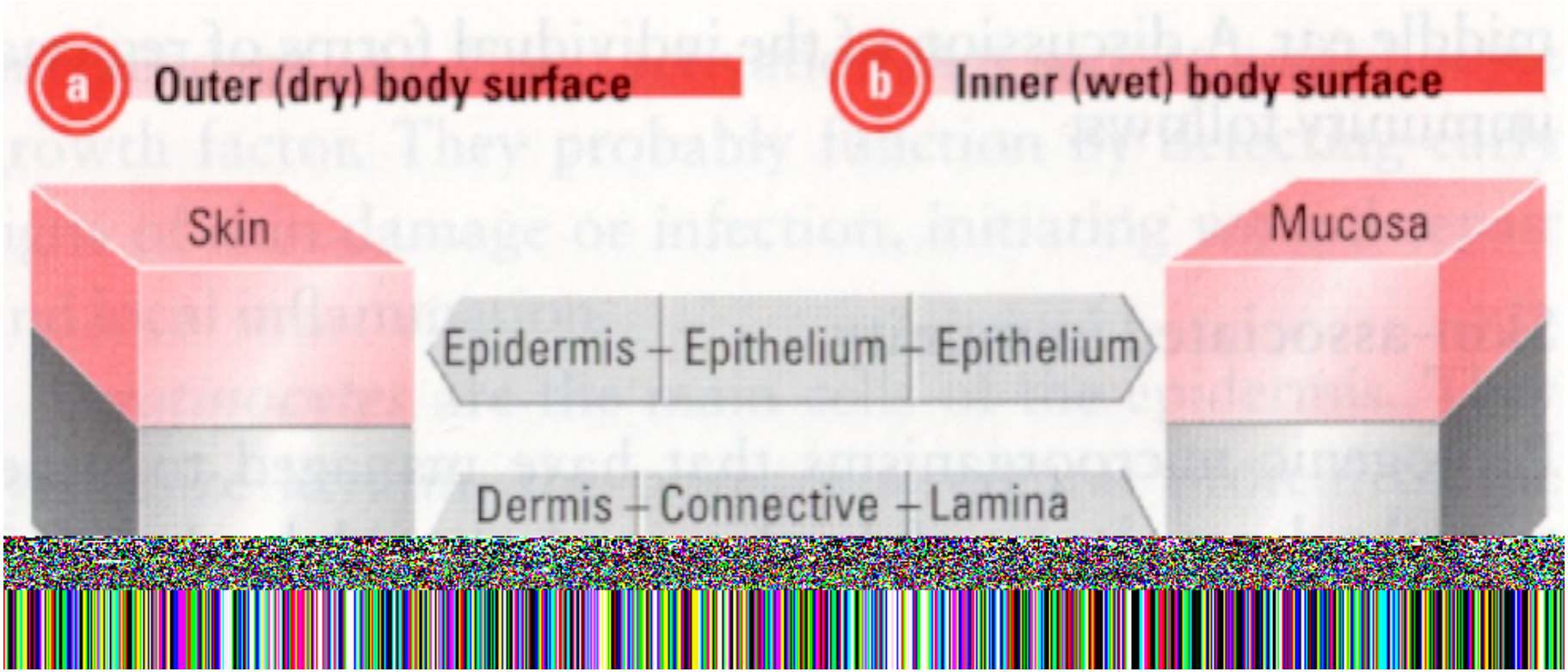
MALT, SALT and Microbiota

Dr. Berki Timea

External skin surface: “dry body surface” 1.7 - 1.8 m^2

Internal mucosal surface: “wet body surface” 400 m^2

Two types of body surfaces



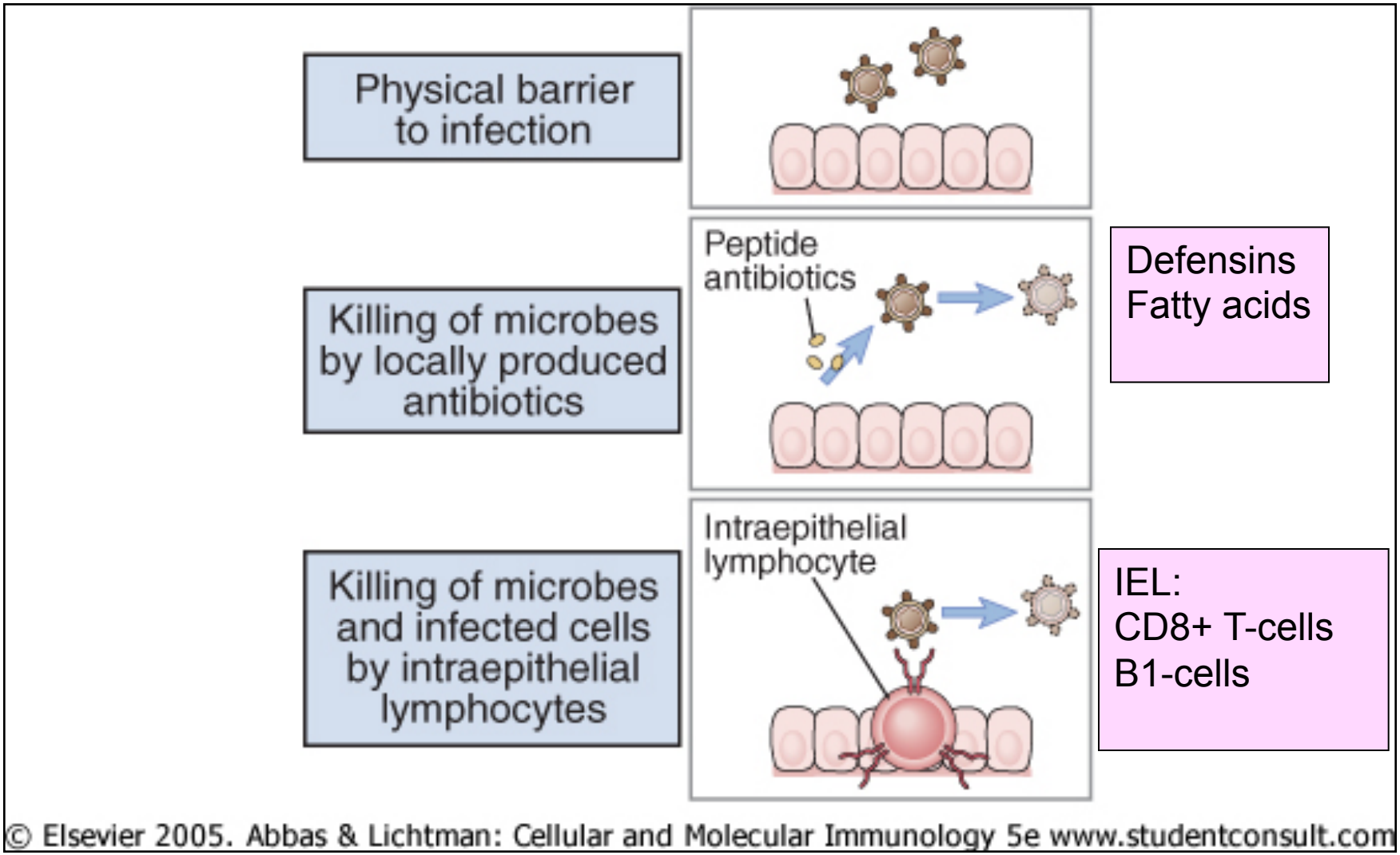
Skin associated immune system (SIS or SALT)

Special structural elements:

- Antigen presenting cells (Langerhans cells, veiled cells, monocytes, tissue macrophages)
- Effector cells (gamma-delta T cells, alpha-beta T cells, B cells, NK cells, granulocytes, mast cells),
- Keratinocytes (cytokine production).

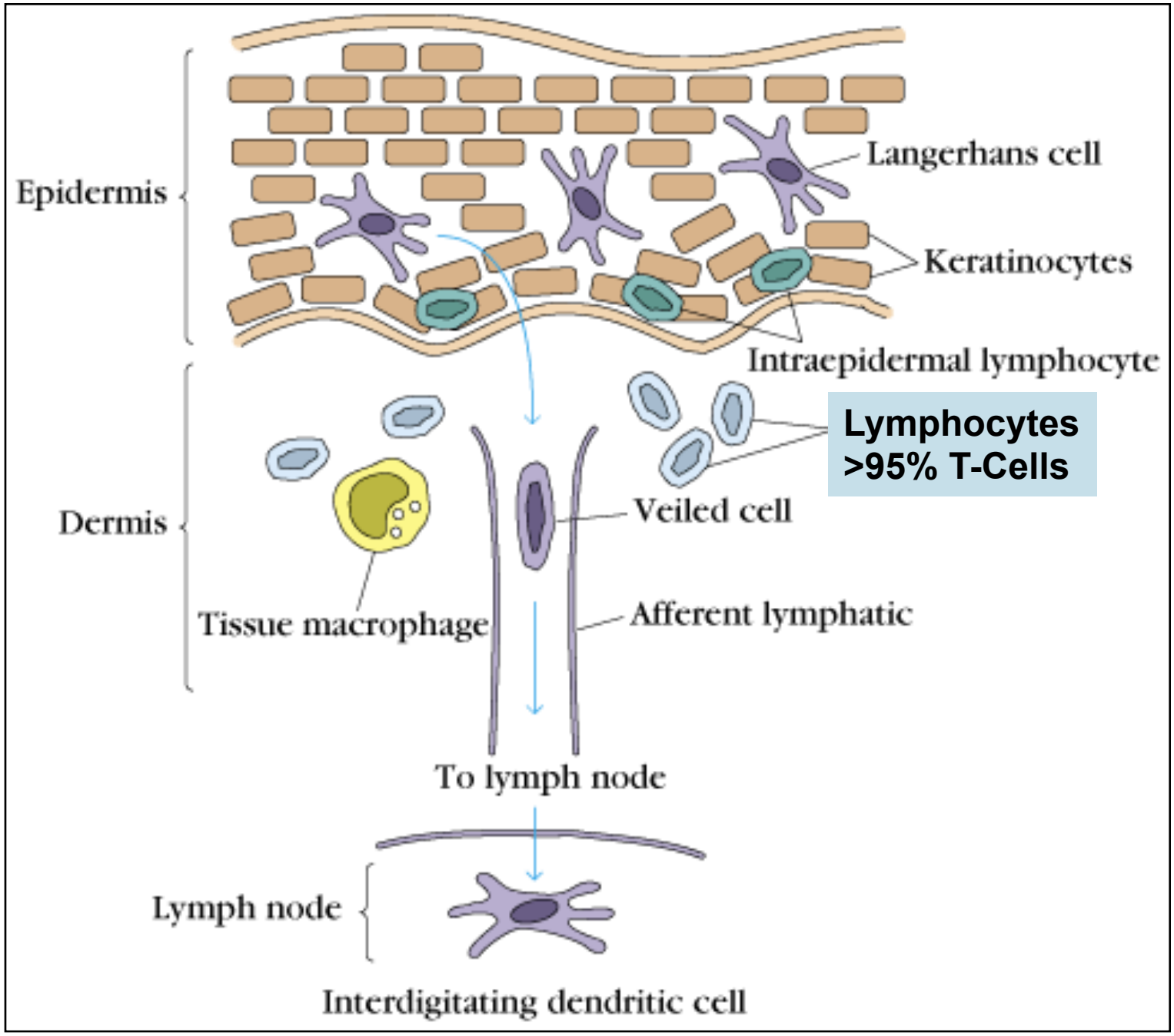
The co-operation between keratinocytes and T cells is similar to the thymus epithelia and thymocyte co-operations.

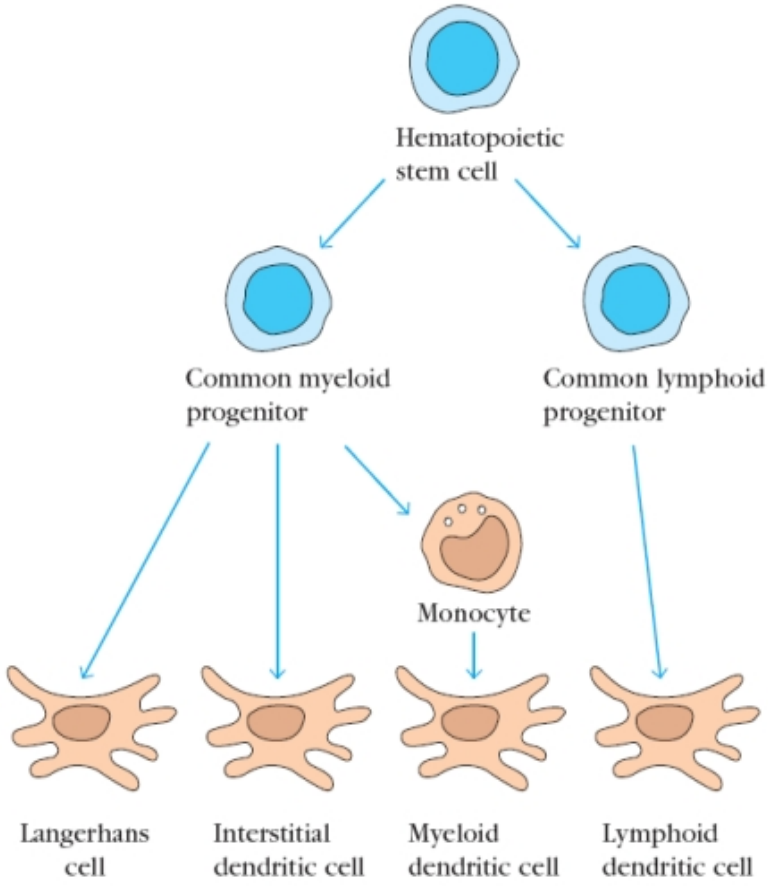
Role of the epithelial Barrier

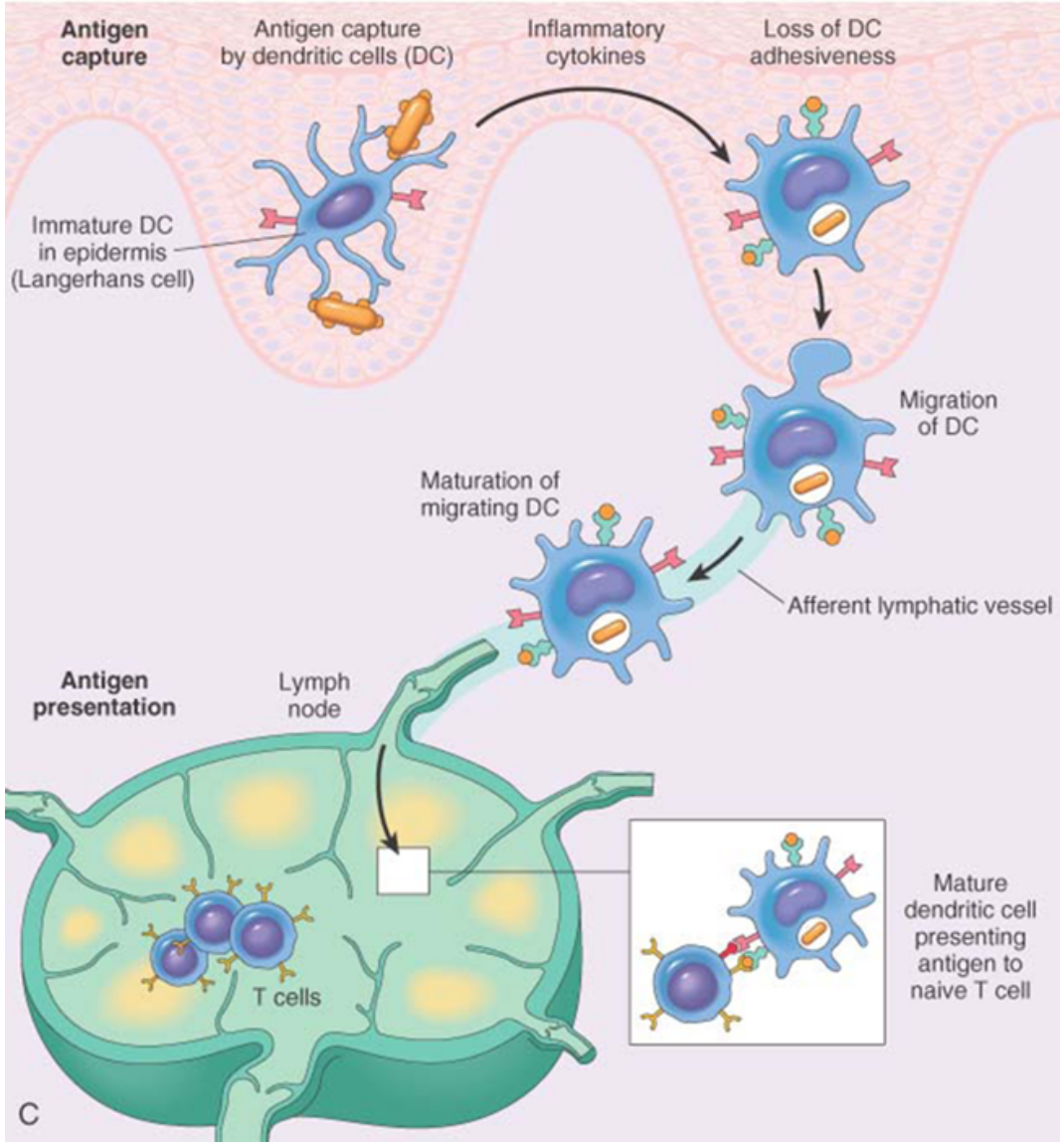


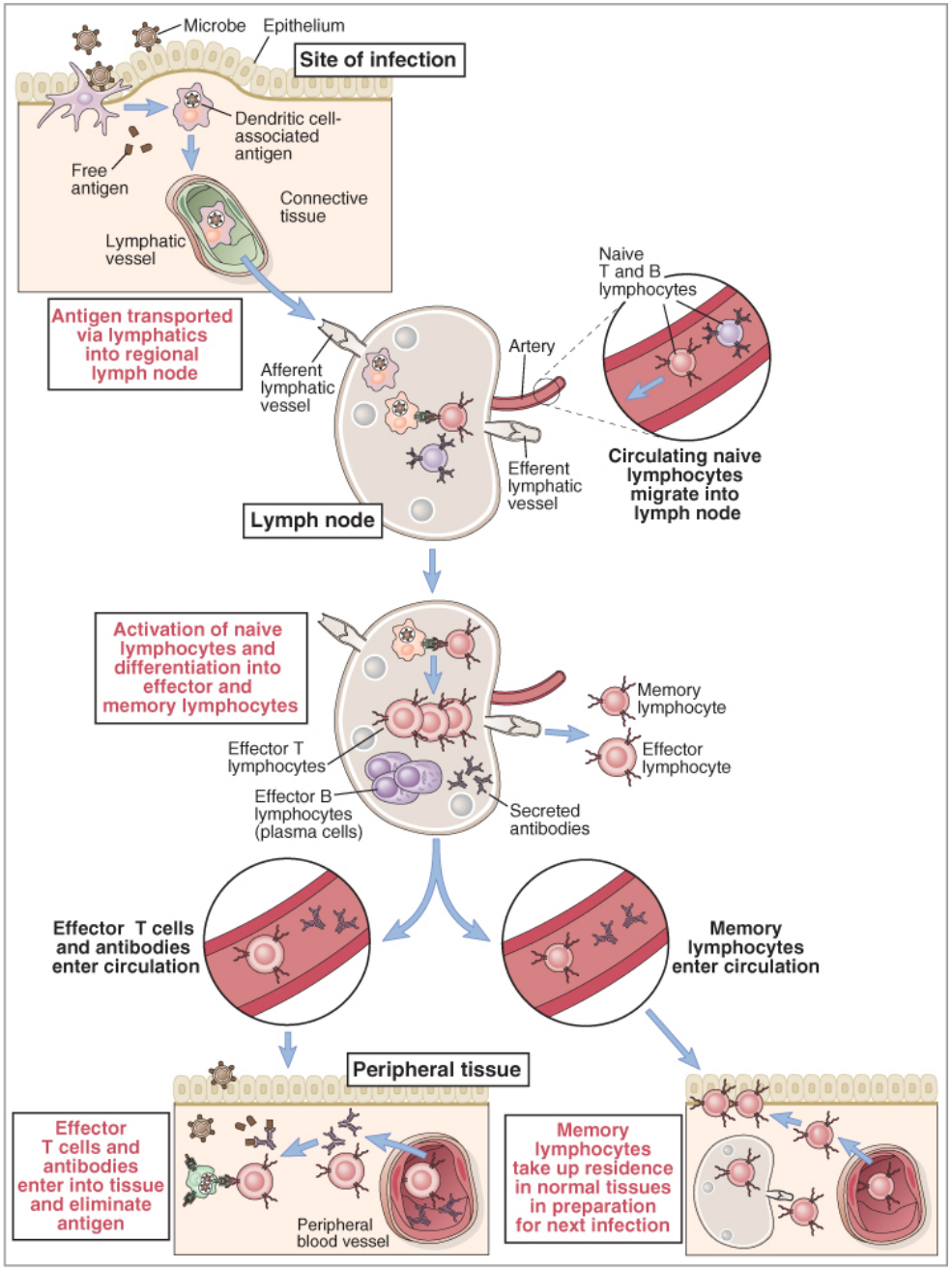
Cytokines produced by human keratinocytes

Interleukines	IL-1α, IL-1β, IL-6, IL-8
Colony stimulating factors	IL-3, GM-CSF, G-CSF, M-CSF
Interferons	IFN-α, IFN-β
Cytotoxic cytokines	TNF-α
Transforming growth factors	TGF-α, TGF-β
Growth factors	PDGF, fibroblast GF


Epidermis
Langerhans cell
Keratinocytes
Intraepidermal lymphocyte
Dermis
Lymphocytes
>95% T-Cells
Veiled cell
Tissue macrophage
Afferent lymphatic
To lymph node
Lymph node
Interdigitating dendritic cell


Hematopoietic stem cell
Common myeloid progenitor
Common lymphoid progenitor
Monocyte
Langerhans cell
Interstitial dendritic cell
Myeloid dendritic cell
Lymphoid dendritic cell


Antigen capture
Antigen capture by dendritic cells (DC)
Inflammatory cytokines
Loss of DC adhesiveness
Immature DC in epidermis (Langerhans cell)
Migration of DC
Maturation of migrating DC
Afferent lymphatic vessel
Antigen presentation
Lymph node
T cells
Mature dendritic cell presenting antigen to naive T cell
C



Afferent immunreaction is local

Effector response is systemic

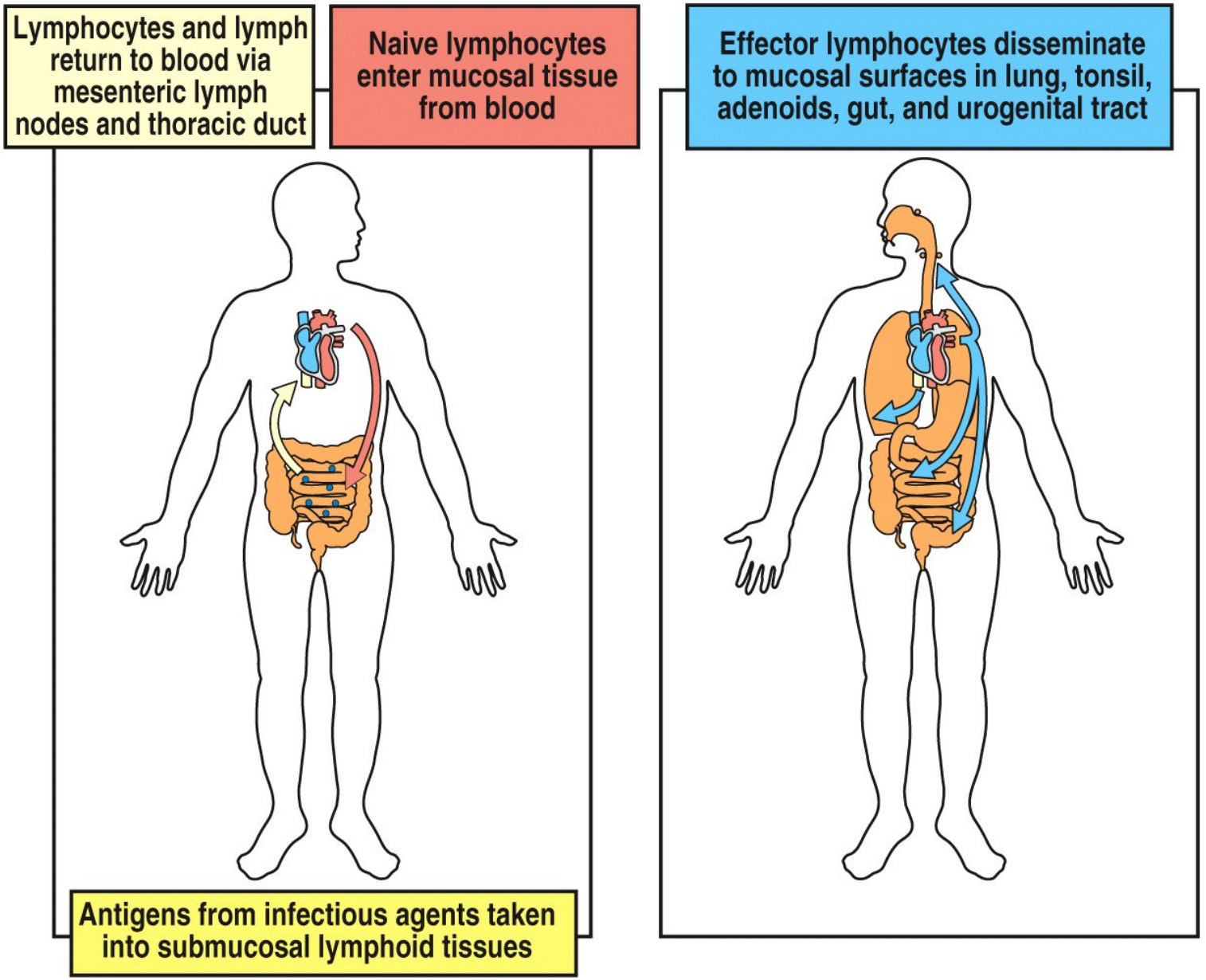


Figure 10-20 Immunobiology, 6/e. (© Garland Science 2005)

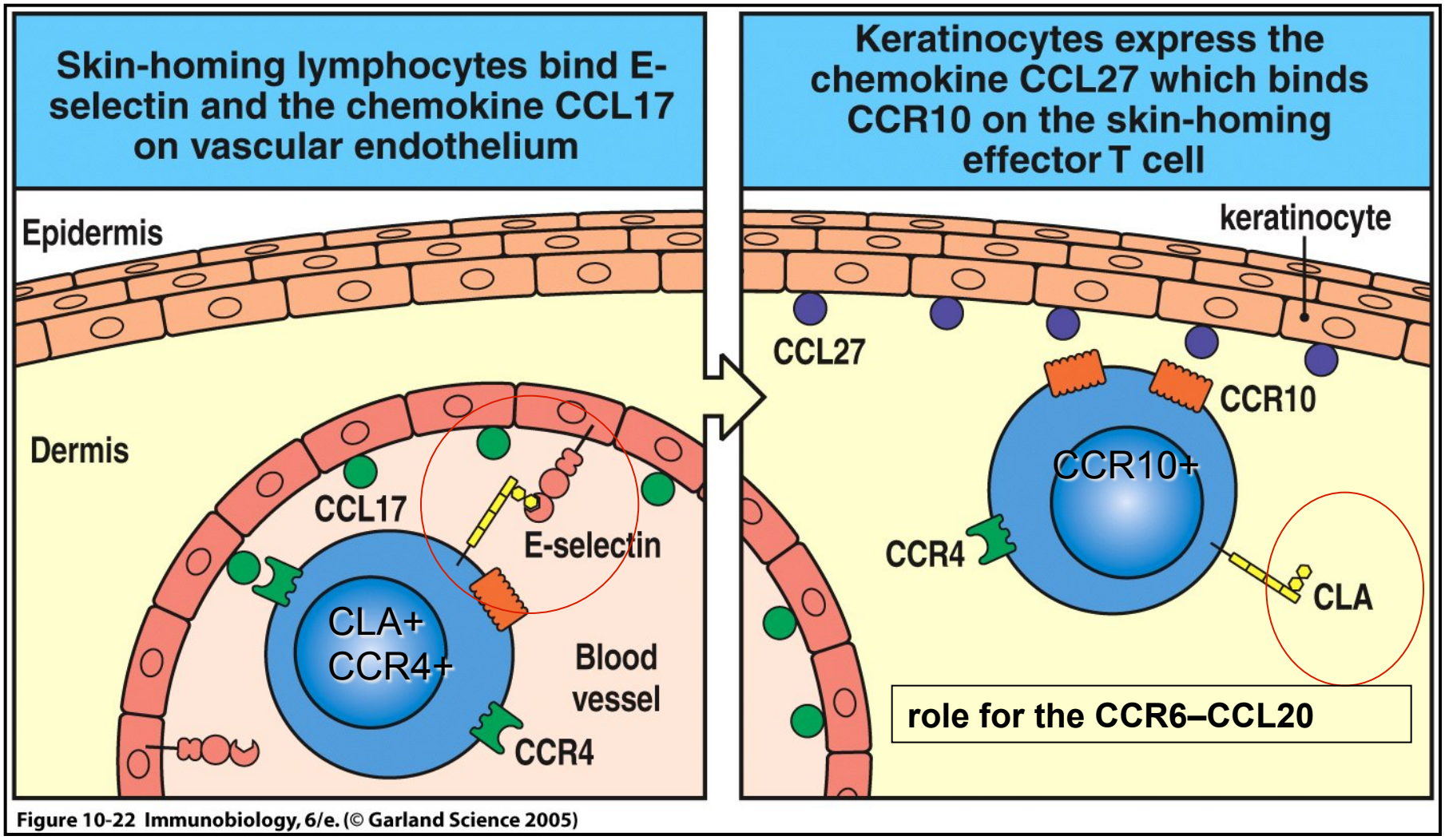
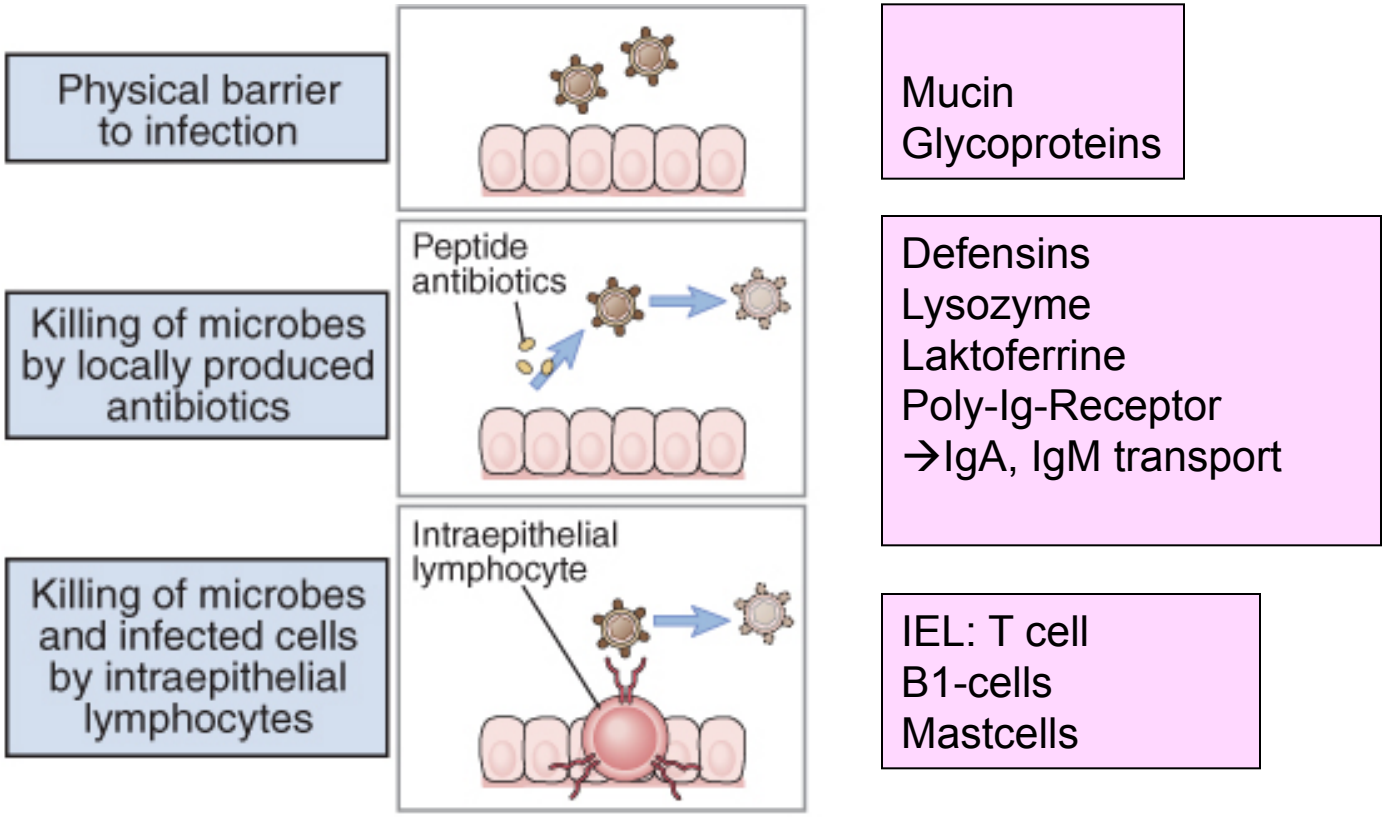


Figure 10-22 Immunobiology, 6/e. (© Garland Science 2005)

CLA: cutaneous-lymphocyte associated antigen

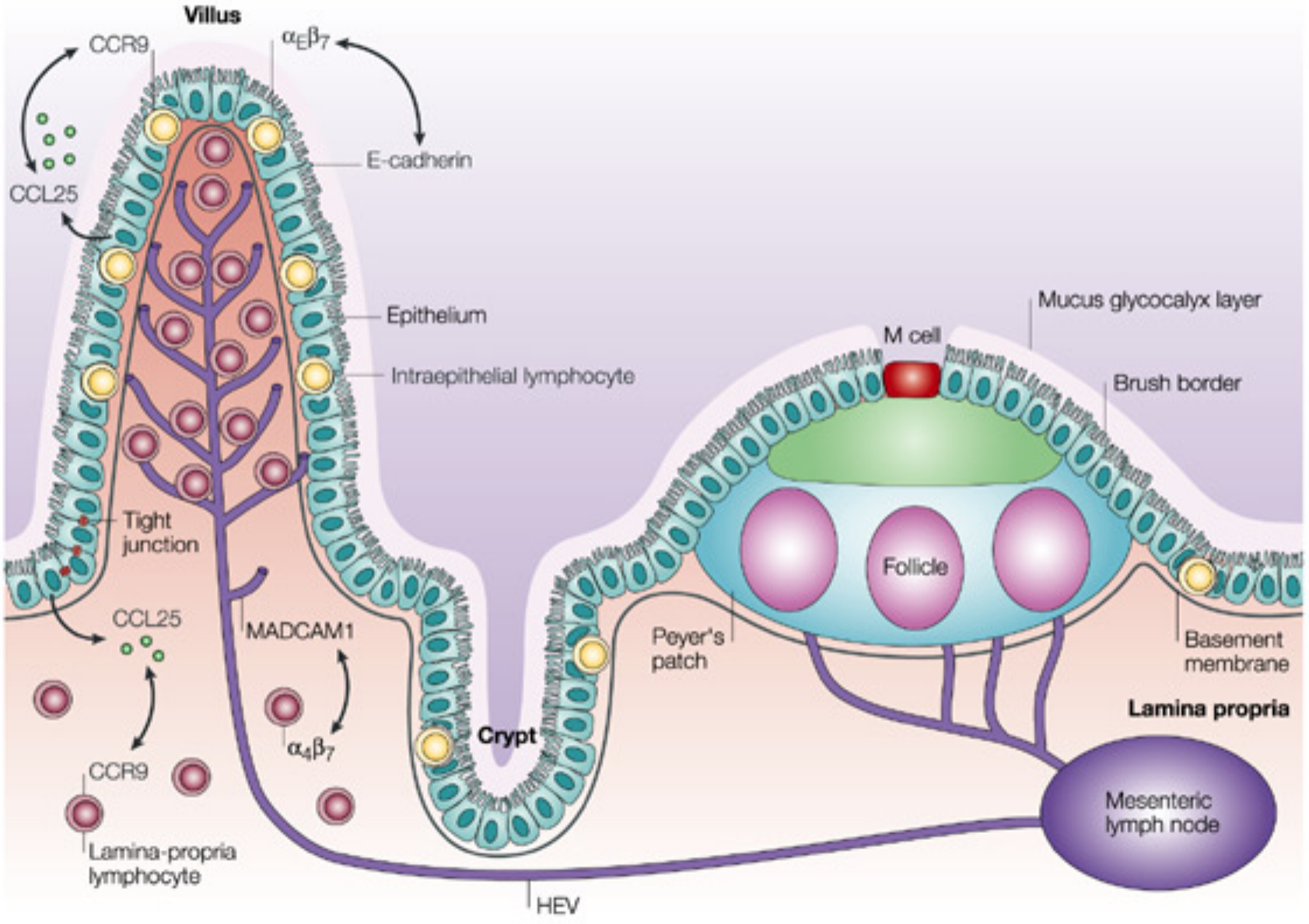
Role of epithelium in MALT



Mucin
Glycoproteins

Defensins
Lysozyme
Laktoferrine
Poly-Ig-Receptor
→IgA, IgM transport

IEL: T cell
B1-cells
Mastcells



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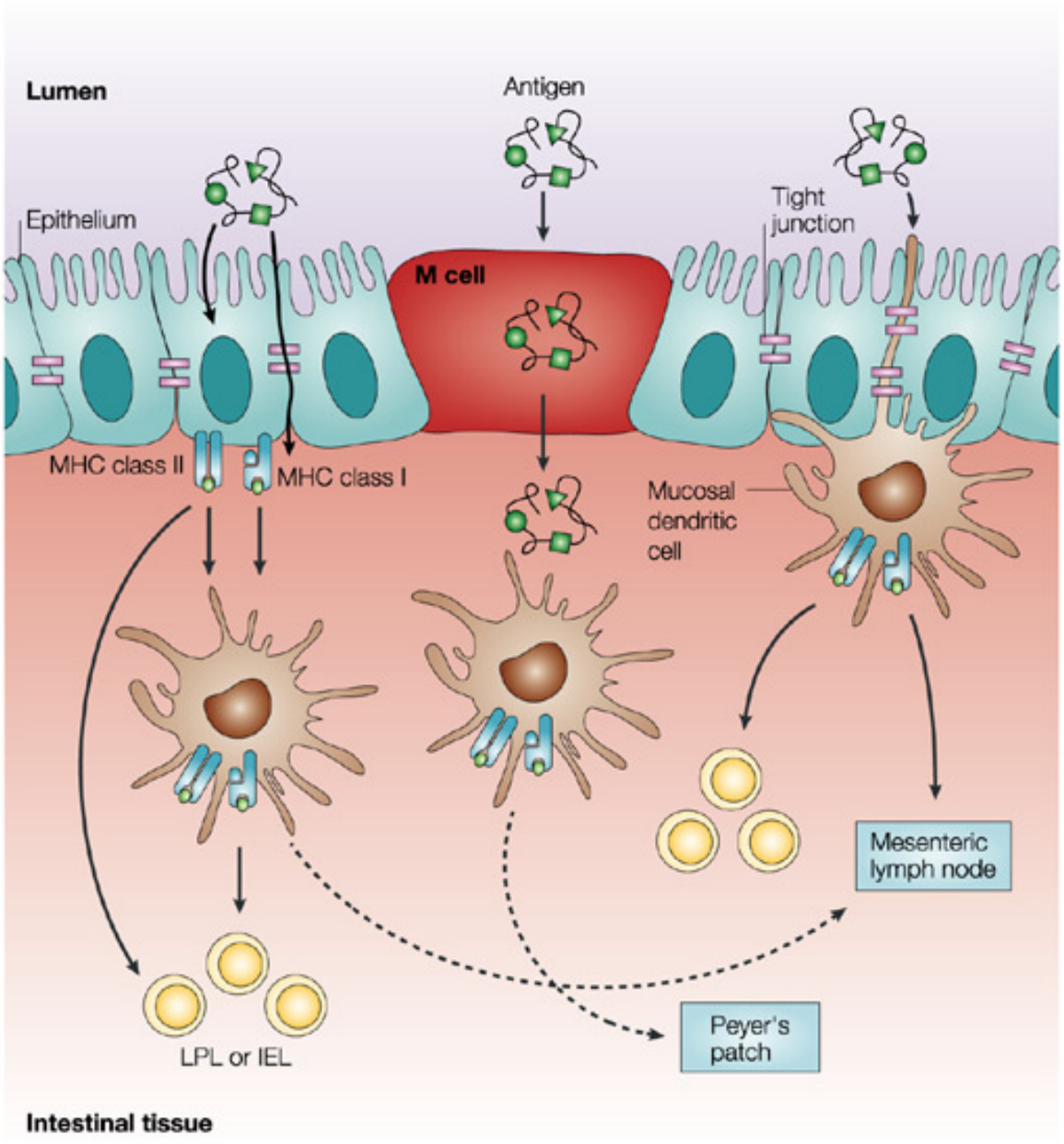

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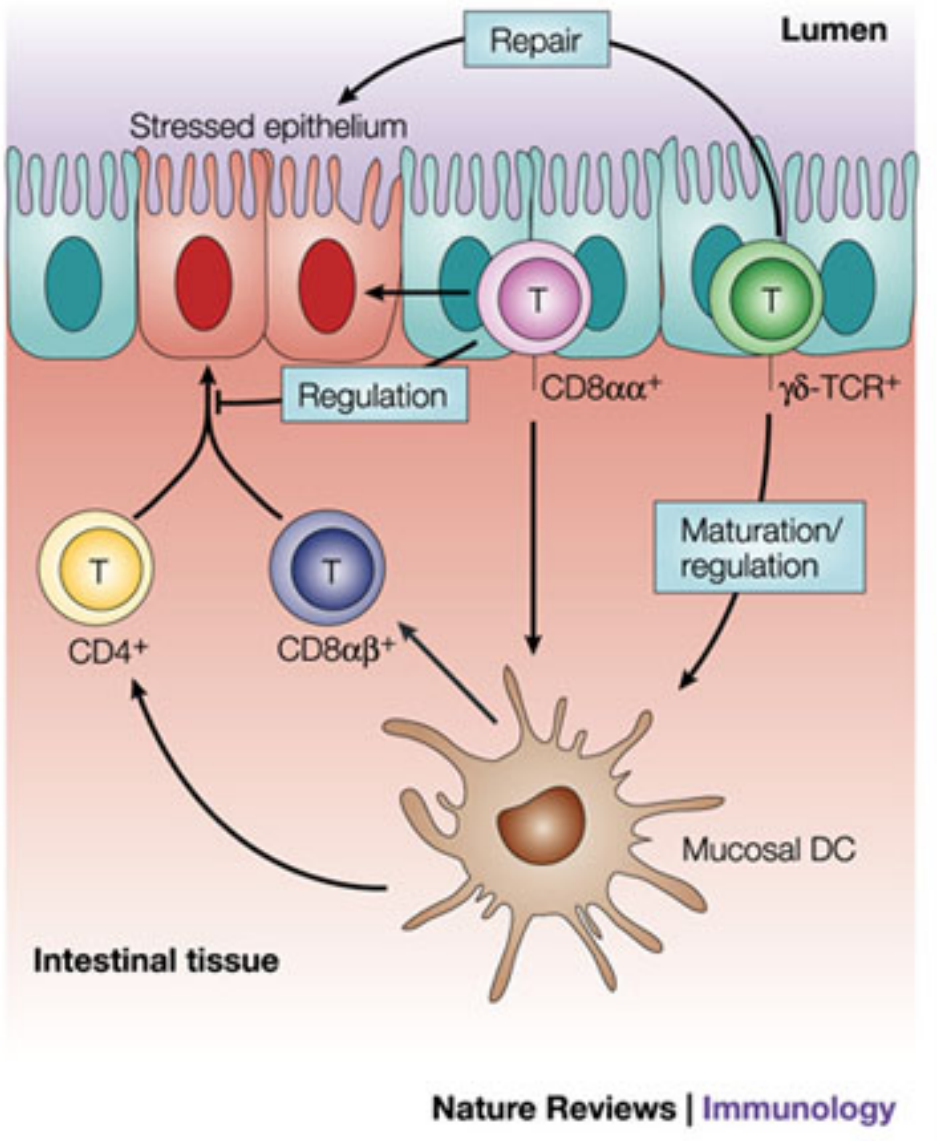
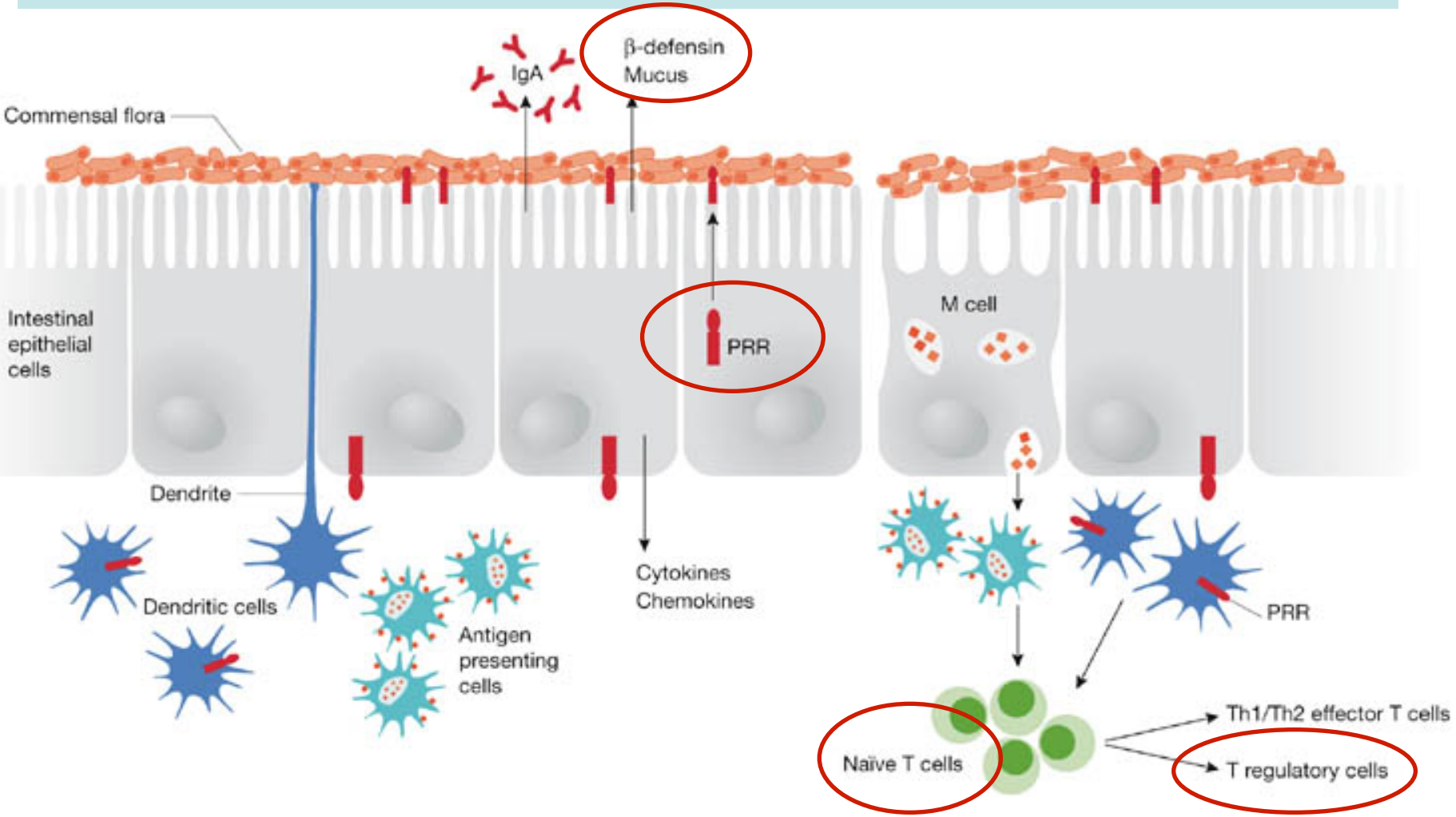
Antigen uptake:

M cells
epithel cells
Dendritic cells

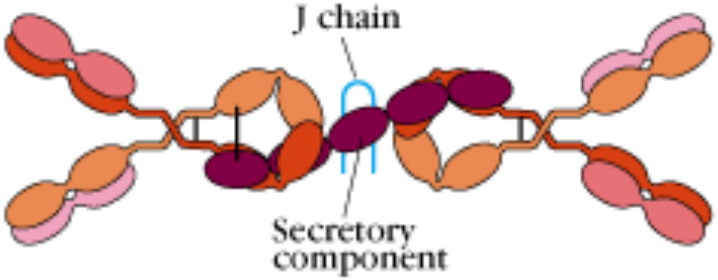
Role of IEL


Repair
Lumen
Stressed epithelium
T
T
Regulation
CD8αα+
γδ-TCR+
Maturation/
regulation
T
T
CD4+
CD8αβ+
Mucosal DC
Intestinal tissue
Nature Reviews | Immunology

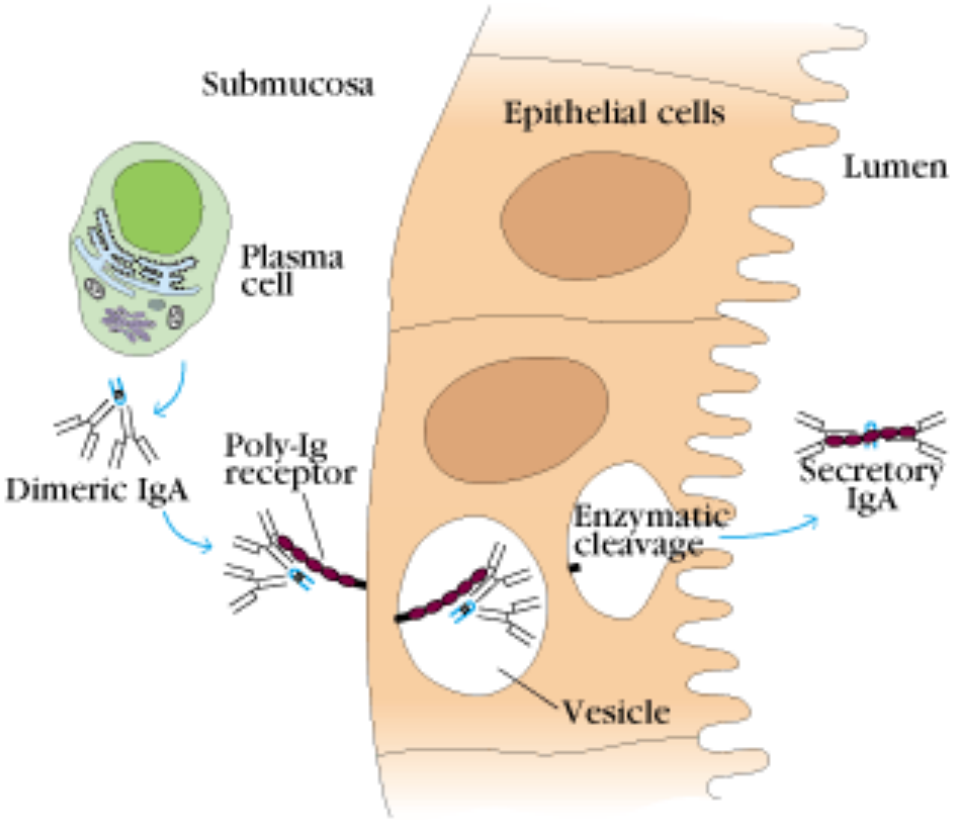
Role of PRR- TLR



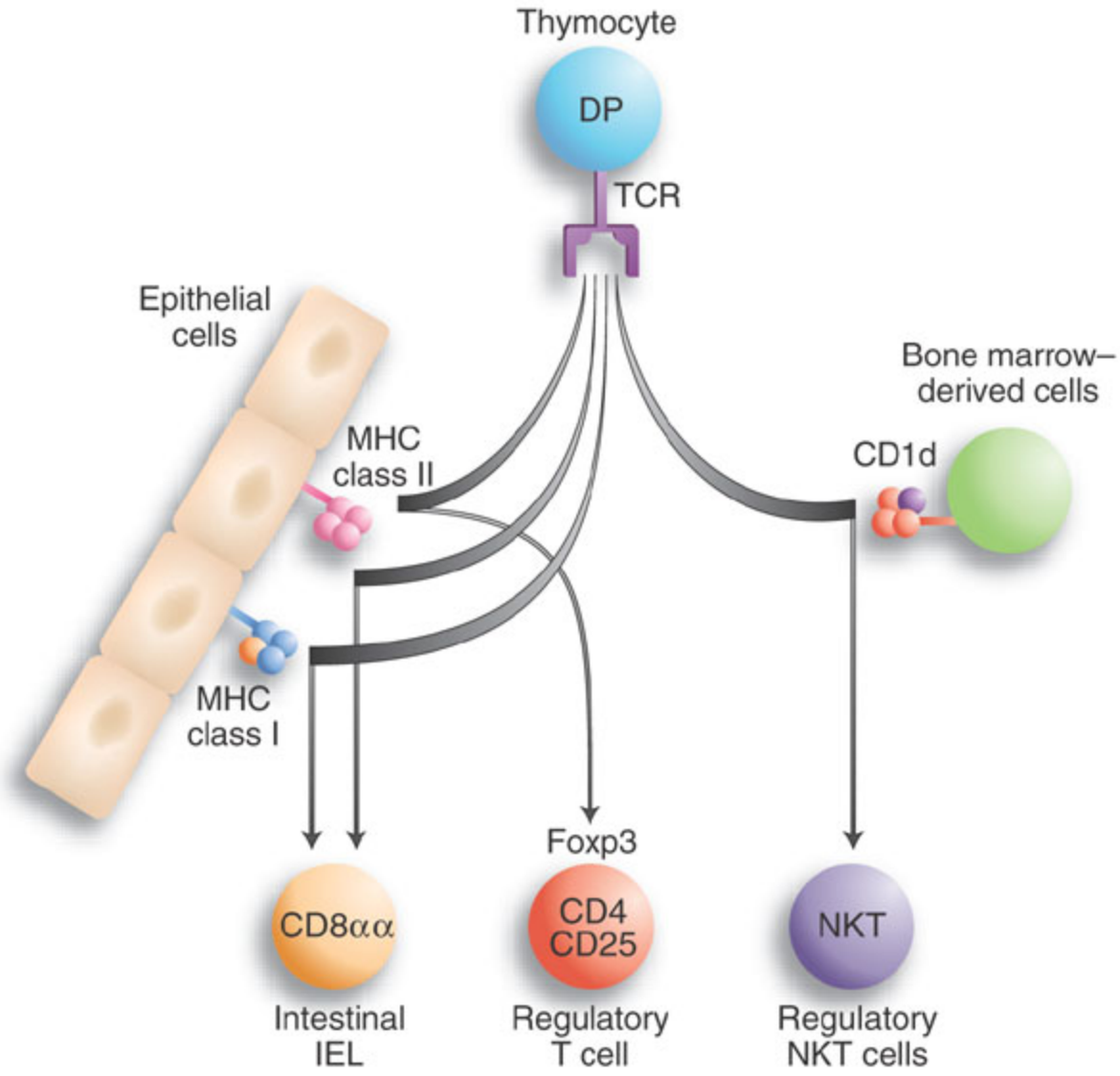
(a) Structure of secretory IgA

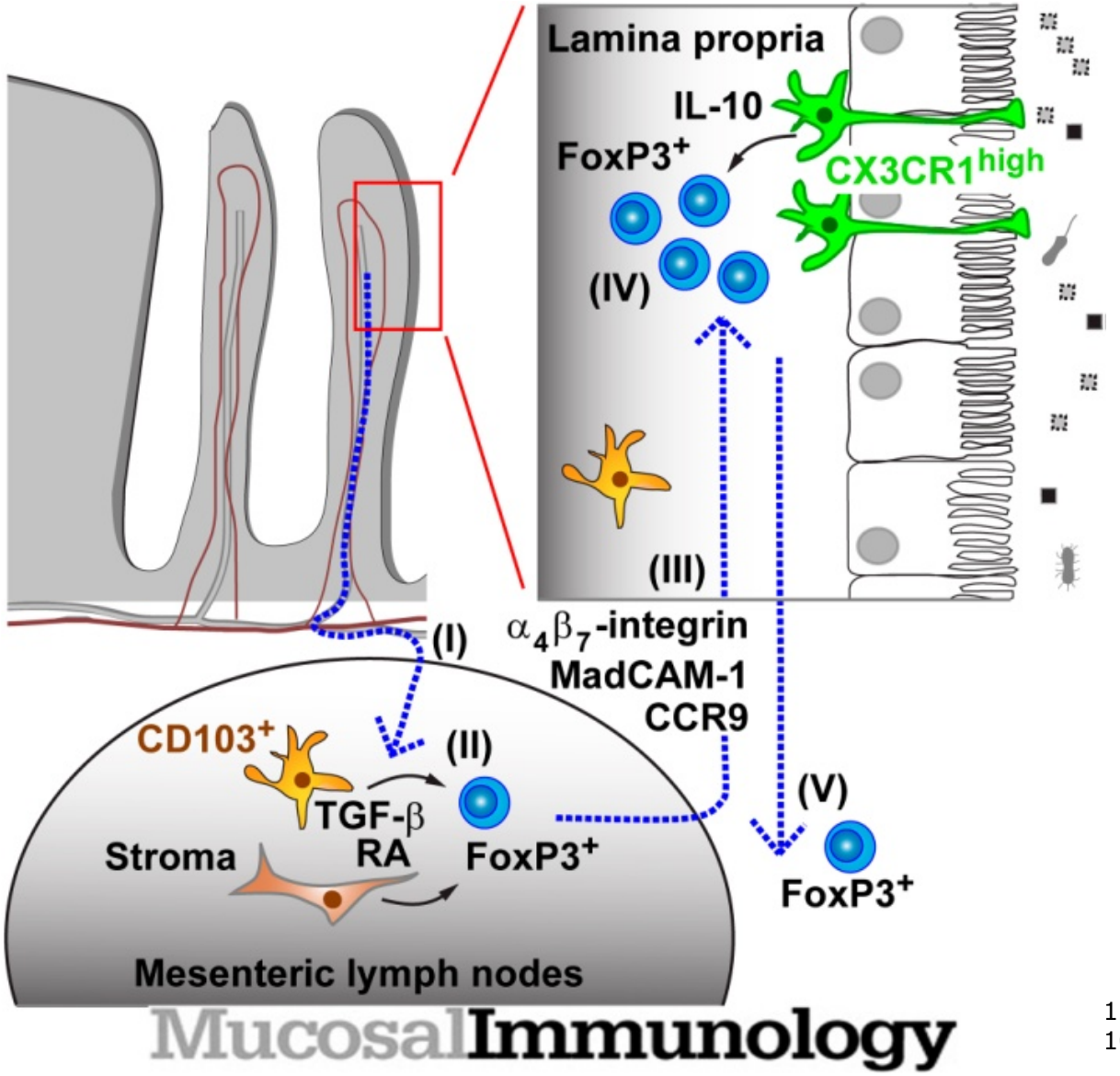


(b) Formation of secretory IgA



Role of intestinal regulatory cells in the development of oral tolerance



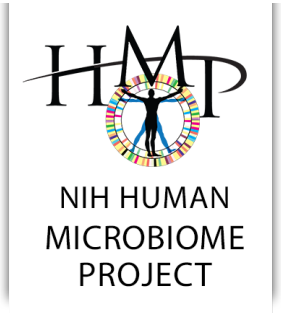


12) 5, 232-239;
1038/mi.2012.4

The Human Microbiome

The Human Microbiome is the collection of all the microorganisms living in association with the human body. These communities consist of a variety of microorganisms including eukaryotes, archaea, bacteria and viruses.

Bacteria in an average human body number ten times more than human cells, for a total of about 1000 more genes than are present in the human genome. Because of their small size, however, microorganisms make up only about 1 to 3 percent of our body mass (that's 2 to 6 pounds of bacteria in a 200-pound adult).

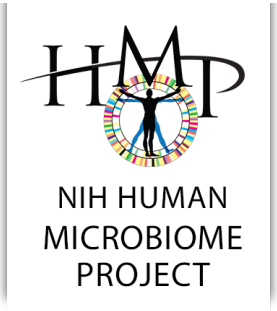


http://hmpdacc.org/

The Human Microbiome (cont.)

These microbes are generally not harmful to us, in fact they are essential for maintaining health. For example, they produce some vitamins that we do not have the genes to make, break down our food to extract nutrients we need to survive, teach our immune systems how to recognize dangerous invaders and even produce helpful anti-inflammatory compounds that fight off other disease-causing microbes.

An ever-growing number of studies have demonstrated that changes in the composition of our microbiomes correlate with numerous disease states, raising the possibility that manipulation of these communities could be used to treat disease.



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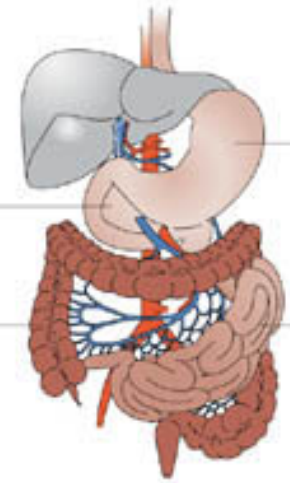
A



Stomach
10^1–10^3 cfu/ml

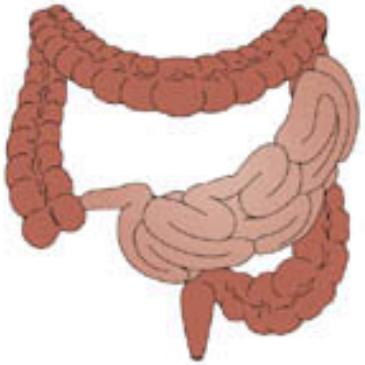
Duodenum
10^1–10^3 cfu/ml

Colon
10^{11}–10^{12} cfu/ml

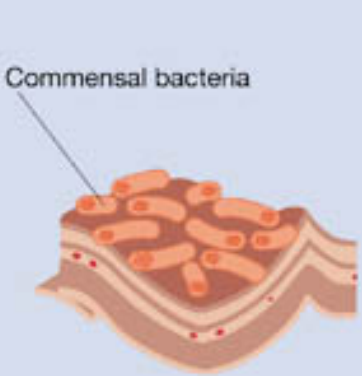
Jejunum/ileum
10^4–10^7 cfu/ml

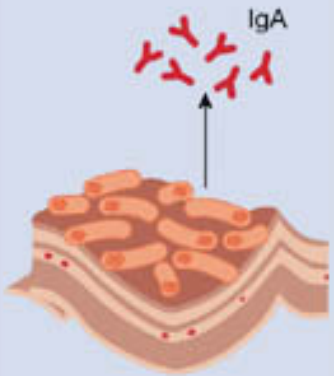
Anaerobic genera	Aerobic genera
Bifidobacterium	*Escherichia*
Clostridium	*Enterococcus*
Bacteroides	*Streptococcus*
Eubacterium	*Klebsiella*

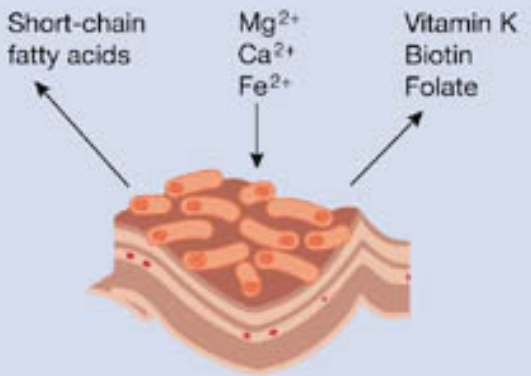
B

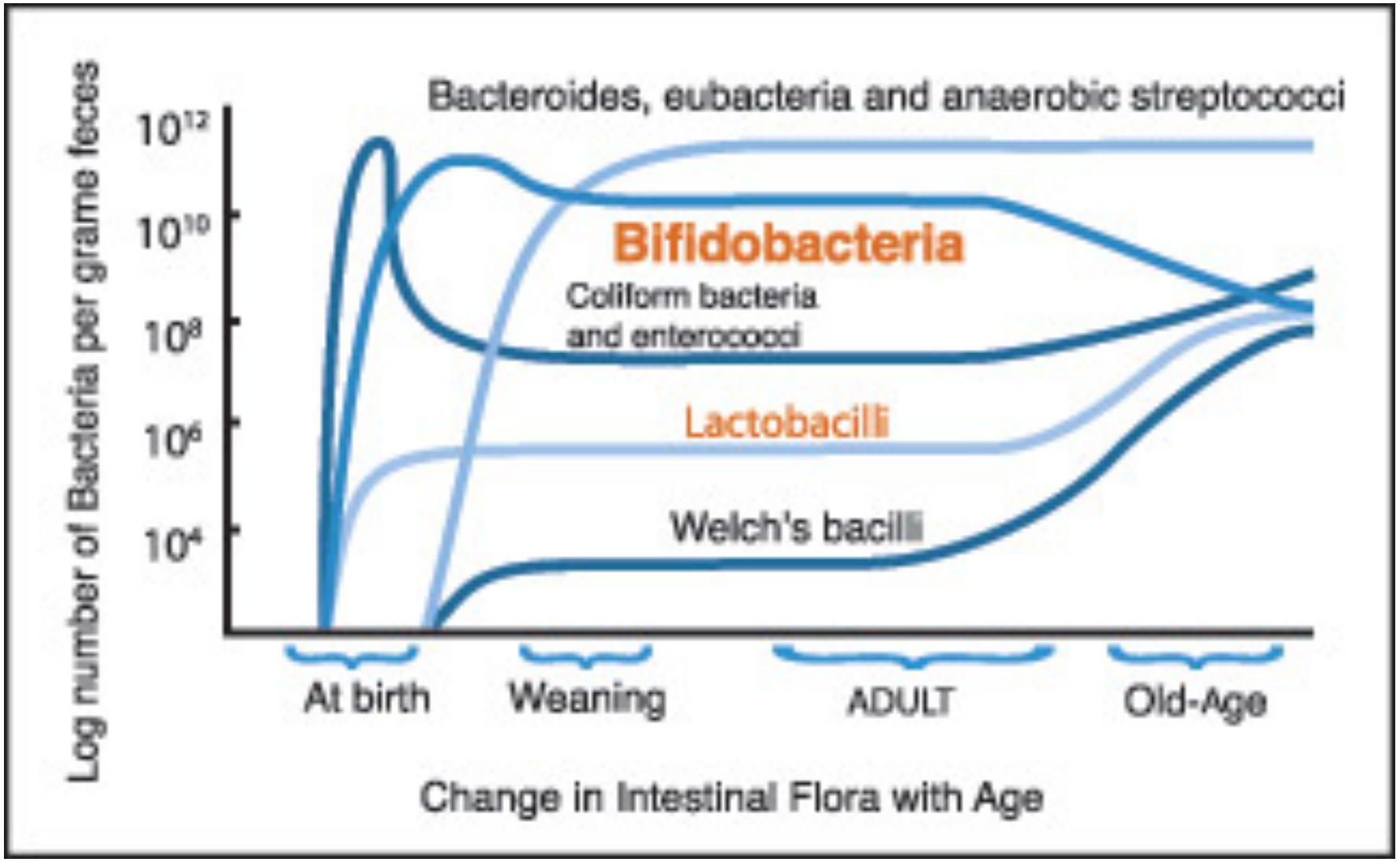


Protective functions	Structural functions	Metabolic functions
Pathogen displacement	Barrier fortification	Control IEC differentiation and proliferation
Nutrient competition	Induction of IgA	Metabolize dietary carcinogens
Receptor competition	Apical tightening of tight junctions	Synthesize vitamins e.g., biotin, folate
Production of anti-microbial factors e.g., bacteriocins, lactic acids	Immune system development	Ferment non-digestible dietary residue and endogenous epithelial-derived mucus
		Ion absorption
		Salvage of energy



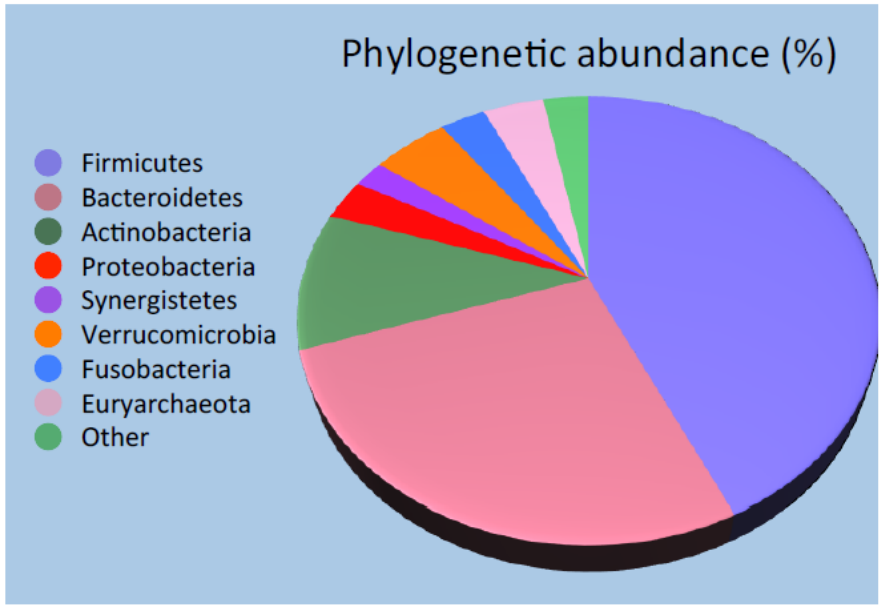


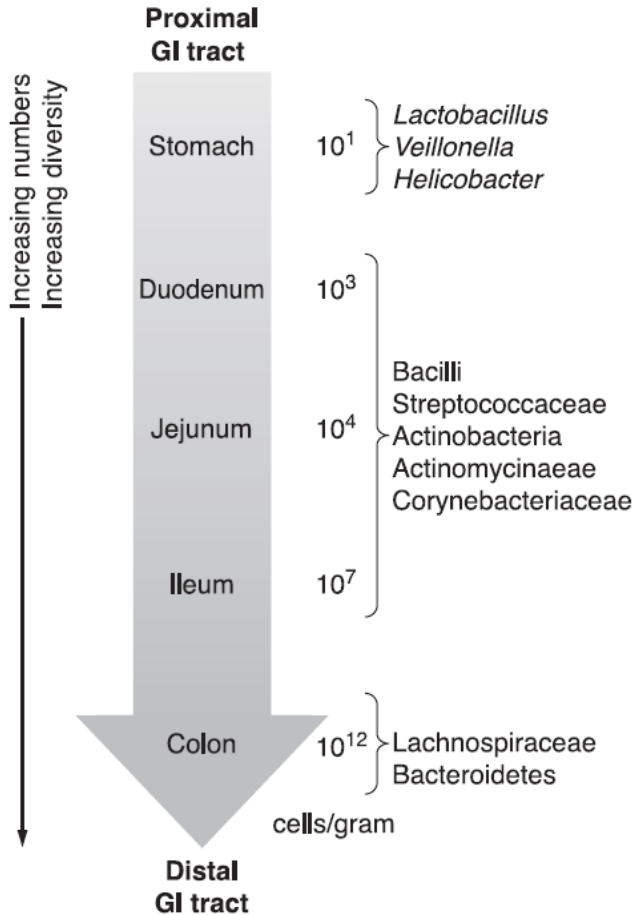



Log number of Bacteria per grame feces
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
Bacteroides, eubacteria and anaerobic streptococci
Bifidobacteria
Coliform bacteria
and enterococci
Lactobacilli
Welch's bacilli
At birth
Weaning
ADULT
Old-Age
Change in Intestinal Flora with Age

Intestinal microbiota: Who is there?

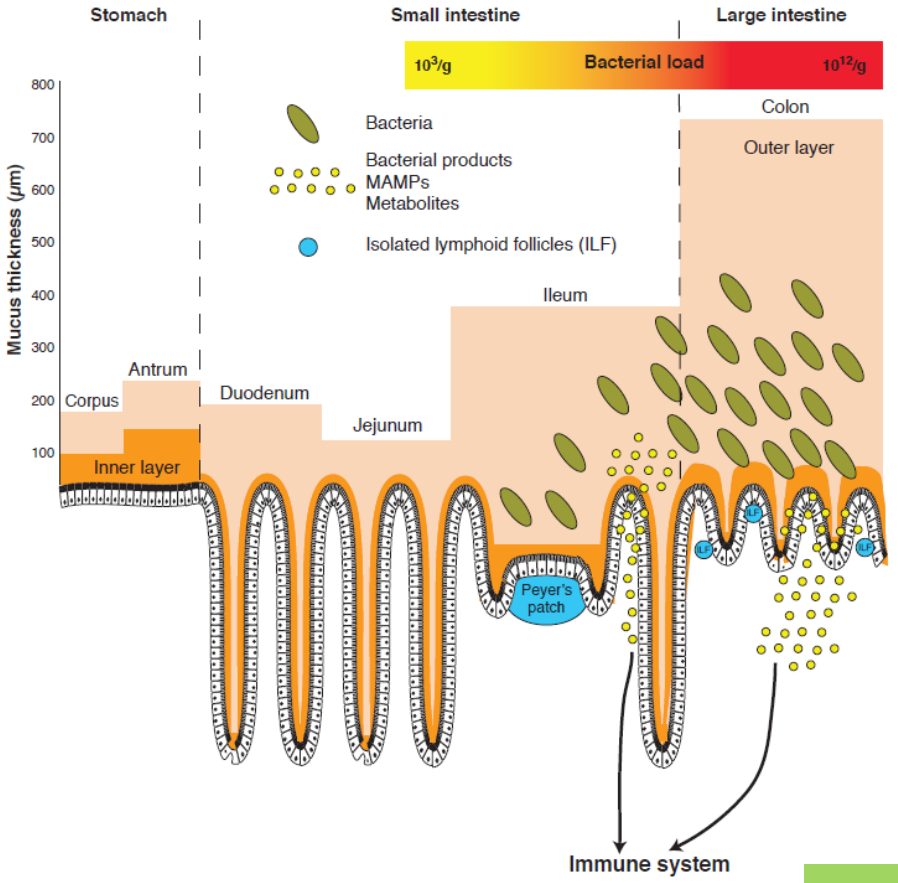
- All mucosal surfaces are colonised with bacteria
- The intestine is a preferred site – over 70% of all bacteria are found in the colon
  - large organ
  - rich in nutrients
- Longitudinal: bacteria increase in number and composition changes from proximal to distal GI tract

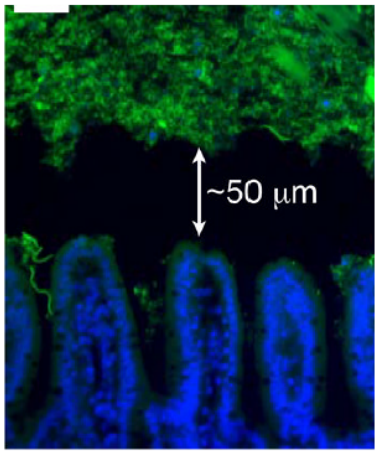


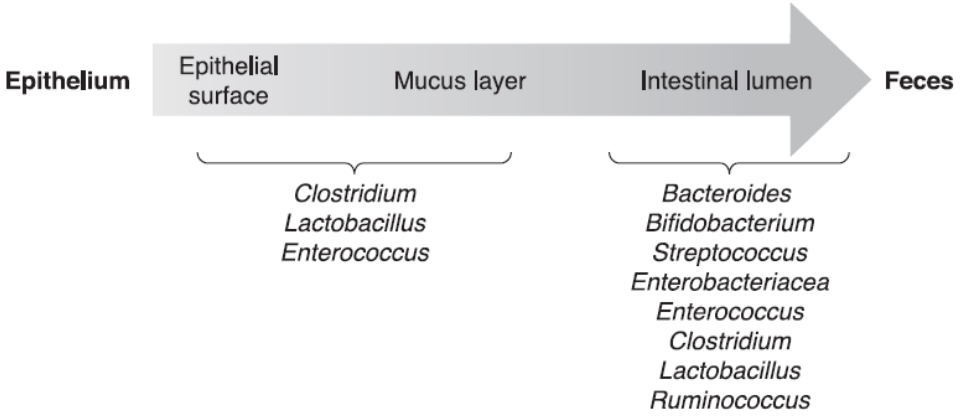


Intestinal microbiota: Where are they?

- Latitudinal: bacterial composition also differs between lumen, mucus, and attached to epithelium







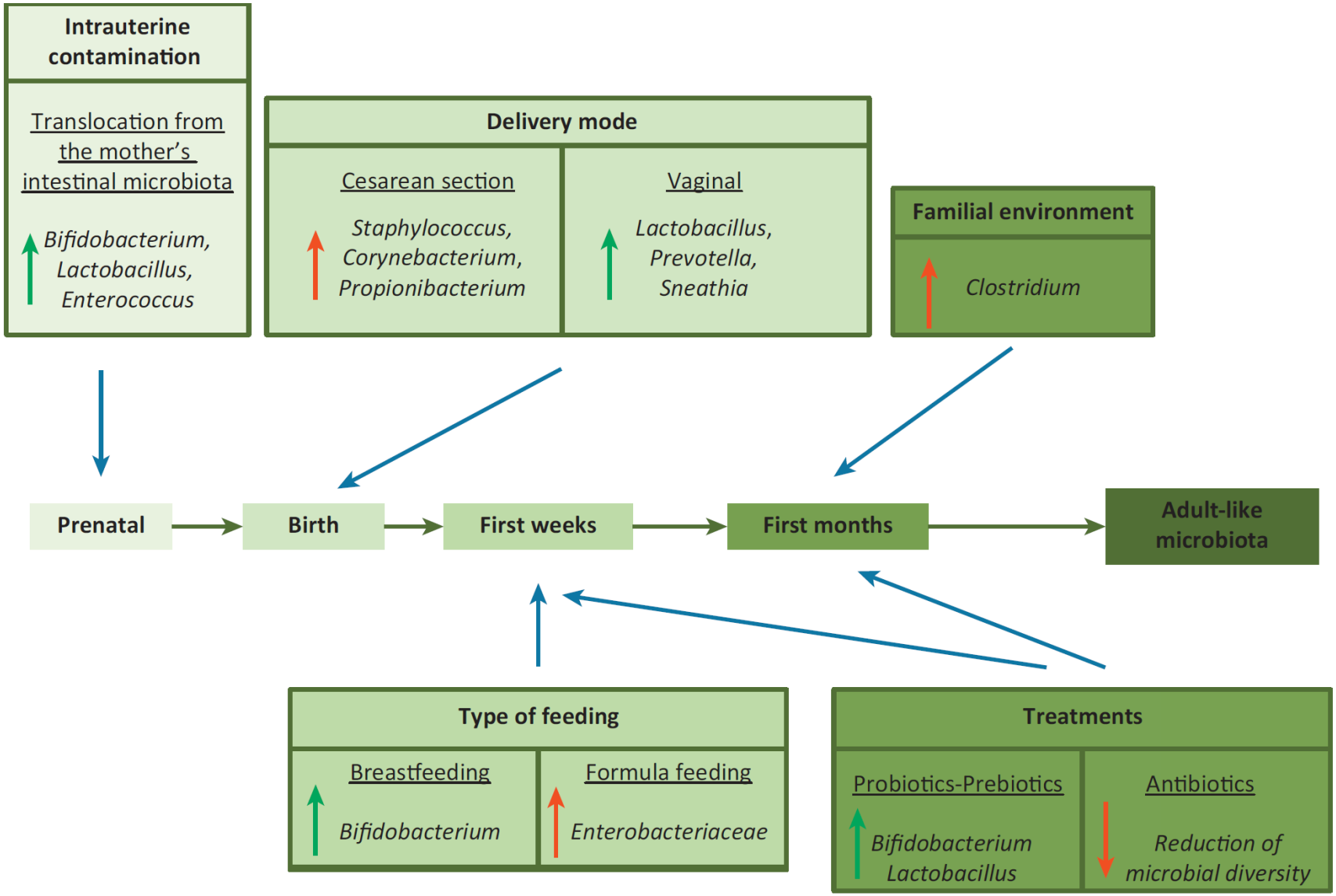
MAMPs – Microbe-associated molecular patterns

Intestinal microbiota in infants

Throughout the human lifetime, the intestinal microbiota performs vital functions, such as:
barrier function, metabolic reactions, trophic effects, and maturation of the host's innate and adaptive immune responses.

Development of the intestinal microbiota in infants is characterized by rapid and large changes in microbial abundance, diversity, and composition. These changes are influenced by medical, cultural, and environmental factors such as:
mode of delivery, diet, familial environment, diseases, and therapies used.

Impact of external factors on the intestinal microbiota of the infant: Mom matters



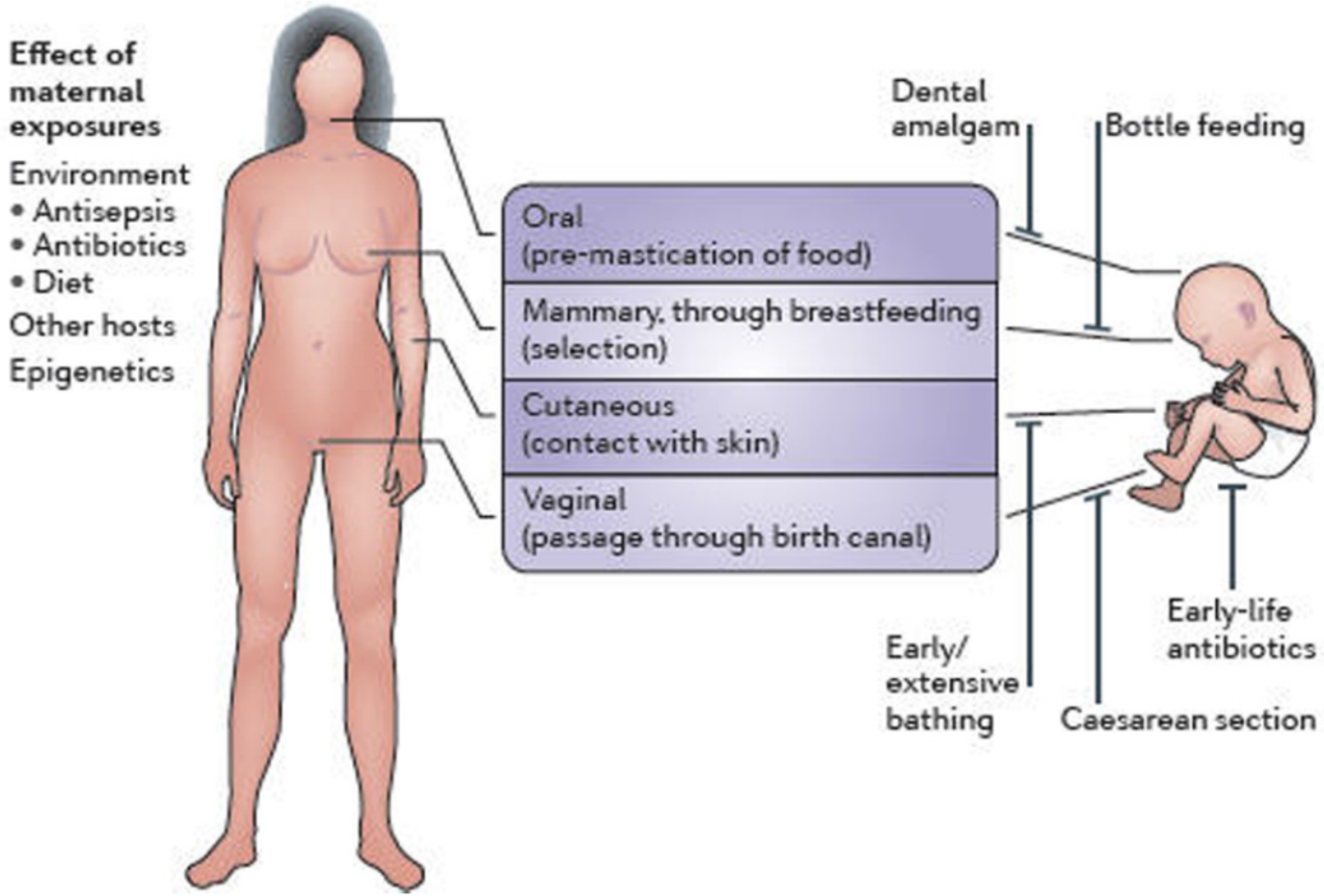
Matamoros S et al, Trends Microbiol, 2013

TRENDS in Microbiology

Figure 1. Impact of external factors on the intestinal microbiota of the infant. Green arrows show beneficial modification; red arrows show modification considered negative for healthy development.

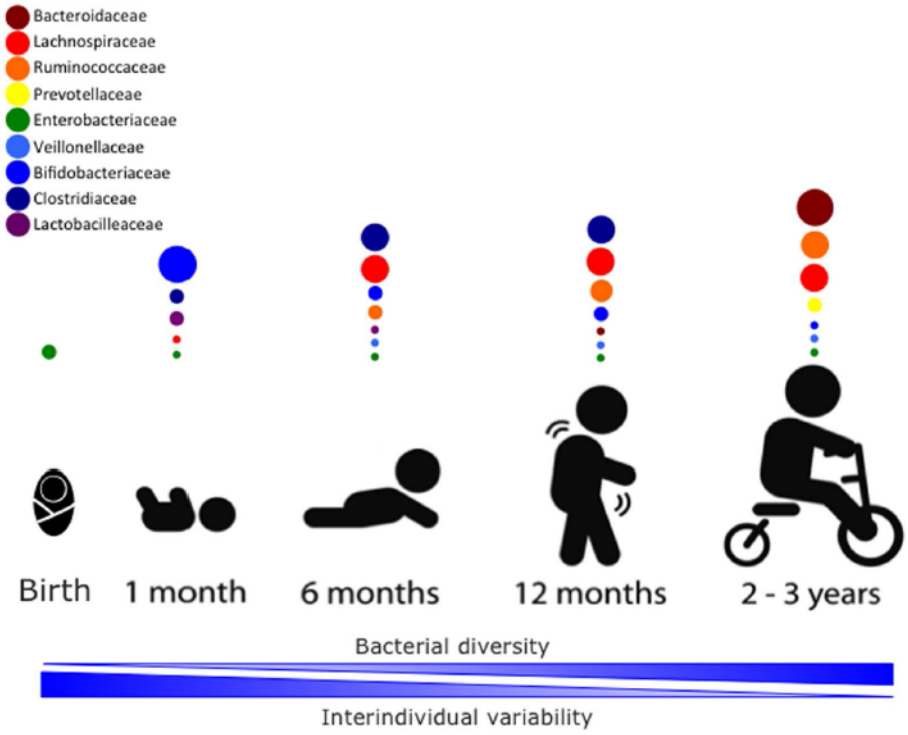
Intestinal microbiota: Where do they come from?

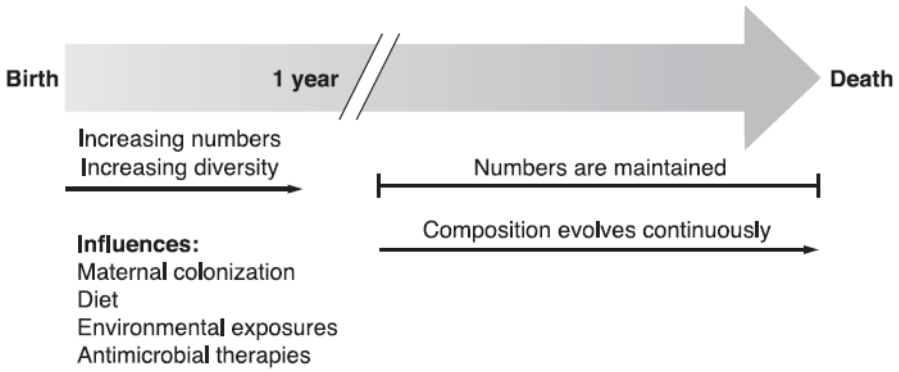
- Initial exposure occurs during passage through birth canal
- During first year of life, heavily influenced by mother and environment



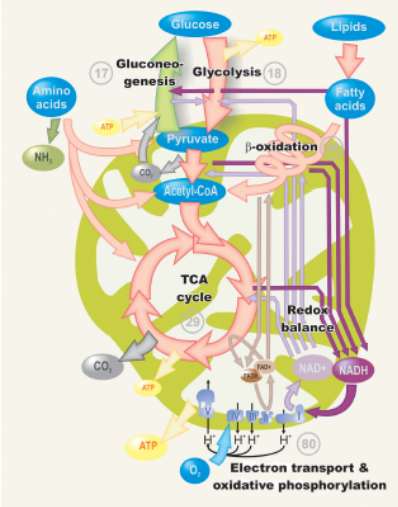
Intestinal microbiota: Where do they come from?

- Microbial stability is established after 1 year
- Composition continues to be influenced by environment; antibiotics, diet, genetics, inflammation, hygiene, lifestyle

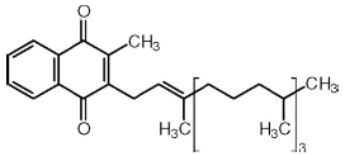




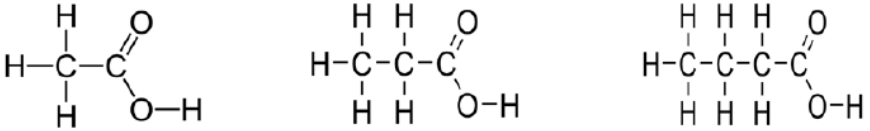
Intestinal microbiota in health



- **Increases the metabolic capacity of the host.**
  - **Digestion of otherwise unused food components.**



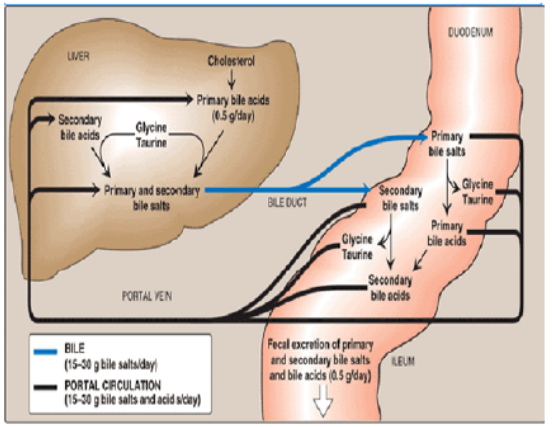
Vitamin synthesis
(eg Vitamin K)

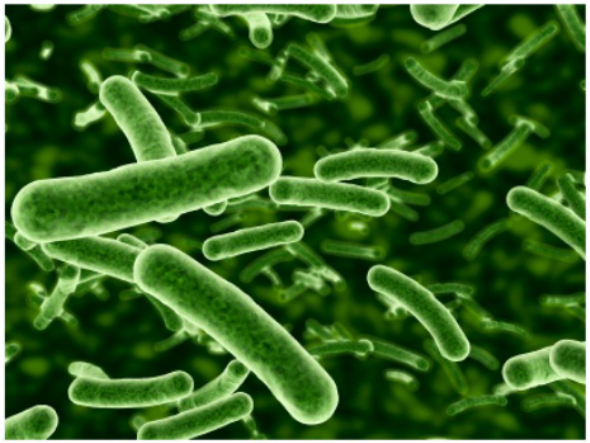


Acetic acid (acetate) Propionic acid (propionate) Butyric acid (butyrate)

Production of short chain fatty acids

Completion of the bile-salt cycle

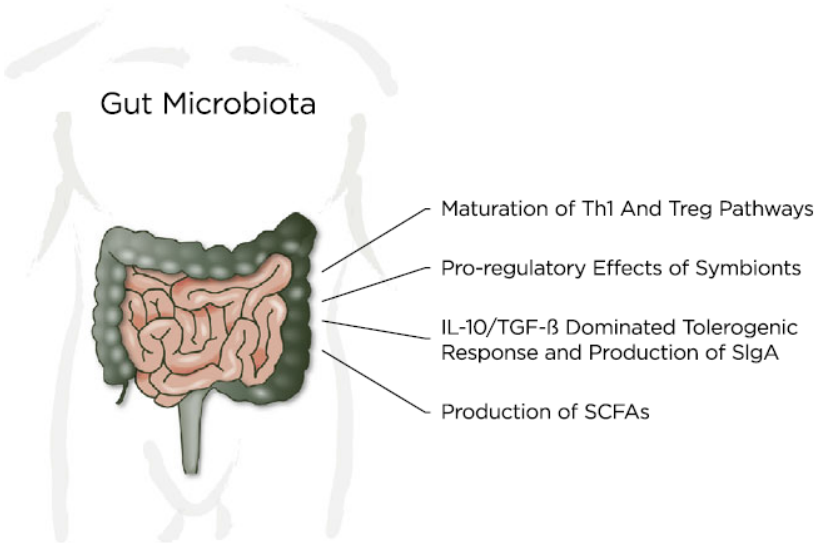




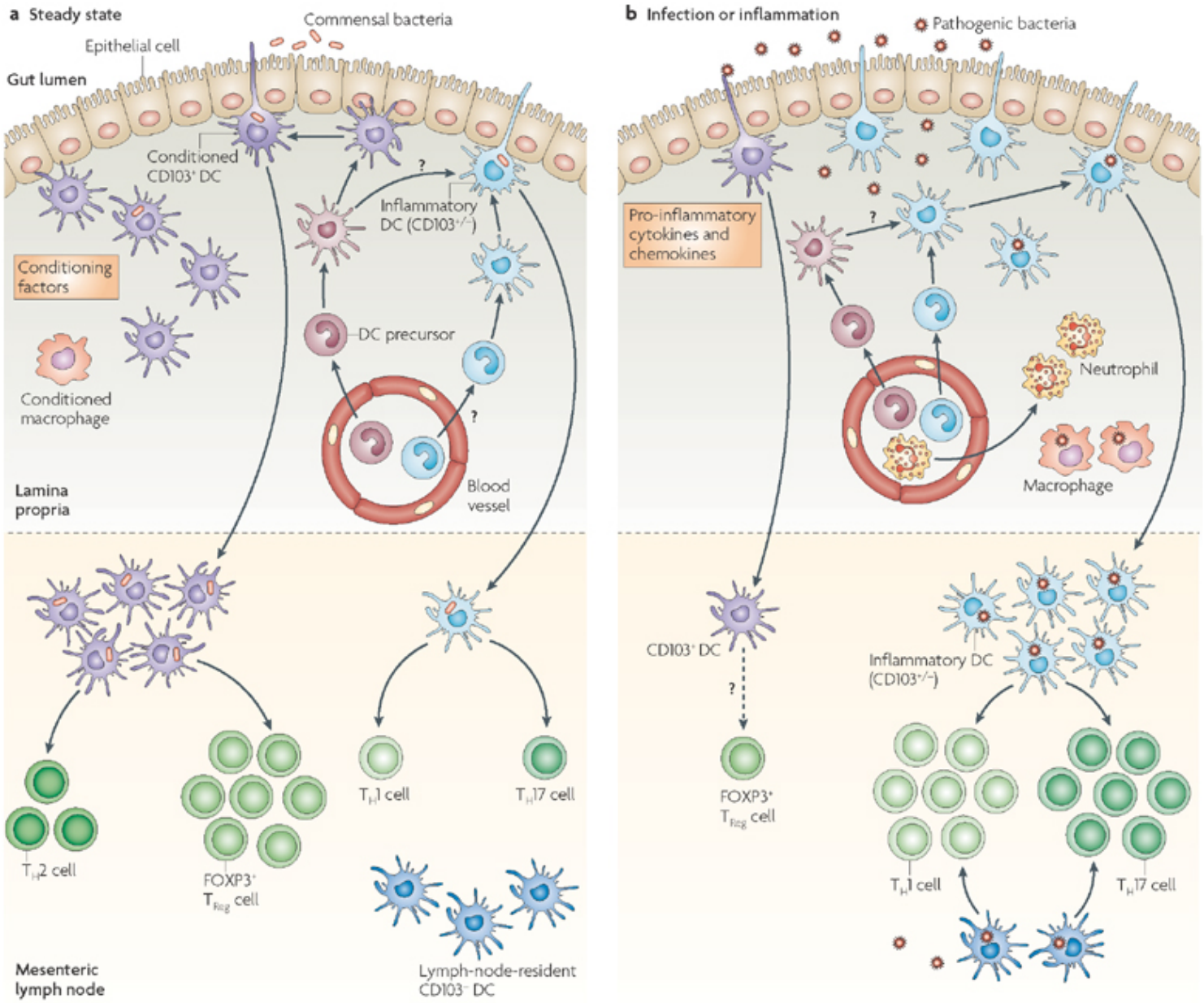
Protect the host from colonization with pathogenic bacteria (Colonization resistance)

Gut microbiota in disease: Allergic disease

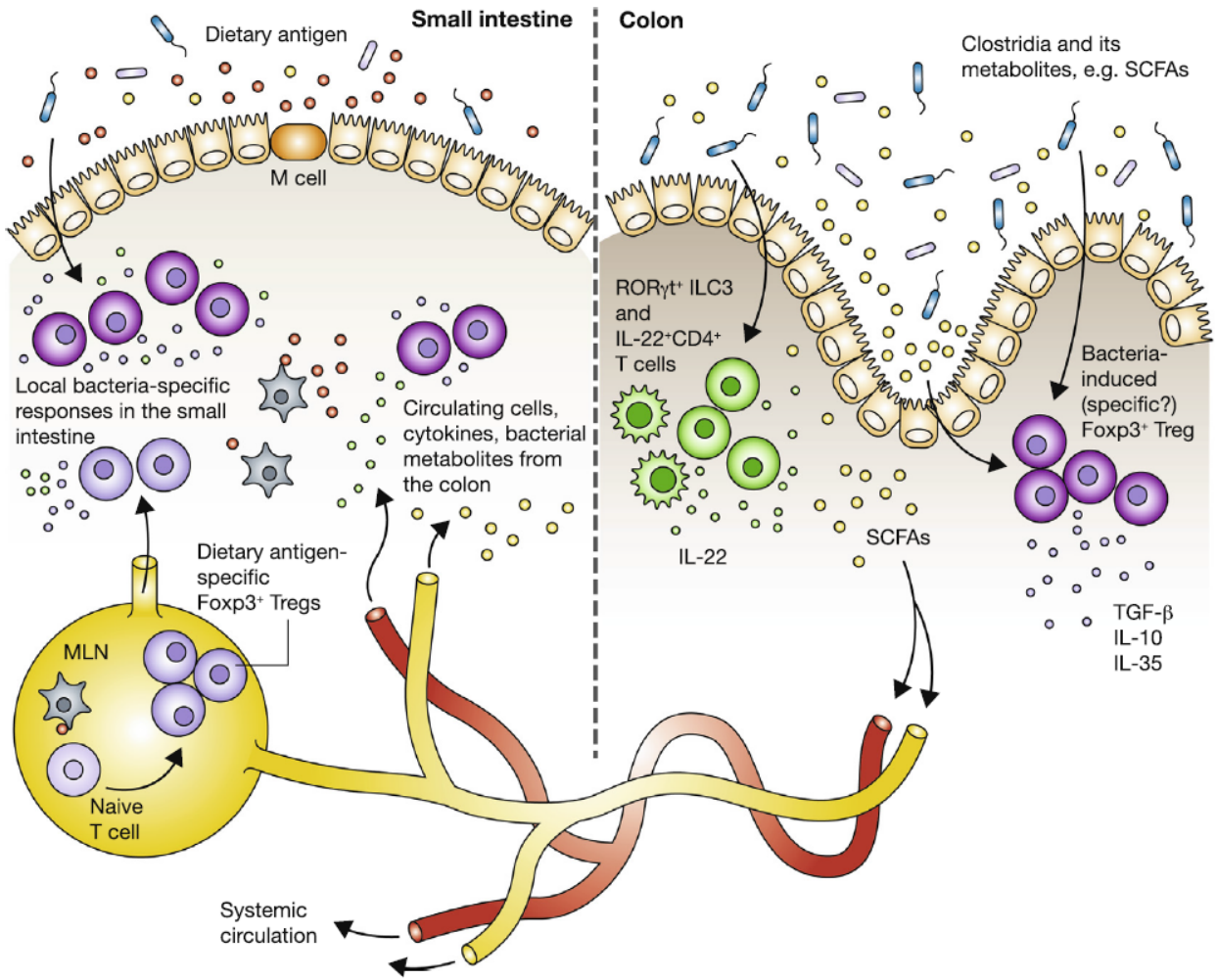
- Massive increase in prevalence of allergic diseases in Westernized countries (>20% over 10 year period)
- Allergic disease is attributed to both genetic predisposition and environmental factors
- Genetic drift over such a short period of time cannot explain increased incidence of disease
- Westernized life-style has introduced several environmental risk factors that disturb the homeostatic balance of gut microbiota
  - Excessive antibiotic use, especially during early life (or even during pregnancy)
  - Shift towards more formula-fed babies
  - Shift towards greater numbers of babies born via Caesarean section
  - Western diet



Pathogen bacteria cause inflammation in the gut wall



Gut microbiota in disease: Food allergy



- Certain types of bacteria produce SCFAs, which can drive induction of regulatory T cells
- Certain types of bacteria promote IL-22 production by CD4+ and ILC, which promotes barrier protection

Table 1. Prevalence of food allergies in adults and children30

Food	Prevalence (%)
Young children	
Cow's milk	2.5
Egg	1.3
Peanut	0.8
Soy	0.4
Tree nut	0.2
Shellfish	0.1
Adults	
Shellfish	2
Peanut	0.6
Tree nut	0.5
Fish	0.4

Table 2. Clinical features of IgE-mediated food allergy

Local oral & orbital	Dermatological	Gastrointestinal	Respiratory	Systemic
Itching of palate/lips	Acute urticaria	Nausea	Nasal itching	Hypotension
Swelling of lips/ tongue	Flushing	Abdominal pain	Rhinorrhoea & nasal obstruction	
Eye itching, redness and watering	Angioedema	Vomiting	Sneezing	
Periorbital oedema	Exacerbation of existing eczema	Diarrhoea	Laryngospasm	
	Morbiliform rash		Dyspnoea, wheeze	

Table 3. Food groups cross reacting with pollens in Oral Allergy Syndrome (adapted from ref22)

Pollen	Allergen	Associated cross-reacting Oral Allergy Syndrome triggers
Birch	*Bet v 1*	Apple, peach, plum, cherry, apricot, almond, carrot, celery, parsley, hazelnut (also possible soy and peanut systemic allergy)
Ragweed	*amb a* allergen group	Melon, cucumber, zucchini, banana, kiwi
Mugwort	*art v 1*	Celery, carrot, parsley, peppers, mustard, cauliflower, broccoli, garlic, onion
Orchard Grass	*dac g* allergen group	Melon, peanut, potato, tomato
Timothy Grass	*Phl p* allergen group	Swiss chard, orange