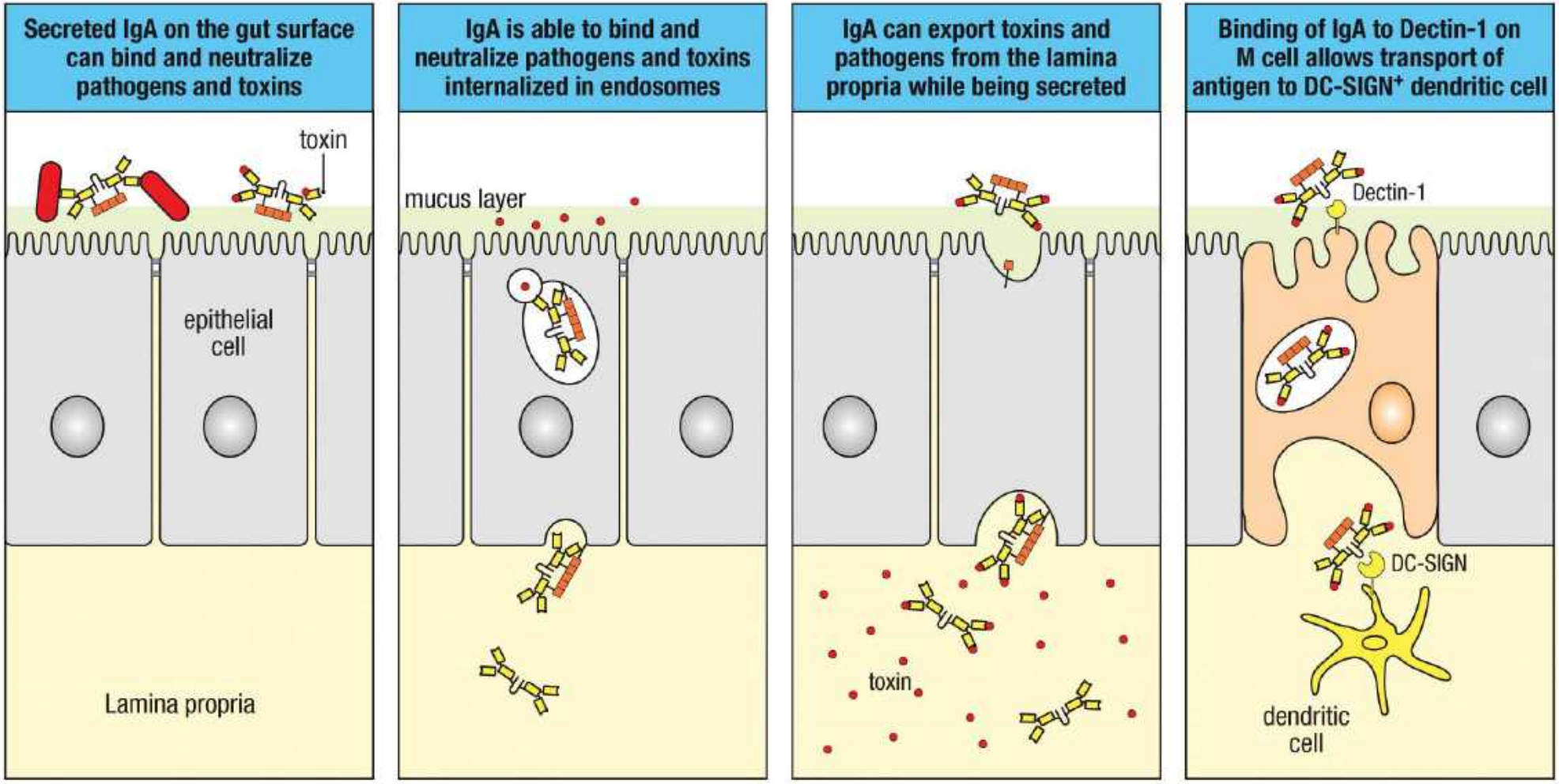
Transcytosis of secretory IgA to the luminal surface



IgA binds to the polymeric Ig receptor (pIgR), also known as transmembrane secretory component (SC) on the basolateral surface and is transported to the apical surface. The portion of the pIgR attached to the Fc region of IgA is then enzymatically cleaved and stays bound to dimeric IgA as SC.

From Gerald Pier, Channing Labs, HMS

Secretory IgA has several functions at epithelial surfaces



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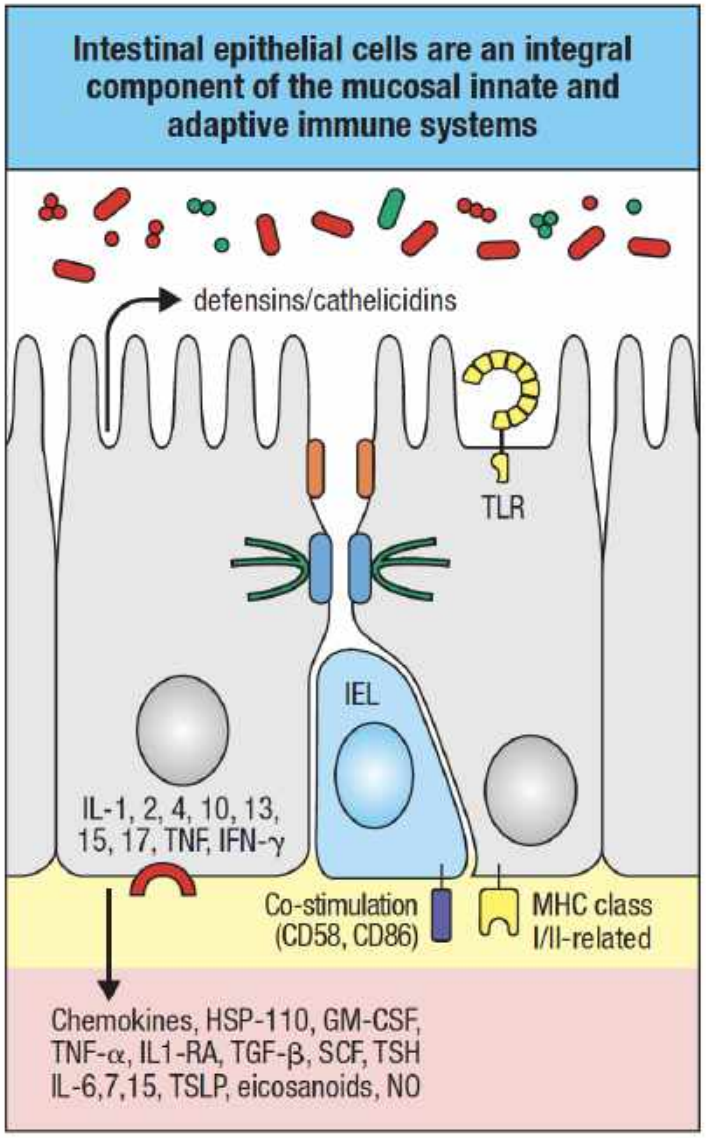
Epithelial cells direct numerous components of the innate and adaptive immune systems at various levels



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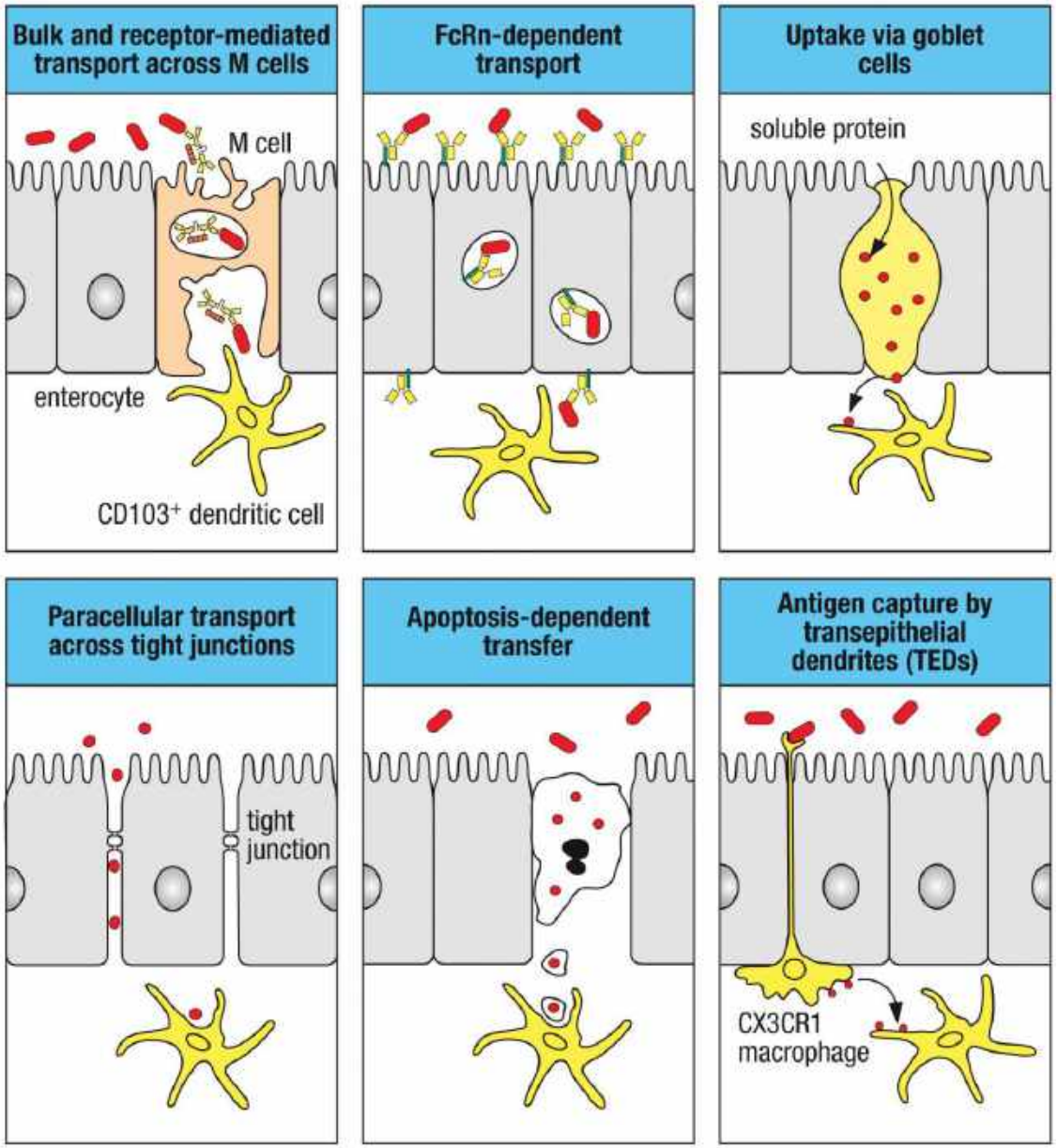
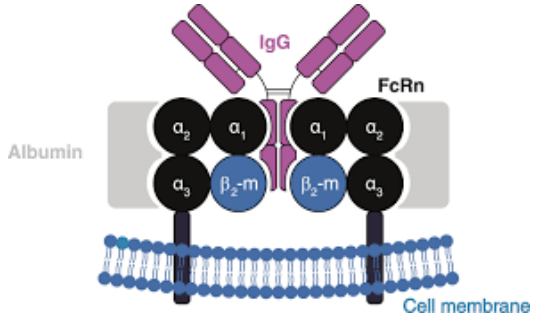
Routes of antigen uptake in the intestine





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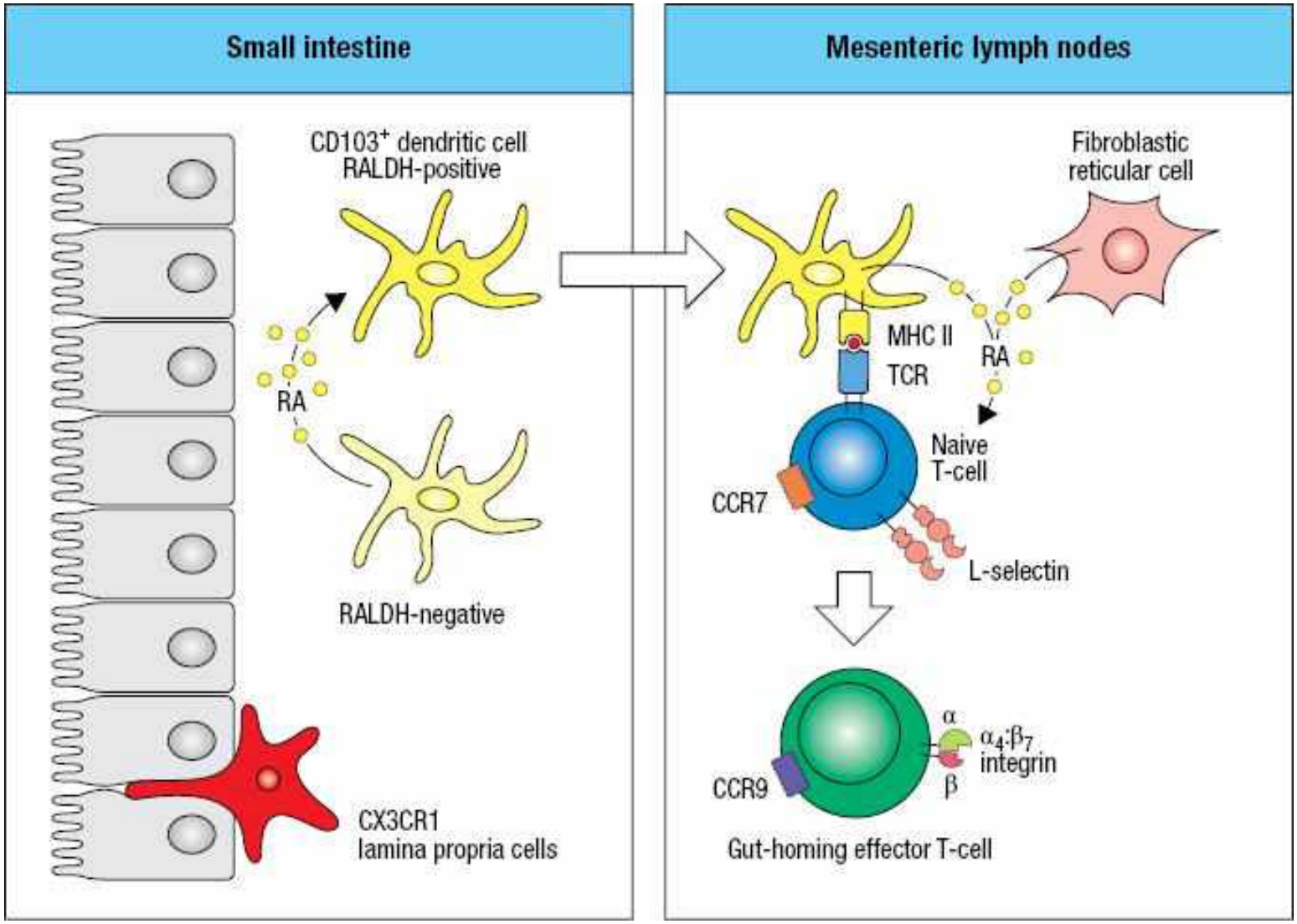
Small intestinal-derived migratory DC induce the expression of gut homing molecules

Retinoic Acid is derived from dietary vitamin A



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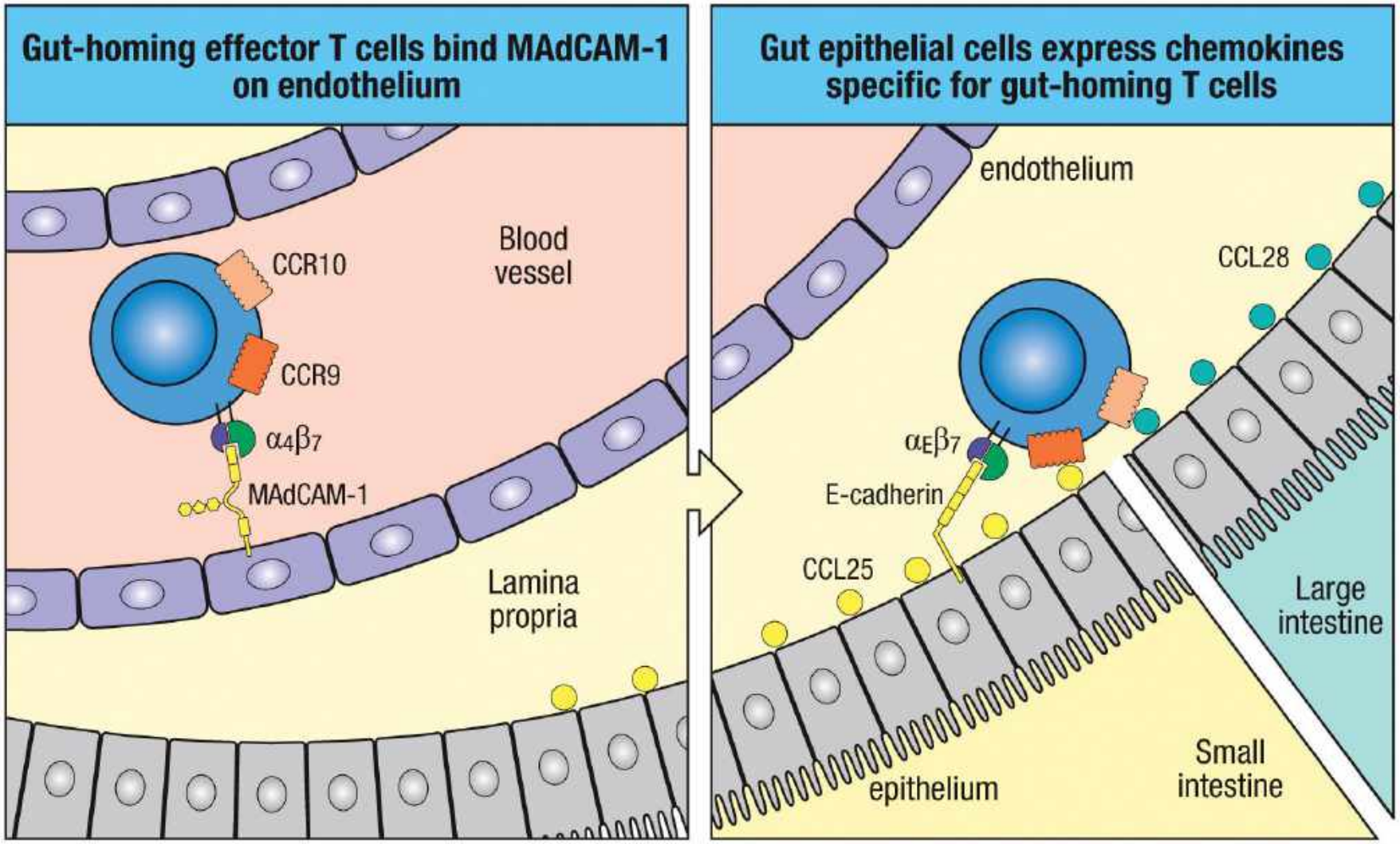
Molecular control of intestine specific homing of lymphocytes



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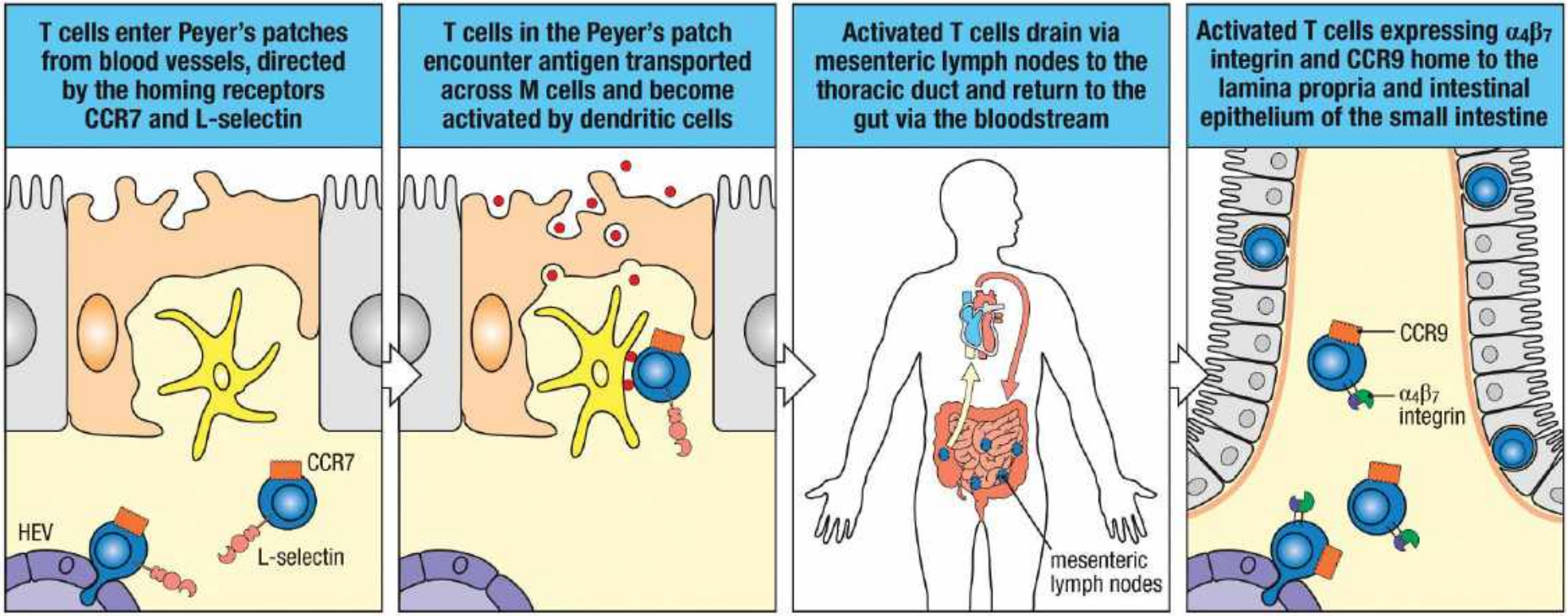
The mucosal immune system contains large numbers of effector lymphocytes even in the absence of disease



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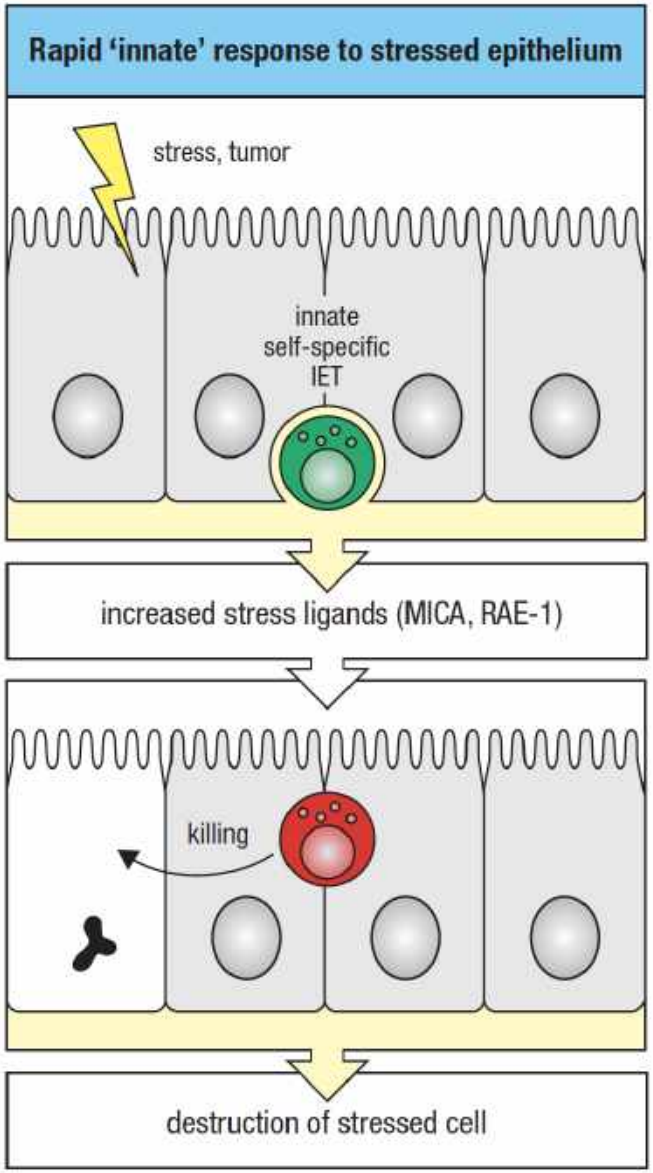
Memory T effector cells accumulate in the intestinal lamina propria, enabling the GALT to respond quickly and effectively to challenge with enteric pathogens.

Antigen challenge redistributes memory T effector cells to "man the barrier" for strategic mucosal defense.

IEL act as sentinels to detect and repair damaged epithelium



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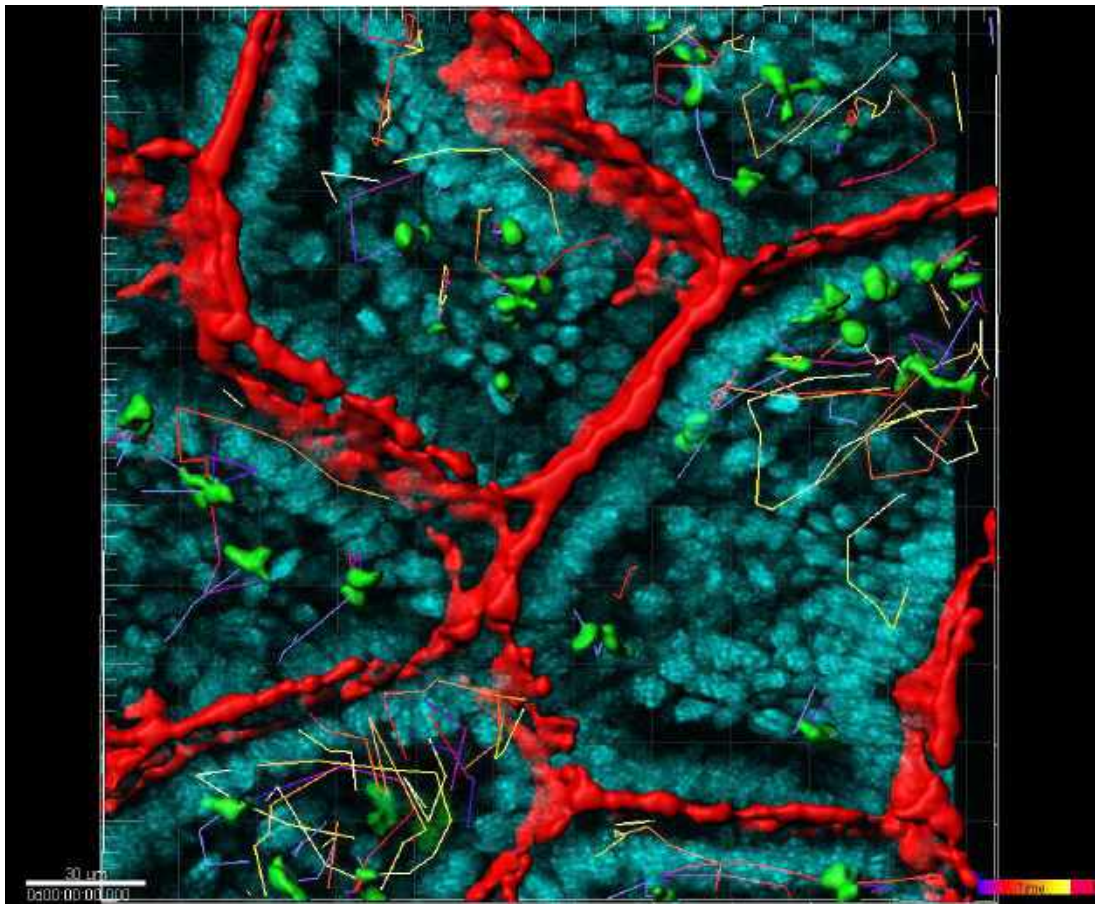
lumen γδ T cell nuclei



Edelblum et al PNAS 2012, 109: 7097

How does the gut-associated lymphoid tissue distinguish innocuous dietary antigens and commensal bacteria from pathogenic microbes

….and mount an appropriate response to each?

	Protective immunity	Mucosal tolerance
Antigen	Invasive bacteria, viruses, toxins	Food proteins; commensal bacteria
Primary Ig production	Intestinal IgA and IgG Specific Ab present in serum	Some local IgA 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

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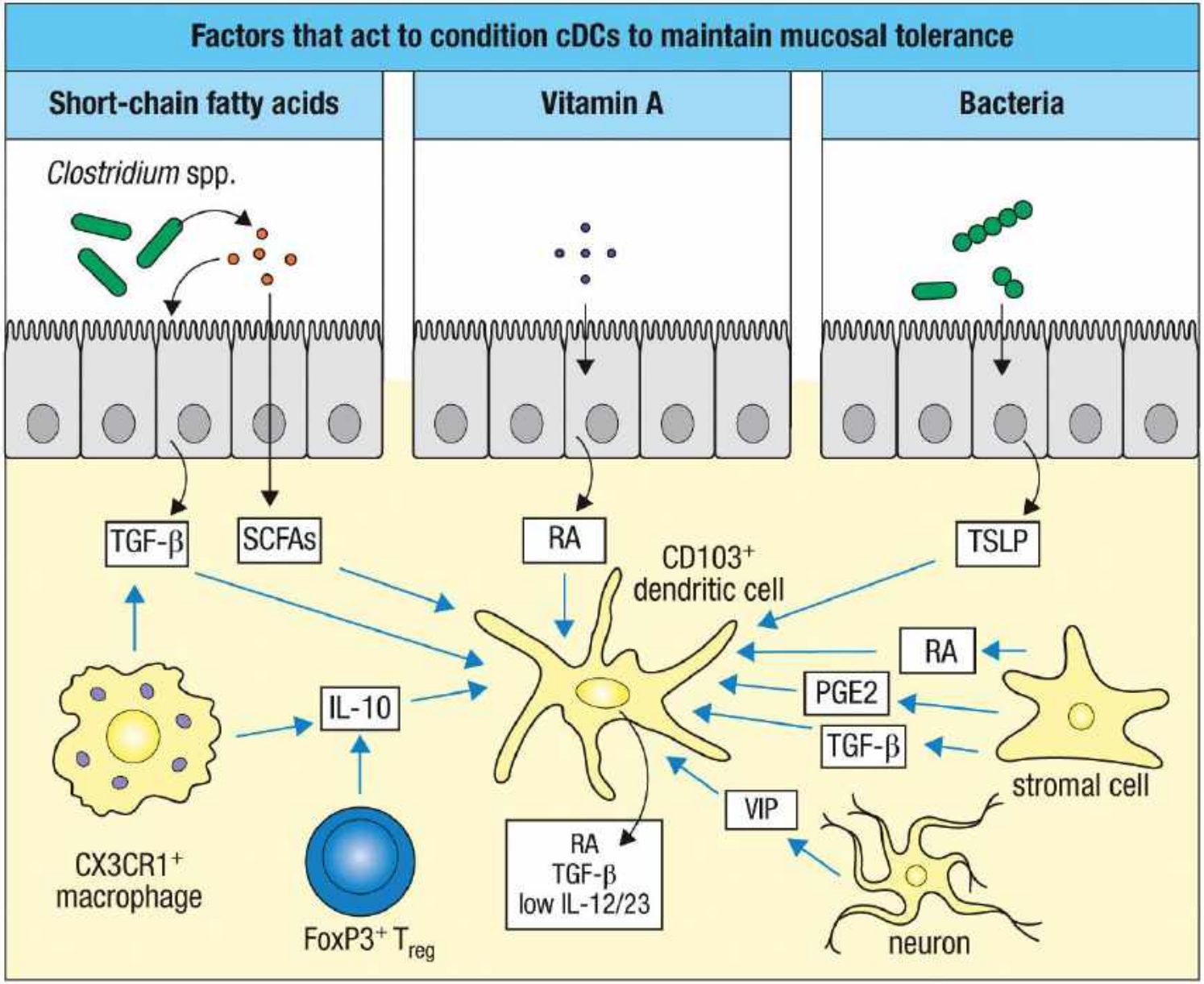

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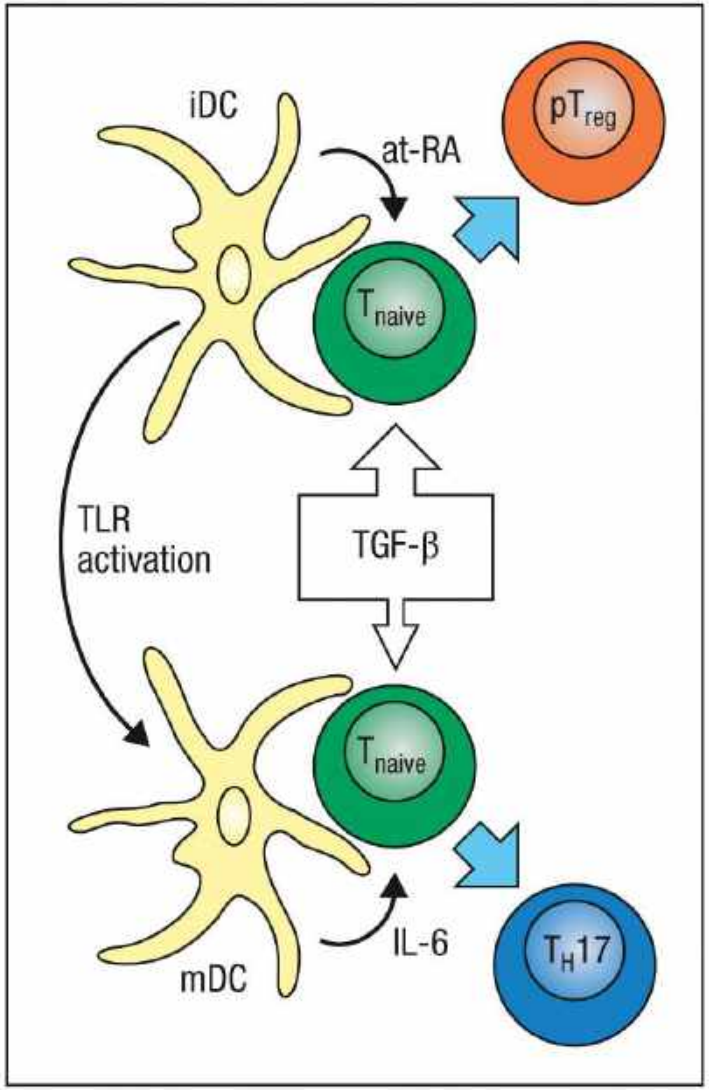
A shared requirement for TGF-β in the differentiation of pTreg and Th17 provides a development link that reflects their complementary roles in promoting mutualism with the microbiota



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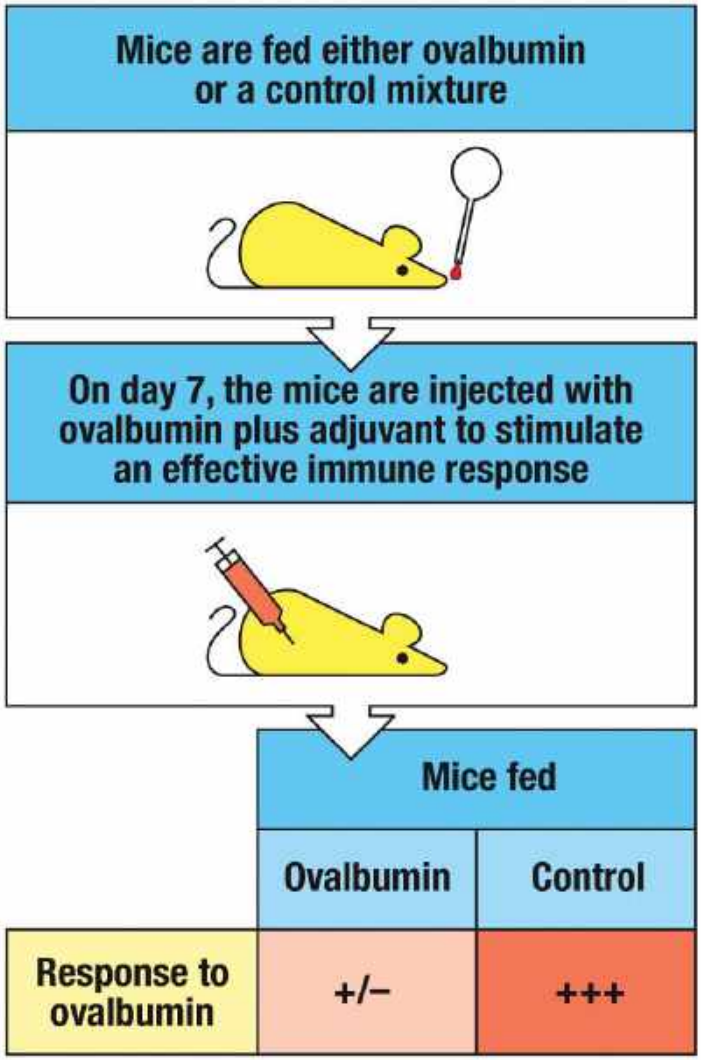
Oral tolerance to dietary antigens can be modeled experimentally



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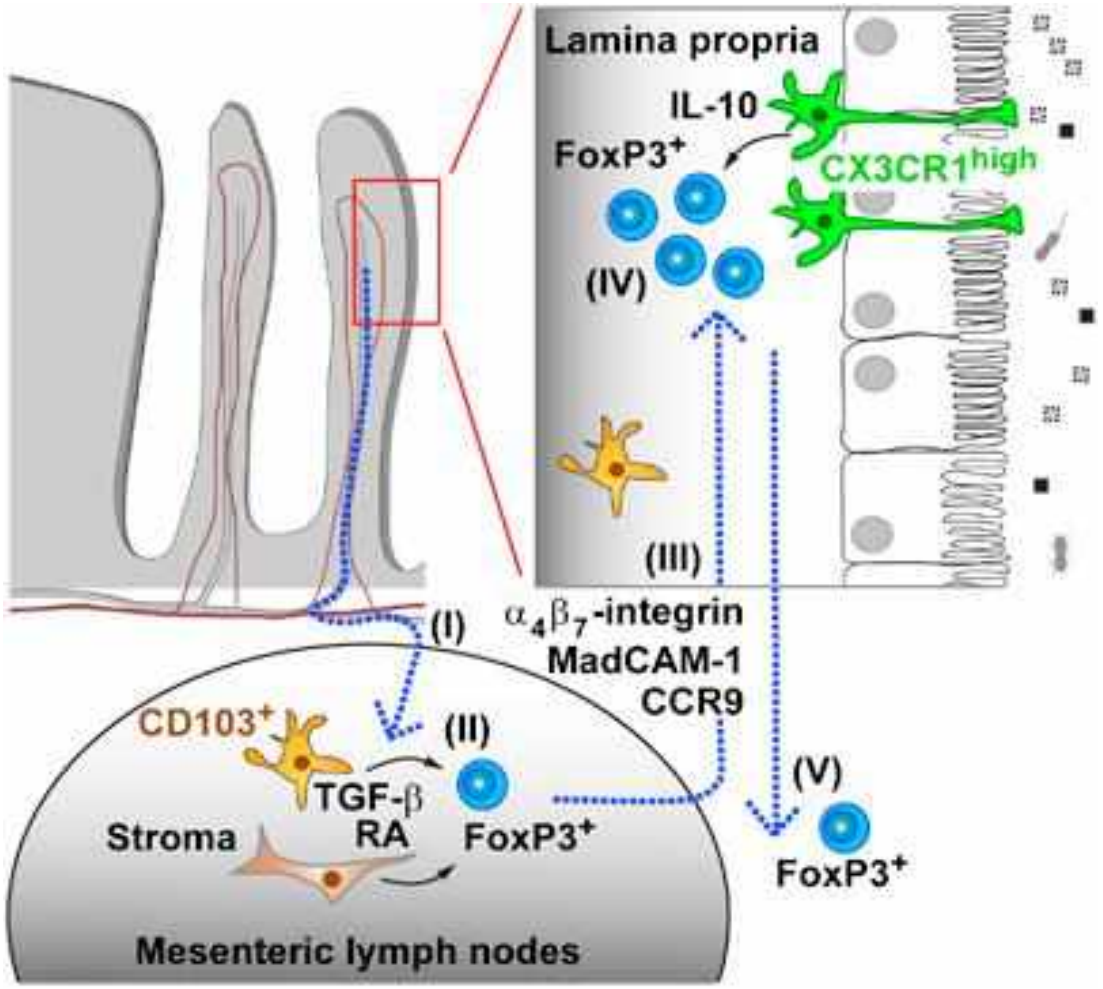
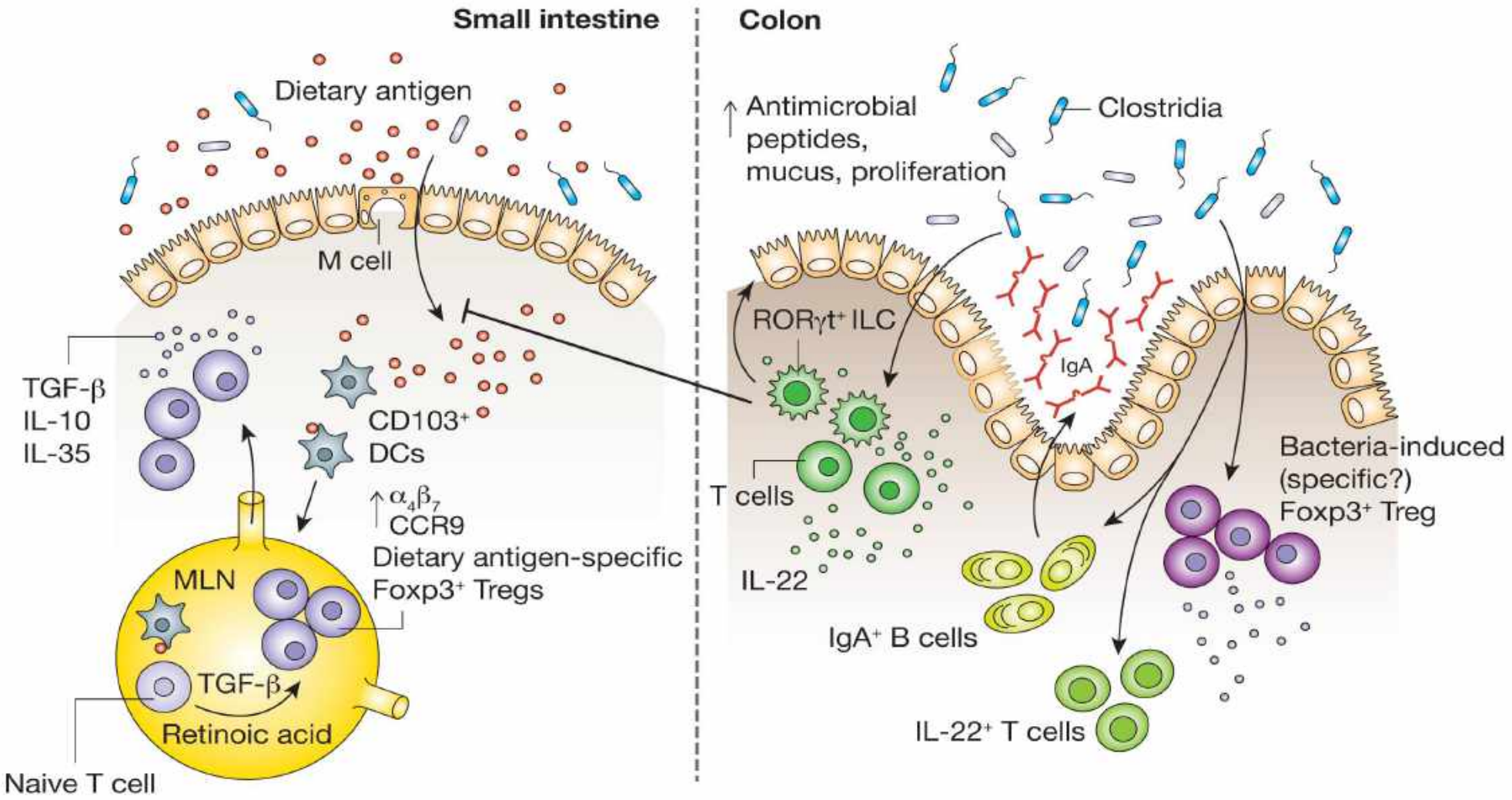
A multistep model of oral tolerance to dietary antigens



I. Antigen loaded $CD103^+$ DC migrate to MLN
II. RA produced by DC and stromal cells in MLN induce homing receptors and favor **TGF-β** dependent conversion of $Foxp3^+$ Tregs
III. Committed Tregs home back to LP
IV. Tregs expand under the influence of IL-10 produced by $CX3CR1^{hi}$ macrophages
V. Some Tregs exit mucosa via lymph or blood-stream to promote systemic tolerance

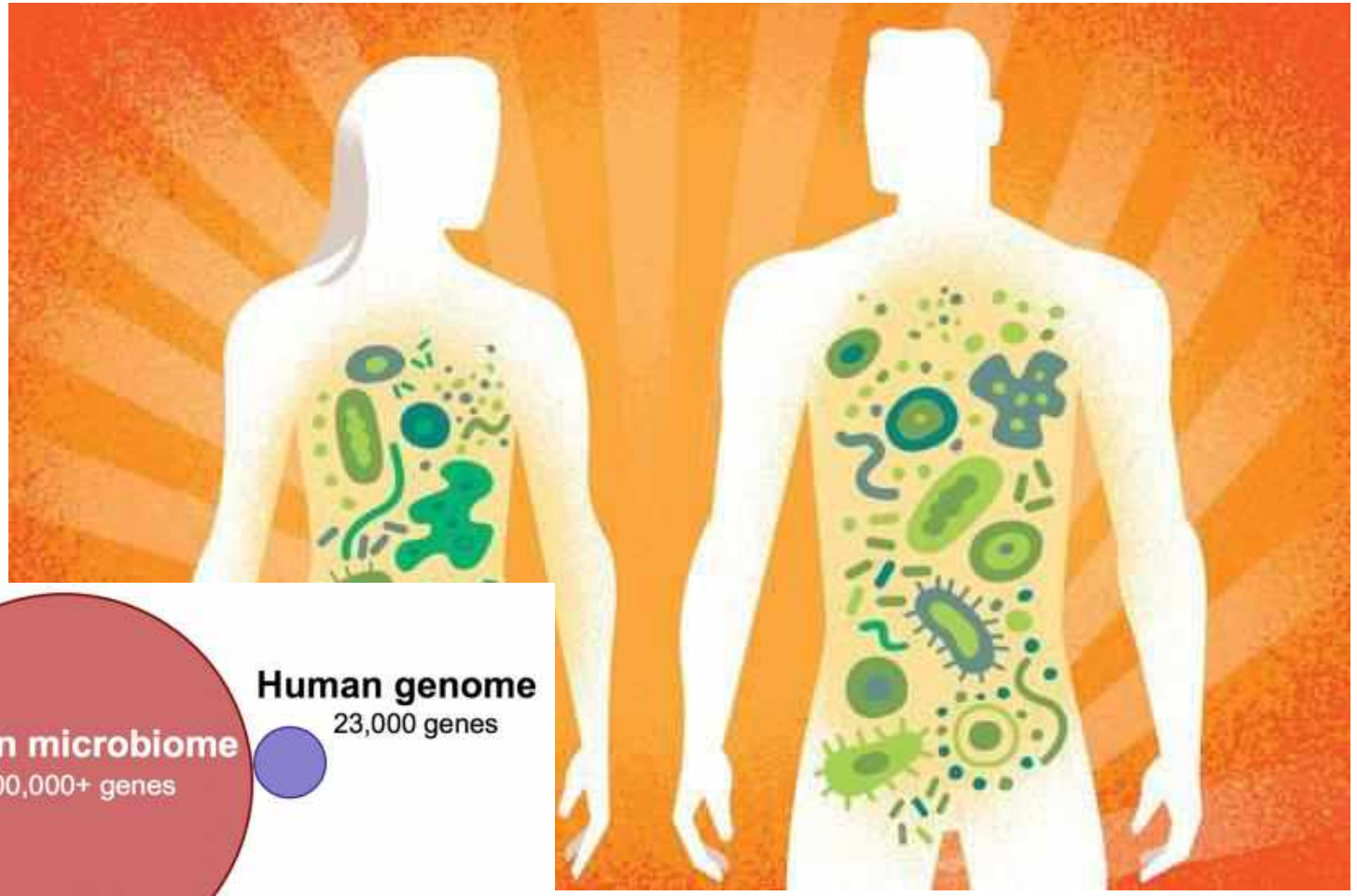
Pabst and Mowat, *Mucosal Immunology* 2012, 5: 232

Tolerance to dietary antigen requires the induction of a bacteria-induced barrier protective response



Stefka, Feehley et al *PNAS* 2014, 111; 13145

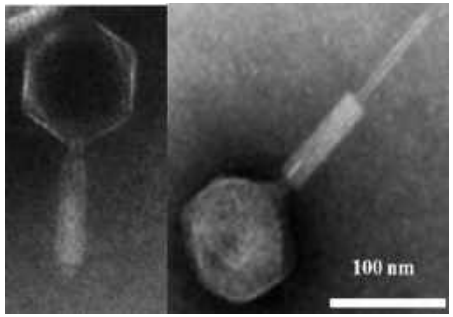
Microbes populate our skin and mucosal surfaces and profoundly influence our health



The microbiome is defined as the collective genomes of the microbes that live on the skin and mucosal surfaces.

bacteria

virus



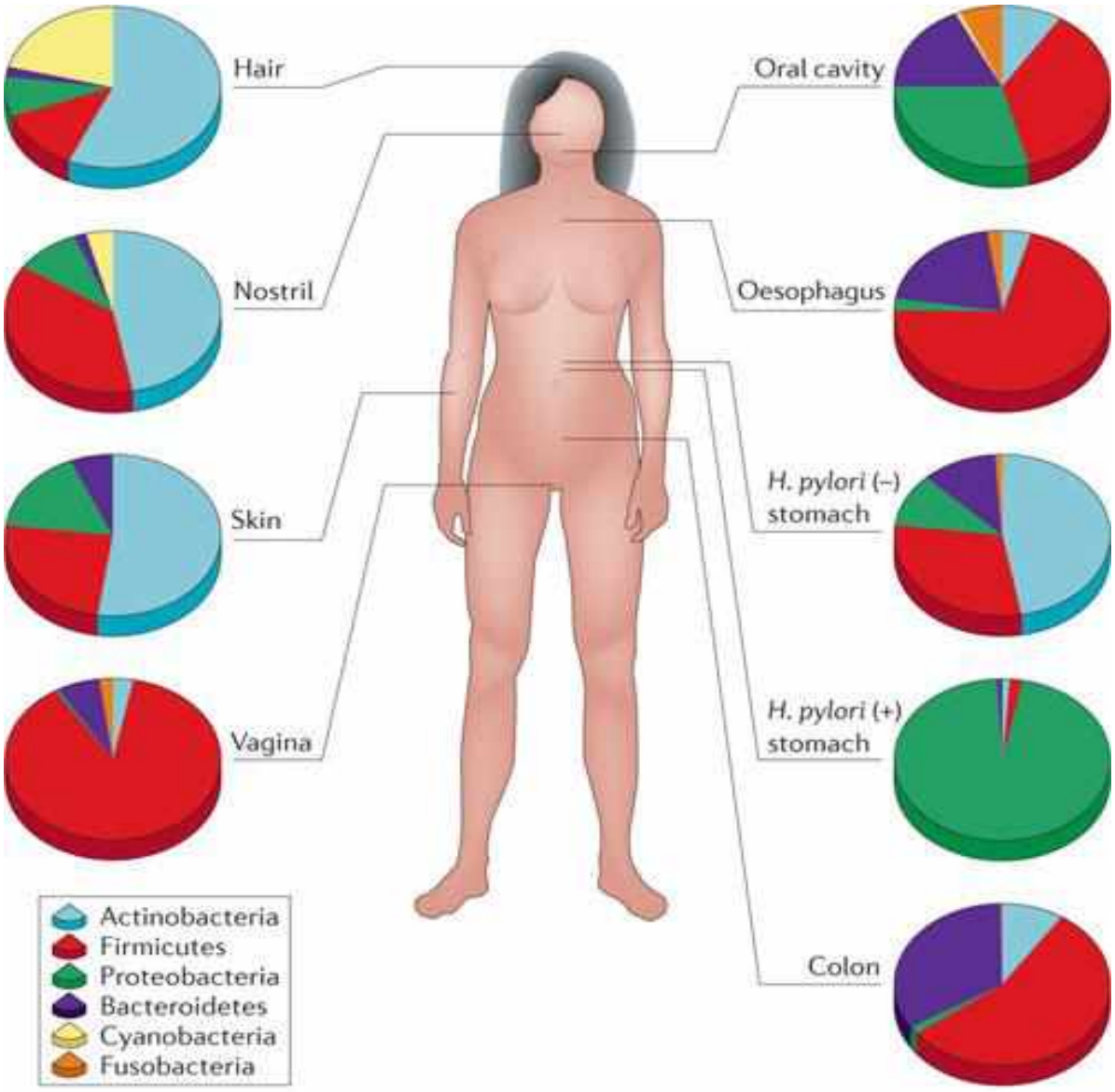
bacteriophage

protozoa

fungus

helminths

The composition of the microbiota varies by anatomical site

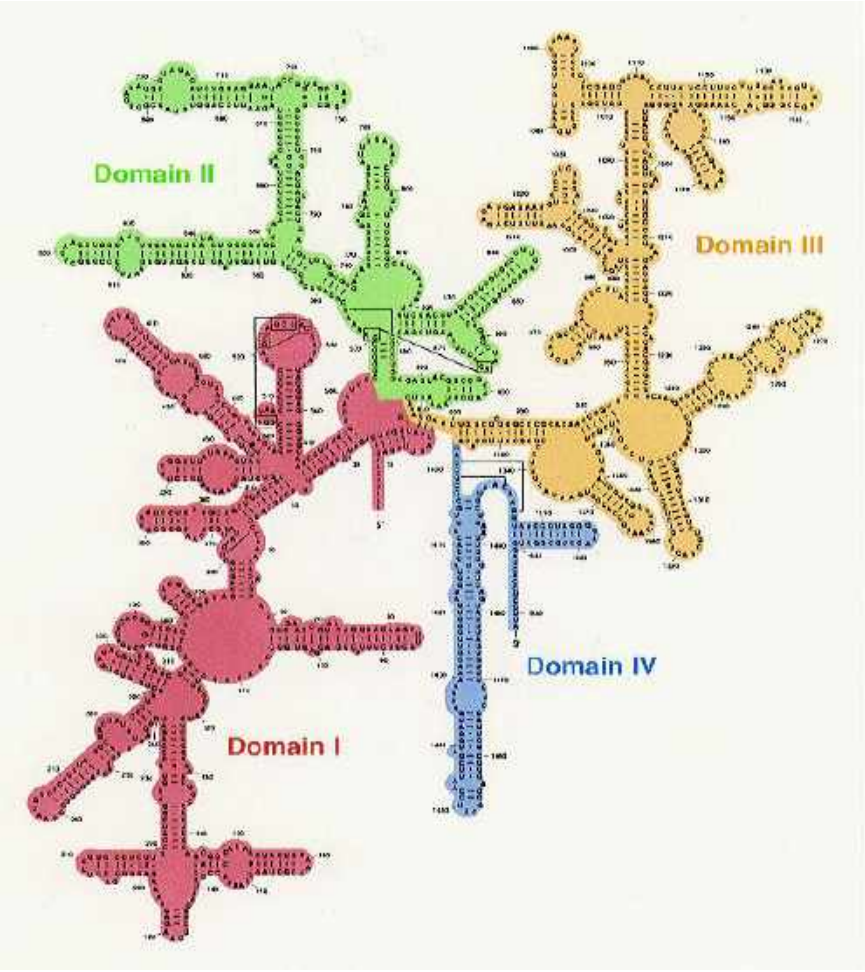


Cho, I. & Blaser, M.J. *Nat. Rev. Genetics* 2012; 13: 260

Culture independent methods of analysis have transformed our understanding of the composition of the microbiome

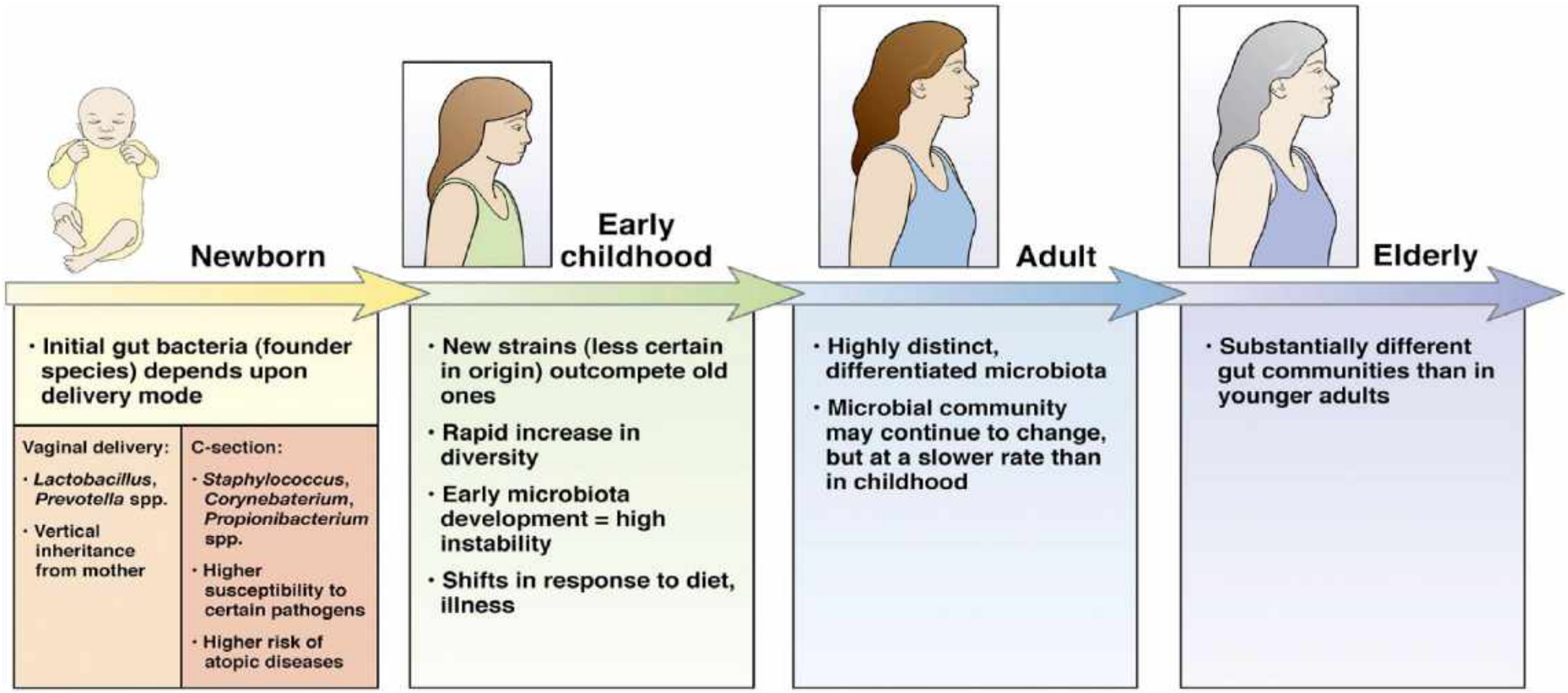
The 16S rRNA gene is highly conserved among bacterial species.

"Universal" primers target conserved regions of this gene and allow for amplification and sequencing of species-specific hypervariable regions for bacterial classification.



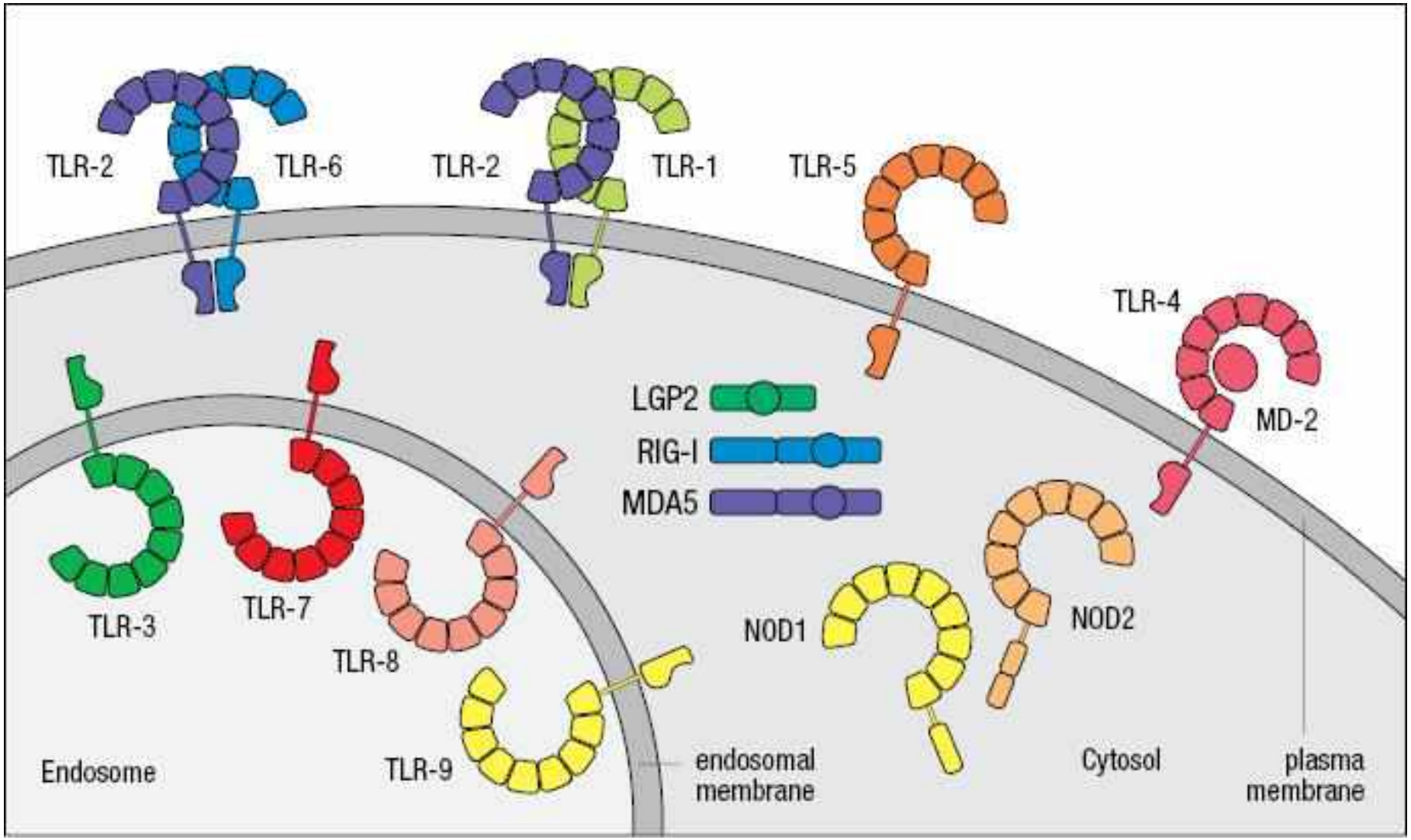
Structure of 16S ribosomal RNA

The gastrointestinal microbiota changes throughout life



Dominguez-Bello, MG et al, *Gastroenterology* 2011, 140:1713

Pathogenic and commensal microbes share the same PAMPS (pathogen associated molecular patterns)



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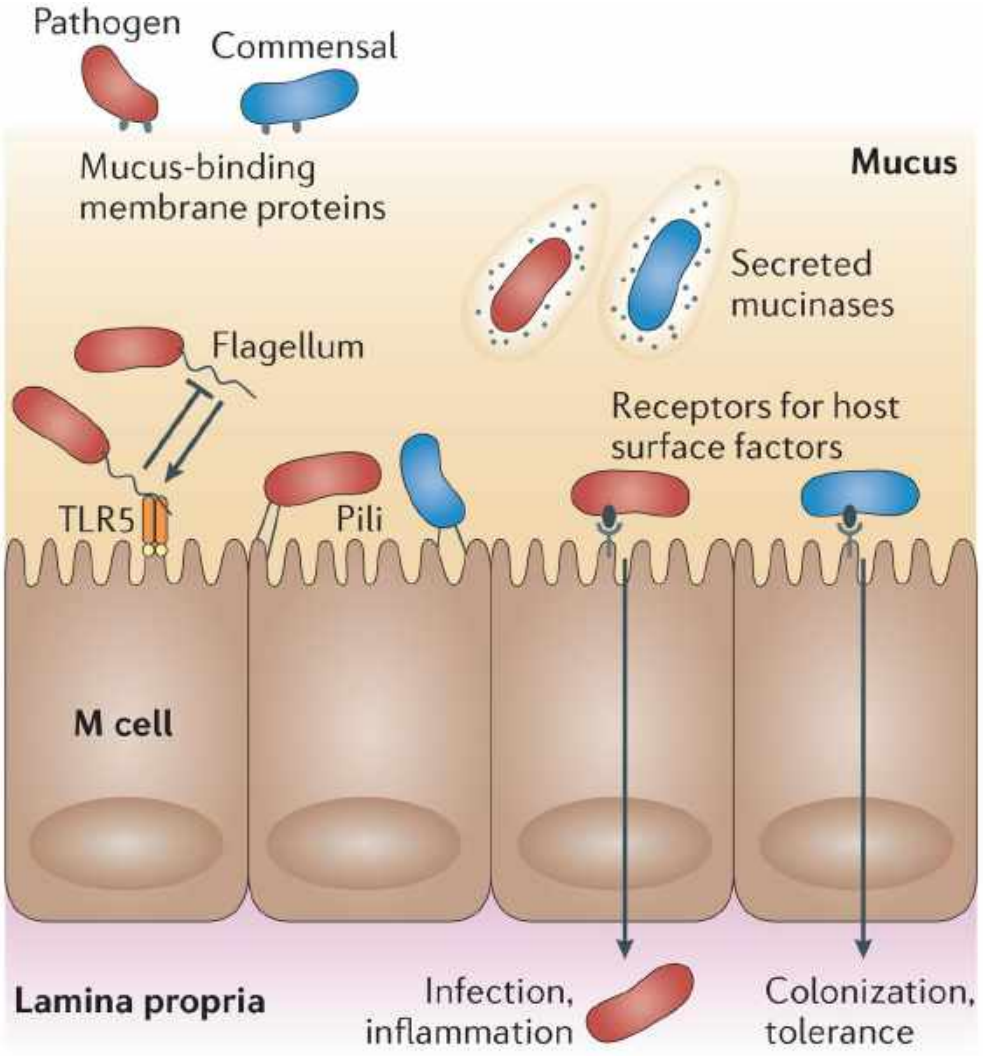
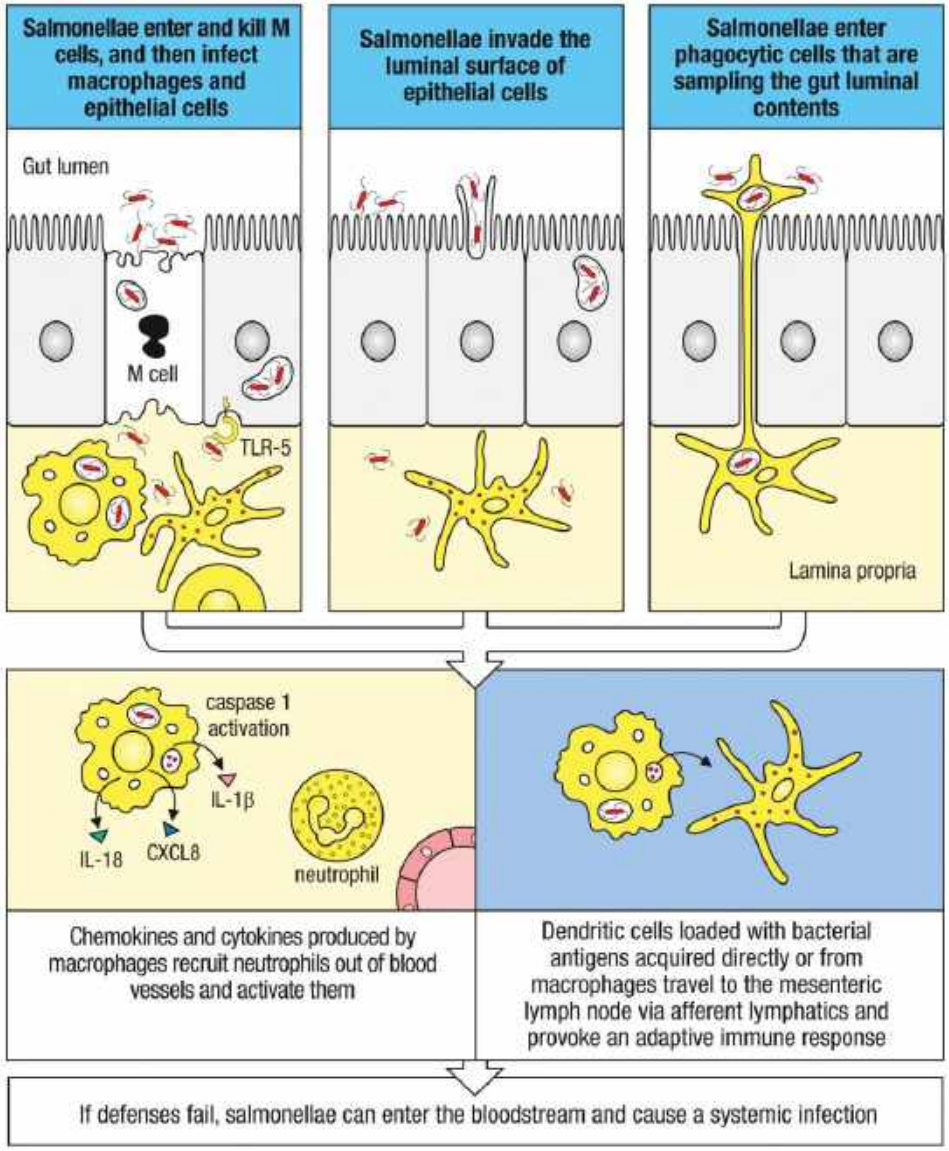
Both pathogens and commensals have access to the gut epithelium



Donaldson, G.P. et al *Nat. Rev. Micro*. 2016; 14: 20

Enteric pathogens cause a local inflammatory response and the development of protective immunity



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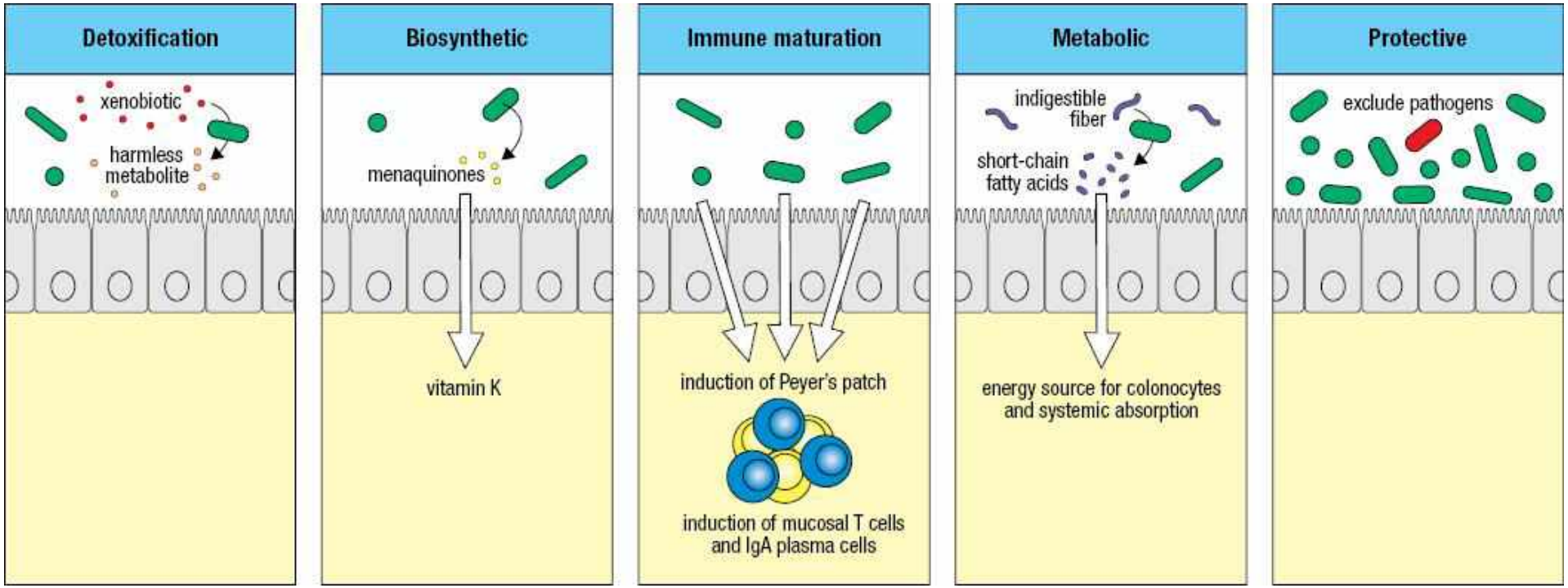
We exist in a dynamic interrelationship with our commensal microbiome!

Healthy individuals “tolerate” their intestinal microbiota but are also constantly receiving signals from the microbiome that have a profound impact on both systemic and mucosal immunity.

The commensal microbiota confers many health benefits to the host



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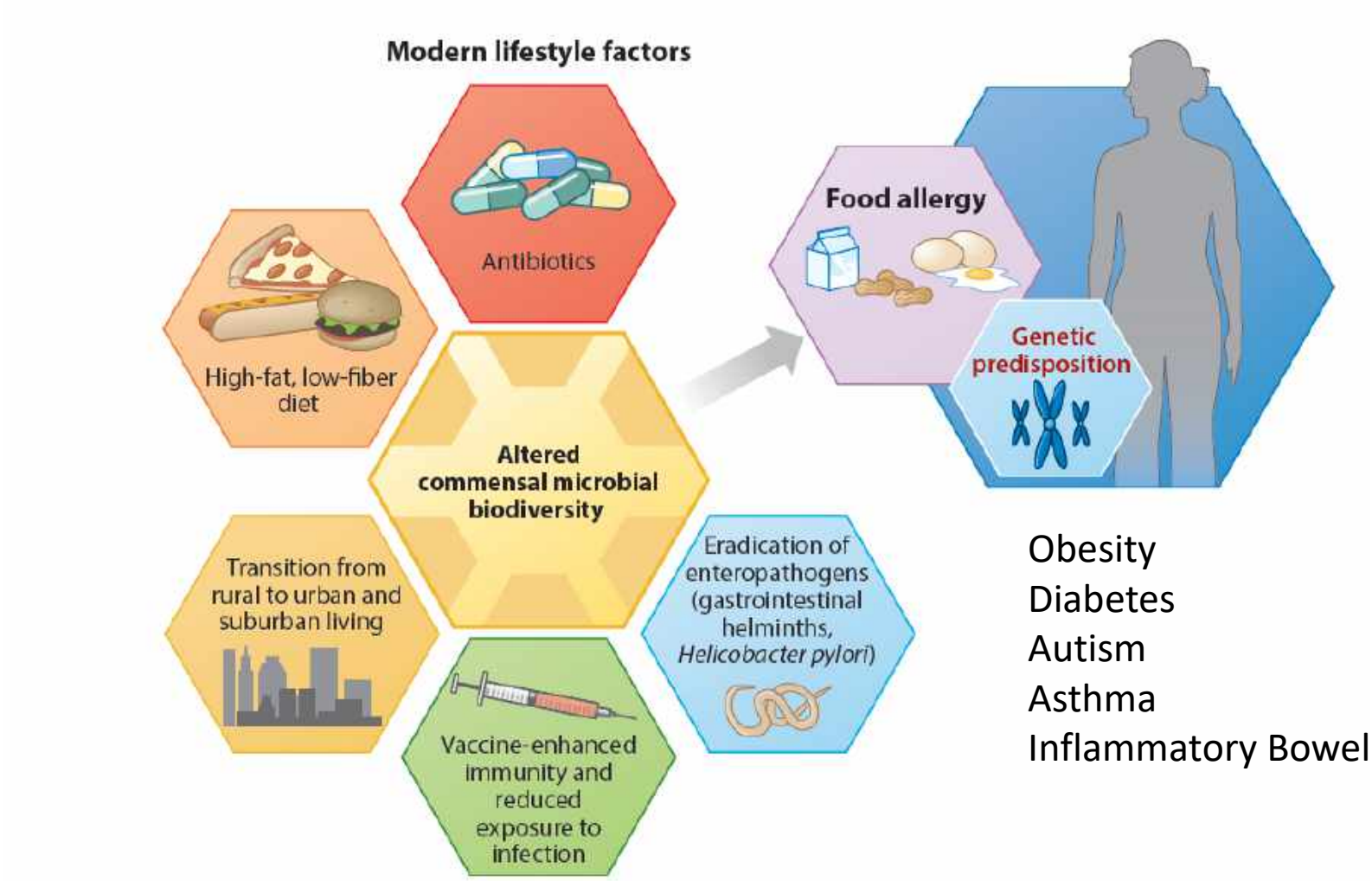
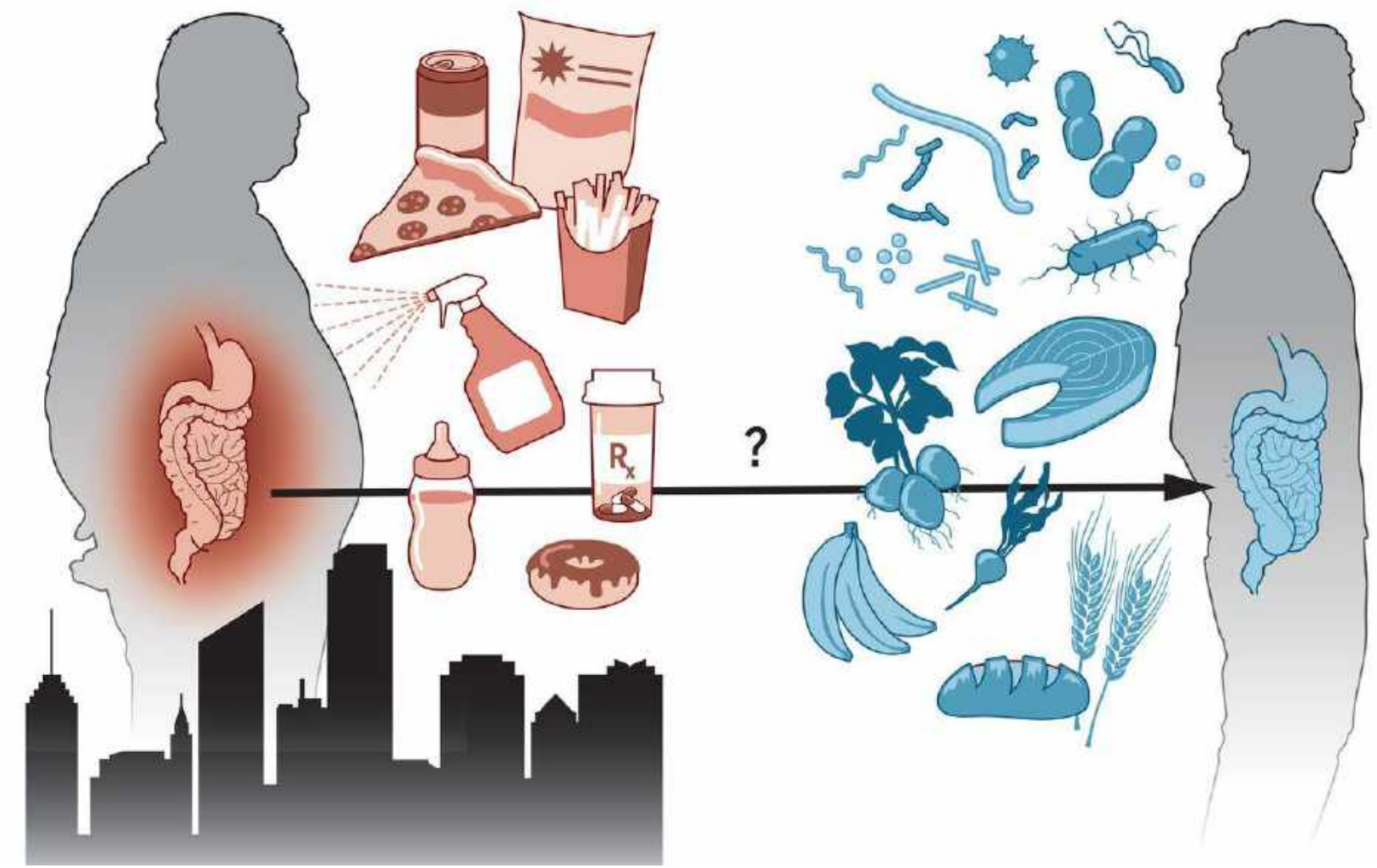
21st century lifestyle factors alter commensal microbial diversity and are driving a dramatic increase in non-communicable chronic disease (NCCD)



Obesity
Diabetes
Autism
Asthma
Inflammatory Bowel Disease

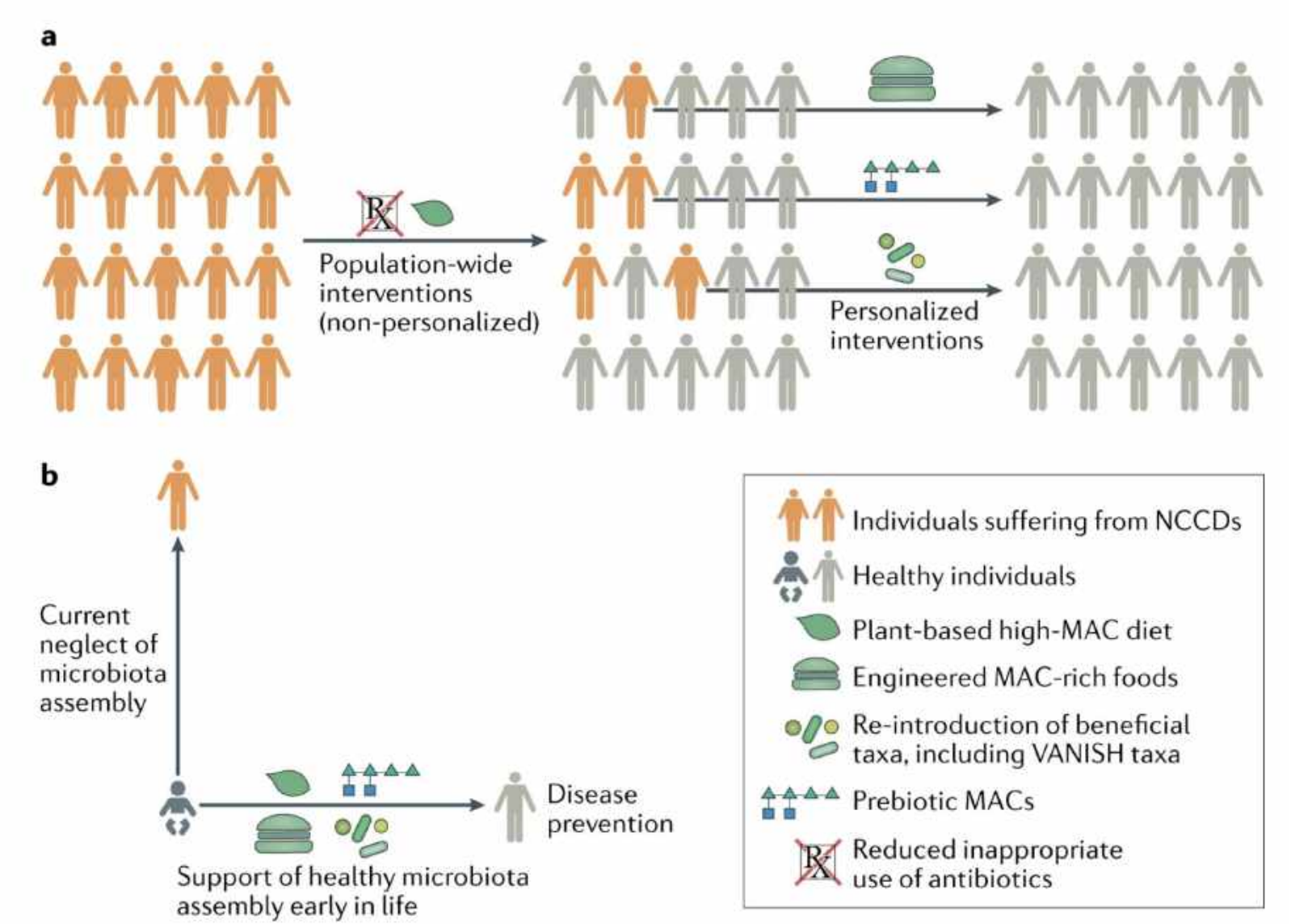
Iweala, O. and Nagler, C. *Ann. Rev. Immunol.* 2019, 37: 377

Most humans on earth consumed largely plant material for greater than 200,000 years; industrialization has changed the human gut microbiota



Sonnenburg, J.L. & Sonnenburg, E.D. *Science* 2019; 366:eaaw9255

Both population-wide and personalized strategies are needed to manipulate the gut microbiota to improve health



Sonnenburg & Sonnenburg *Nat. Rev. Micro*. 2019; 17: 383

Mucosal Vaccines

Mucosal (oral/nasal) vaccines are the preferred method for vaccination in the developing world; many don't require cold chain.

Mucosal vaccines are easily administered (needle-free), non-invasive and cost-effective.

Only mucosal vaccination elicits a protective secretory IgA response.

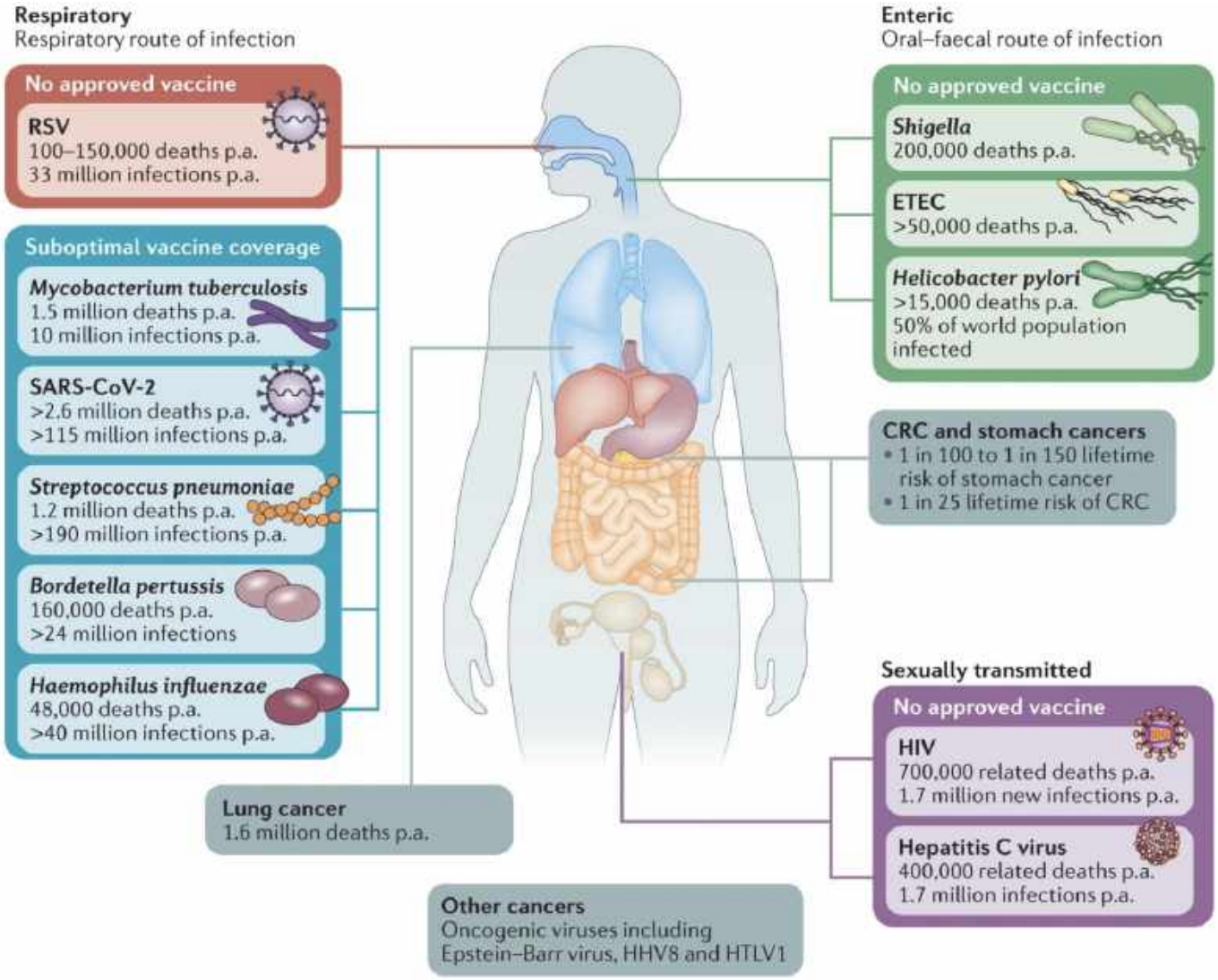
unicef

Eradicating polio

We are closer than ever to ending polio.

Burden of mucosal diseases with unmet vaccine needs

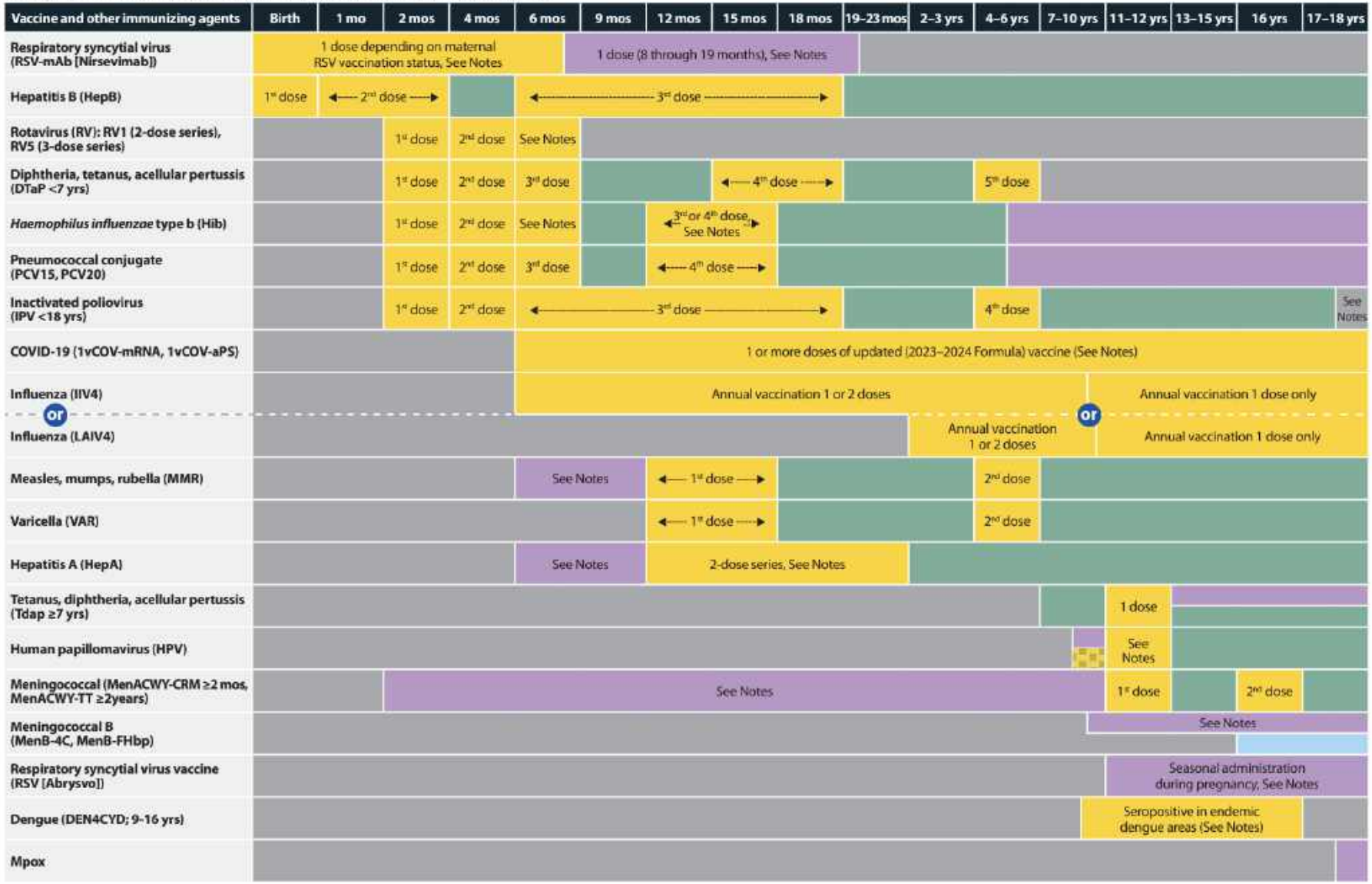
p.a., per annum



Lavelle, E.C. & R. W. Ward *Nat. Rev. Immunol.* 2022; 22: 236

Table 1 Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars.
To determine minimum intervals between doses, see the catch-up schedule (Table 2).



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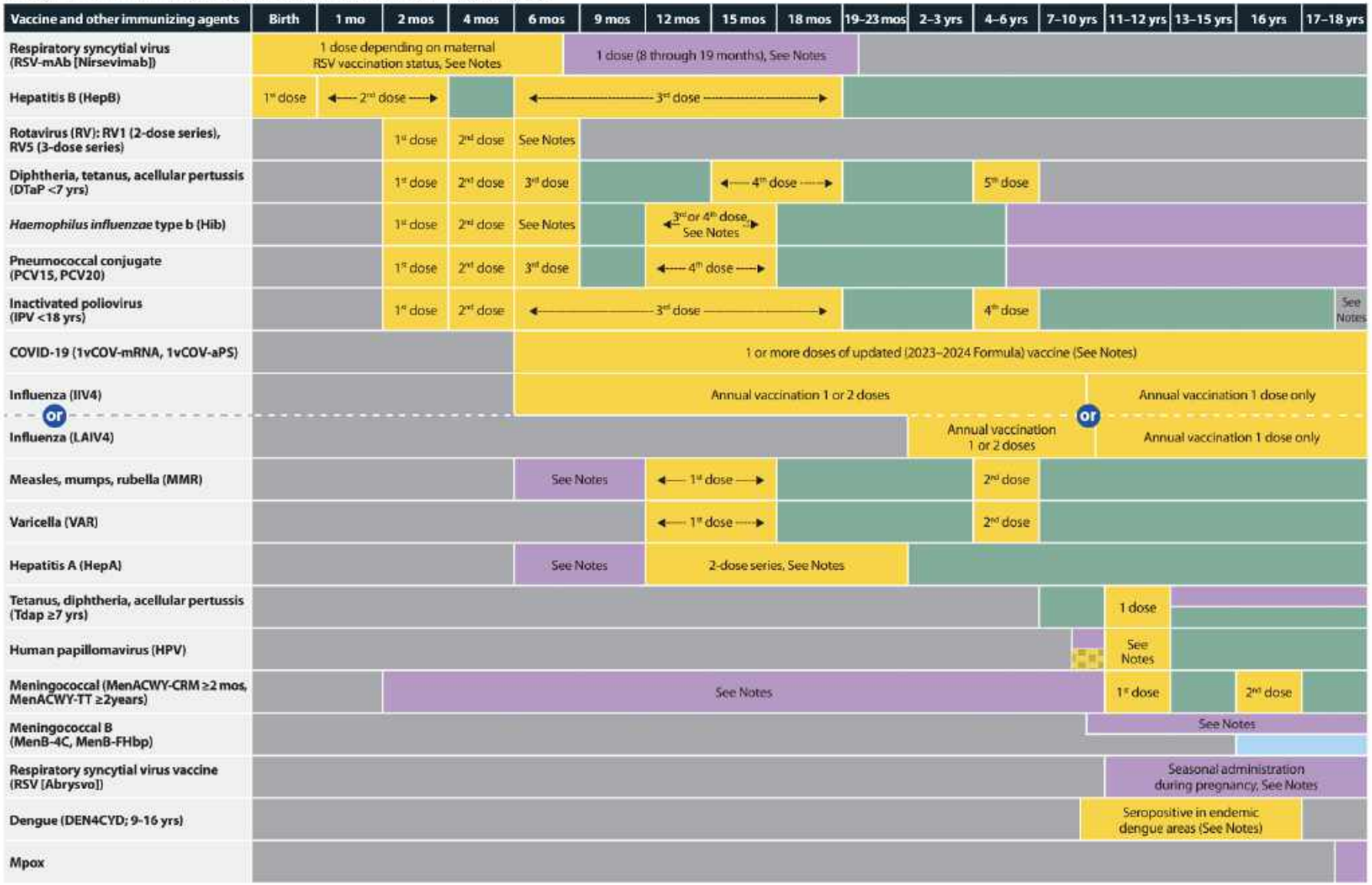
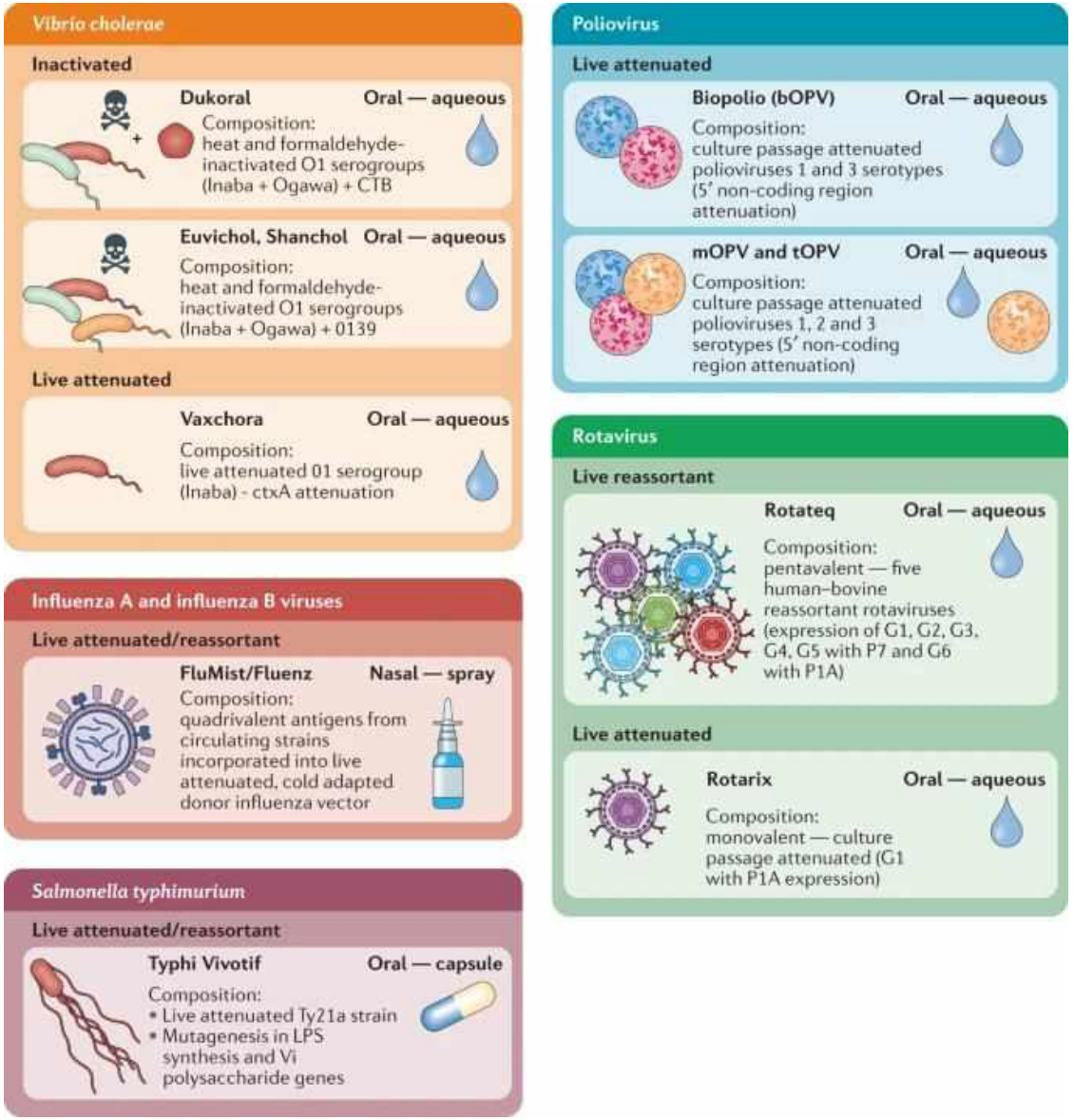


Licensed Mucosal Vaccines



All are live-attenuated or inactivated whole cell preparations

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Mucosal adjuvants

Adjuvants that are effective parenterally are generally toxic or unstable when given orally.

The tendency of the GALT to induce tolerance to soluble antigens has made identification of effective mucosal adjuvants difficult.

Microbial products such as cholera toxin, *E. coli* heat-labile toxin and oligodeoxy-nucleotides containing a bacterial CpG motif can act as effective mucosal adjuvants and induce both mucosal and systemic immune responses to co-administered protein antigens.

Questions?

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