Basic Immunology

Suppression of the immune response
Suppressor mechanisms of immune functions

19th lecture
November 3rd, 2025
Zoltán Kellermayer

Main steps of the immune response

Recognition

Molecular and cellular co-operations

Activation

Differentiation and clonal expansion

Effector functions

Memory formation

Suppression

Factors involved in suppression

1. Antigen as the main regulator

2. Need for costimulation

3. Regulatory T cells

4. Regulation of the humoral immune response
    - Regulatory B cells
    - Antibody feedback
    - Anti-idiotype antibodies

1. Antigen as the main regulator

Activates T and B cells

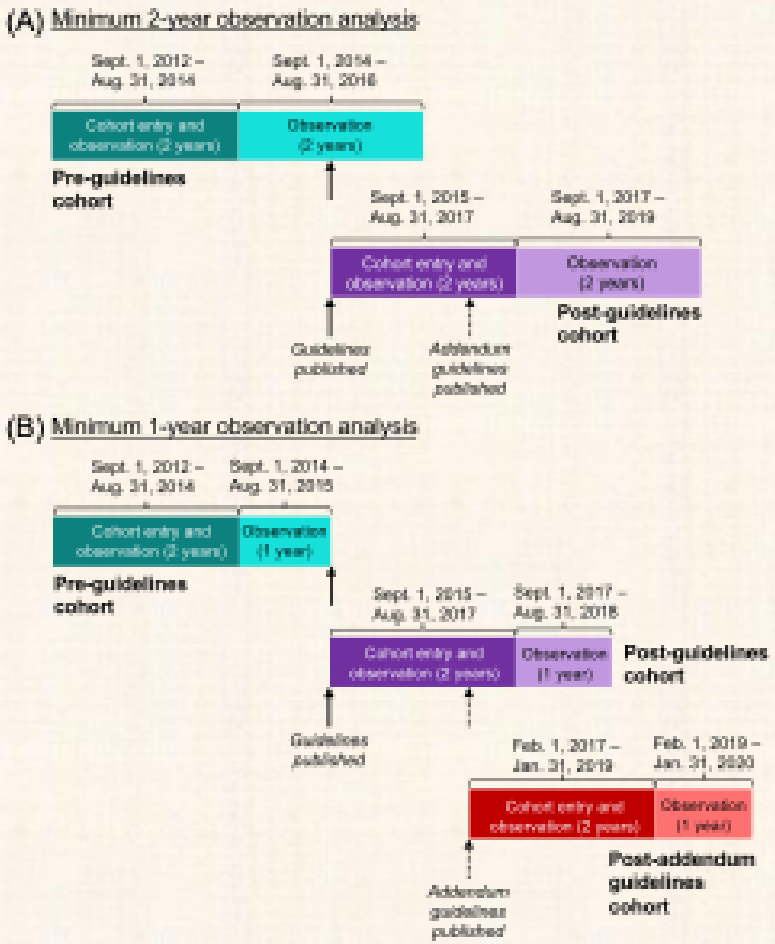
Antigen nature, dose (time, amount), location influence the immune response

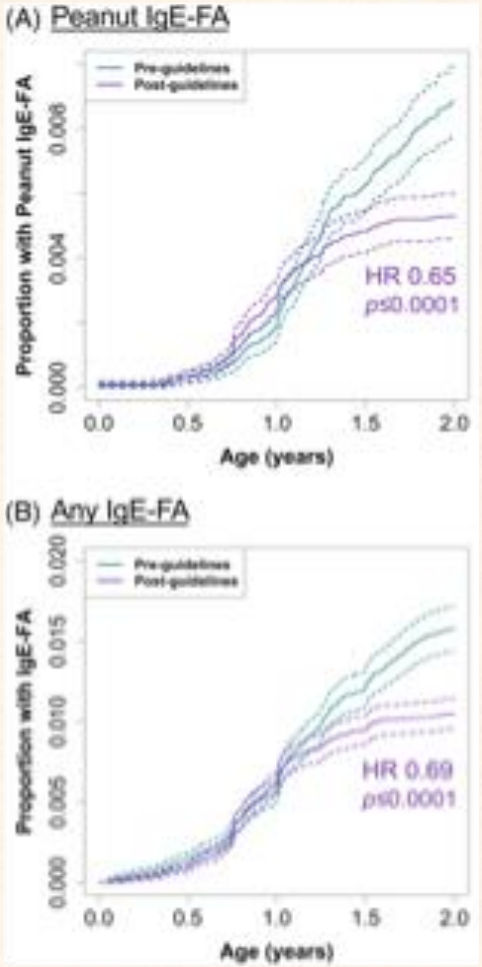
T_H1 vs T_H2

Withdrawal/elimination of the antigen stops further activation

1. Antigen as the main regulator: timing

Peanut allergy: when should peanut (as antigen) be introduced?

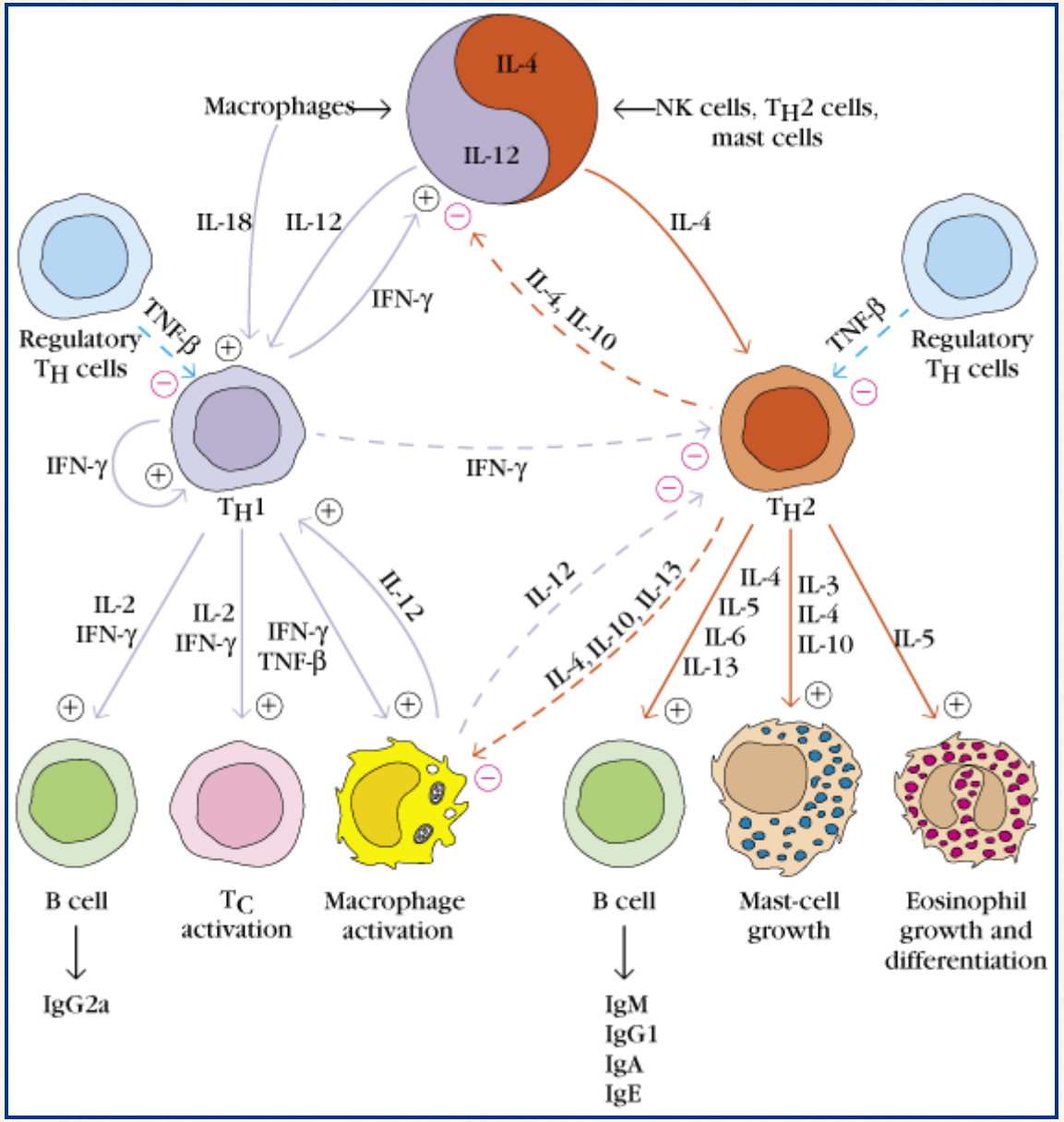




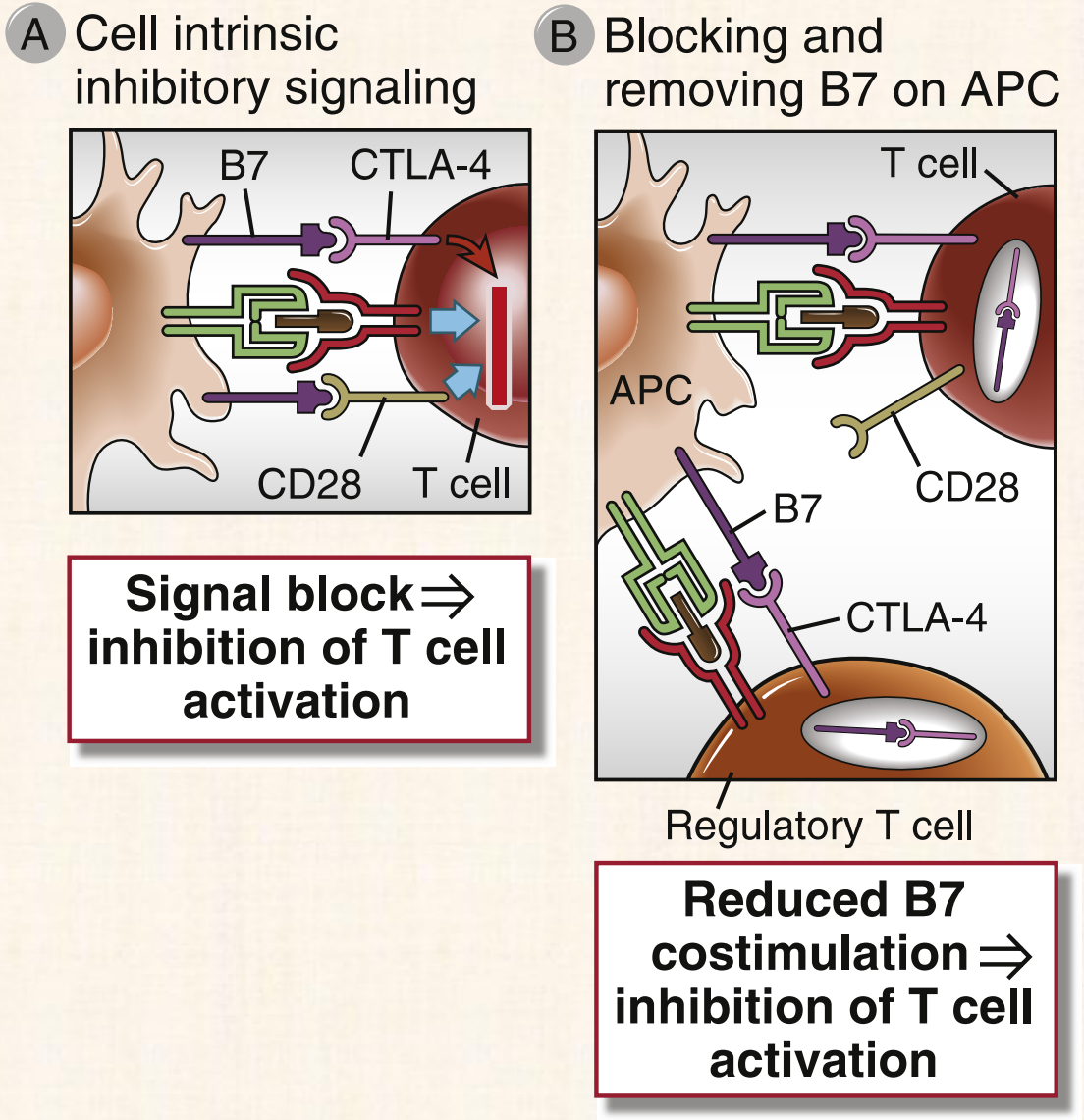
Introducing peanuts earlier led to a lower incidence of peanut allergy

Gabryszewski SJ et al: Guidelines for Early Food Introduction and Patterns of Food Allergy. Pediatrics, 2025

1. Antigen as the main regulator: influencing the cytokine balance



2. Need for costimulation

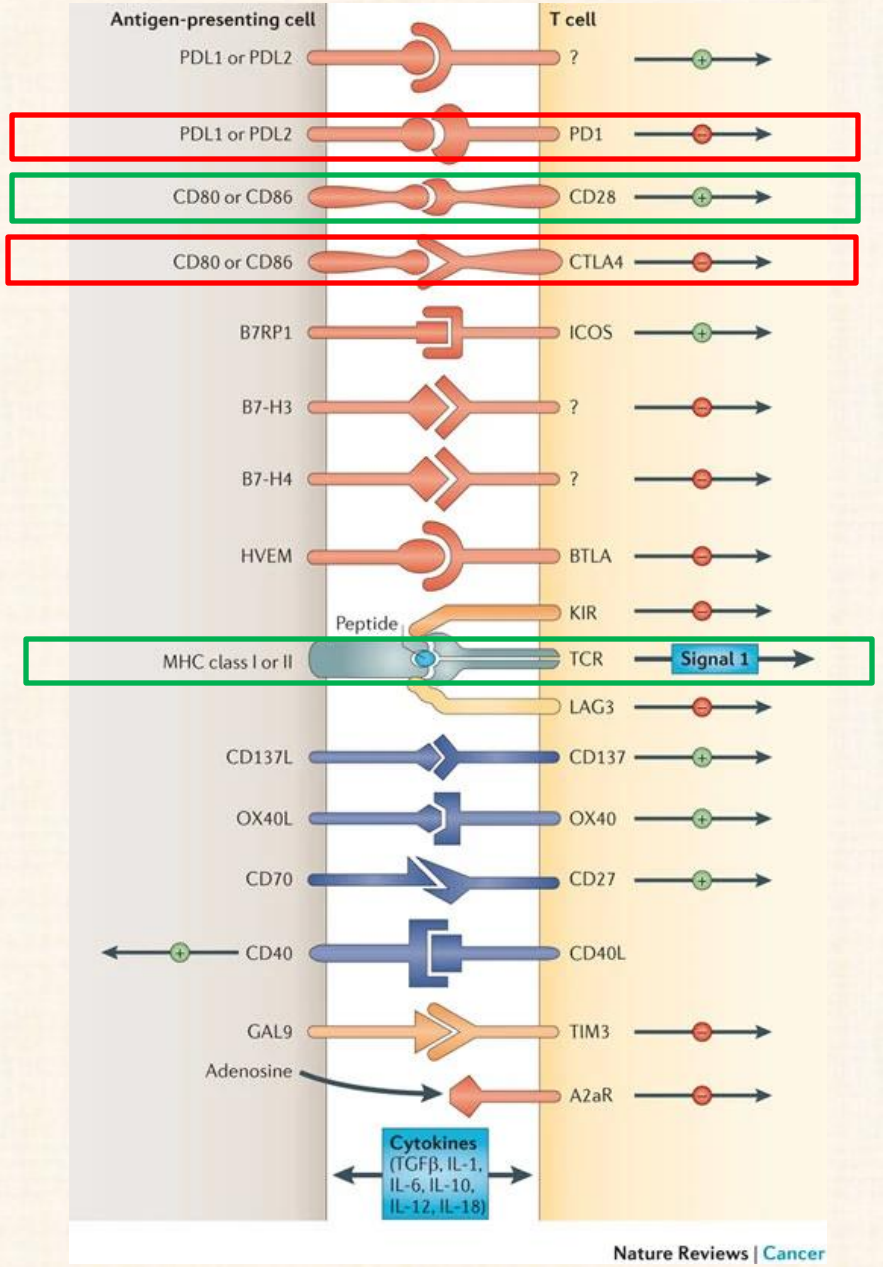


CD28: constitutively expressed on T cells
CTLA-4: expressed after activation
higher affinity towards B7

Fig 15-6

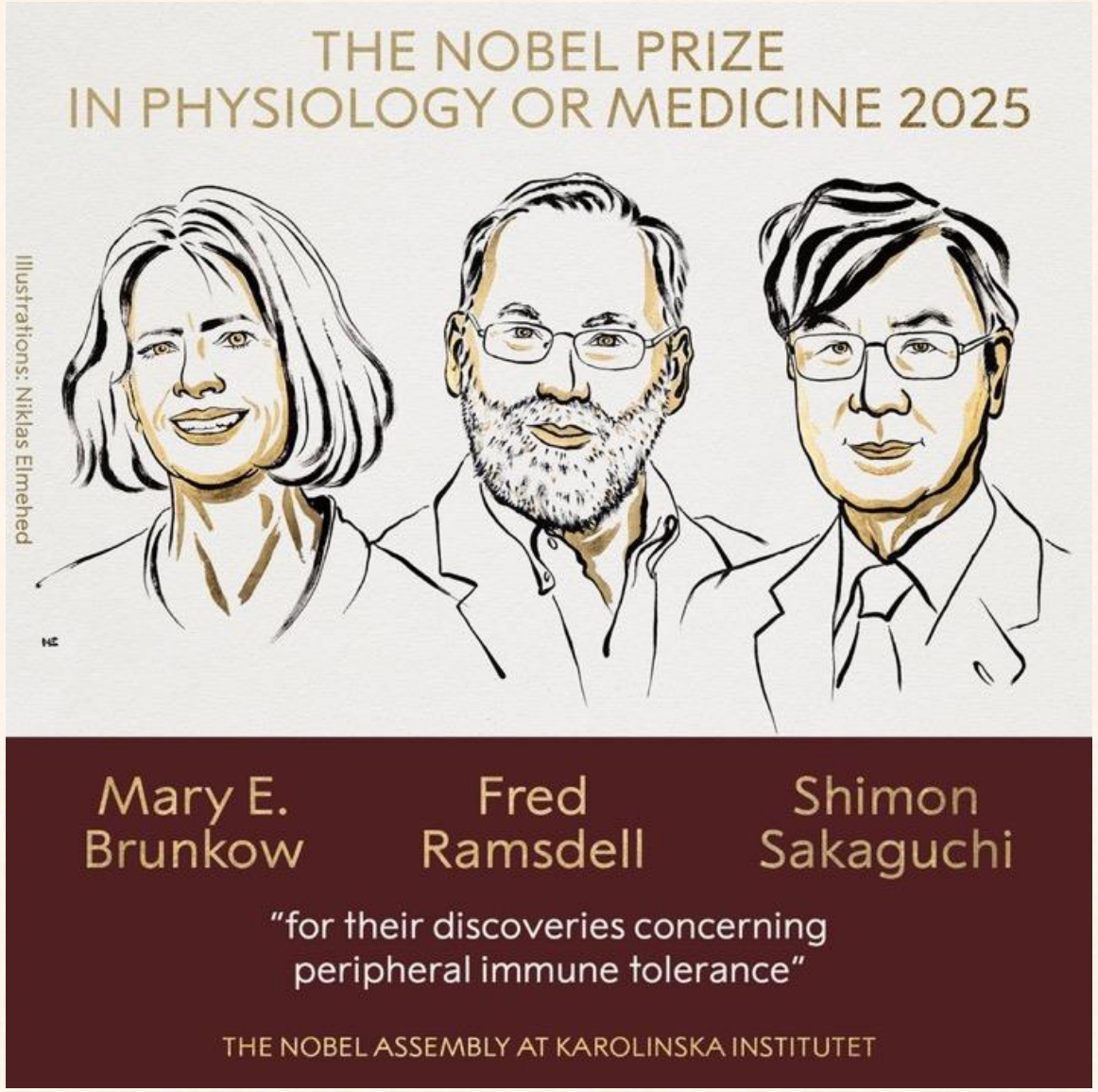
2. Need for costimulation: Immune checkpoints

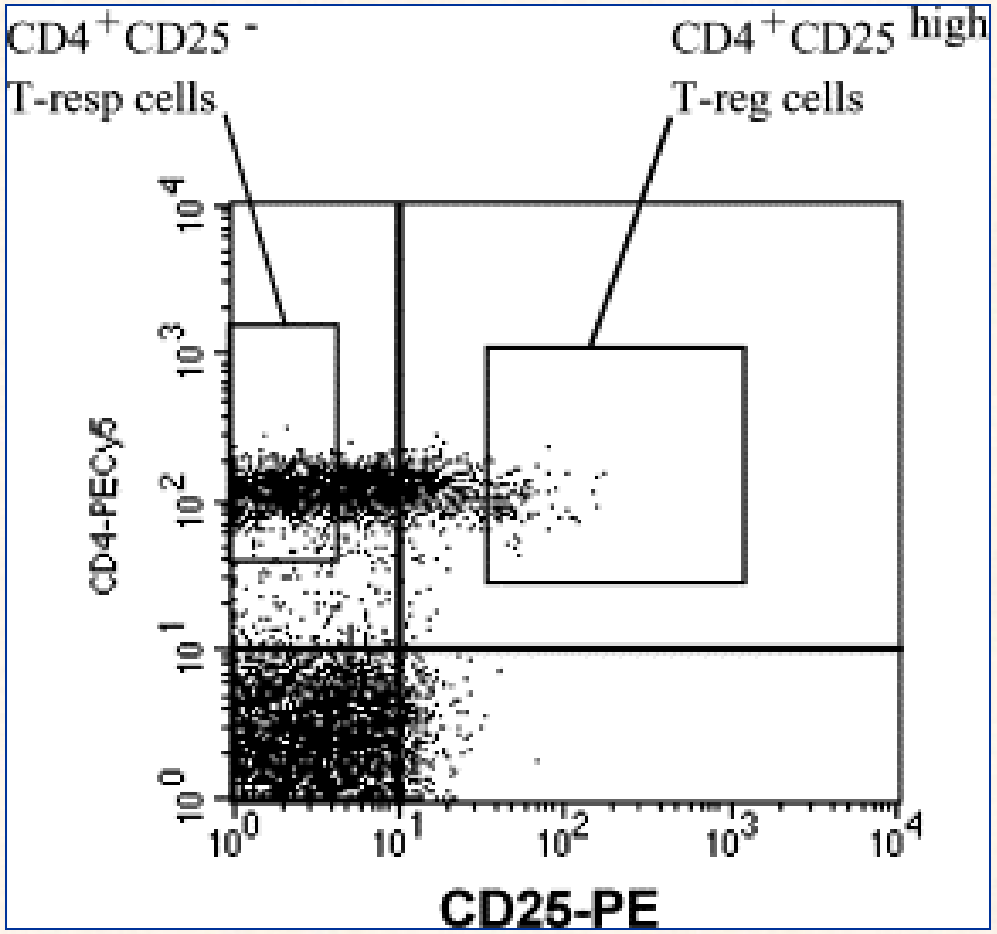
Antigen presenting cell



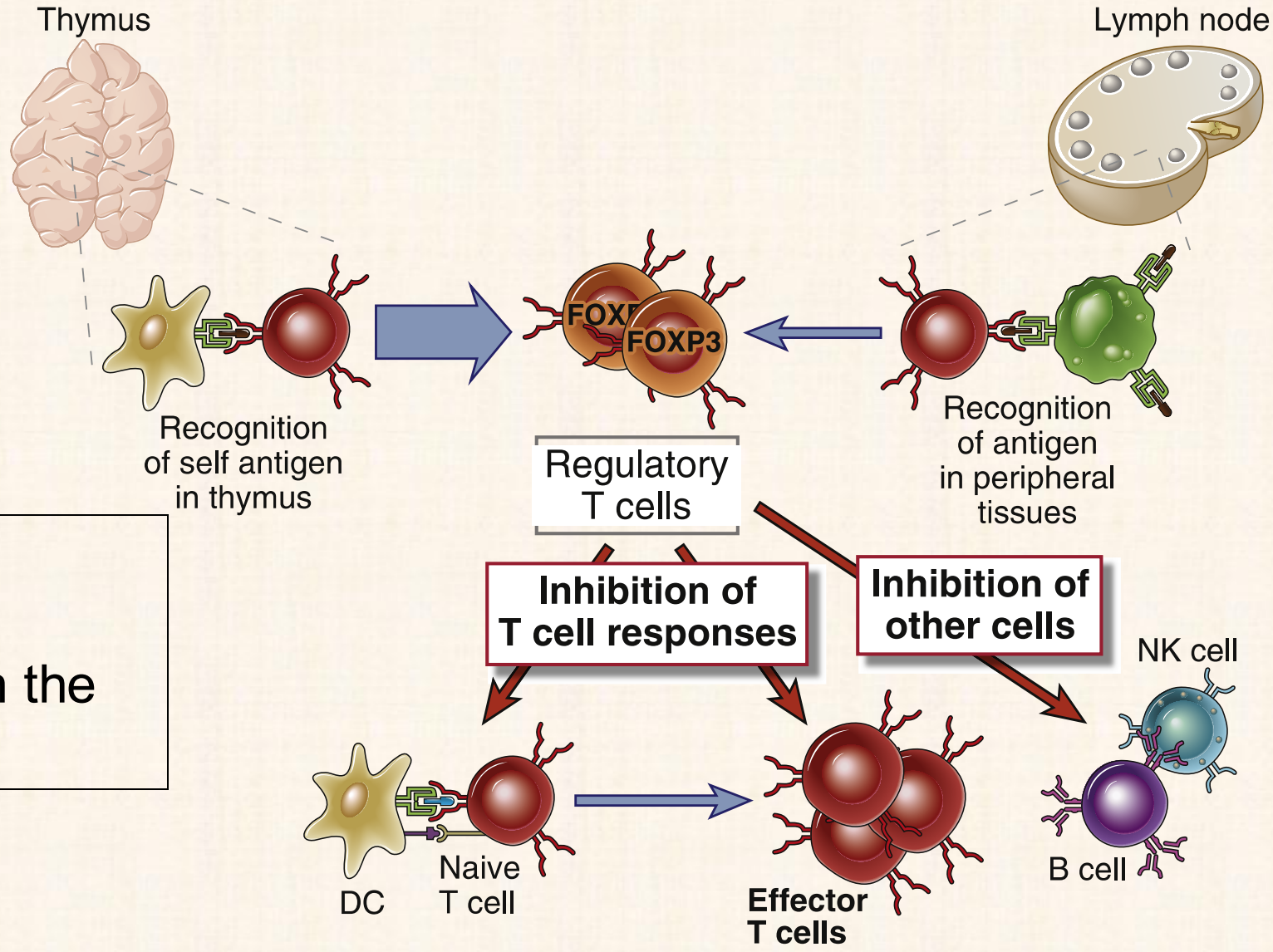
T cell

3. Regulatory T cells (T_{reg}) are $CD3^{+}CD4^{+}CD25^{hi}$





3. Main functions of regulatory T cells



Natural Treg

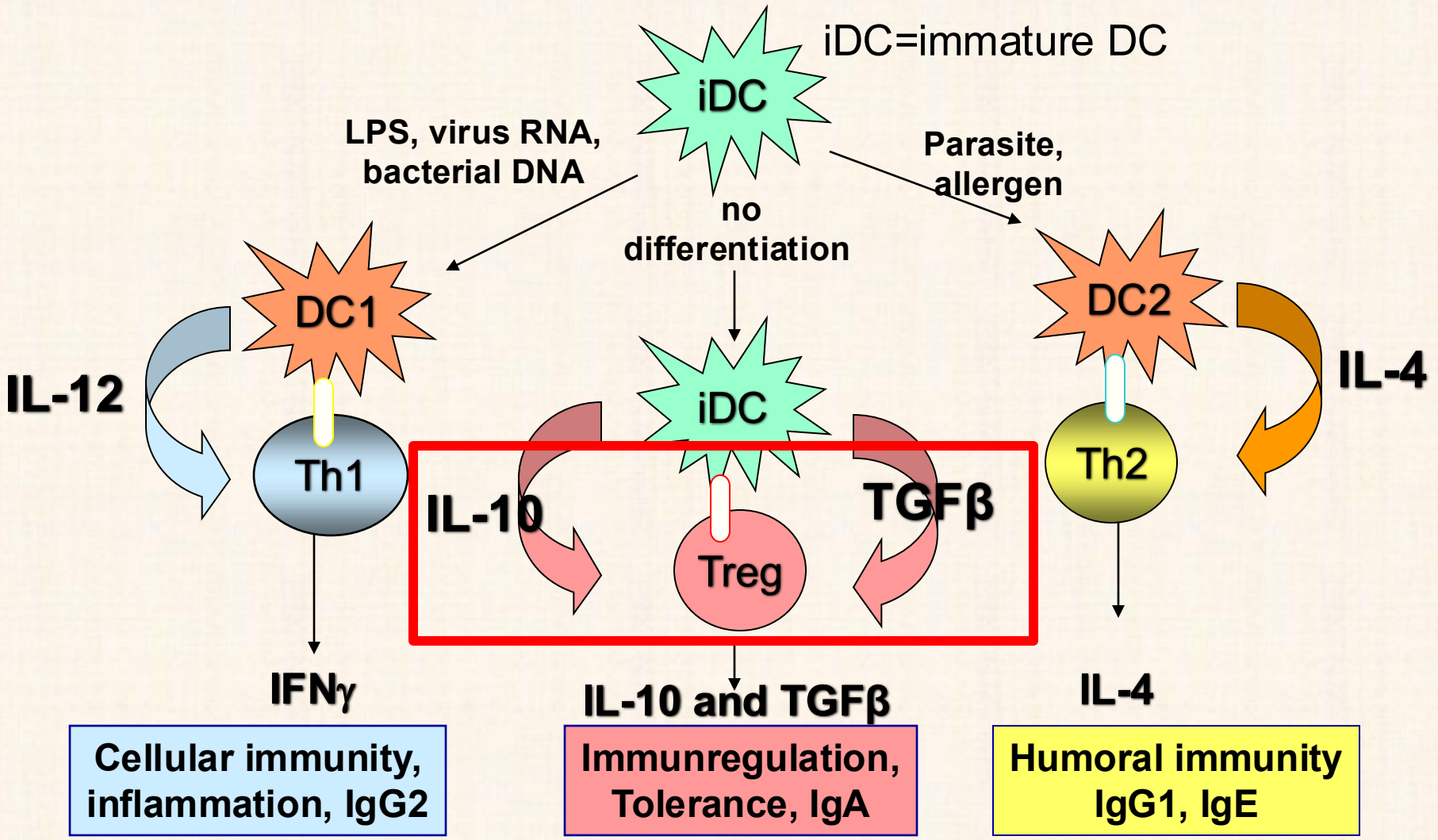
Differentiate in the thymus

Induced Treg

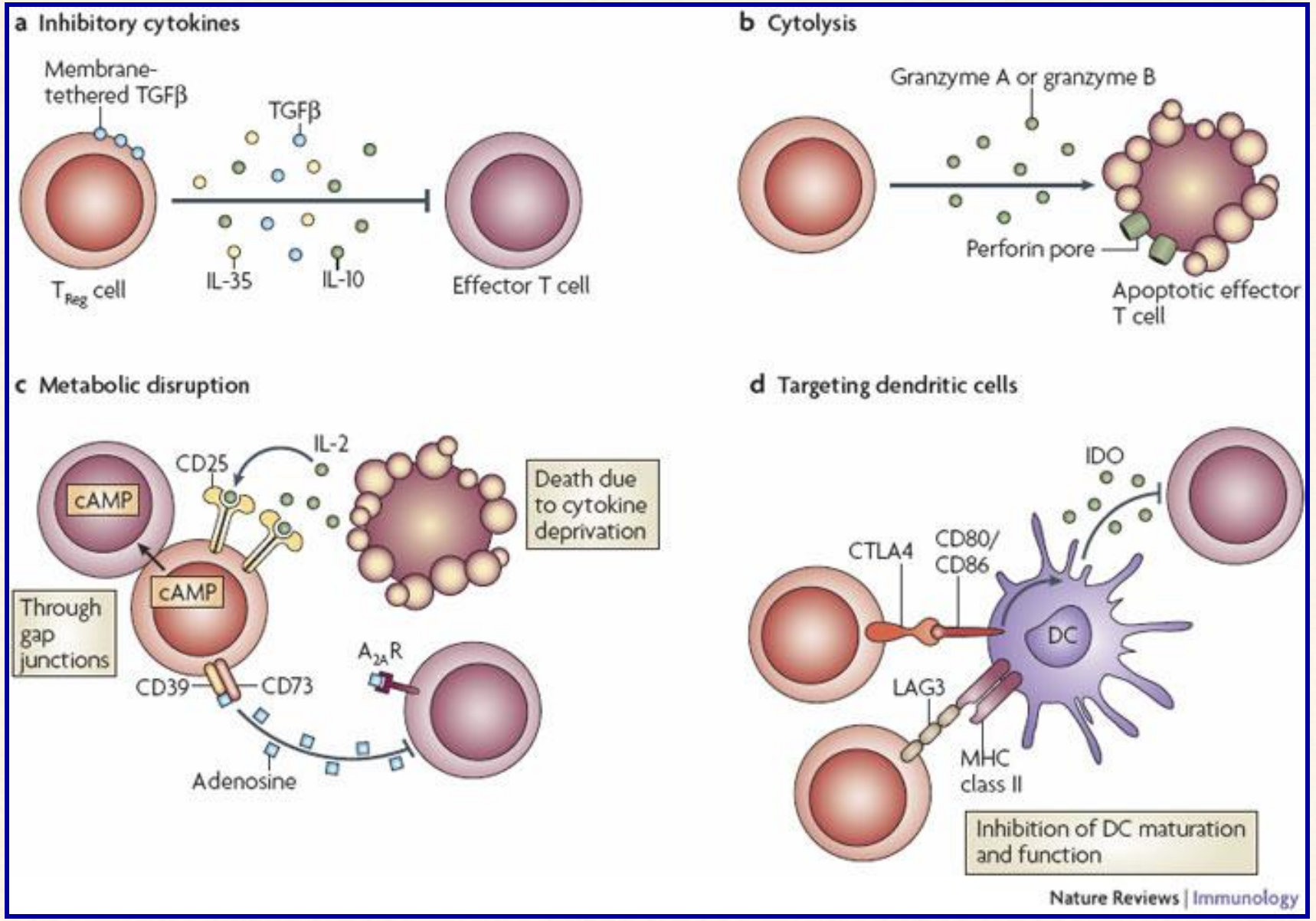
Differentiate in the periphery

Fig 15-7

3. Development of induced T_{reg} cells



3. T_{reg} suppression mechanisms



3. Inhibitory cytokines secreted by T_{regs}

TGFβ (Transforming Growth Factor β)

Inhibits classical (M1) macrophage activation
Suppresses neutrophils
Promotes T_{reg} differentiation (but under certain circumstances, also T_H17!)
Induces IgA isotype switch
Promotes local tissue repair

IL-10

Inhibits IL-12 production by DCs and macrophages
Inhibits expression of co-stimulatory molecules on DCs and macrophages
Inhibits expression of class II MHC molecules on DCs and macrophages

3. T_{reg} overview

Phenotype: $CD3^+$ $CD4^+$ $CD25^+$ $FoxP3^+$

FoxP3 Mutation: IPEX Syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)

Origin: Thymus (natural) or periphery (induced)

Suppression mechanism:

- Cytokine secretion: IL-10, TGFβ
  - *IL-10$^{-/-}$ mice: colitis*
- Blocking costimulation via CTLA-4
- IL-2 “consumption” via IL-2Rα (CD25, high-affinity IL-2R)
- cytolysis

4. B cell suppression

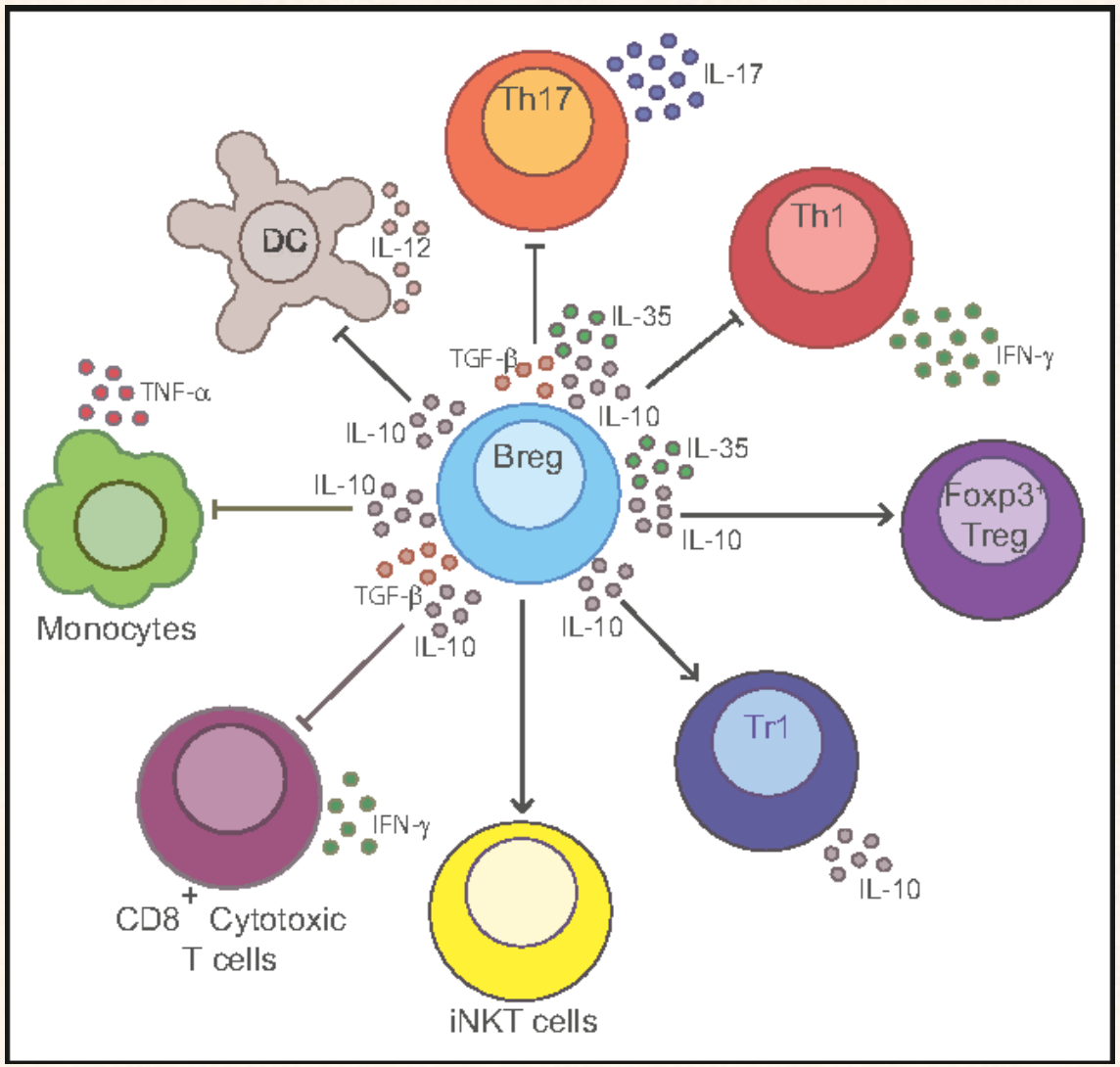
Regulatory B cells (B_{reg})

High levels of antibodies block further B cell activation

IgG + antigen immunocomplex inhibits B cell function by binding to FcγRIIb

(IgM + antigen immunocomplex promotes further B cell activation!)

4. Regulatory B cells



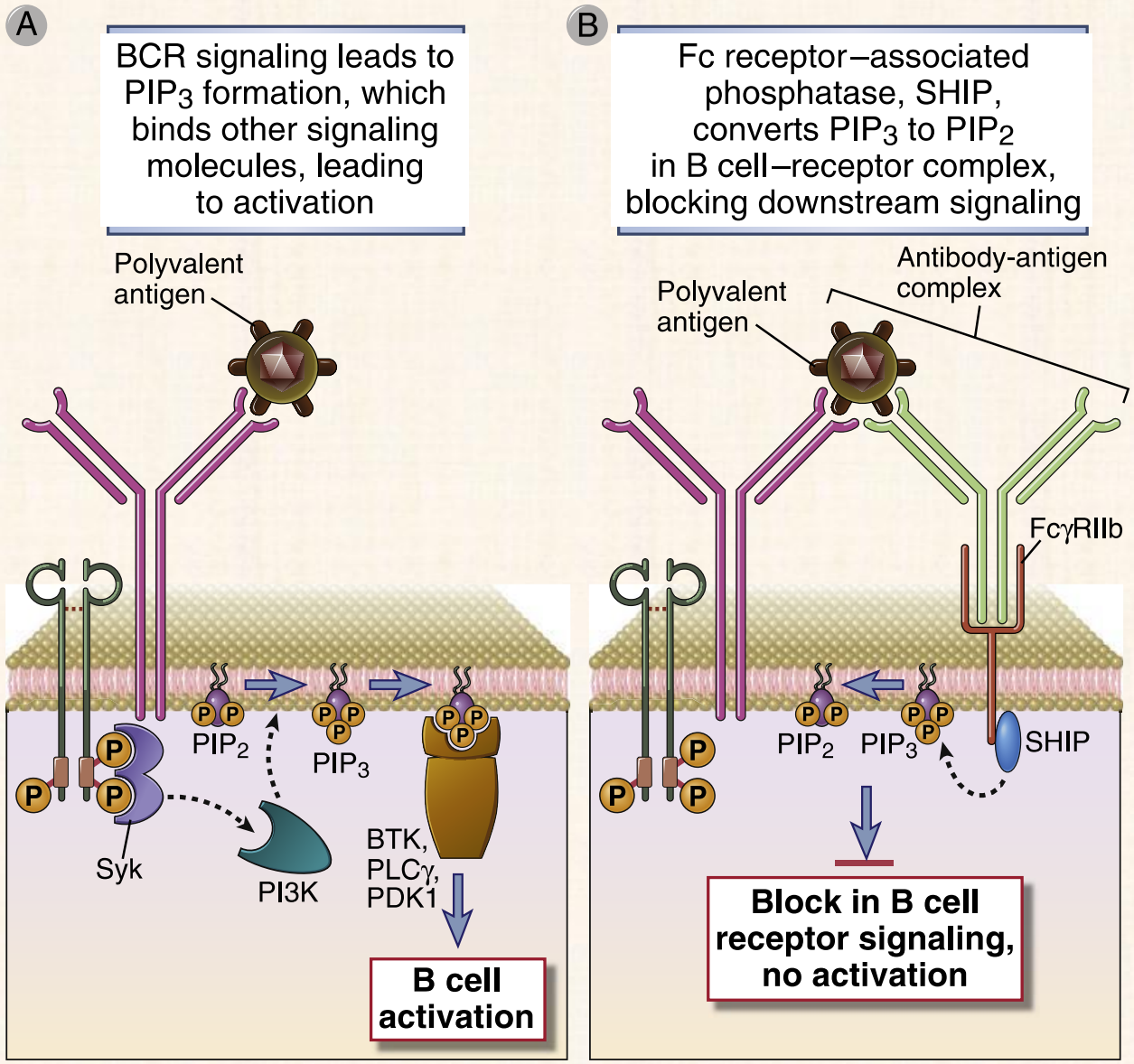
B_{reg} cells produce **IL-10**, IL-35, and TGF-β

Prohibit the expansion of pathogenic T cells and other pro-inflammatory lymphocytes

Promote T_{reg} cells

No definitive phenotype identified yet

4. Suppression via antibody feedback



FcγRIIb: inhibitory FcR (contains ITIM!)

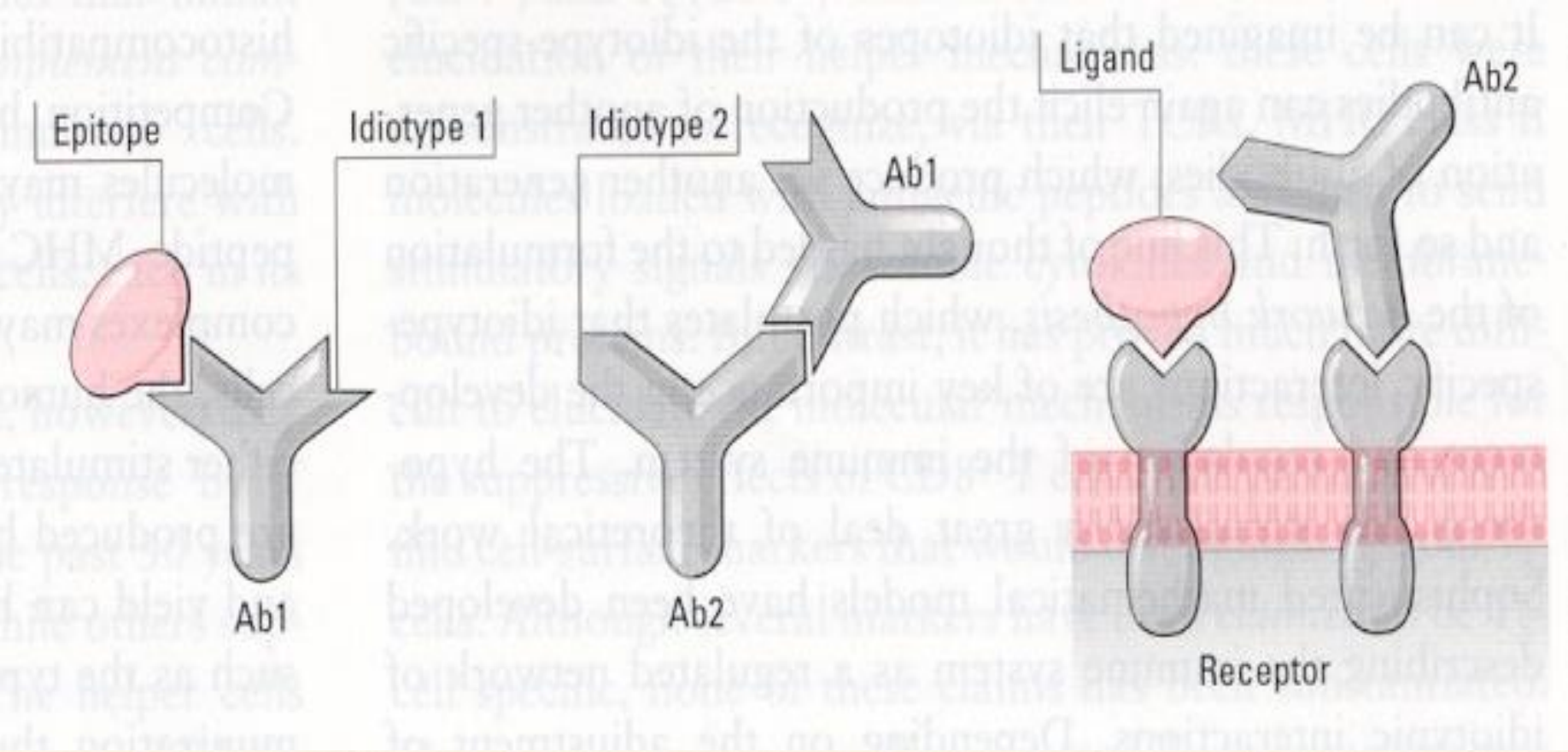
Simultaneous binding of antigen + IgG leads to B cell inhibition

Fig 12-21

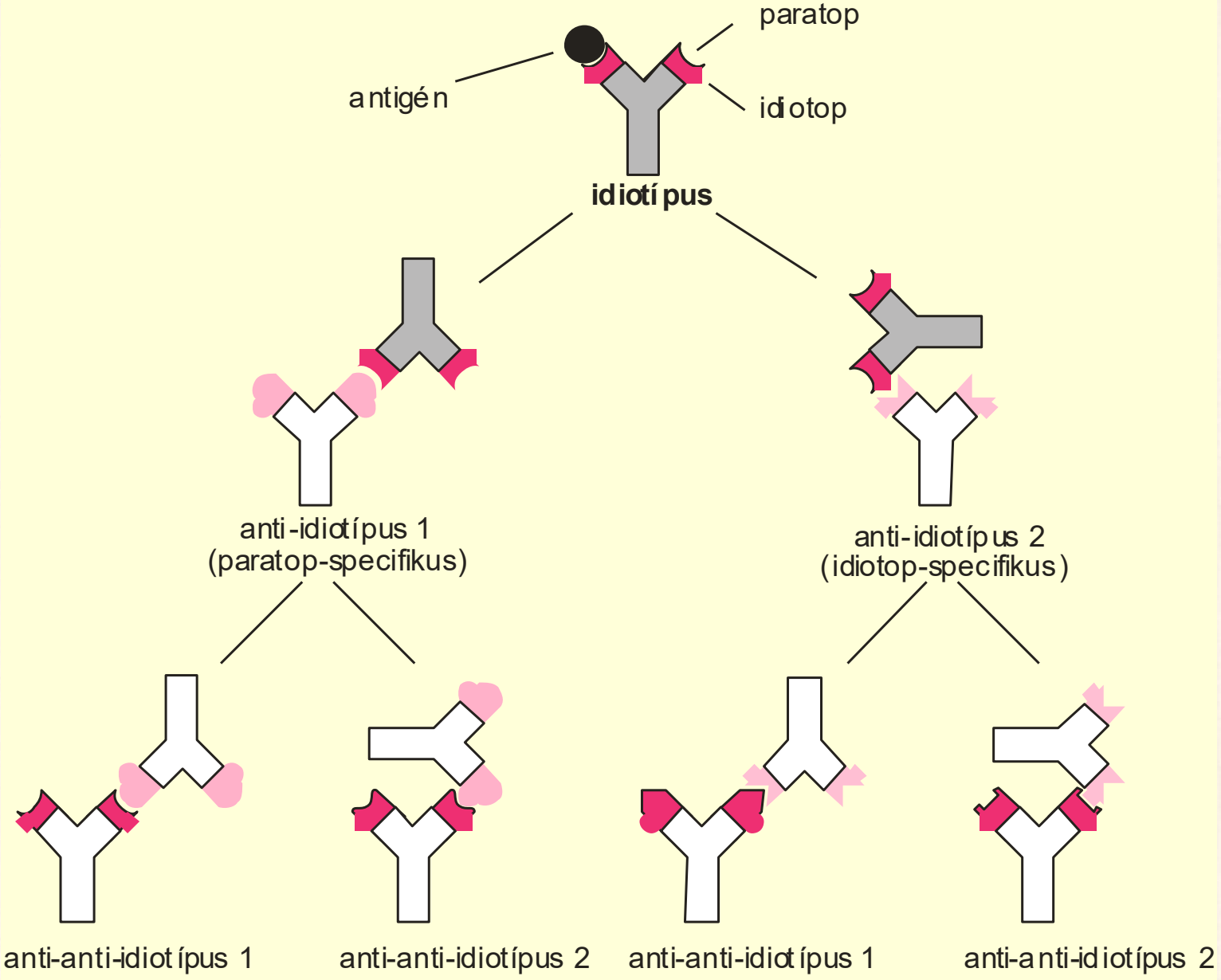
4. Anti-idiotype antibodies

Affinity maturation (somatic hypermutation) leads to formation of new structures capable of inducing an immune response

Antibodies will be directed against the idiotype of the original antibody



4. Anti-idiotype network



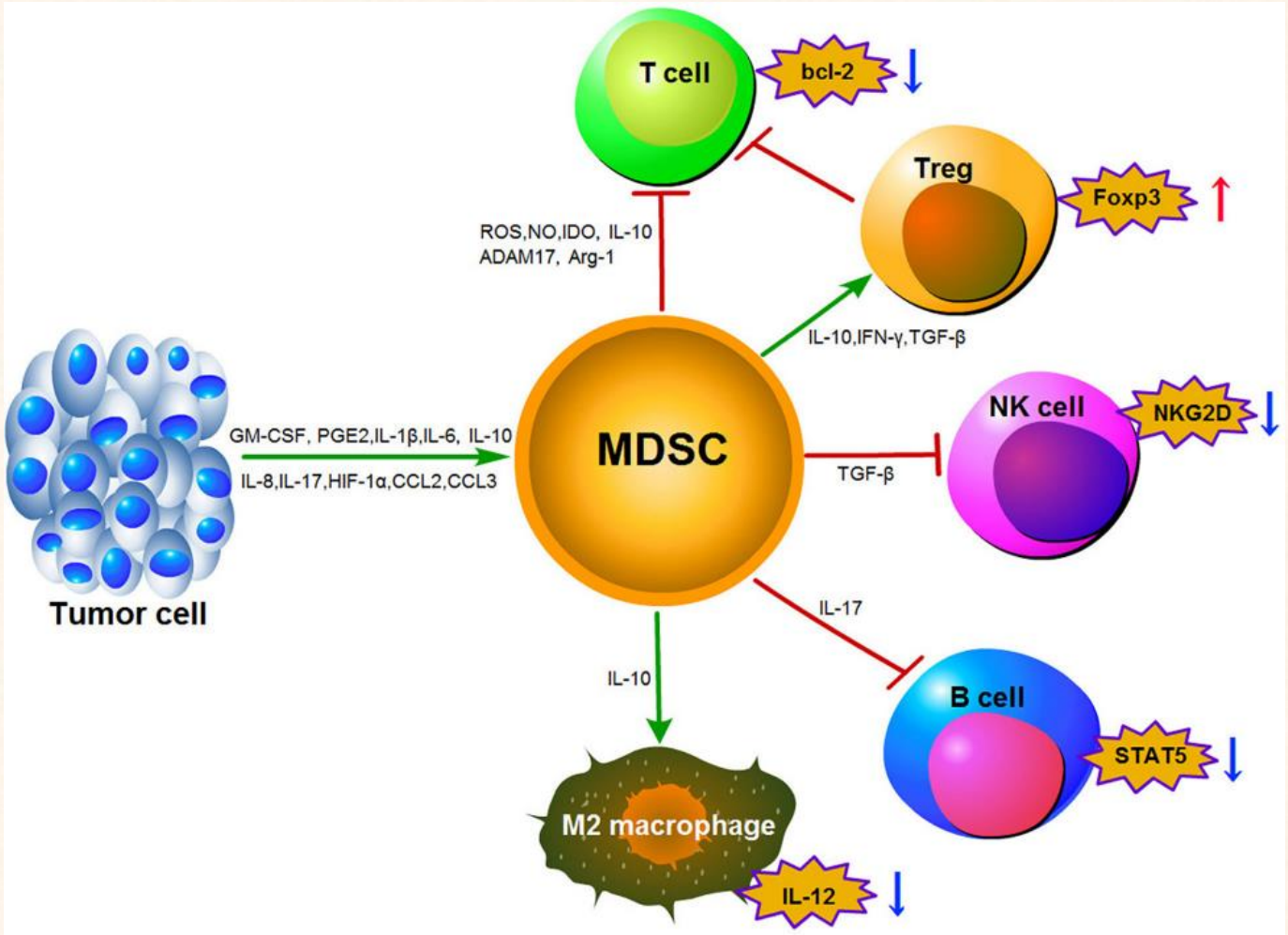
4. Functions of the anti-idiotype network

Suppression of B and T cells

Functional memory formation

Biological mimicry (insulin – anti-insulin – anti-anti-insulin)

+1a: Pathological suppression: Myeloid Derived Suppressor Cells (MDSCs)

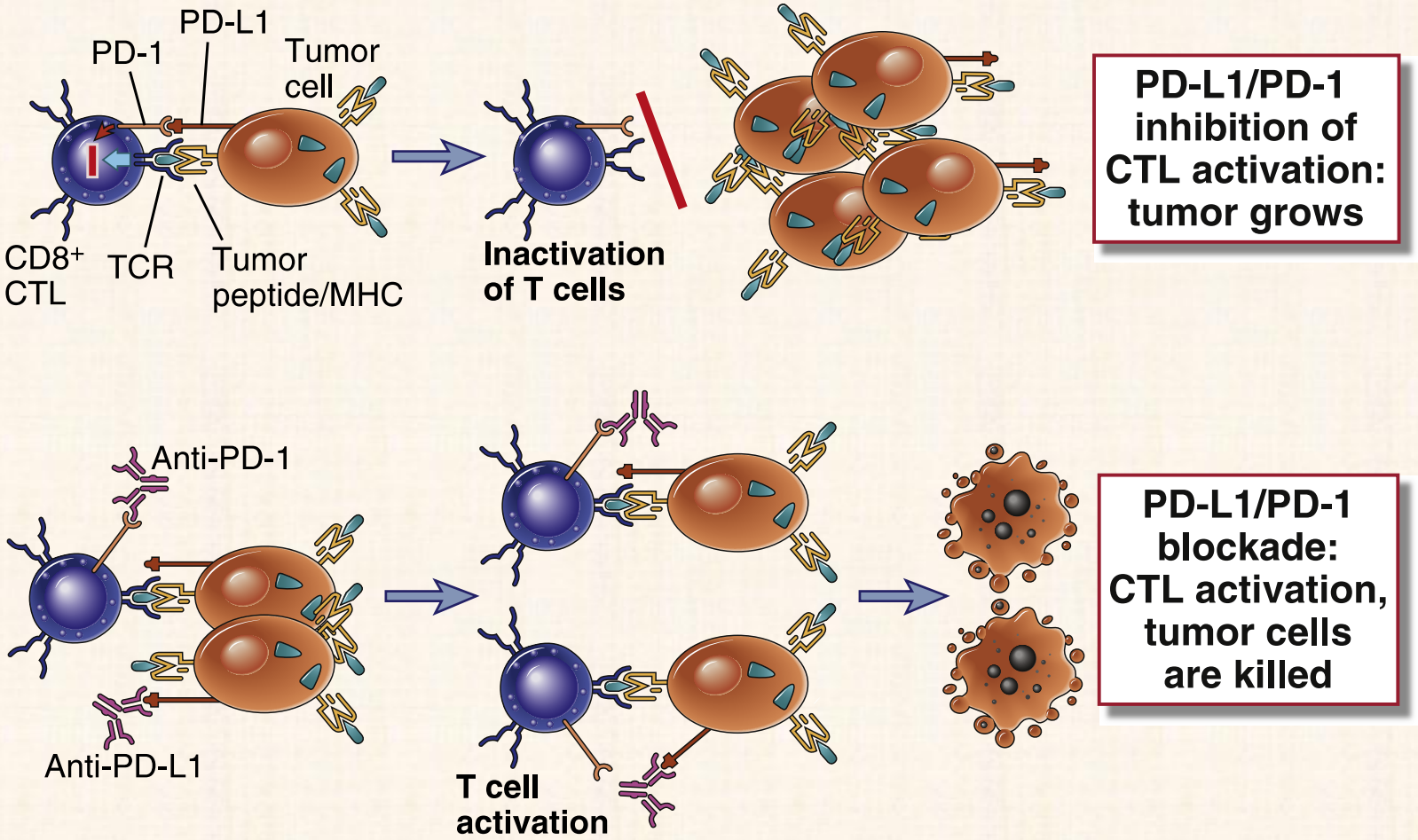


Yin K et al 2020. Front. Oncol. 10:610104. doi: 10.3389/fonc.2020.610104

Tumor microenvironment induces differentiation of MDSCs from various myeloid cells (neutrophils, monocytes, dendritic cells)

MDSCs suppress the anti-tumor immune response, promoting tumor growth

+1b: Pathological suppression: Tumors inhibit T cells via immune checkpoint



Tumors express inhibitory molecules that lead to blockade of T cell activation (see slide #7)

Targeting these inhibitors is a promising area of tumor immunotherapy (*Nobel Prize for in Physiology or Medicine, 2018, James P Allison and Tasuku Honjo*)

Basic Immunology

Regional immunity
Immune components of the oral cavity

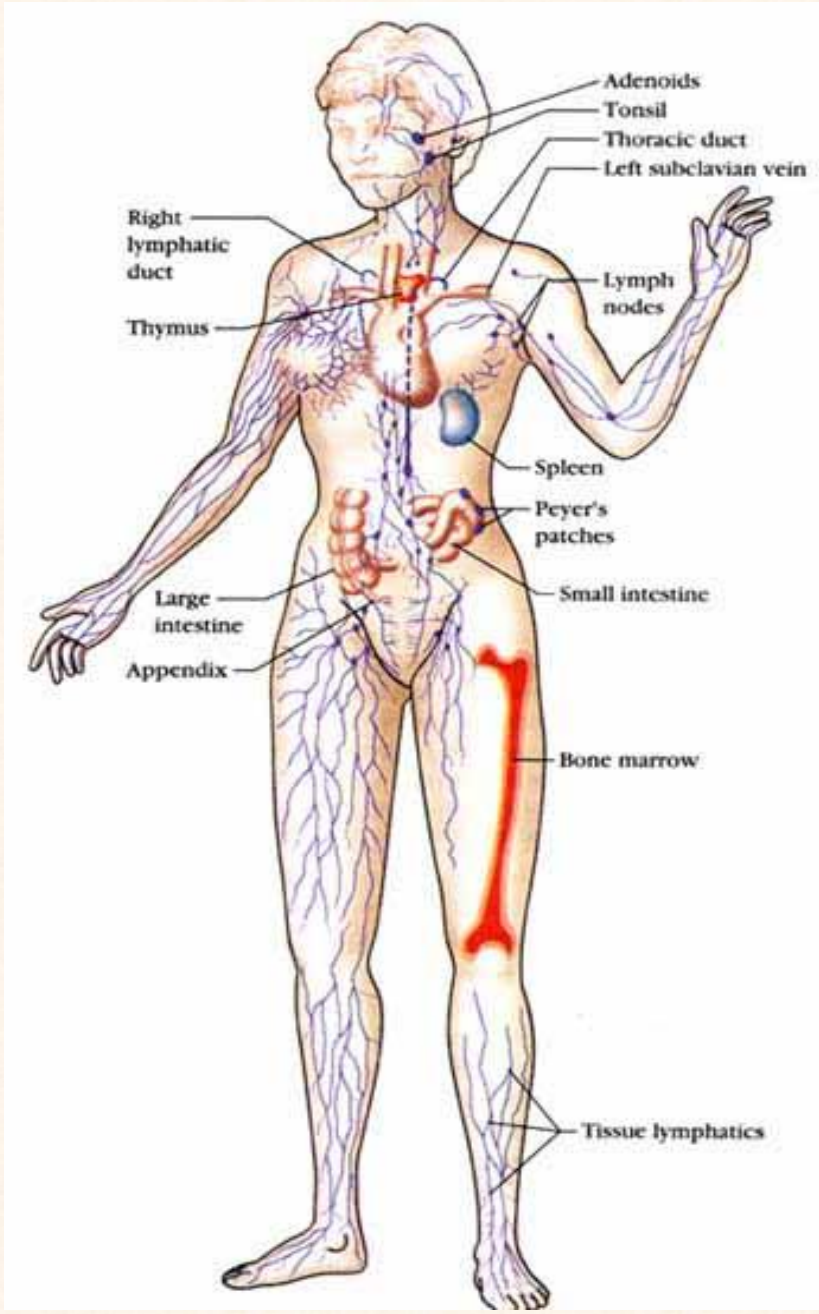
20th lecture
November 3rd, 2025
Zoltán Kellermayer

Regional immune system

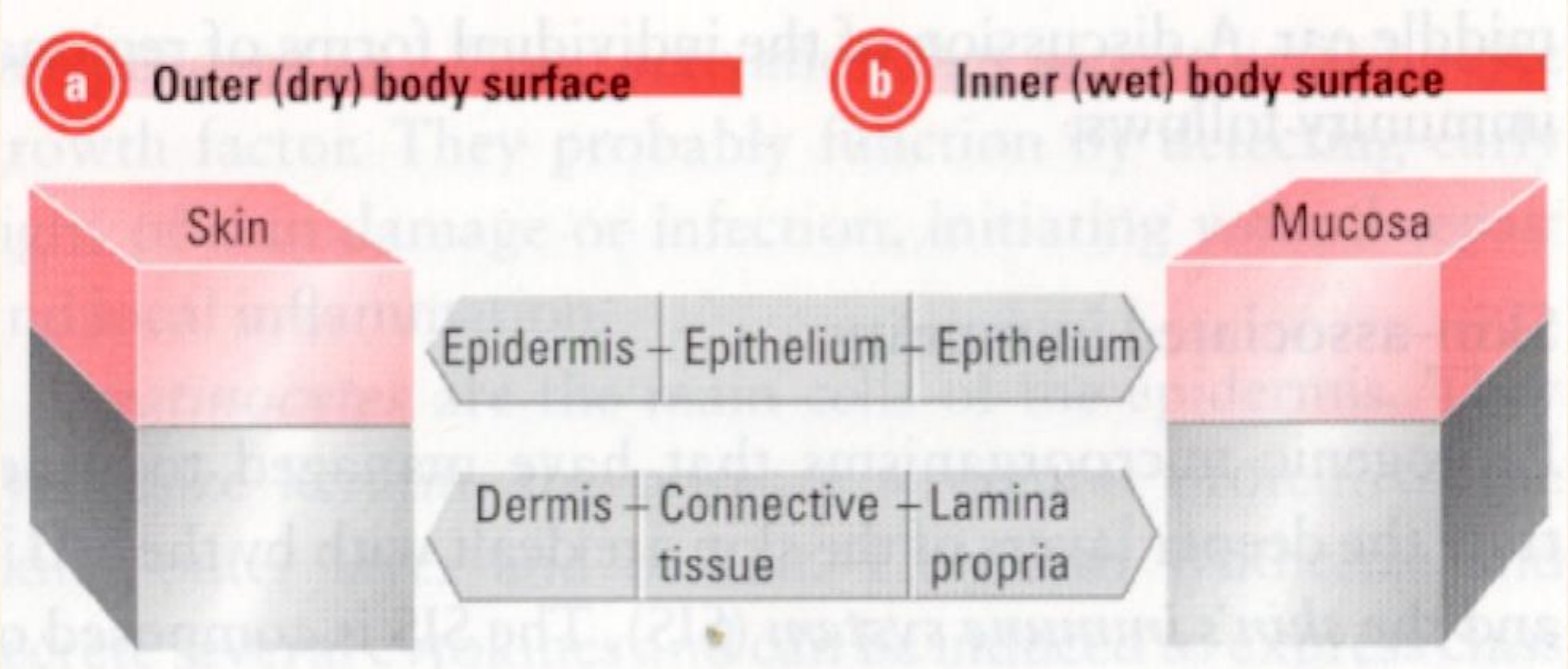
The collection of *immune cells* and *molecules* with specialized functions at a particular anatomic location

Gastrointestinal tract
MALT: Mucosa Associated Lymphoid Tissue

Cutaneous immune system
SALT: Skin Associated Lymphoid Tissue



Two types of body surfaces



Physical barrier

Immune cells

Draining secondary lymphoid tissues…

Intestinal immune system: introduction

Surface: 200 m^2

~$5x10^{10}$ total lymphocytes (blood: 10^{10})

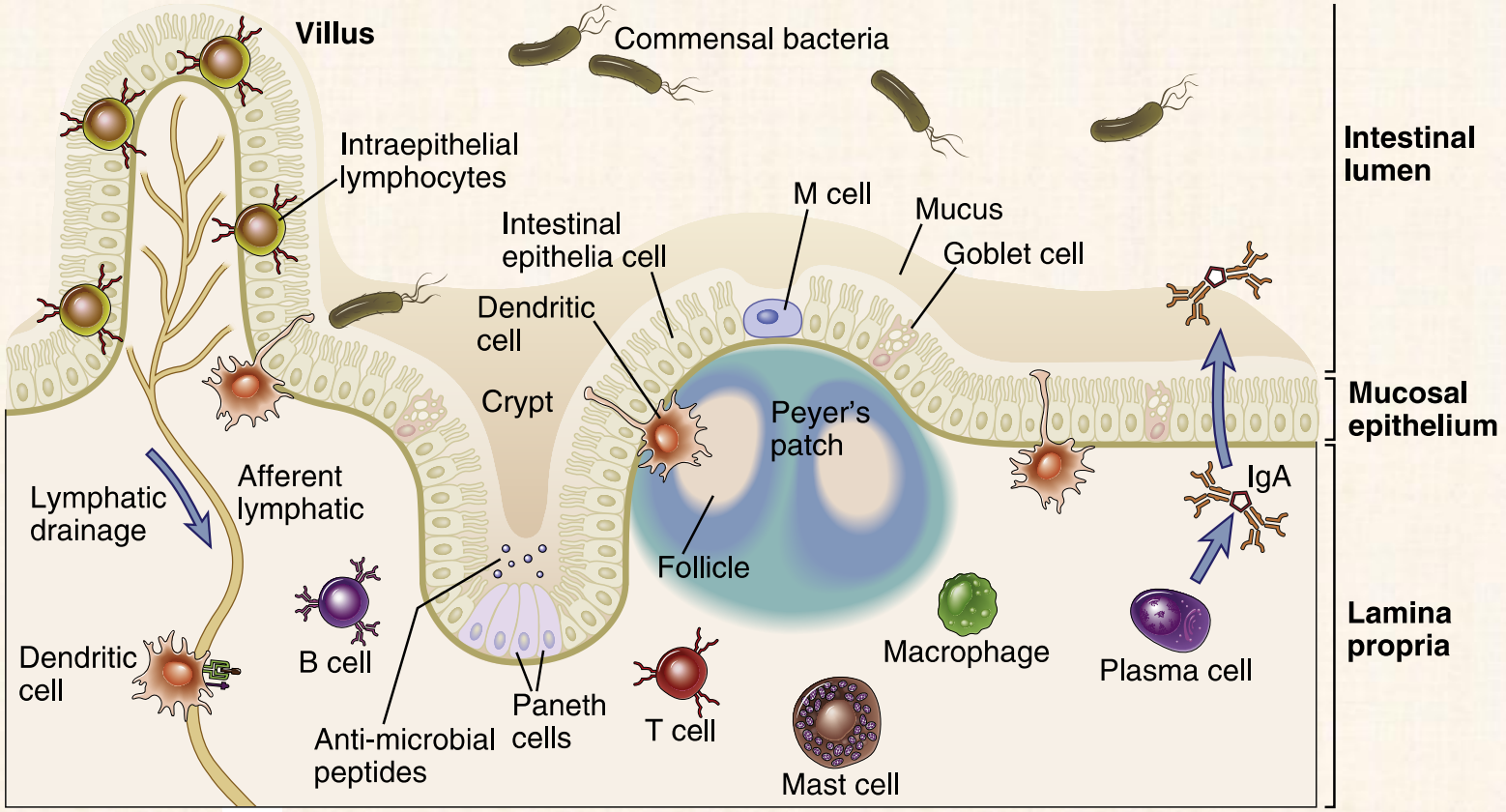
Huge amount of microbes: 10^{14}

Harmless (beneficial) antigens: food + microbiome

Immune system has to find the small number of dangerous pathogens within the large amount of harmless antigens

Delicate balance between tolerance and attack

Overview of the intestinal immune system



Special structures

M cells

Migrating APCs

Peyer's patches

IgA

Effector cells: T cells, innate lymphoid cells (ILCs), NK cells, MAIT cells, macrophages, eosinophils, mast cells, granulocytes

Fig 14-1

Lymphoid tissues in the gastrointestinal tract

Organized MALT (O-MALT)

Antigen recognition, activation of antigen specific lymphocytes, induction of effector and memory cells

”*Programmed*” lymphoid tissues: develop in utero, in defined locations at defined times

Peyer’s patch, Tonsils

”*Inducible*” lymphoid tissues: develop/mature after birth, depending on antigenic stimulus

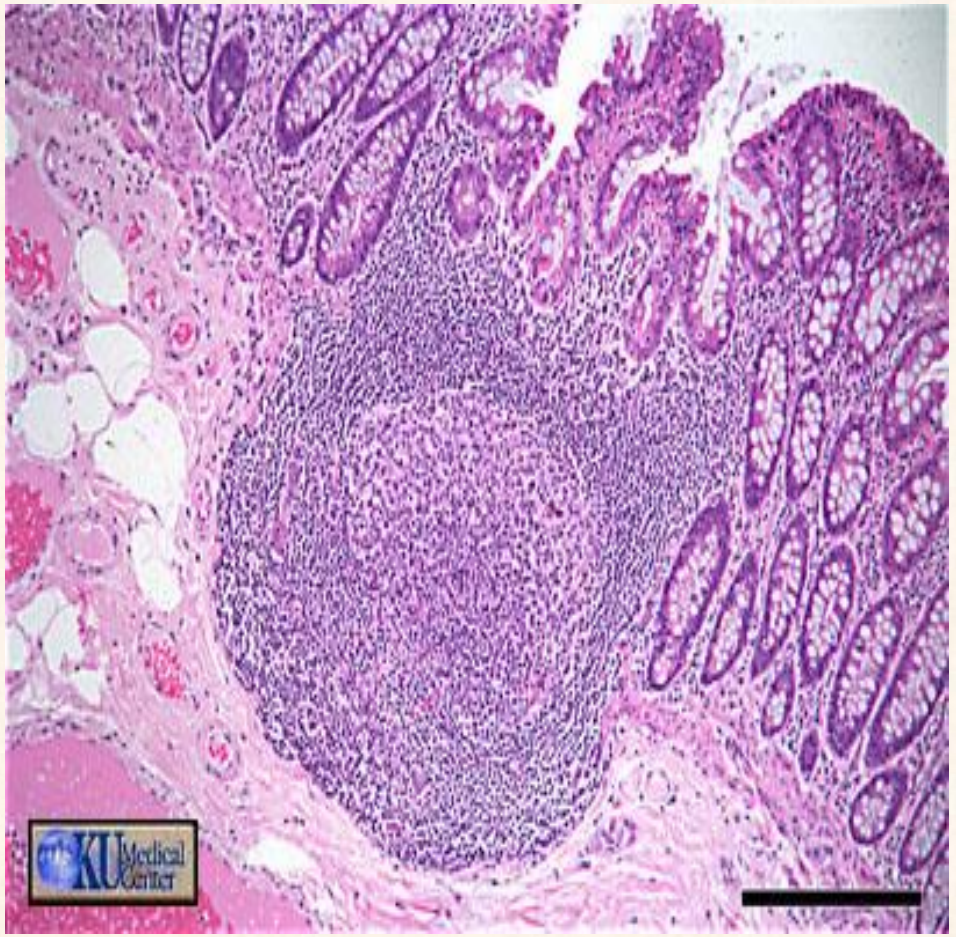
Cryptopatch - isolated lymphoid follicle spectrum

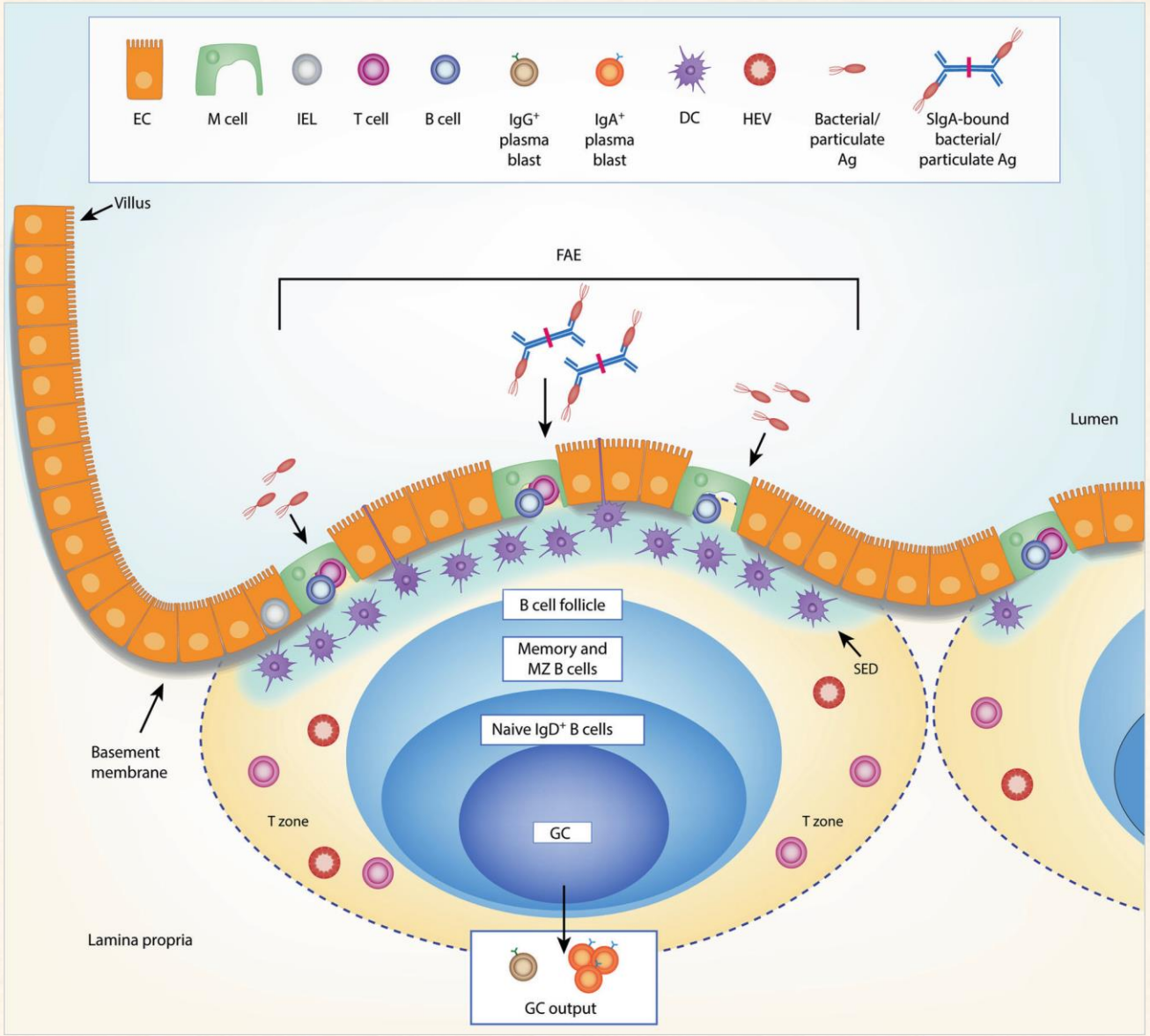
Diffuse MALT (D-MALT)

Effector tissue

Memory cells, activated effector cells, plasma cells in a diffuse pattern

Programmed lymphoid tissues in the gastrointestinal tract: Peyer's patch

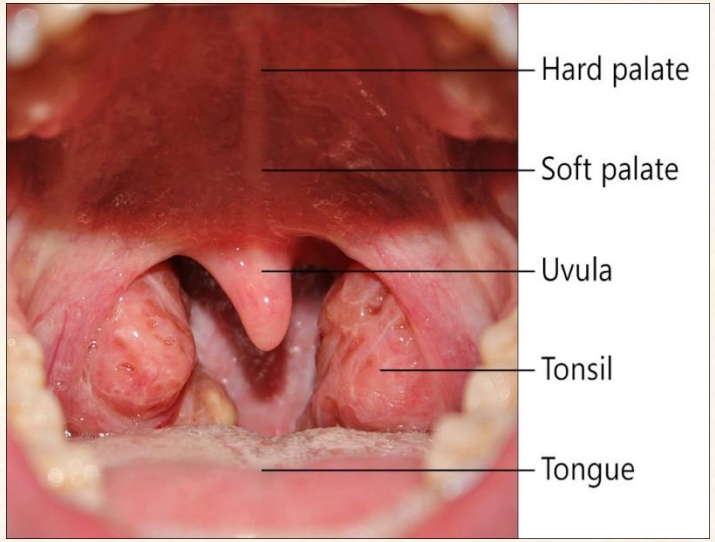


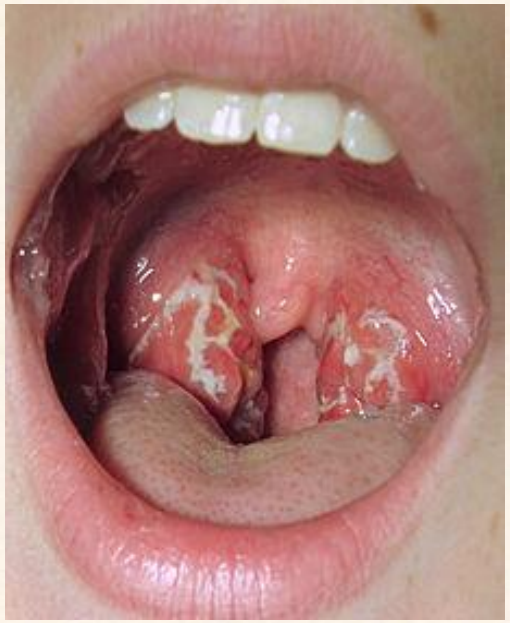


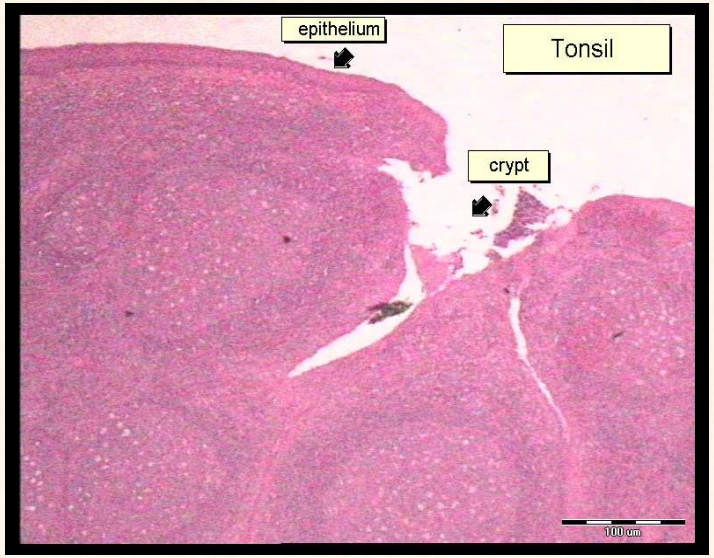
SED: Subepithelial dome
FAE: Follicle associated epithelium

UM Mörbe et al 2021. Mucosal Immunology 14:793-802

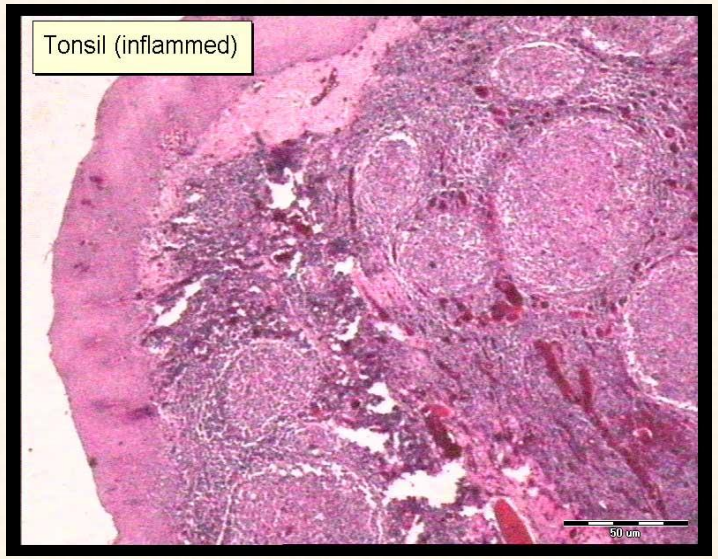
Programmed lymphoid tissues in the gastrointestinal tract: tonsils





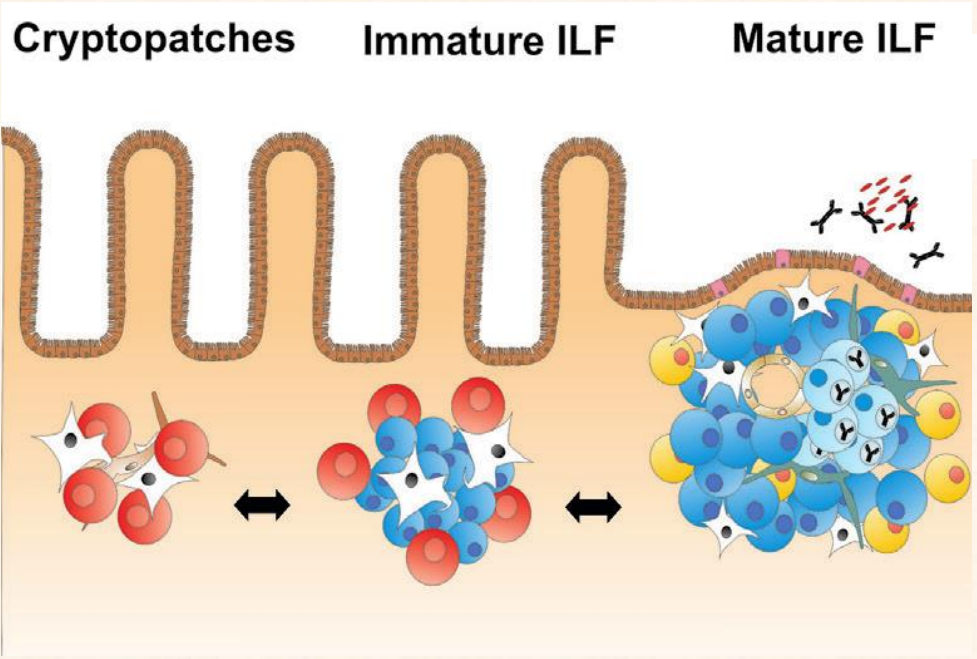


Normal tonsil



Inflamed tonsil

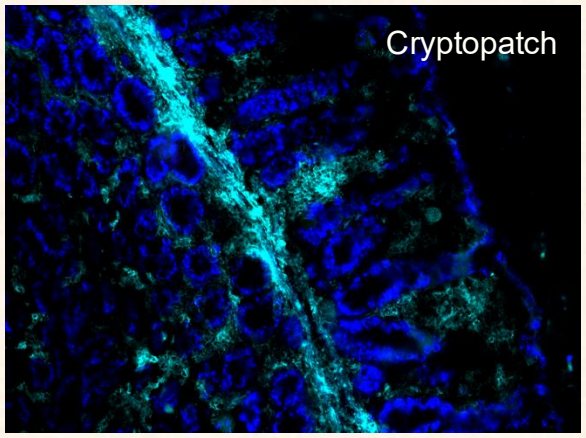
SILT (Solitary intestinal lymphoid tissues): inducible and dynamic components of the MALT

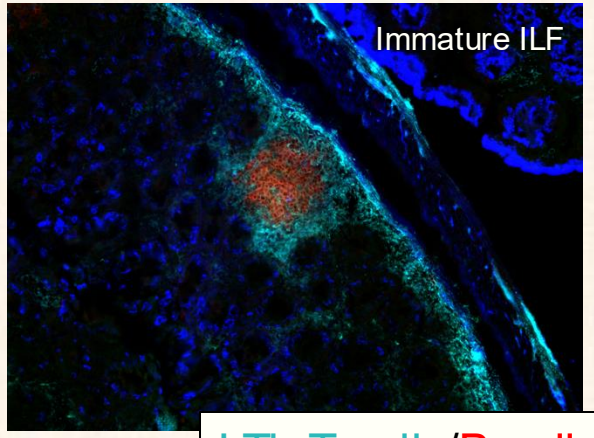


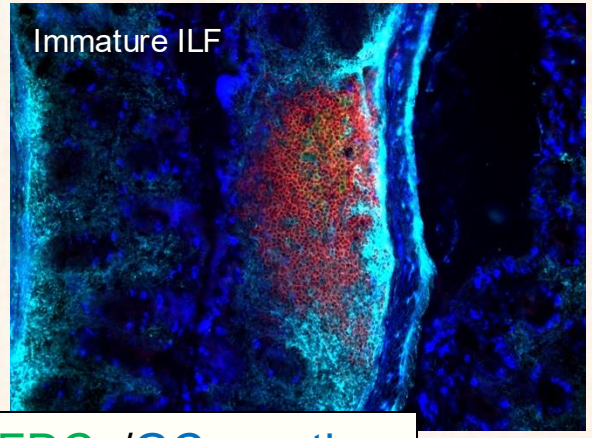
Buettner M and Lochner M (2016) Development and function of secondary and tertiary lymphoid organs in the small intestine and the colon. Front Immunol.

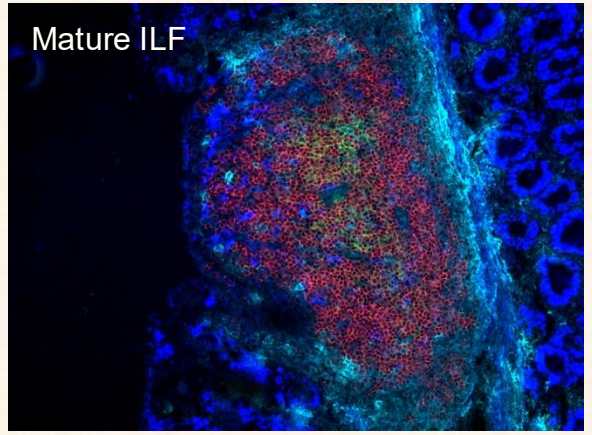
ILF: Isolated lymphoid follicle
LTi: Lymphoid tissue inducer cell

Low antigen burden: spectrum shifts towards cryptopatches
High antigen burden: spectrum shifts towards ILFs









LTi+T cells/B cells/FDCs/GC reaction

Innate immunity of the intestinal immune system: epithelial cells

Epithelial cells

Goblet cells: mucus secretion

- mucus: inner (dense) and outer (less-dense) layer
- antigen sampling…

Paneth cells: anti-microbial peptide secretion (defensins, REGIII)

M-cells: antigen transport

…all derived from Intestinal (epithelial) stem cells (ISC)

Epithelial cells express PRRs (TLRs, NLRs) in a tightly regulated manner

PRR ligation can lead either to inflammation (against invading pathogens) or to tolerance (against commensal bacteria)

M cells transport antigens from the intestinal lumen to the underlying cells

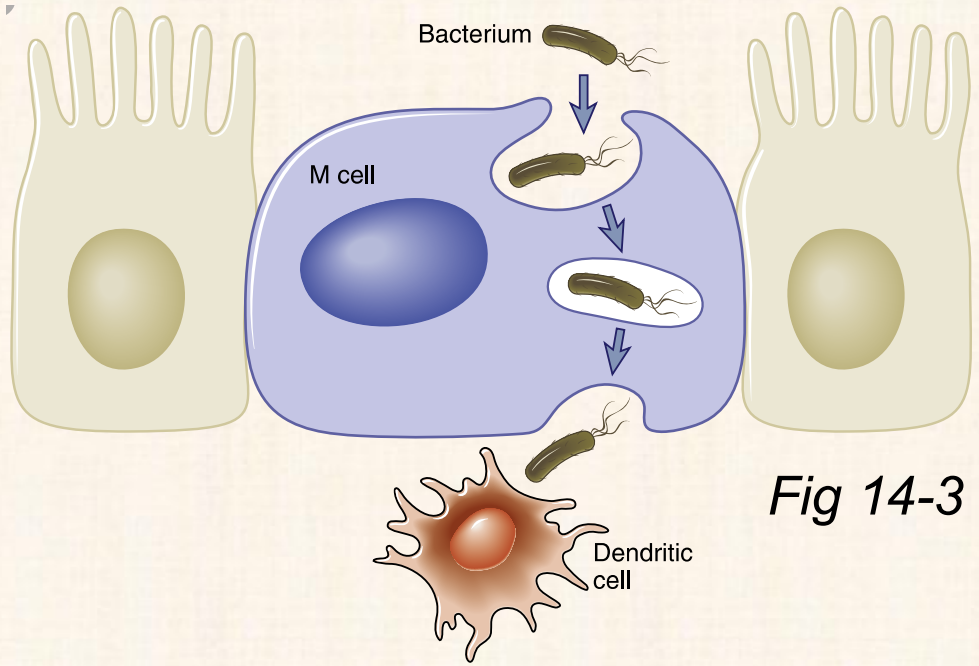
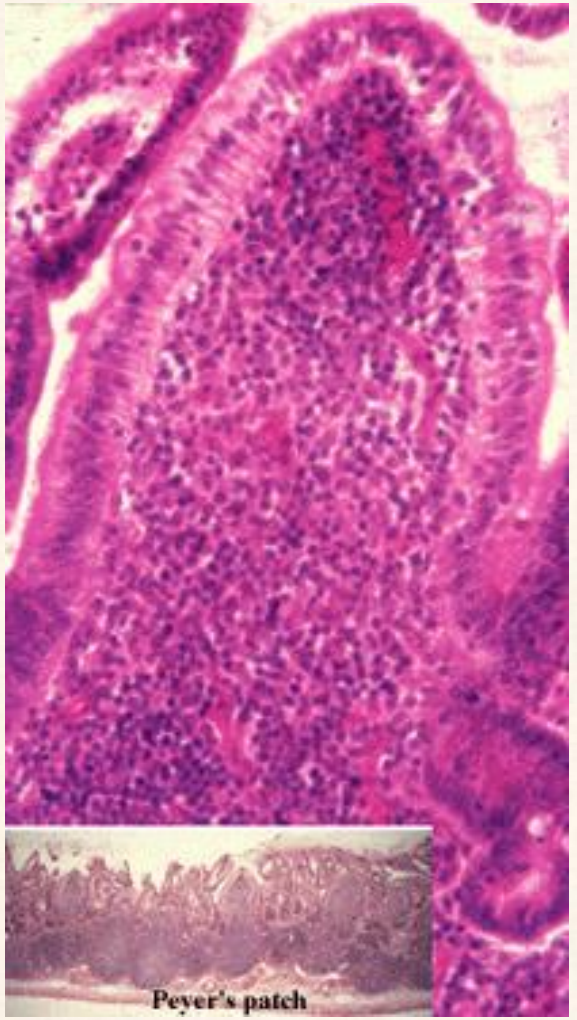
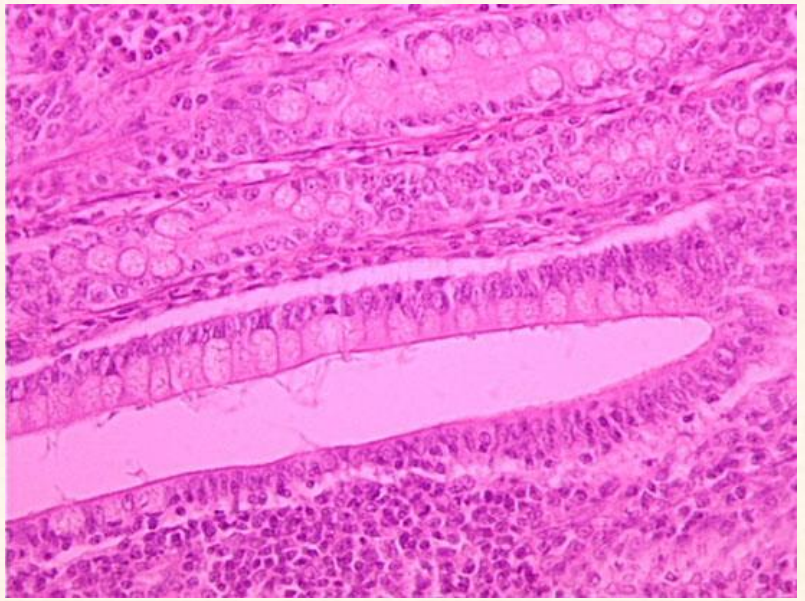


Fig 14-3

Abbas, Lichtmann and Pillai. Cellular and Molecular Immunology. 8th edition.





M cell region

(Not antigen presentation!)

Innate immunity of the intestinal immune system

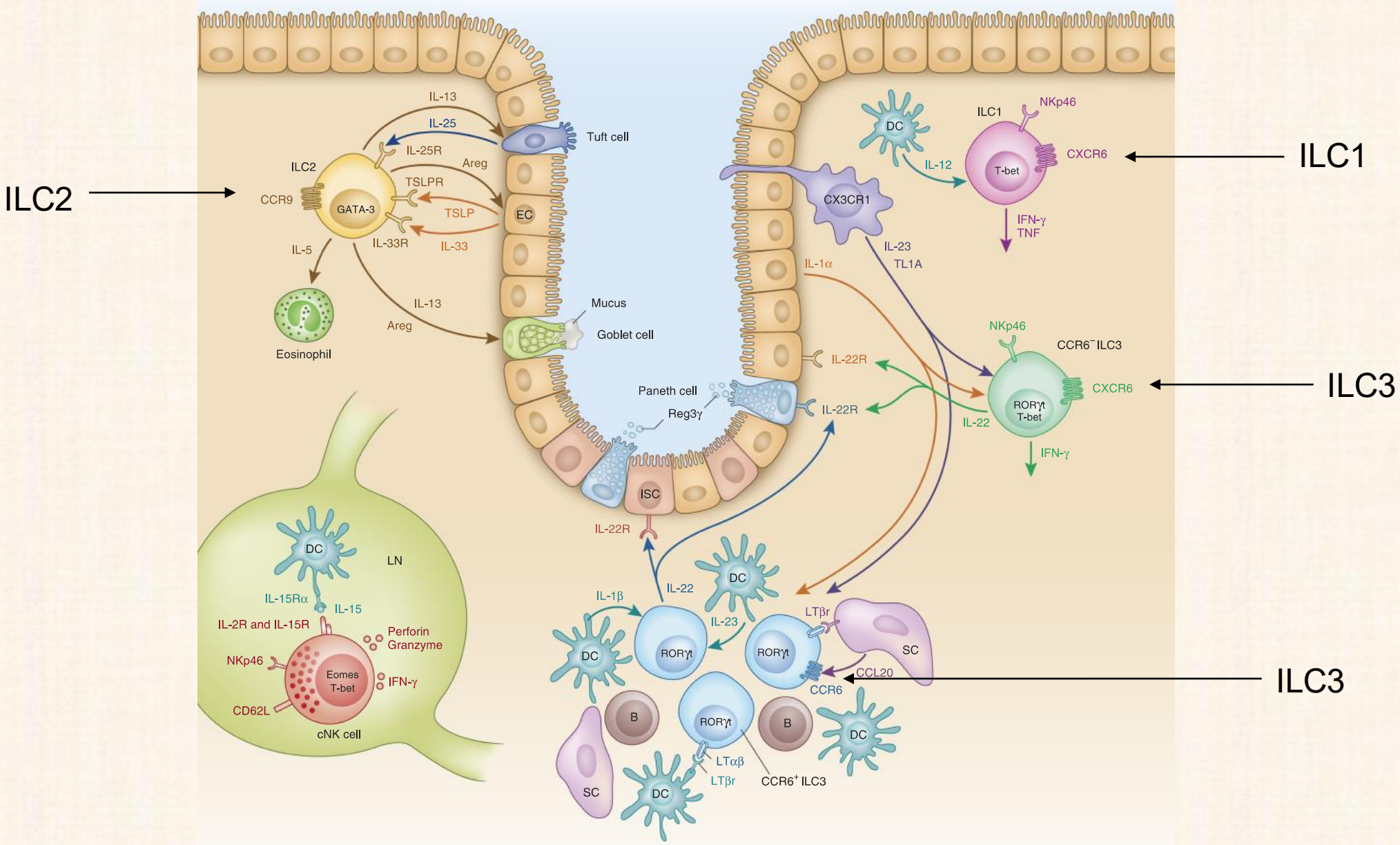
Dendritic cells, Macrophages

- Antigen presentation in mLNs
- Usually promote tolerance (IL-10, TGFβ)
- DCs: express retinal dehydrogenase → secrete retinoic acid → imprinting of gut-homing molecules

Innate lymphoid cells

- Lymphoid cells, but do not express antigen receptors
- Secrete cytokines
- ILC1: NKs + non-cytotoxic ILC1s
- ILC2: immune response against helminths, allergy (IL-5, IL-13)
- ILC3: mucosal healing (IL-22), inflammation (IL-17a) (+ LTi cells)

Innate lymphoid cells (ILCs)

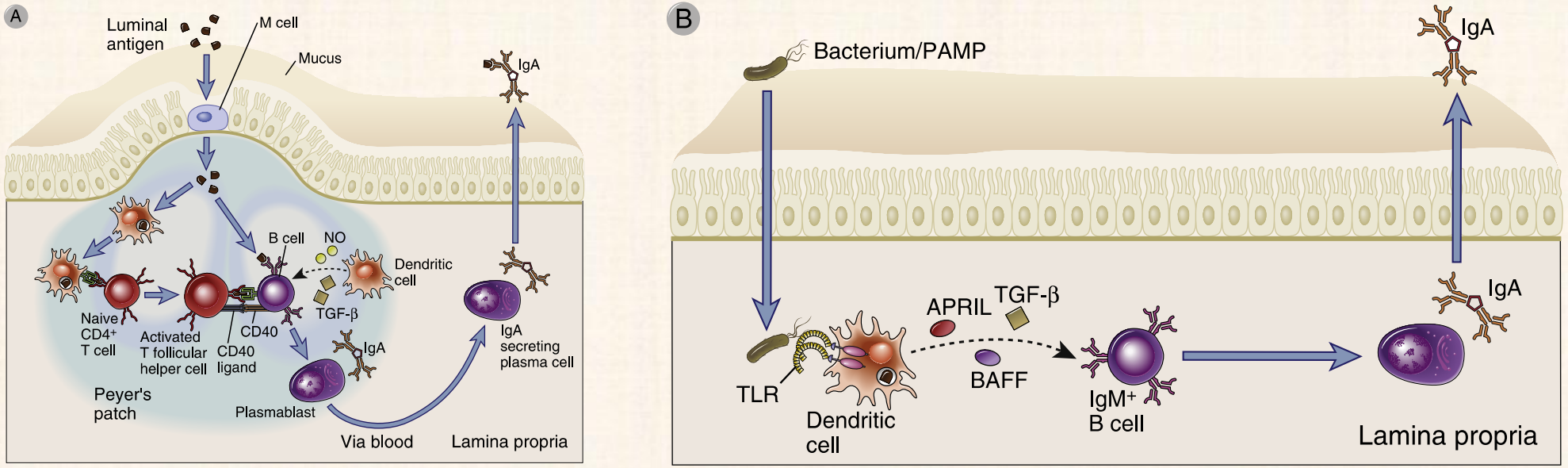


Klose CSN and Artis D (2016) Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nature Immunology

Adaptive humoral immune response in the intestine

IgA is the main antibody in the mucosa

- ~2g IgA produced per day
- Large amounts of TGFβ (produced by epithelial cells and DCs) induce IgA isotype switch
- Neutralizing immunity: prevents microbes/toxins from binding to/crossing the epithelium
- Within lymphoid follicles (PP, ILF) and dispersed throughout the lamina propria
- IgA: dimer, transported across the epithelium via *poly-Ig receptor* (=transcytosis)



T-dependent IgA production

T-independent IgA production

Fig 14-7

IgA is transported across the mucosal epithelial cells

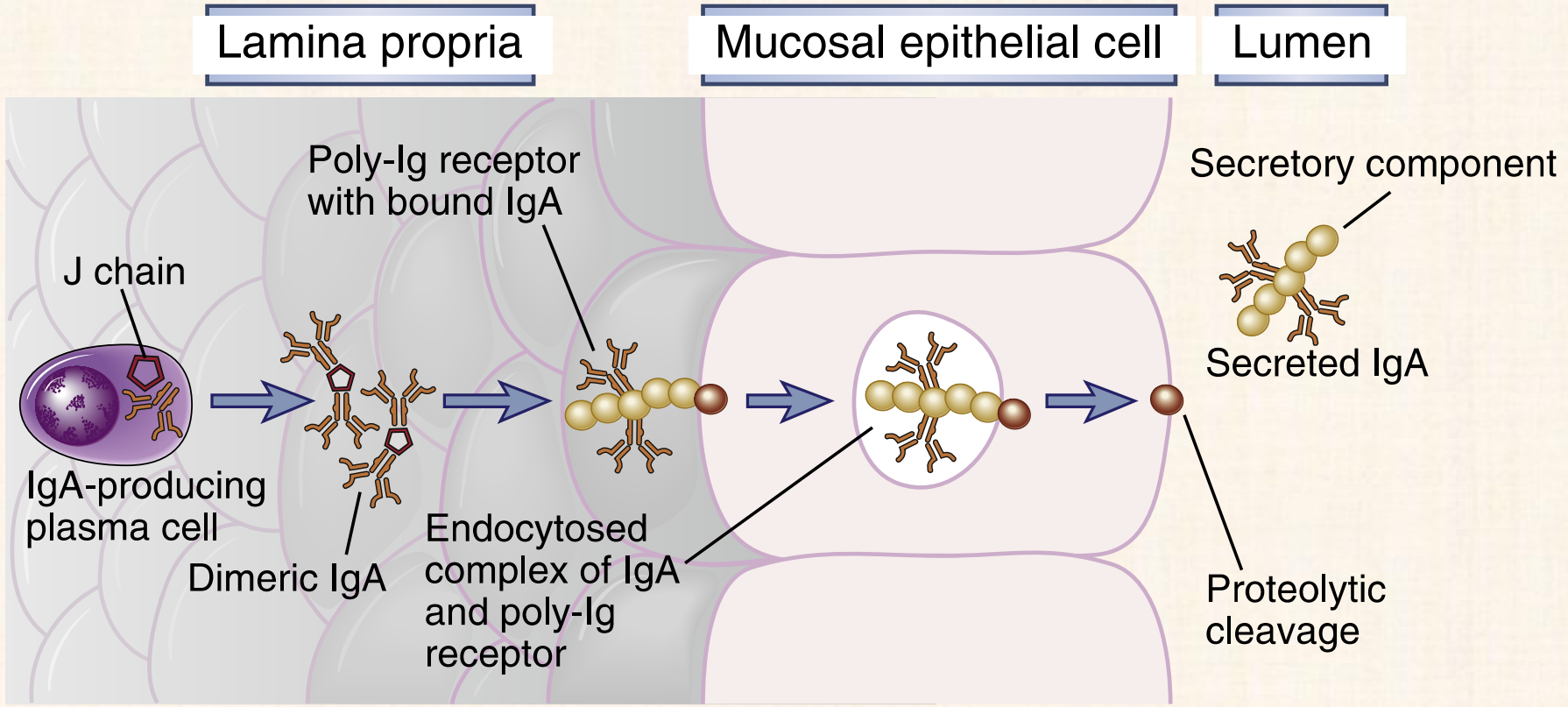


Fig 14-8

Intestinal T cell responses

Location

- Dispersed:
  - Intraepithelial lymphocytes: mainly $CD8^+$ or γδ T cells
  - Lamina propria lymphocytes: mainly $CD4^+$ effector/memory cells
- Organized lymphoid tissues:
  - Peyer's patches
  - Isolated lymphoid follicles
  - mainly $CD4^+$ T cells (Tregs, follicular helper T cells)

Types of T cells

- T_H17 *(~ILC3!)*
  - produce IL-17, IL-22
  - important in immune response against certain (extracellular) pathogenic bacteria
- T_H2 *(~ILC2!)*
  - produce IL-4, IL-13
  - important in immune response against helminths
- Regulatory T cells (Tregs)
  - produce TGFβ, IL-10
  - important in inducing tolerance against non-pathogenic microbes

Homing to mucosal lymphoid tissues

	Endothelium	Leukocyte
Adhesion molecule	MAdCAM-1	α4β7
Chemokine	CCL25	CCR9
	CCL28	CCR10

Vedolizumab: mAb against α4β7, used in inflammatory bowel diseases

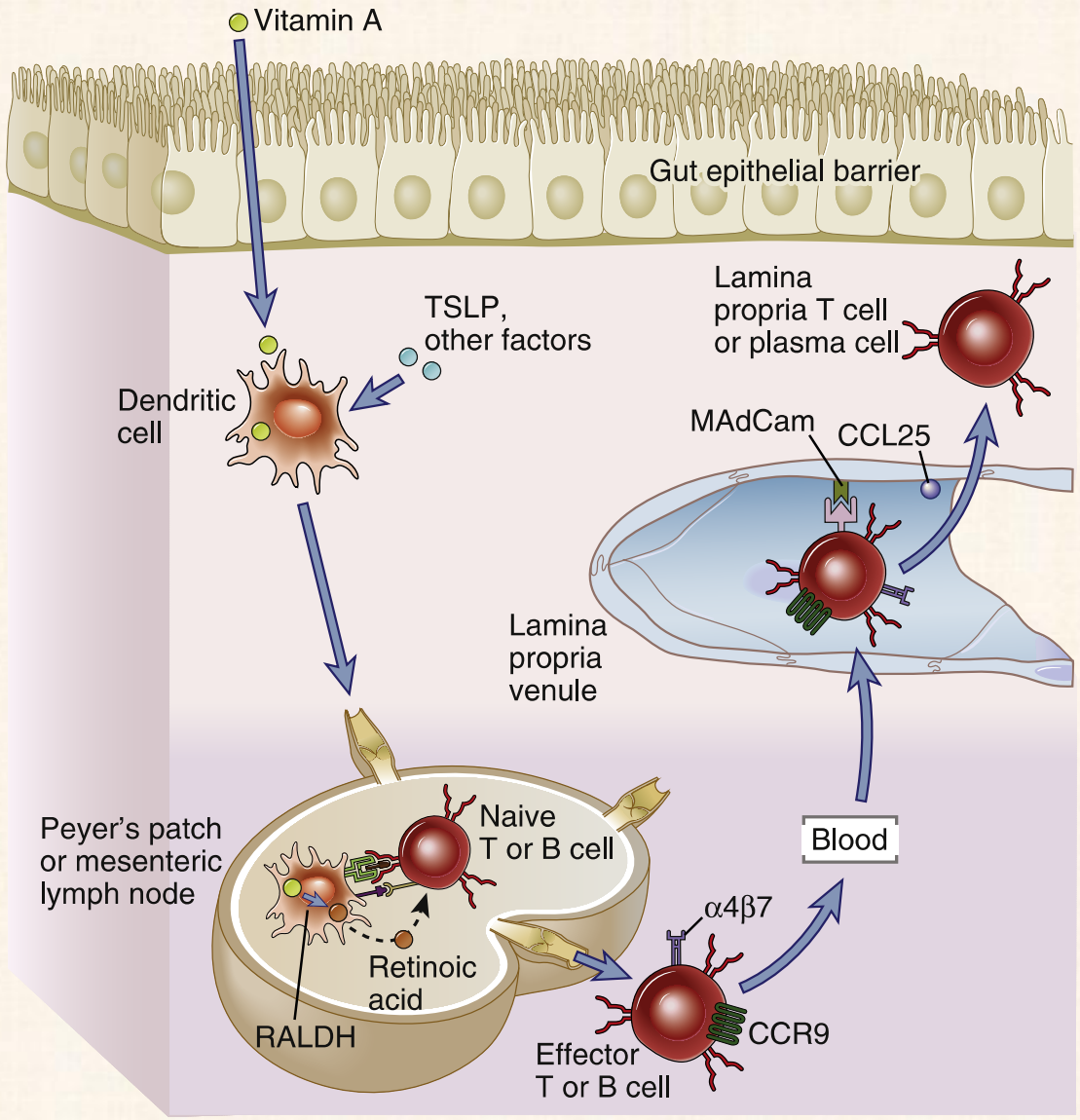


Fig 14-5

Intestinal microbiome

10^{14} cells (10x cells of the human body!)

Required for and regulate immunity of the intestine and also influence systemic immunity

Identification: 16S rRNA sequencing (specific for bacterial strains)

Extraintestinal consequences

- Rheumatoid arthritis
- Allergic diseases (asthma)

Example:

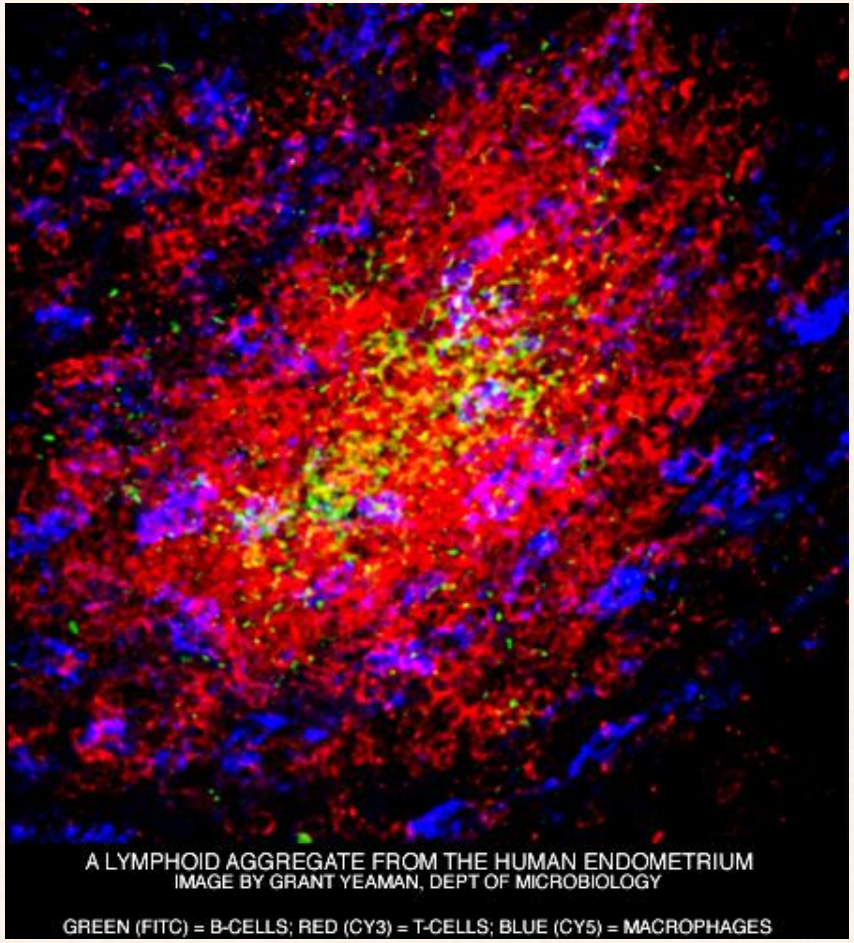
- *Clostridium difficile* infection: usually caused by alteration of normal flora by antibiotic use
- Treatment: fecal transplantation (bacterial flora from healthy donors)

Other mucosal surfaces in the body

Features shared with the intestinal tract:
- epithelial barrier, mucus and antimicrobial factors
- lymphoid tissues beneath the epithelium
- antigen sampling
- secretory IgA as prevention

Airways
- Innate: surfactant protein; alveolar macrophages
- Adaptive: IgA, IgE (allergic reactions)

Genitourinary tract
- Innate: epithelial layer, DCs (Langerhans cells)
- Adaptive: IgG
- Relevance: STDs, HIV pathogenesis



Oral cavity

Inductive site and **effector organ** of immunity

Systemic and **local** immunity (sublingual vaccines!)

Part of the mucosa-associated lymphoid tissues, with **specialized components**

Stratified squamous epithelium + “hard” tissues *(teeth)*

Chewing: causes ongoing damage

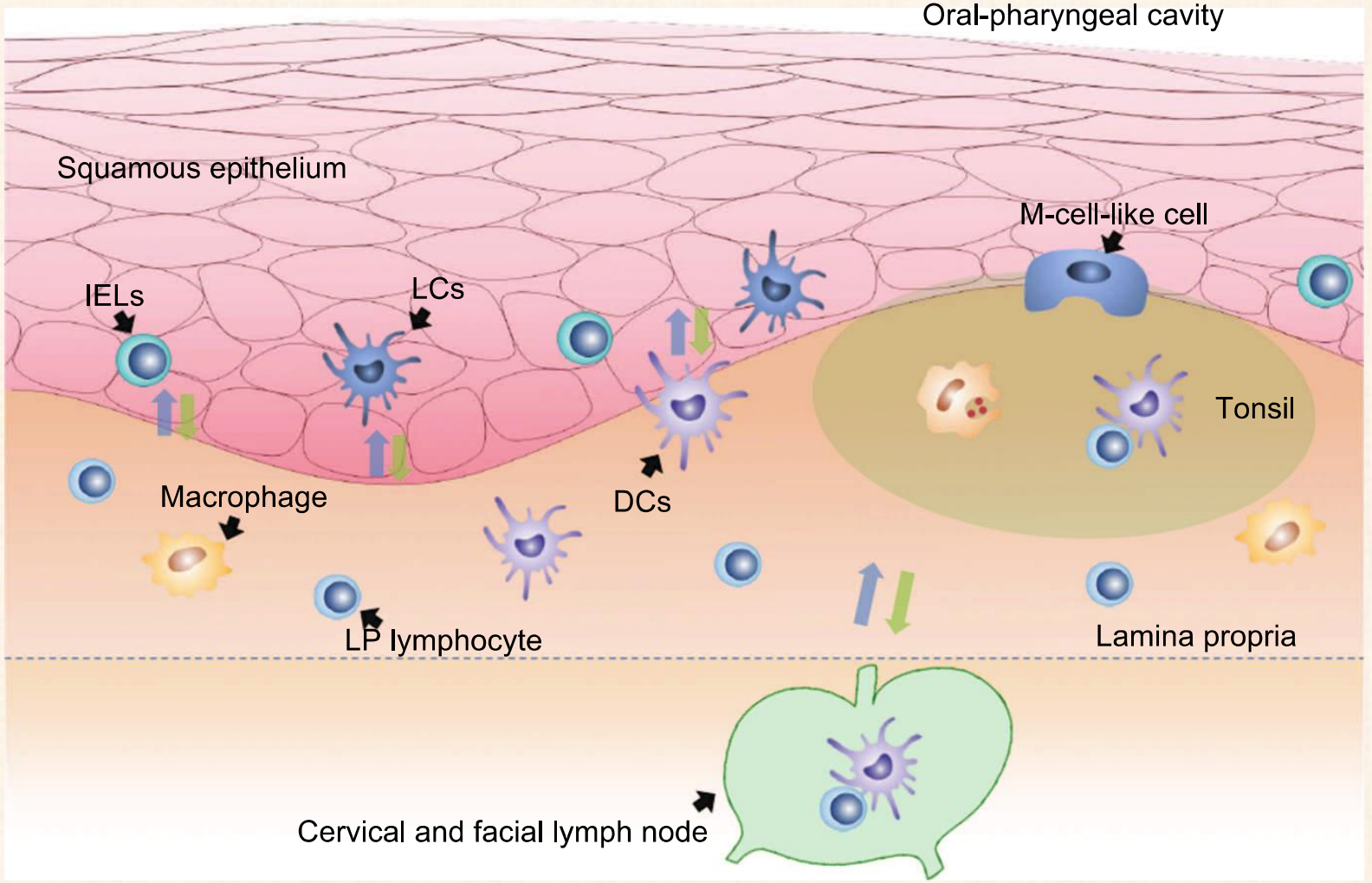
Thick and and dense physical barrier

Permeable: periodontal epithelium

Constant **antigen exposure**: ~100 million bacteria/ml of saliva (~700 species)
~500kg of food annually

Innate and **adaptive** components

Immunity of the oral cavity



DC: dendritic cell LC: Langerhans cell LP: lamina propria IEL: intraepithelial lymphocyte

The mucosal immune system in the oral cavity – an orchestra of T cell diversity. Wu RQ et al, Int J Oral Sci. 2014 6:125-32.

Cellular components

Epithelial cells

- First line (physical + chemical) barrier
- Express PRRs (TLRs, NLRs)
- Can produce inflammatory cytokines (IL-1β, IL-6, GM-CSF)
- Different types and thickness (influences permeability!)
  - keratinized, thick (>50 layers, dorsal tongue)
  - non-keratinized, thick (~30 layers, buccal mucosa)
  - non-keratinized, thin (~10 layers), rich in Langerhans cells (mouth floor)
  - junctional epithelium

NK cells

Langerhans cells, dendritic cells, macrophages: antigen presenting cells

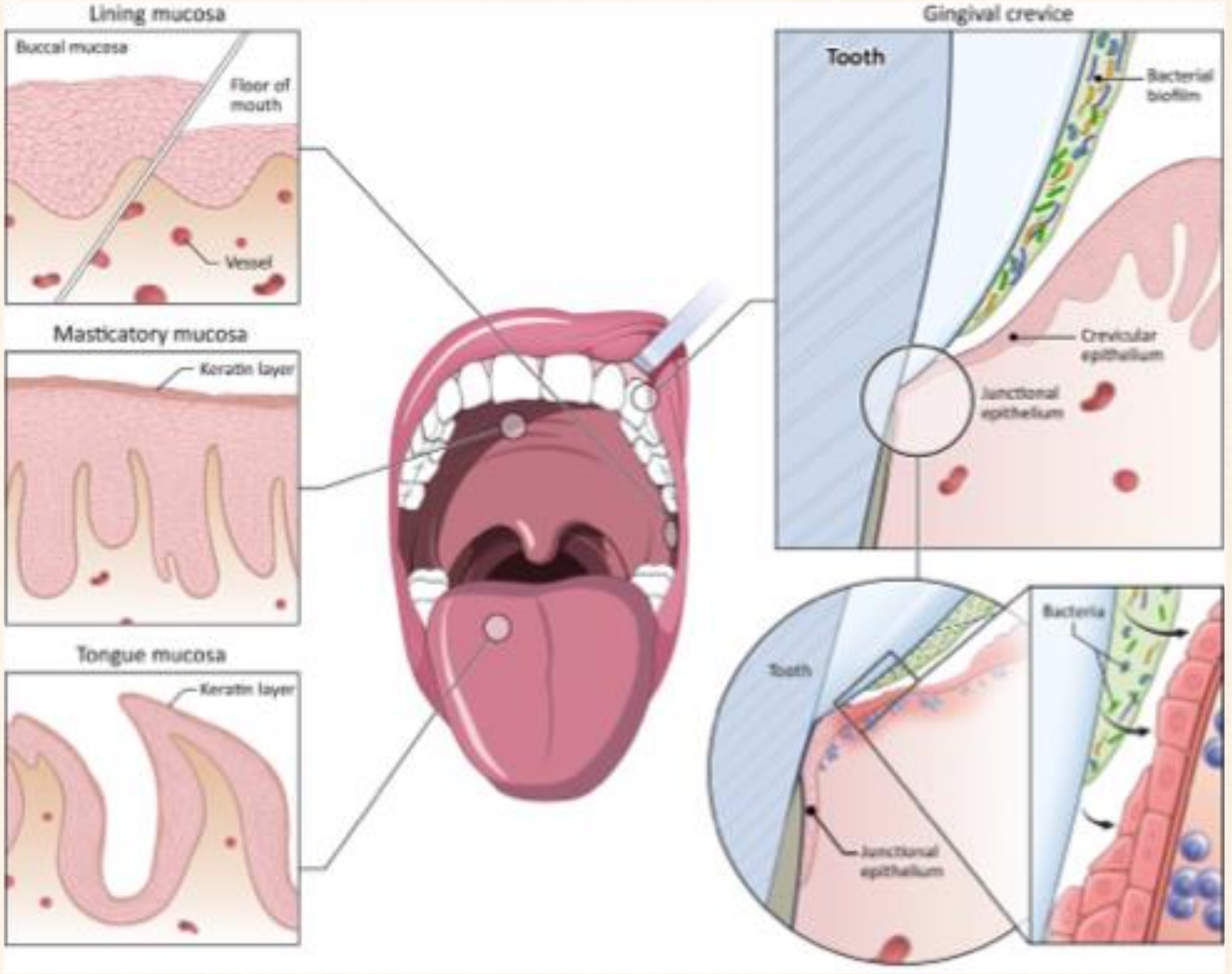
Mast cells

CD8αα+ intraepithelial lymphocytes

T cells: rare in healthy mucosa, T_H17s important in pathology (eg Candida albicans)

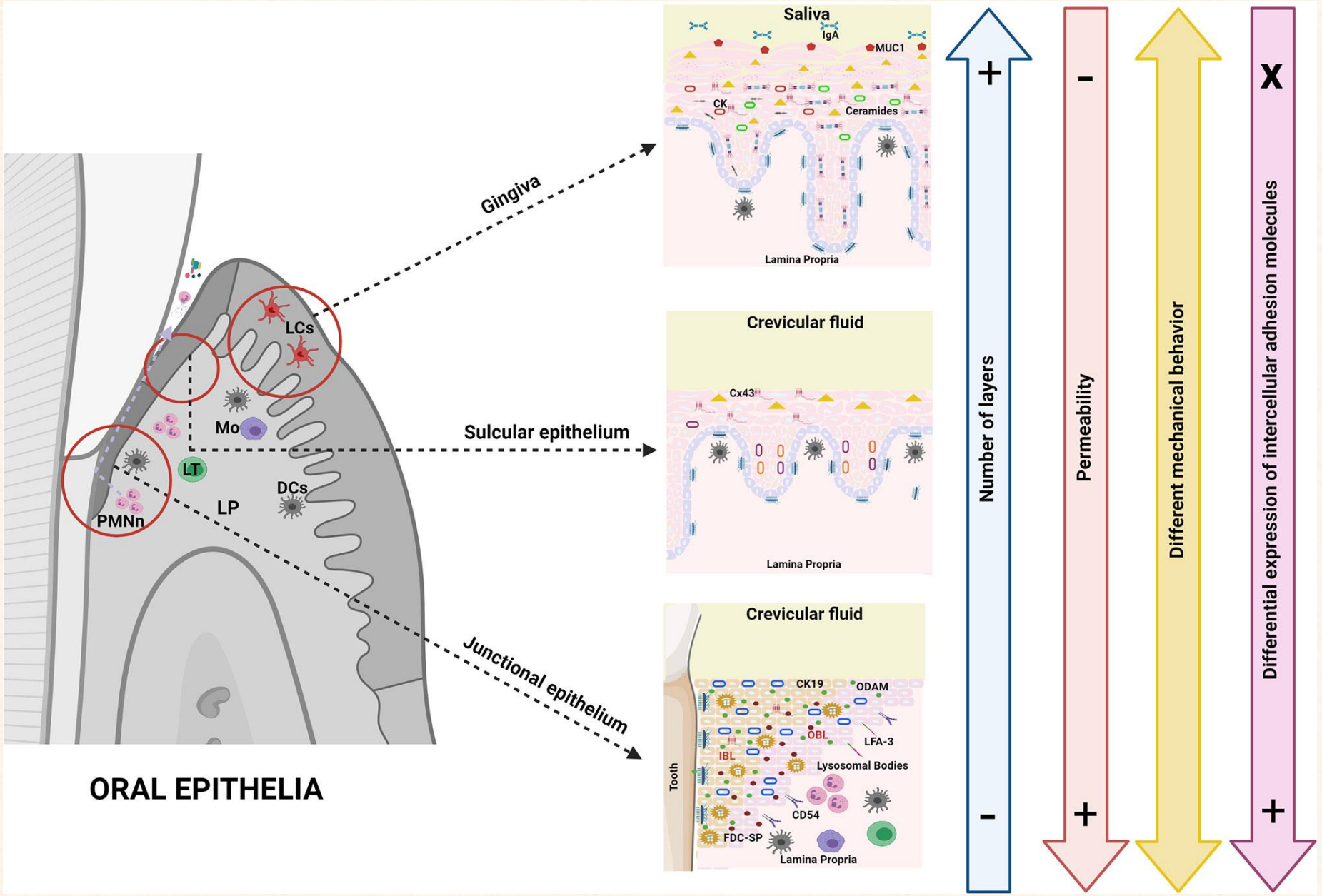
B cells: mainly IgA^+, few IgG^+

Oral epithelial barriers



Tissue-specific immunity at the oral mucosal barrier. Moutsopoulus N et al. Trends Immunol 2018

Oral epithelial barriers



Oral versus Gastrointestinal Mucosal Immune Niches in Homeostasis and Allostasis. Suarez LJ et al. Front Immunol 2021.

Saliva

750-1000 ml/day

3 pairs of major glands (parotid, submandibular, sublingual) + several minor glands

Important in:

- physico-chemical protection of teeth
- immunity of oral mucosa
- mucosal healing

Contains lots of proteins with innate and adaptive immunologic features

Low concentrations of the various factors, but synergistic effect

Xerostomia: Increased susceptibility to oral candidiasis, worse dental caries

Salivary antibodies

Types

IgA: usually dimer (from the salivary gland),
IgG: lower amounts (from serum or local plasma cells)
IgM and IgE: very low amounts

IgA$^+$ B cells

Activated in NALT (nasopharynx-associated lymphoid tissue, tonsillae + adenoids, *Waldeyer's ring)*

Migrate to salivary gland stroma (and mucosa)

IgA

Transported across epithelial cells via polymeric Ig receptor + secretory component
Constitutively secreted into saliva

Salivary IgA function

Neutralization

Agglutination

Surface immune exclusion

Opsonization (FcαRI) – antigen presentation, degranulation, cytokine production

Catalyze oxygen burst

Salivary antimicrobial proteins

Defensins

Disrupt pathogen membranes; antibacterial, antifungal, antiviral activity

Lactoferrin

Iron-binding protein; neutralizes bacteria and viruses, disrupts bacterial membrane

Cathelicidins

Destruct bacterial membranes; bind LPS

Lysozyme

Hydrolyzes peptidoglycan, effective mainly against Gram+ bacteria

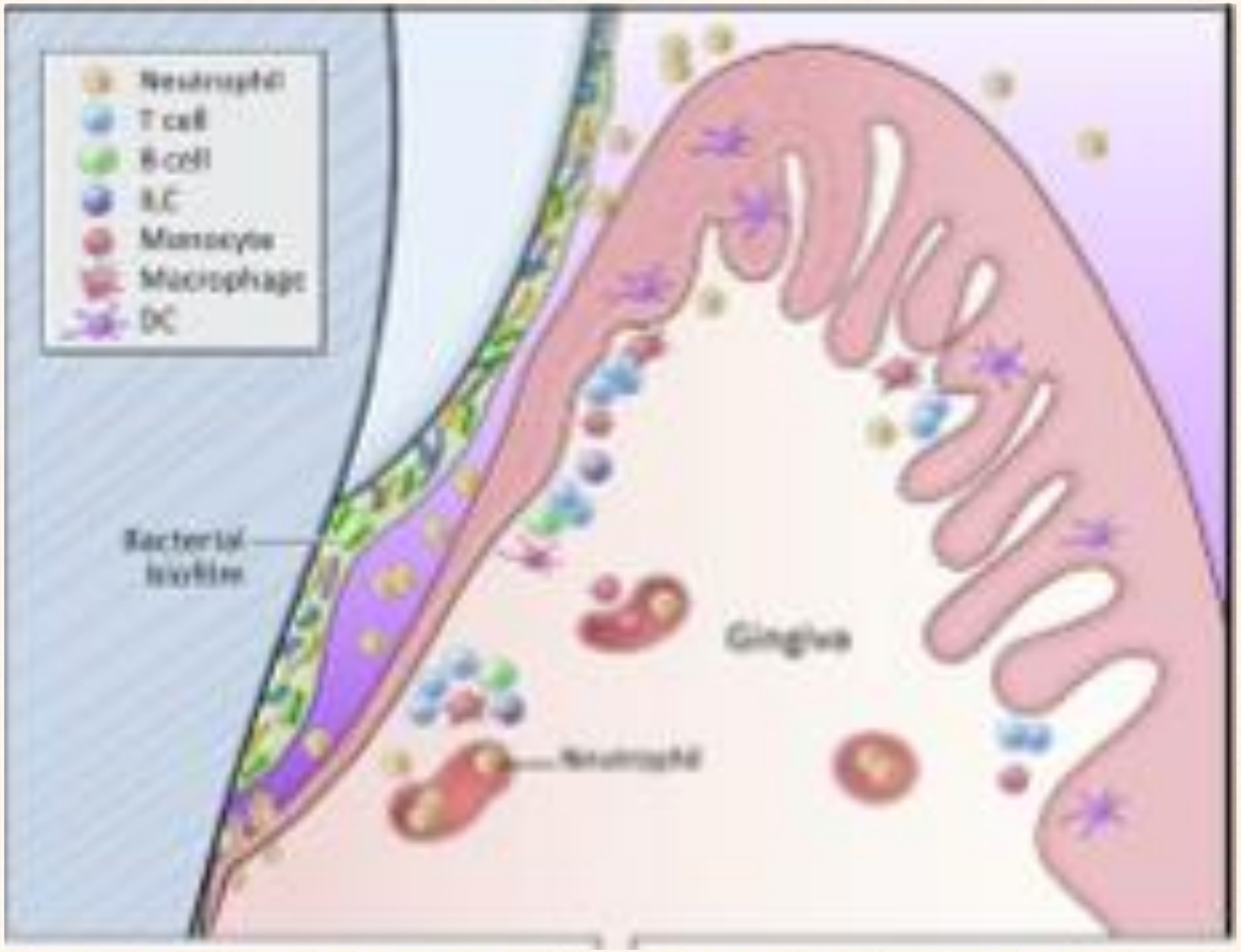
α-Amylase

Cleaves the α-1,4-glycosydic bond; can bind LPS, influences bacterial adhesion

Mucins

Secretory and membrane-bound form, entrap and agglutinate pathogens

Gingival crevicular fluid (GCF)



Tissue-specific immunity at the oral mucosal barrier. Moutsopoulus N et al. Trends Immunol 2018

Gingival crevicular fluid (GCF)

Exudate from gingival capillaries

Accumulates around the necks of the teeth

Normally ~1ml/day, significantly increases in periodontitis and gingivitis

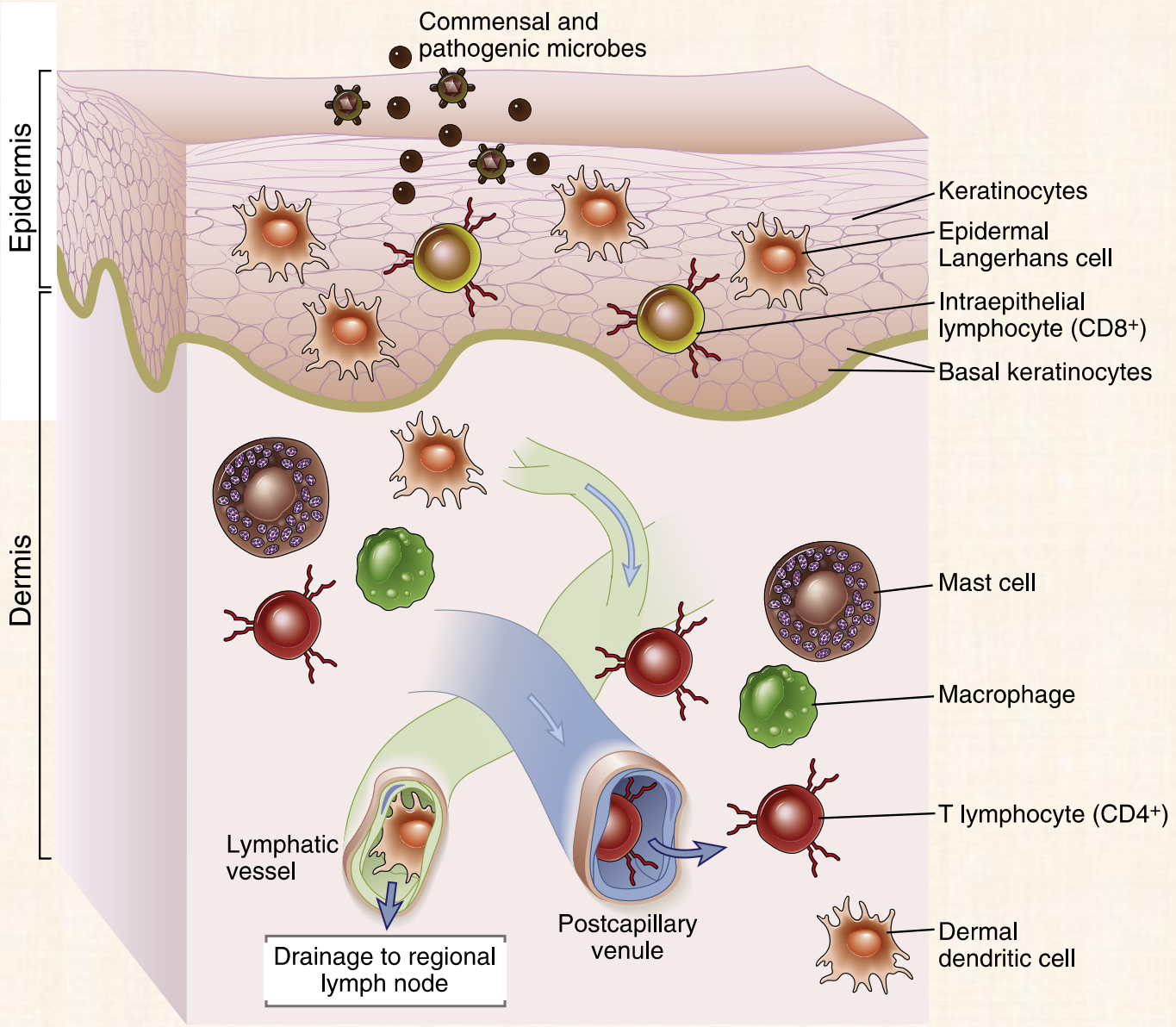
Content:

humoral components: antibodies (IgG), cytokines, digestive enzymes, antimicrobial proteins

cellular components: leukocytes, lymphocytes

Function: cleans the crevice between the tooth and the gingival epithelium

Cutaneous immune system



$2m^2$
$\sim 2x10^{10}$ lymphocytes
Physical barrier

(Sun)burns
Microbes
Traumas

Fig 14-9

Cells of the cutaneous immune system

Keratinocytes

Physical barrier

Cytokines: TNF, IL-1, IL-6, IL-18, IL-25, IL-33 (inflammation); IL-10 (regulation)

Chemokines: CCL27

Growth factors: PDGF, FGF, GM-CSF

Anti-microbial peptides: defensins, cathelicidins

Activation: through PRRs (TLRs, NLRs)

Dendritic cells, macrophages

Mainly Langerhans cells

Migrate to regional lymph nodes following phagocytosis of antigens

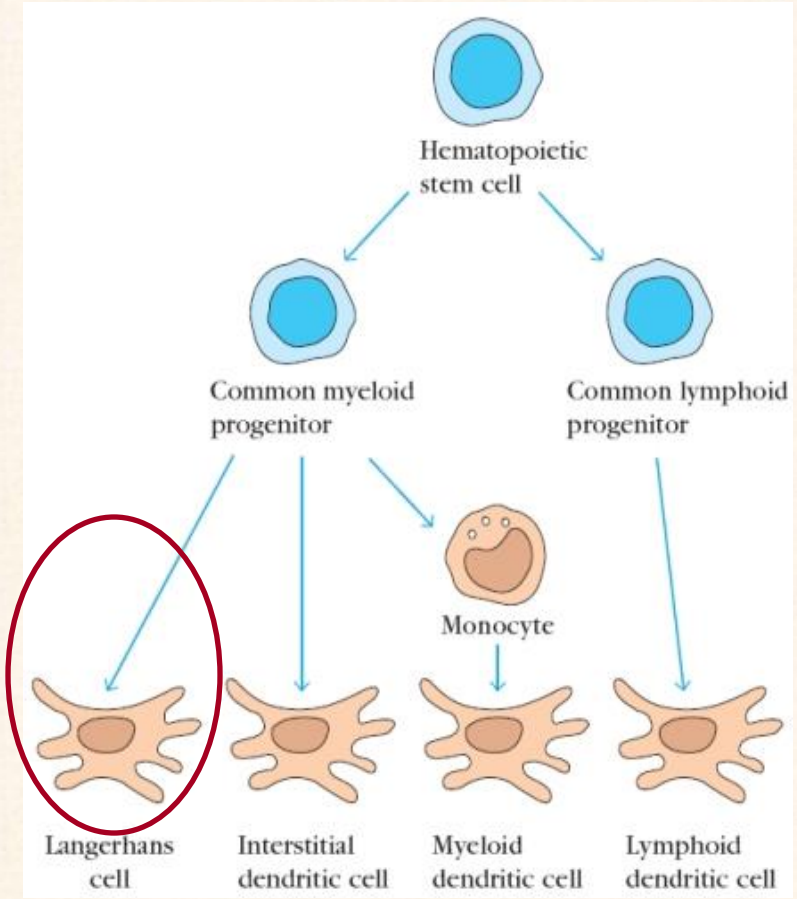
Present antigens to T cells, imprint skin-homing properties

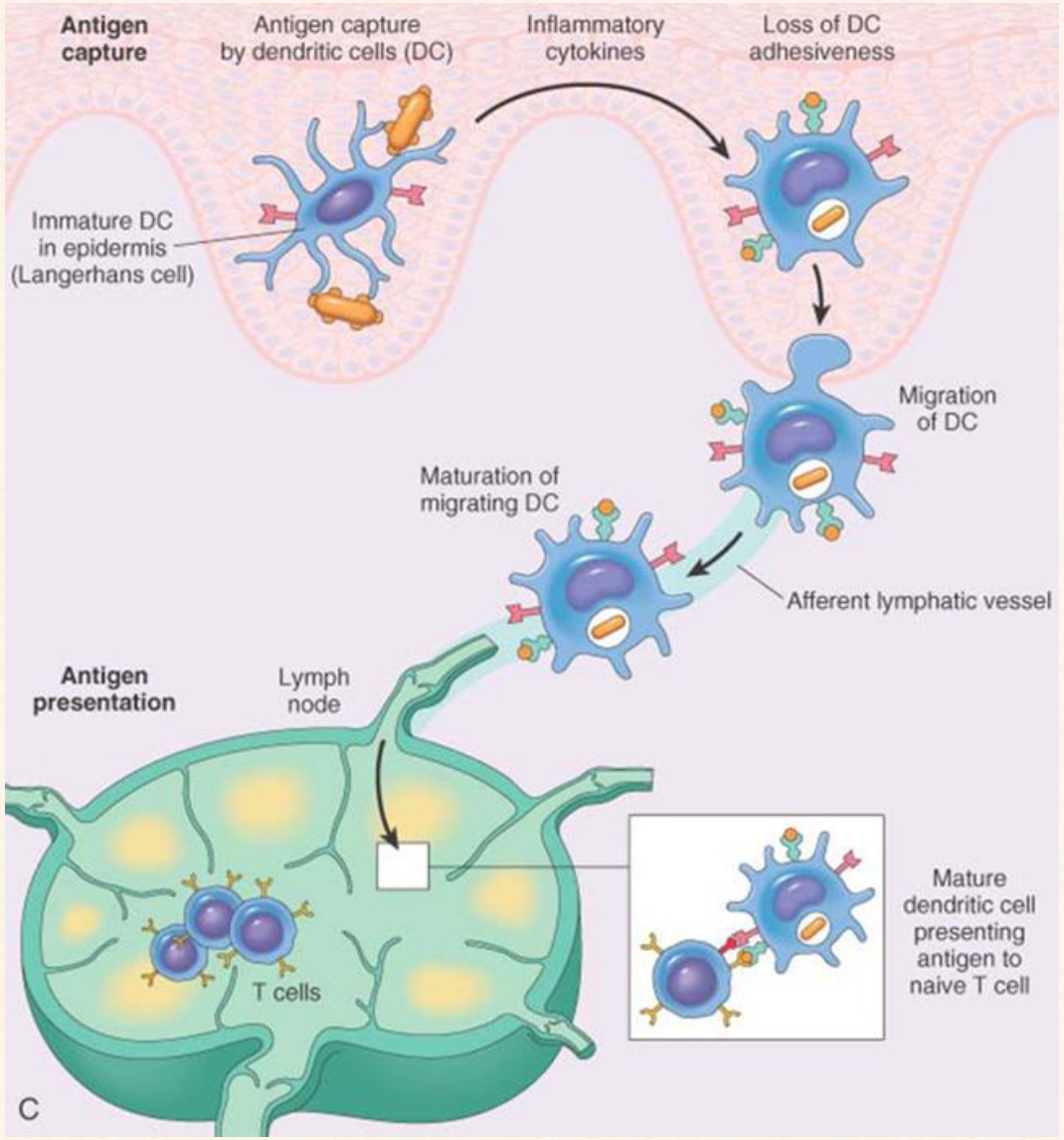
T cells

Intraepidermal: mainly $CD8^+$ or γδ T cells

Dermal: $CD4^+$ (T_H1, T_H2, T_H17, T_{reg}), mostly memory T cells

Dendritic cells





Homing to the skin

	Endothelium	Leukocyte
Adhesion molecule	E-selectin	CLA
Chemokines	CCL17	CCR4
	CCL1	CCR8
	CCL27	CCR10

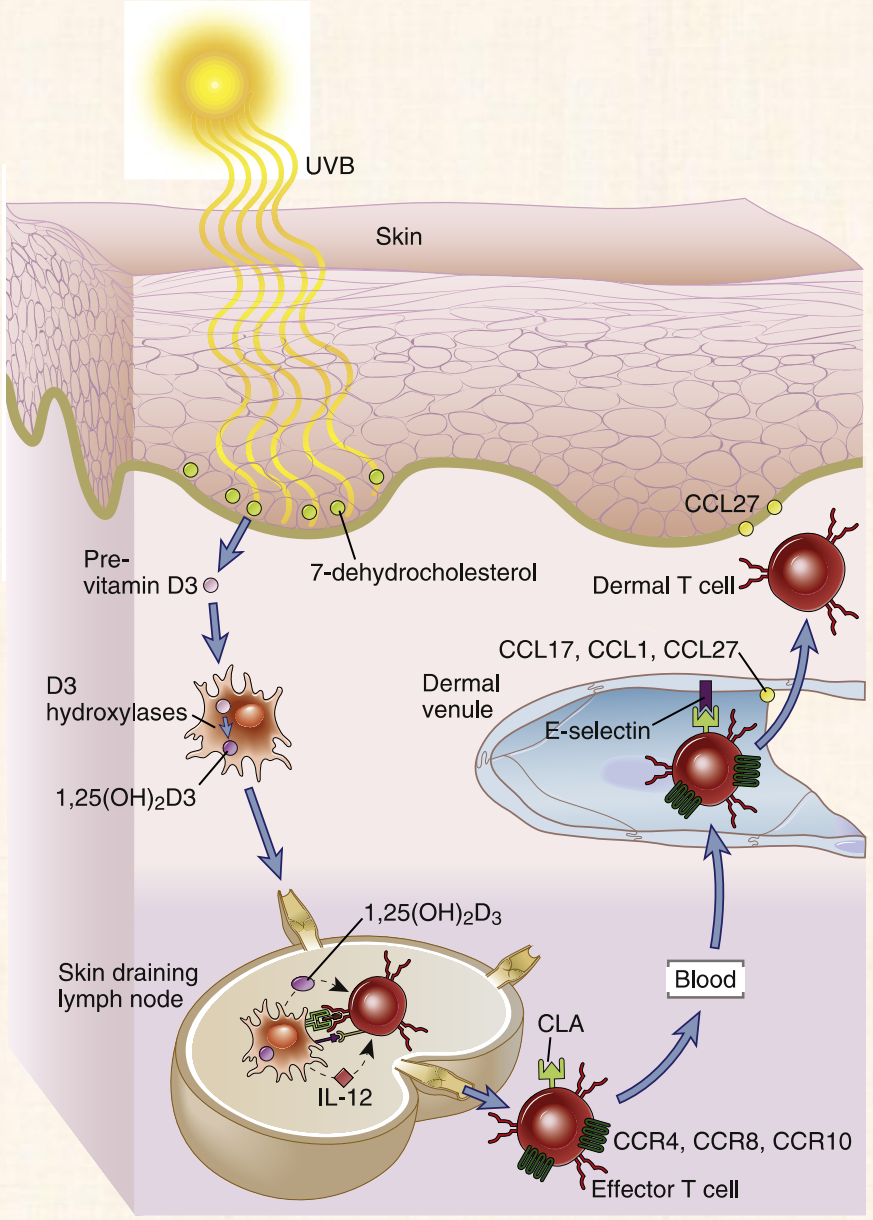


Fig 14-9

Dichotomy of the immune systems