

Basic Immunology

Regional immunity

Mucosa and skin associated immune system

21st lecture

April 23rd, 2026

Zoltán Kellermayer

Regional immune system

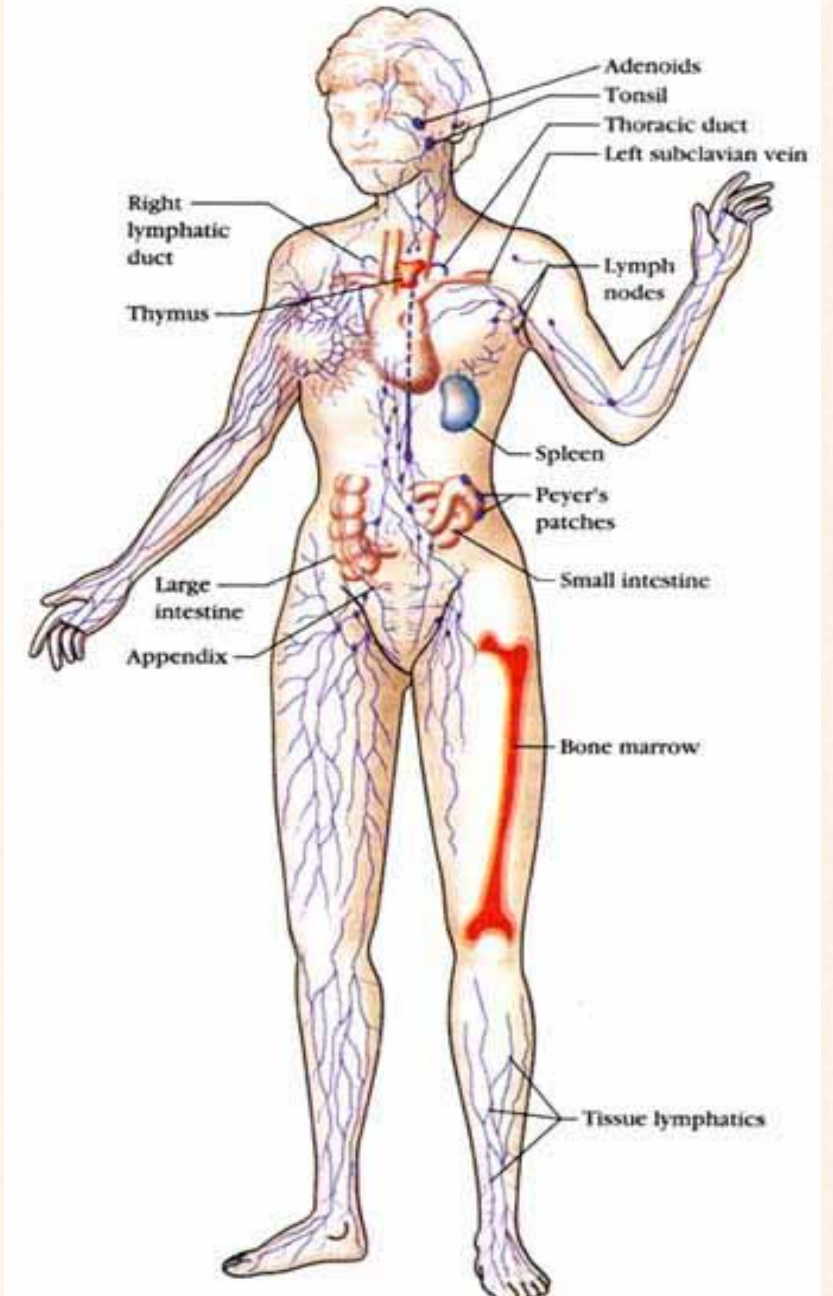
The collection of *immune cells and molecules* with specialized functions at a particular anatomic location

Gastrointestinal tract

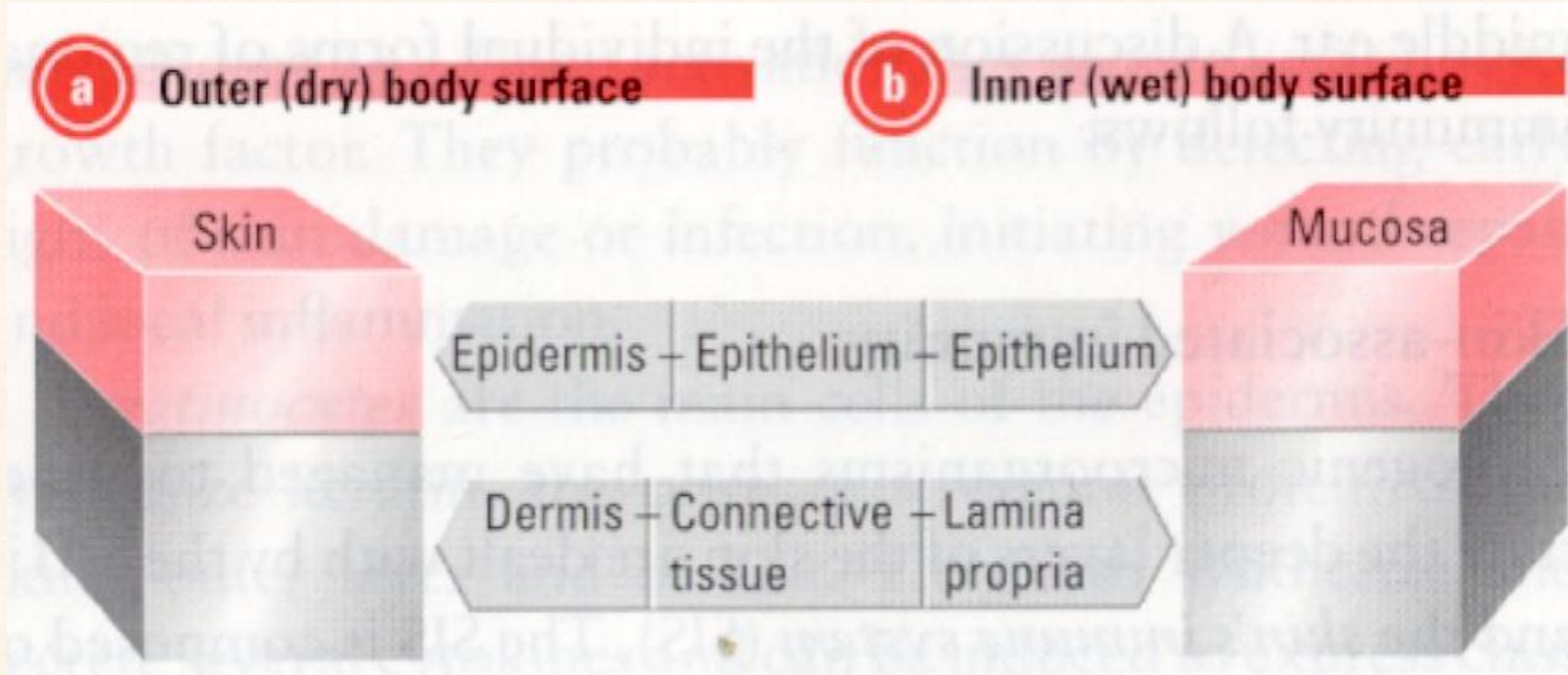
MALT: Mucosa Associated Lymphoid Tissue
gastrointestinal, bronchopulmonary,
urogenital tract

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 m²

~5x10¹⁰ total lymphocytes (blood: 10¹⁰)

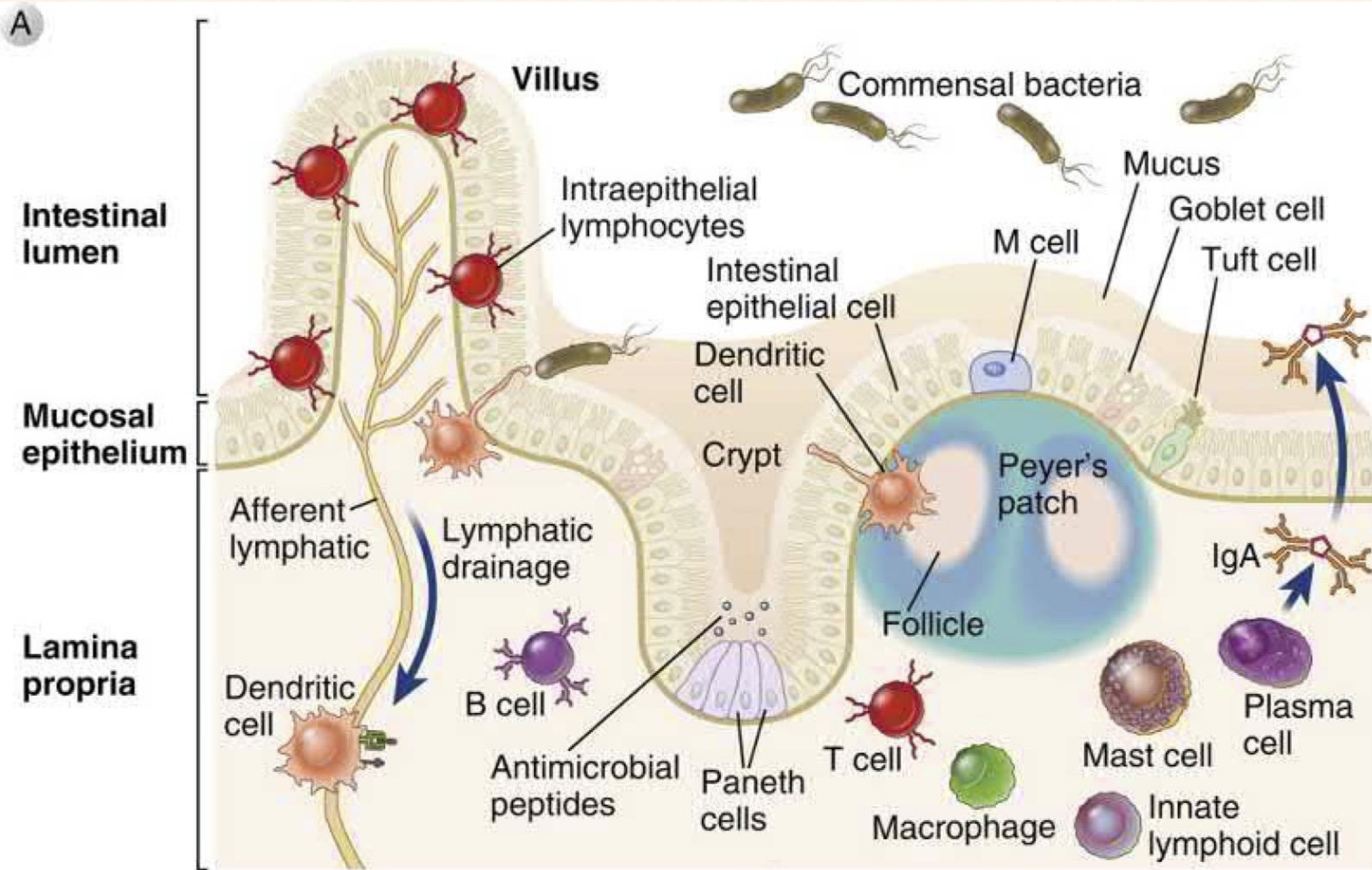
Huge amount of microbes: 10¹⁴

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

Specialized epithelial 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

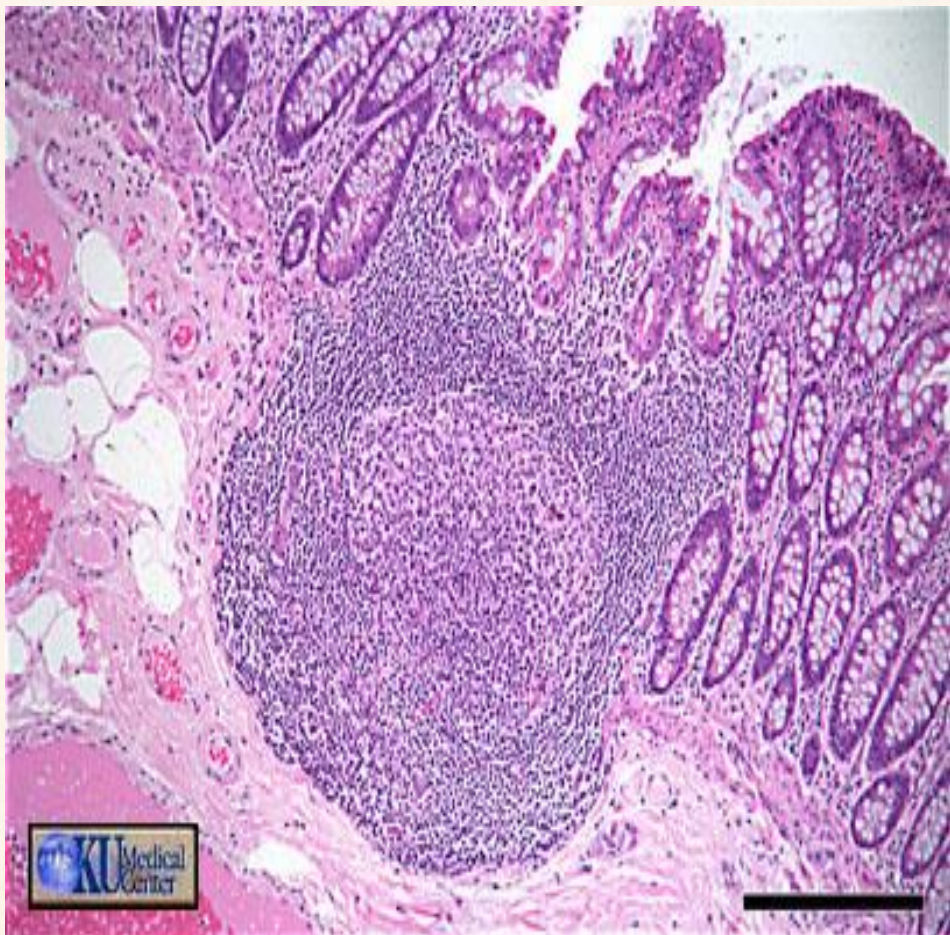
Cryptopatch - isolated lymphoid follicle spectrum

Diffuse MALT (D-MALT)

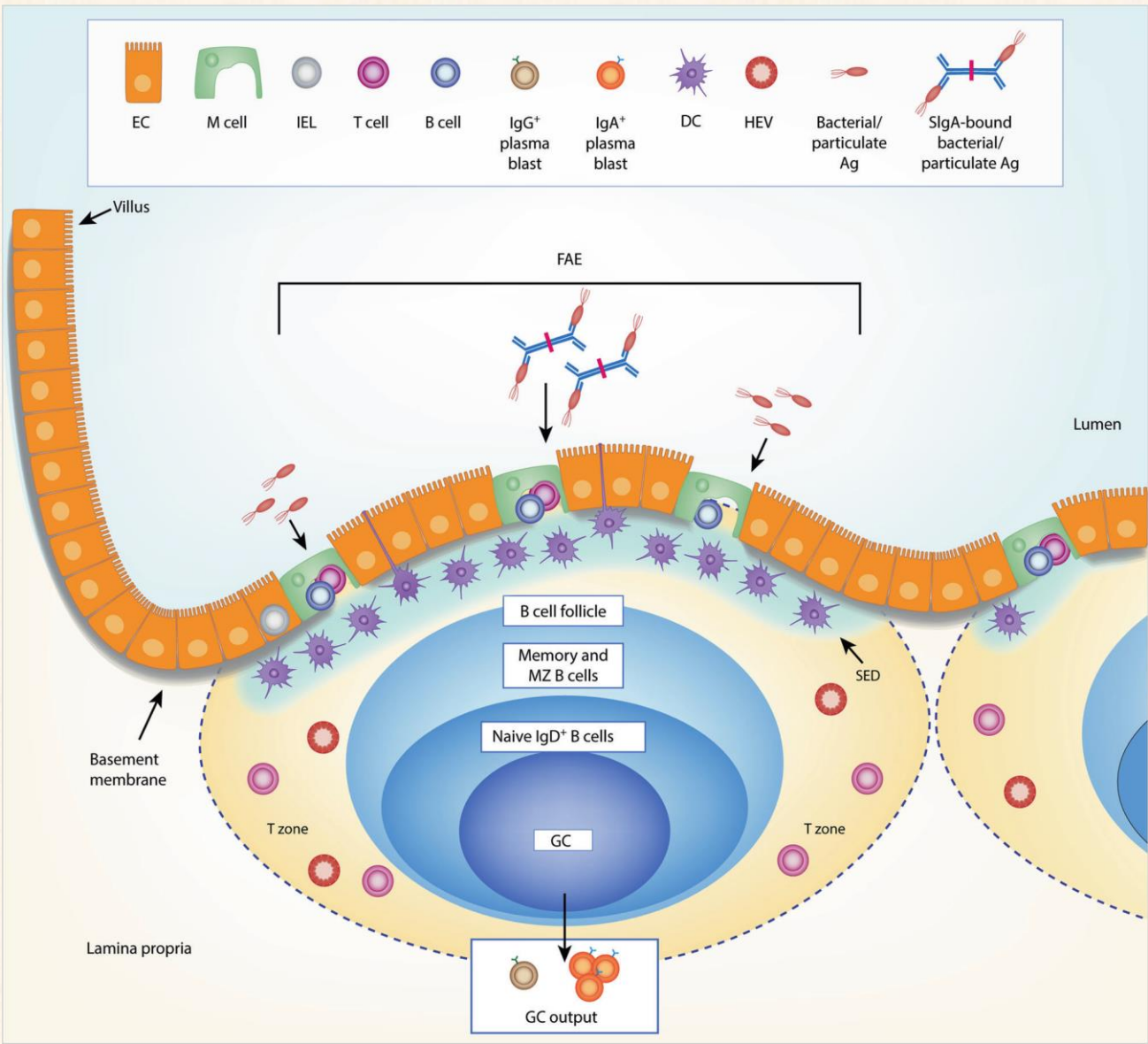
Effector tissue

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

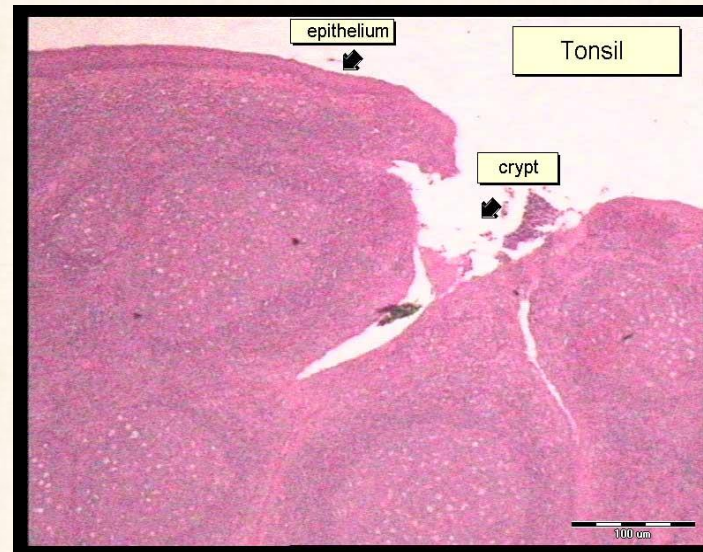
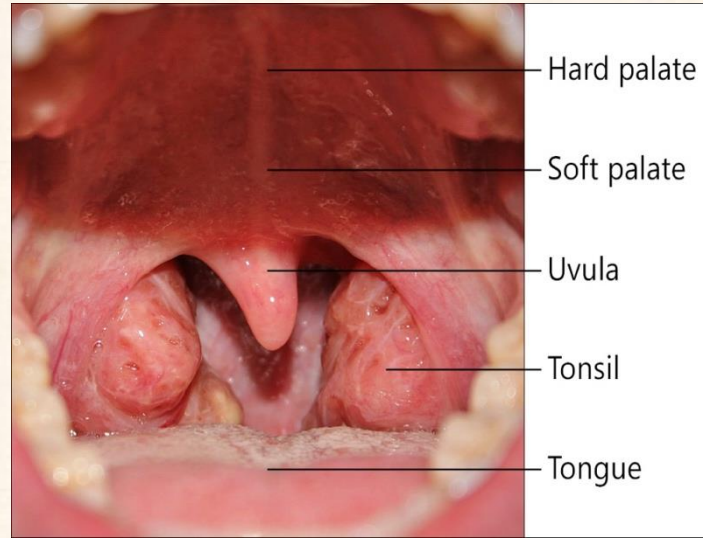
Programmed lymphoid tissues in the gastrointestinal tract: Peyer's patch



SED: Subepithelial dome
 FAE: Follicle associated epithelium



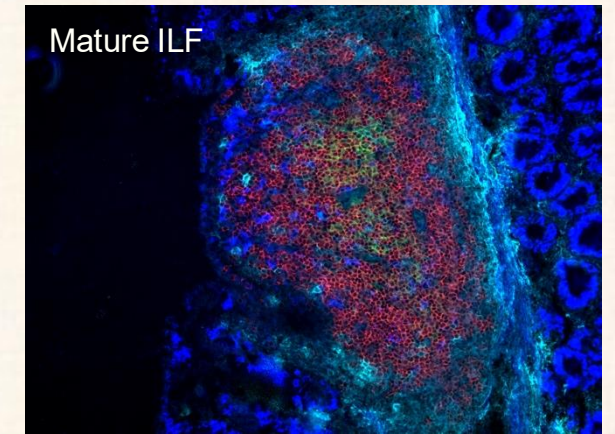
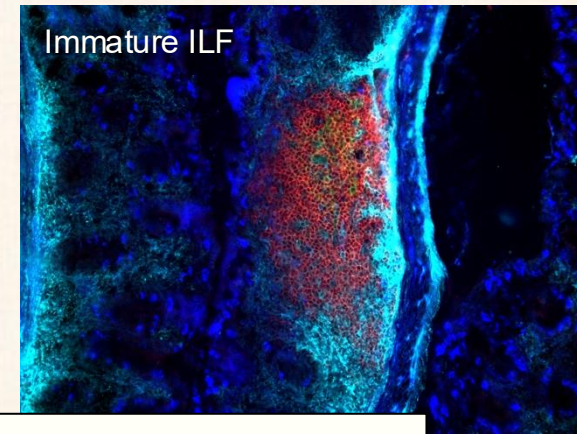
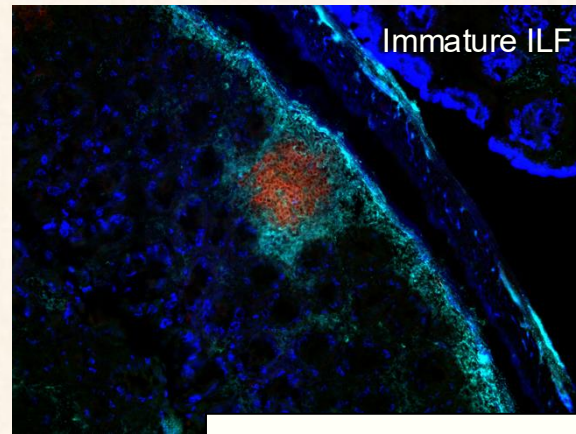
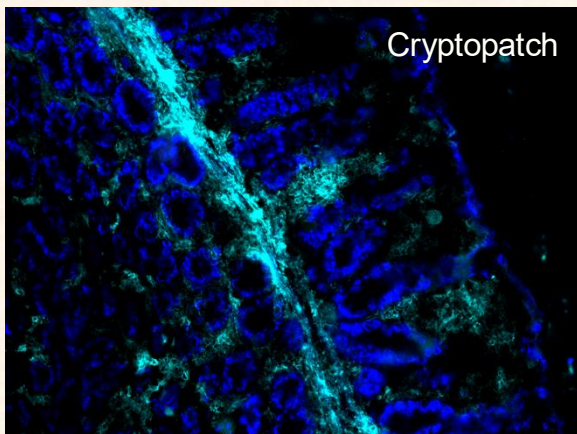
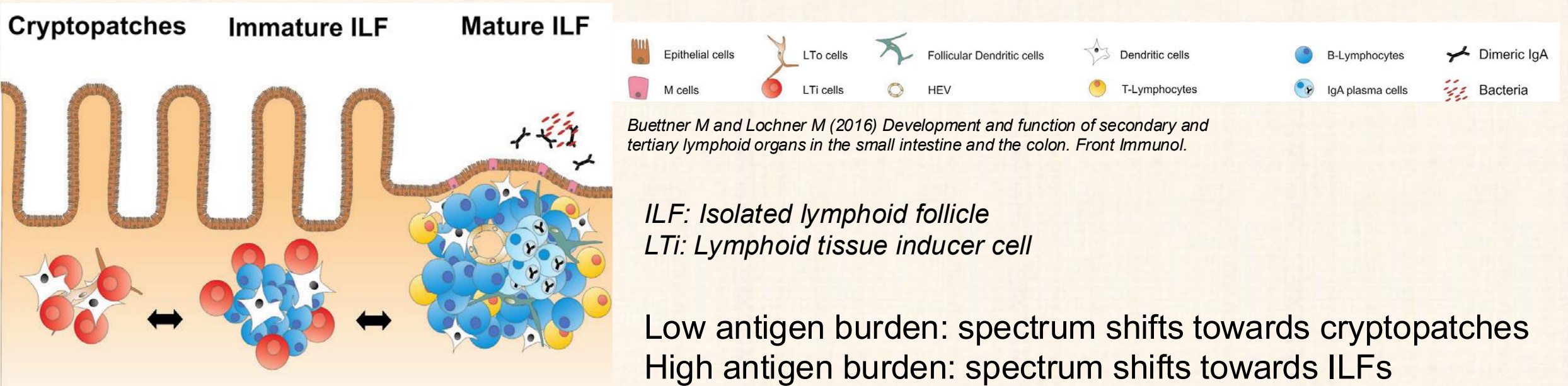
Programmed lymphoid tissues in the gastrointestinal tract: tonsils



Normal tonsil

Inflamed tonsil

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



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

Innate immunity of the intestinal immune system: epithelial cells

Epithelial cells

Goblet cells: constant mucus secretion

mucus: small intestine: 1 layer; colon: 2 layers - inner (dense) and outer (less-dense) layer
antigen sampling...

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

M-cells: antigen transport

Tuft cells: Type 2 immune response (against helminths)

...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

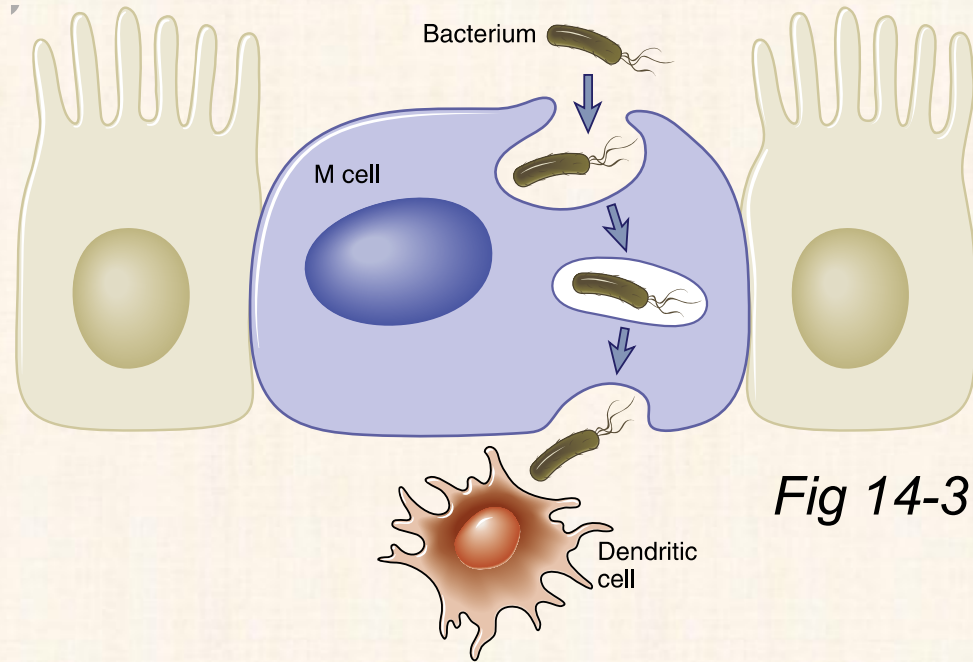
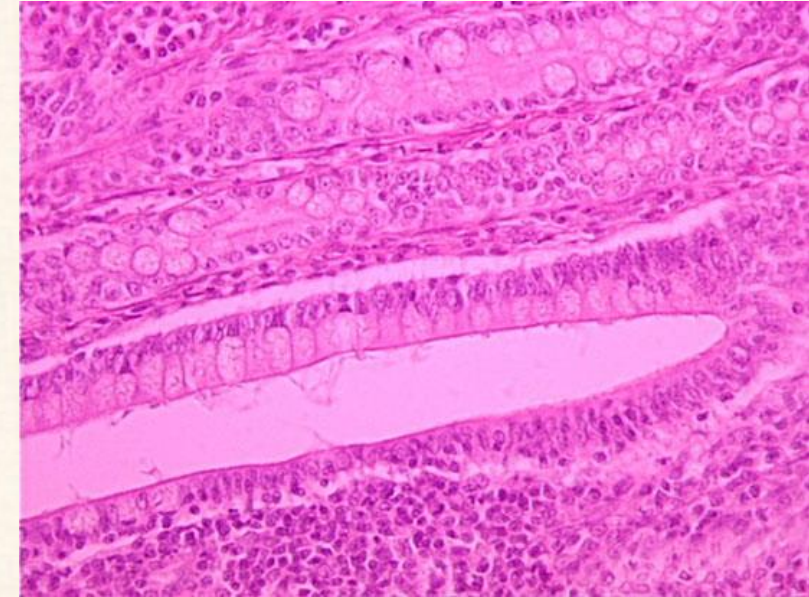
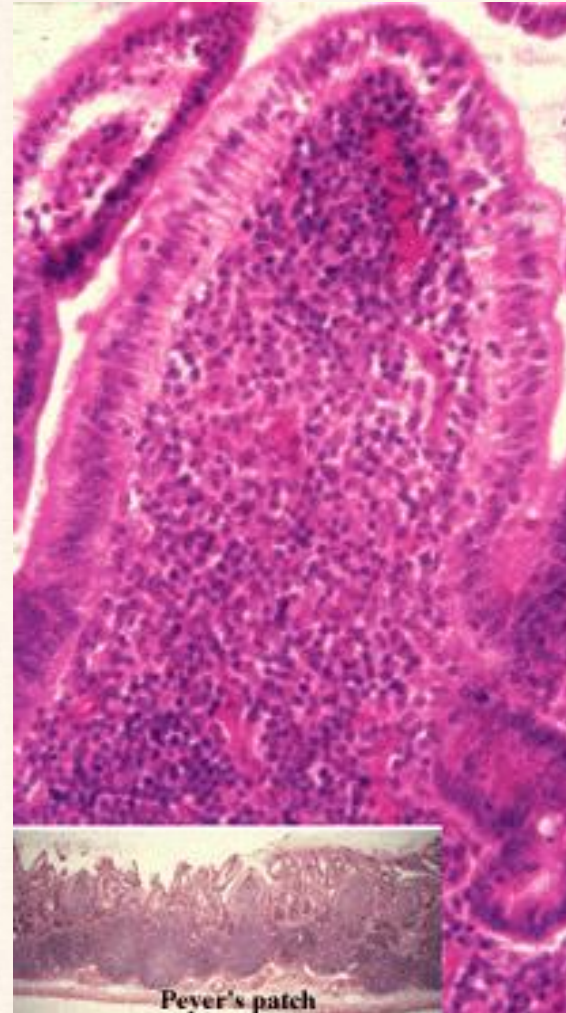


Fig 14-3

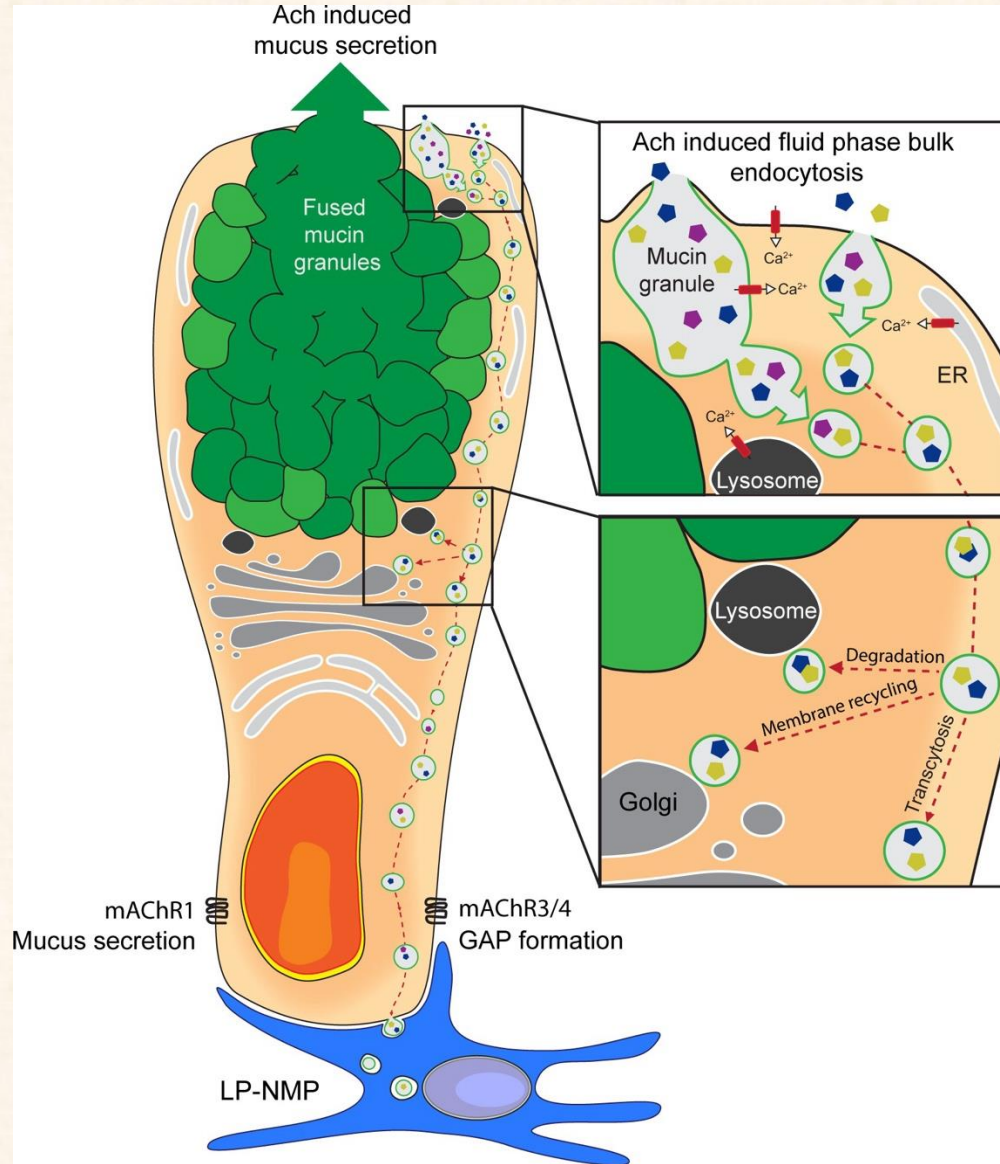
Abbas, Lichtmann and Pillai. *Cellular and Molecular Immunology*. 8th edition.
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(Not antigen presentation!)



M cell region

Goblet cells: not only mucus secretion...



GAP: Goblet cell associated Antigen Passages

Transport of luminal antigens to underlying mononuclear phagocytes

Innate immunity of the intestinal immune system

Dendritic cells, Macrophages

Antigen presentation in mLNs

Usually promote tolerance (IL-10, TGF β)

DCs: express retinal dehydrogenase \rightarrow secrete retinoic acid \rightarrow imprinting of gut-homing molecules

Innate lymphoid cells

Lymphoid cells, but do not express antigen receptors

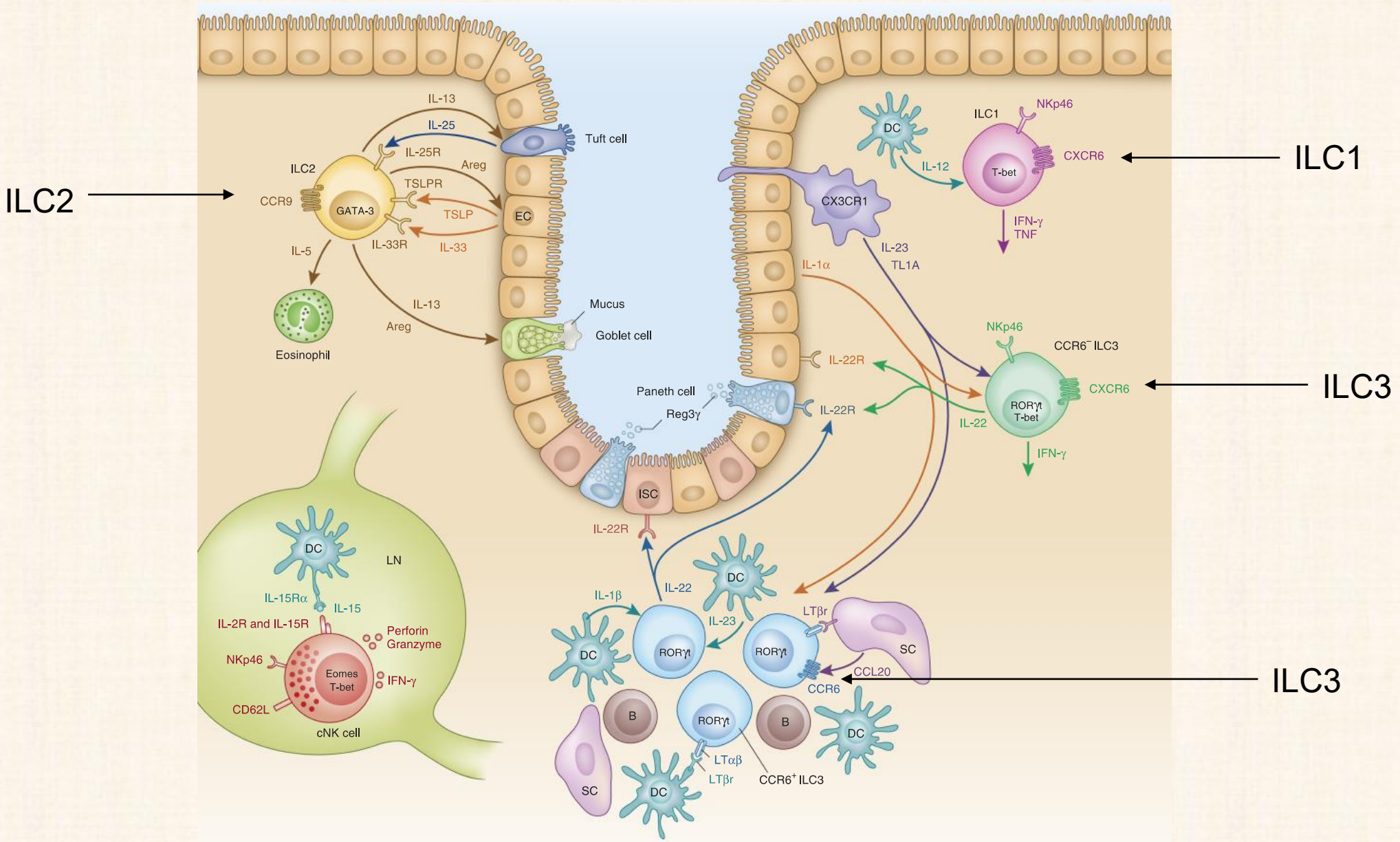
Secrete cytokines

ILC1: NKs + non-cytotoxic ILC1s

ILC2: immune response against helminths, allergy (IL-5, IL-13)

ILC3: mucosal healing (IL-22), inflammation (IL-17a) (+ LT α i 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

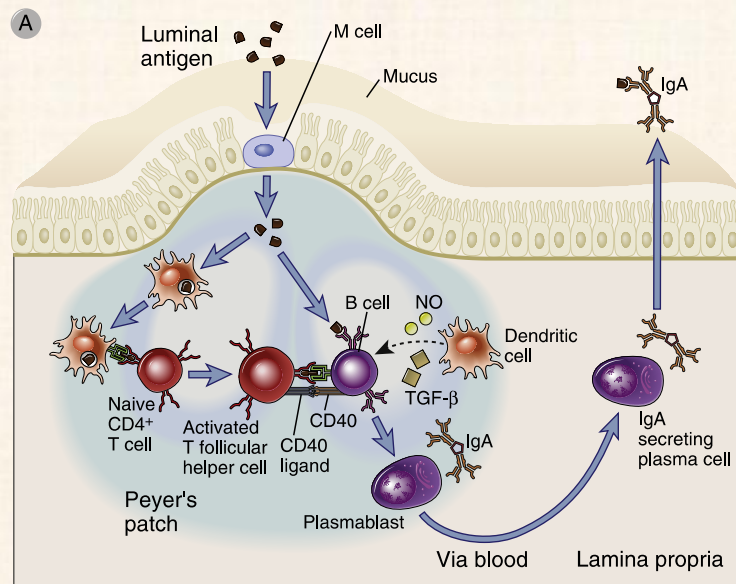
~2g IgA produced per day

Large amounts of TGF β (produced by epithelial cells and DCs) induce IgA isotype switch

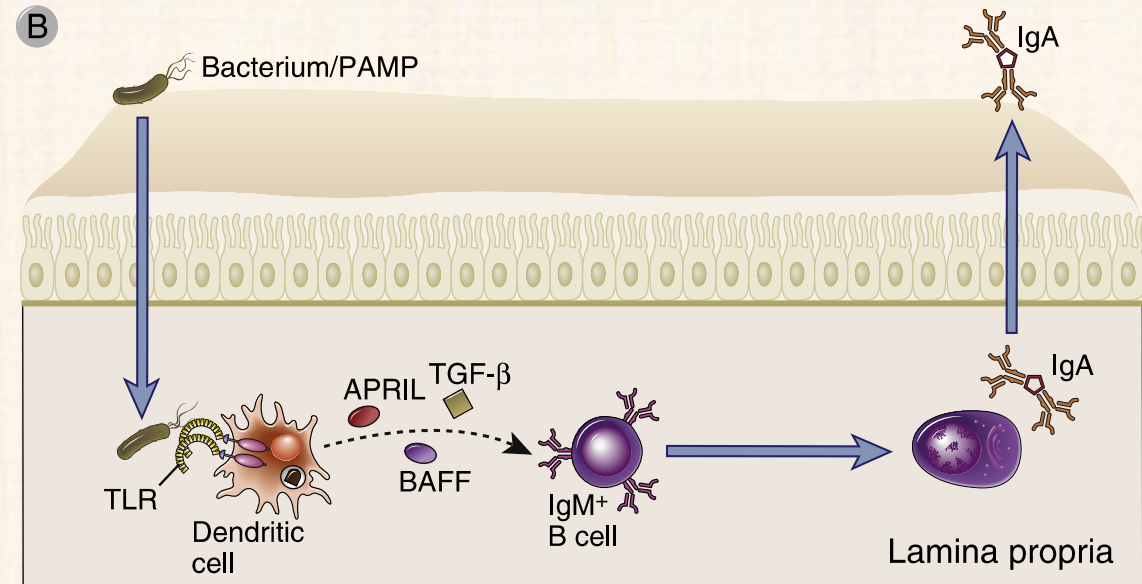
Neutralizing immunity: prevents microbes/toxins from binding to/crossing the epithelium

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

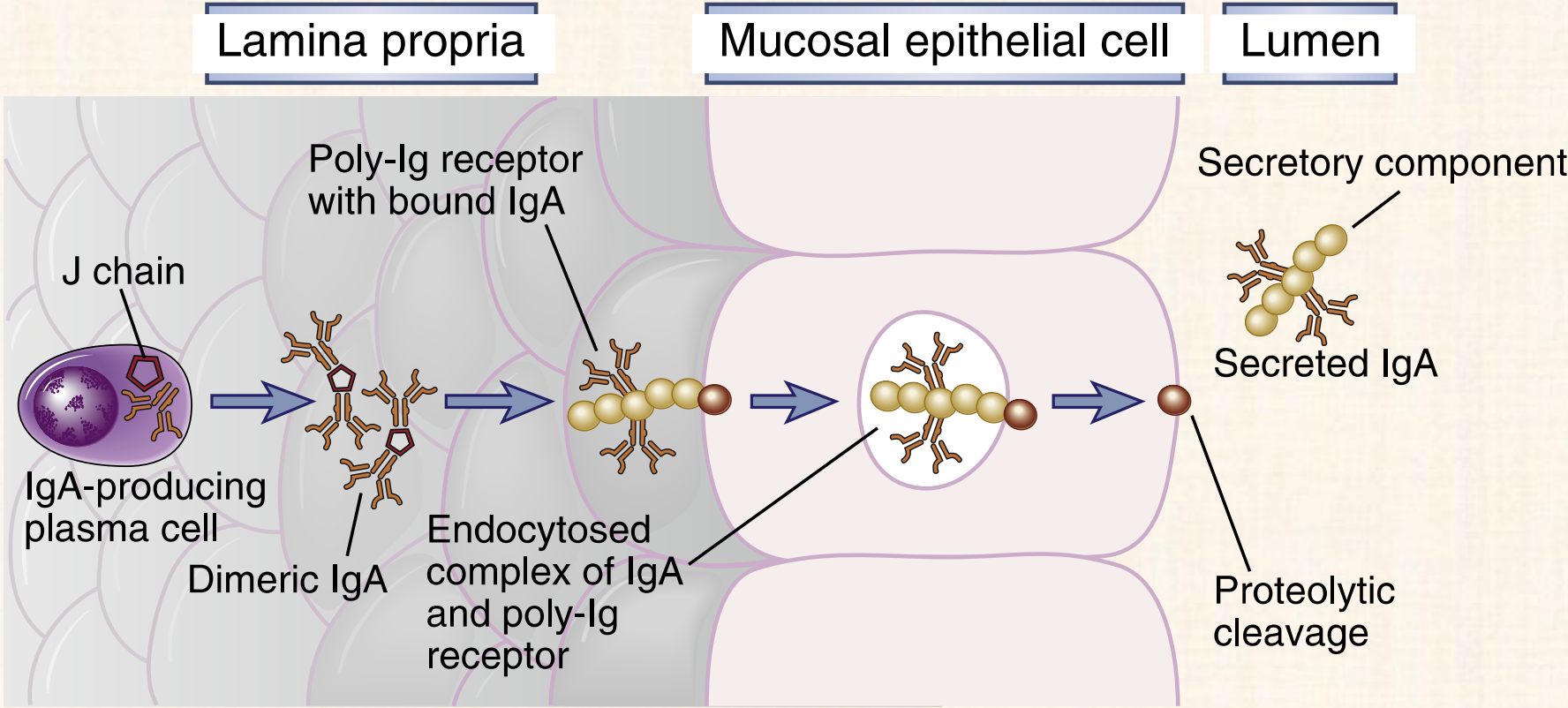


Fig 14-8

Intestinal T cell responses

Location

Dispersed:

Intraepithelial lymphocytes: mainly CD8⁺ or $\gamma\delta$ 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 TGF β , IL-10

important in inducing tolerance against non-pathogenic microbes

Homing to mucosal lymphoid tissues

	Endothelium	Leukocyte
Adhesion molecule	MAdCAM-1	$\alpha 4\beta 7$
	CCL25	CCR9
Chemokine	CCL28	CCR10
	CCL20	CCR6

Vedolizumab: mAb against $\alpha 4\beta 7$, used in inflammatory bowel diseases

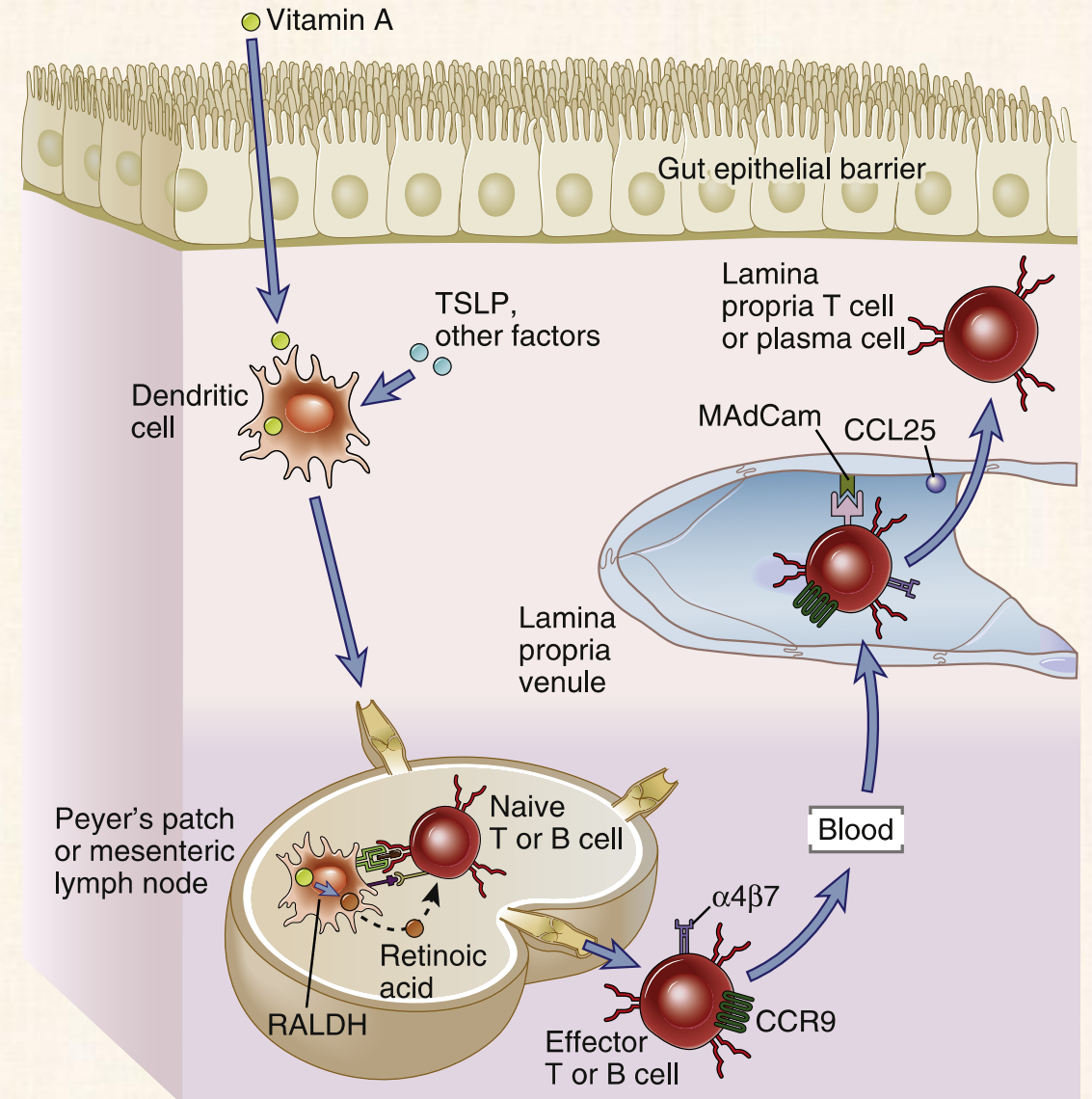


Fig 14-5

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:

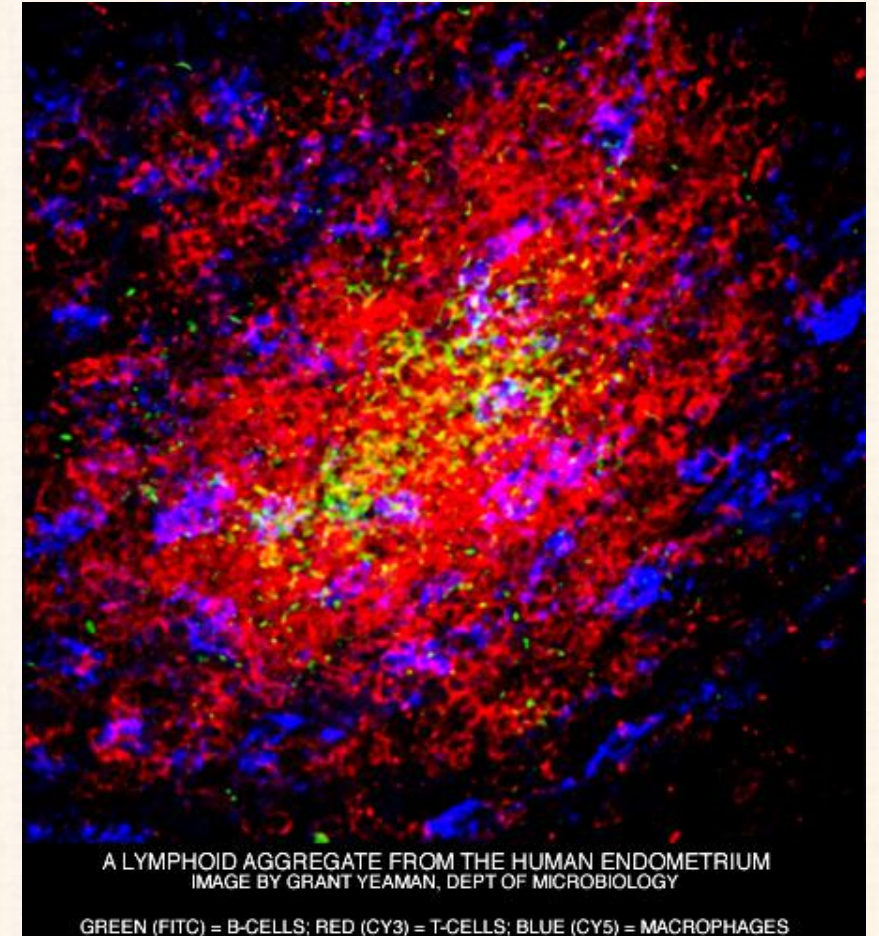
- epithelial barrier, mucus and antimicrobial factors
- lymphoid tissues beneath the epithelium
- antigen sampling
- secretory IgA as prevention

Airways

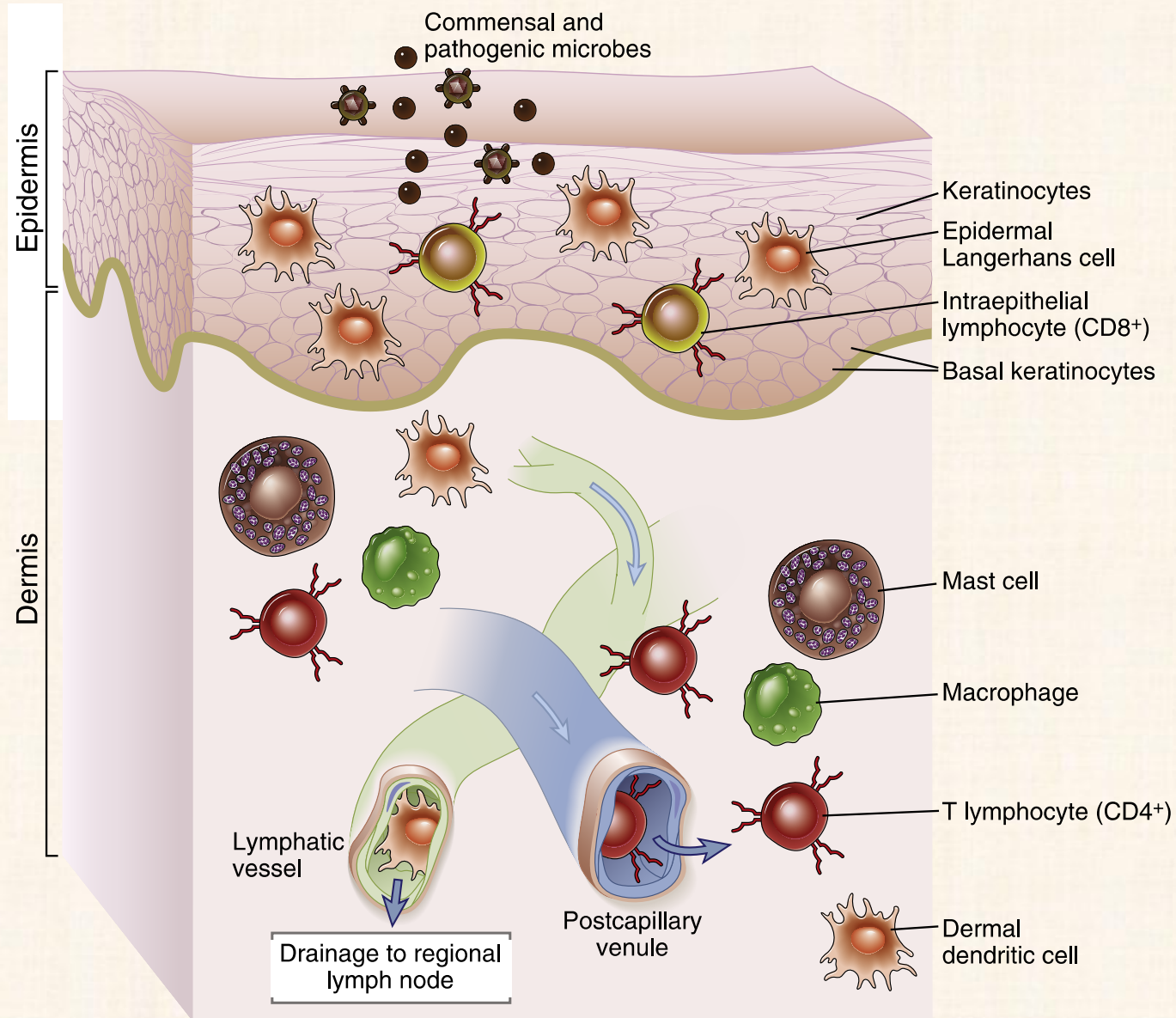
- Innate: surfactant protein; alveolar macrophages
- Adaptive: IgA, IgE (allergic reactions)

Urogenital tract

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



Cutaneous immune system



2m²
~2x10¹⁰ lymphocytes
Physical barrier

*(Sun)burns
Microbes
Traumas*

Fig 14-9

Cells of the cutaneous immune system

Keratinocytes

Physical barrier

Cytokines: TNF, IL-1 β , 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

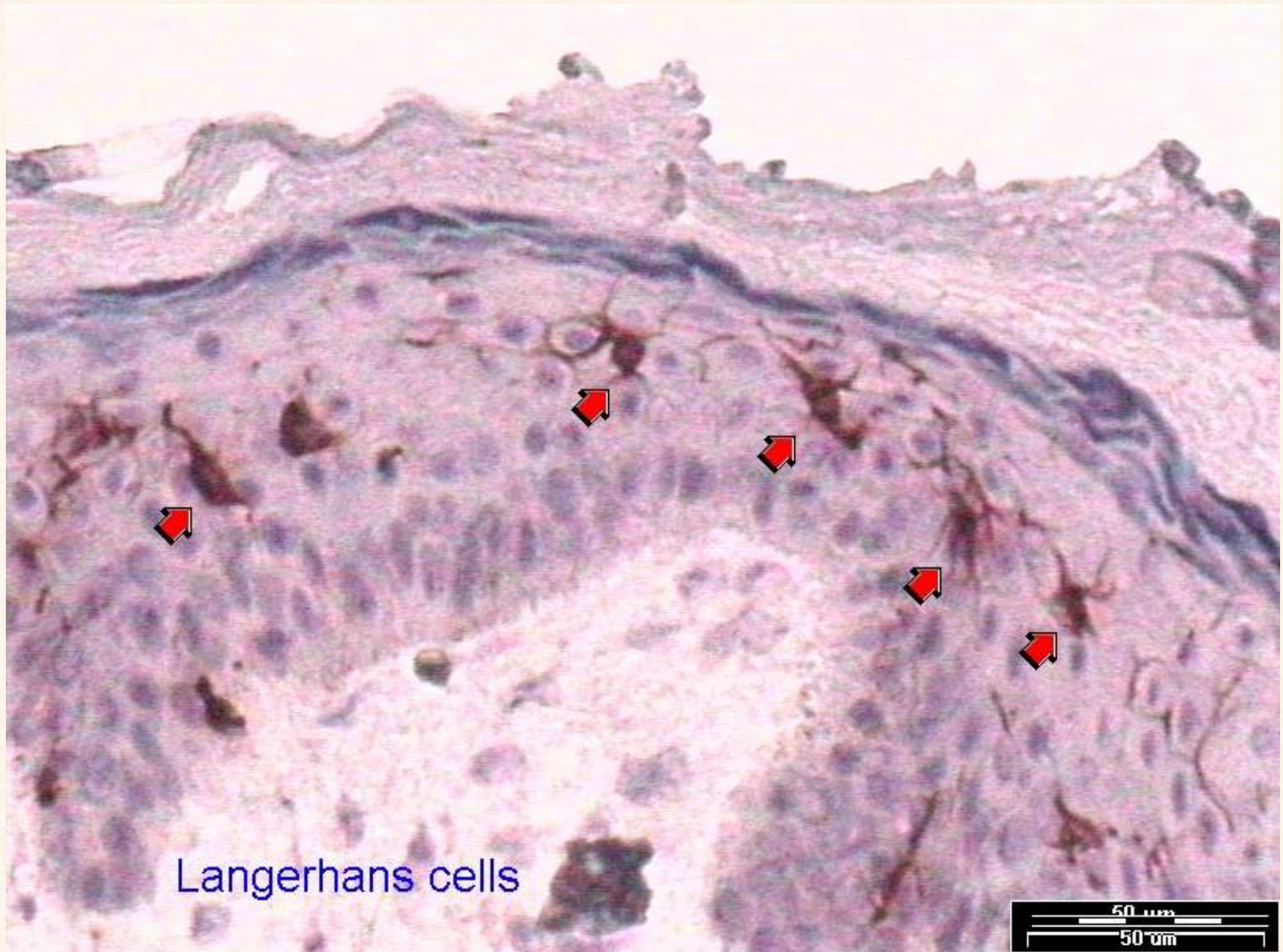
Migrate to regional lymph nodes following phagocytosis of antigens

Present antigens to T cells, imprint skin-homing properties

T cells

Intraepidermal: mainly CD8⁺ or $\gamma\delta$ T cells

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



Langerhans cells

50 μm
50 μm

Homing to the skin

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

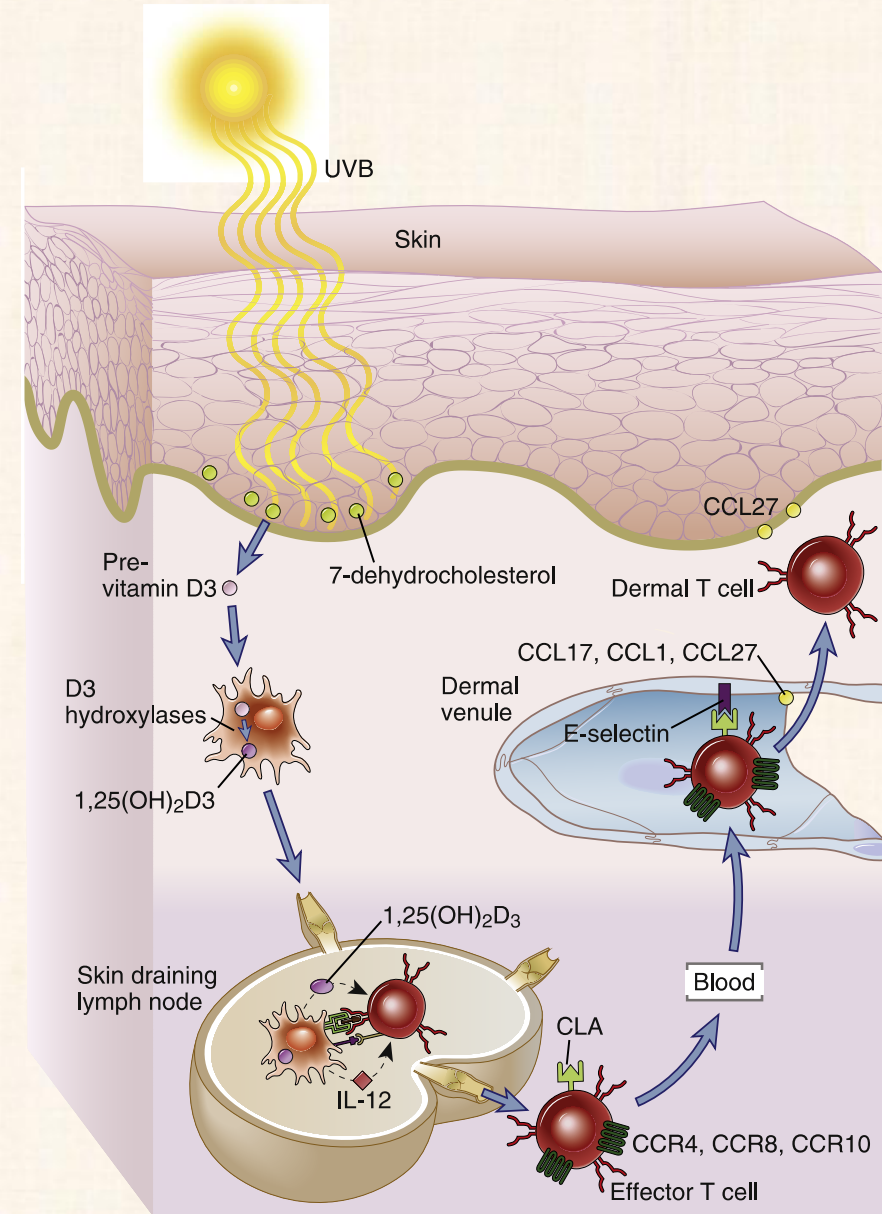
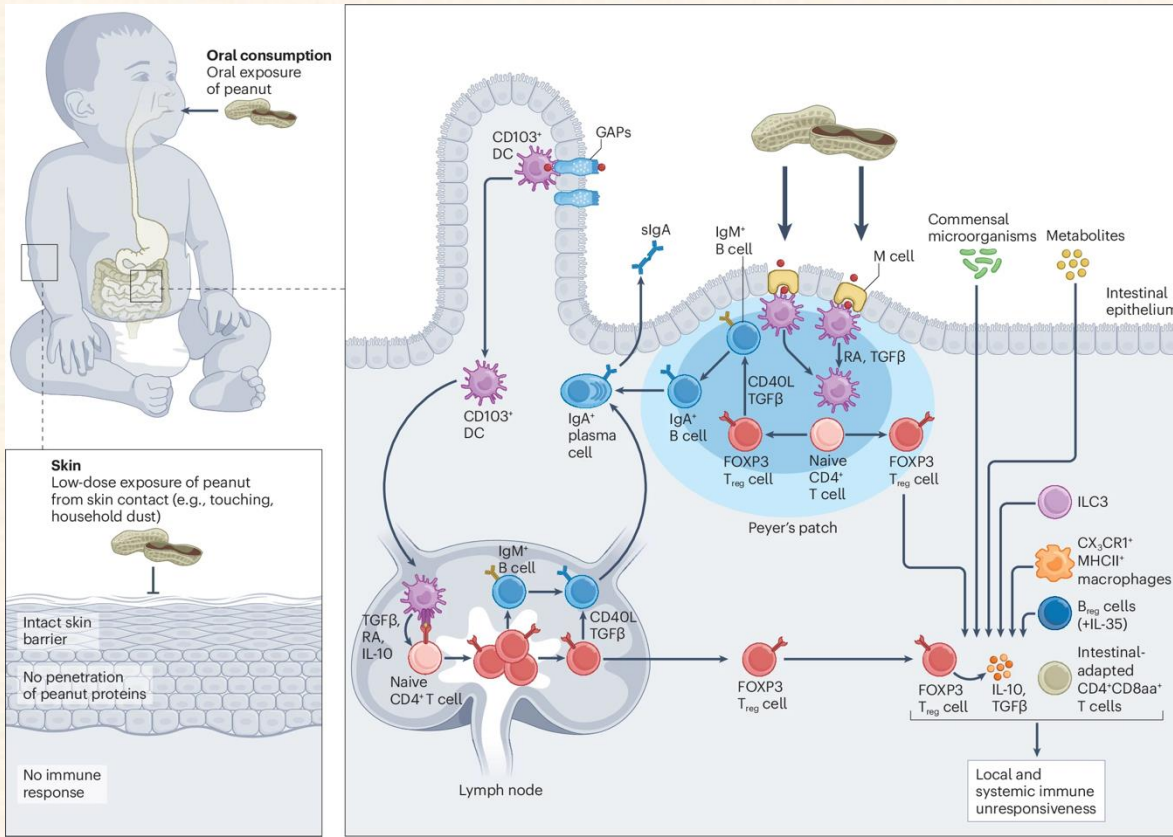
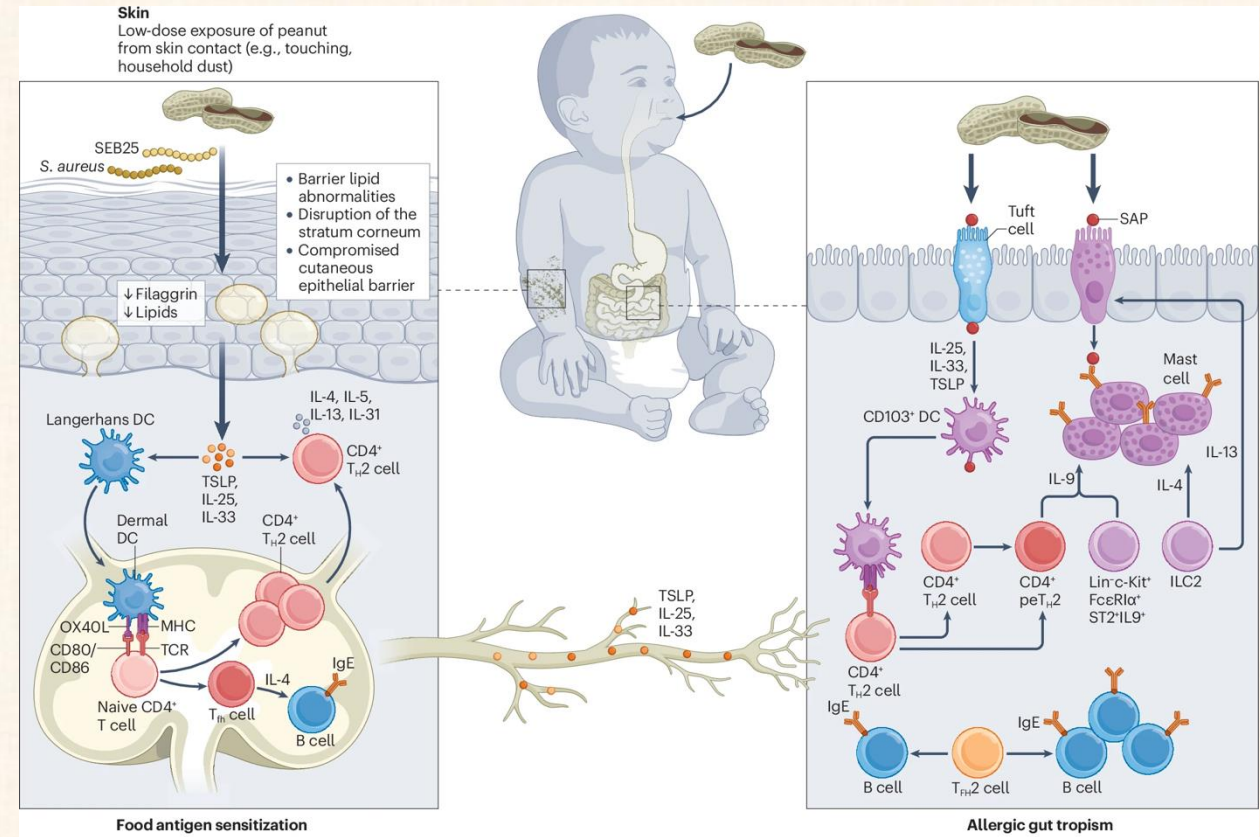


Fig 14-9

Mucosal vs skin immunity



Oral entry: tolerance



Entry through skin: sensitization

Basic Immunology

Suppression of the immune response
Suppressor mechanisms of immune functions

22nd lecture
April 23rd, 2026
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-idiotypic antibodies

1. Antigen as the main regulator

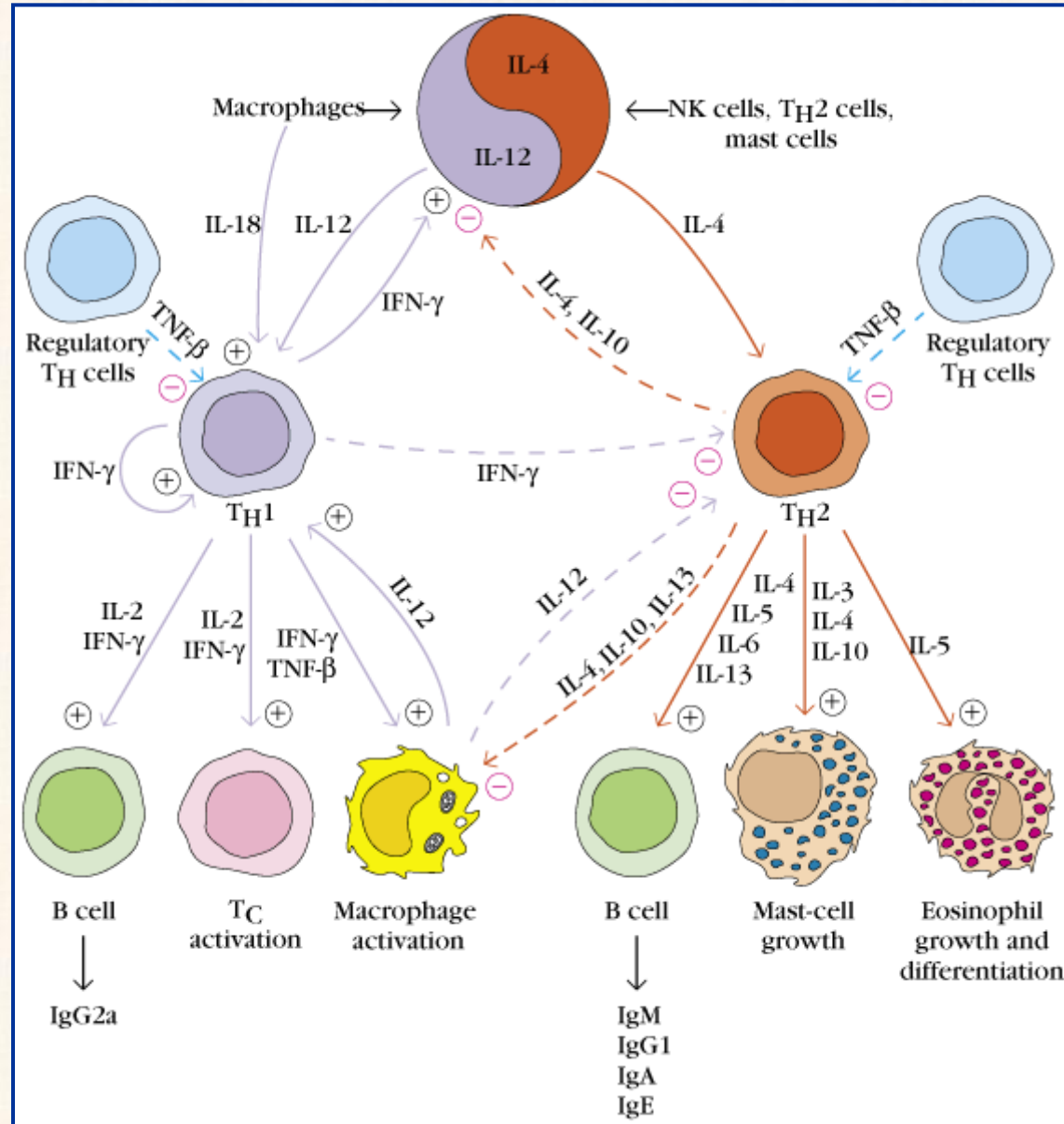
Activates T and B cells

Antigen nature, dose (short vs long term), location (skin vs mucosa) influence the immune response

T_H1 vs T_H2

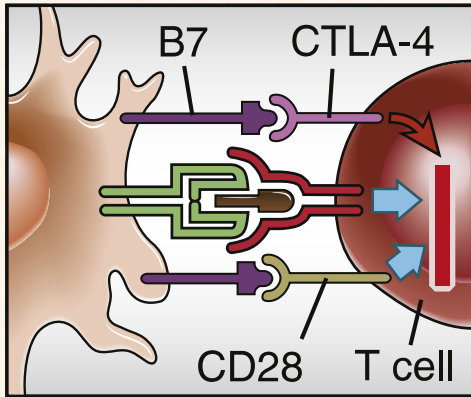
Withdrawal/elimination of the antigen stops further activation

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



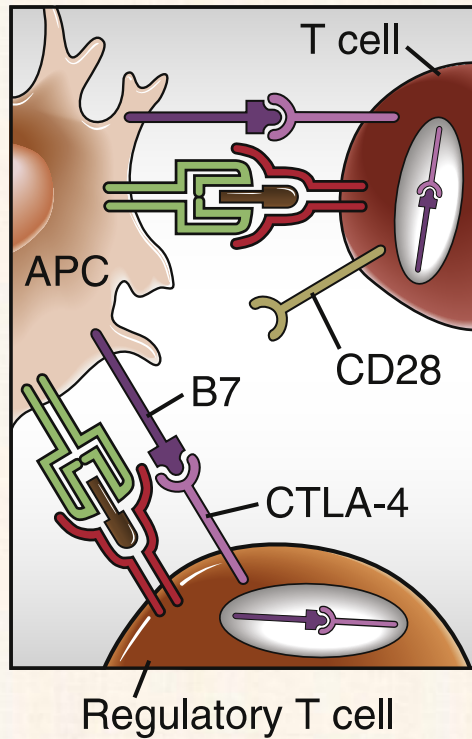
2. Need for costimulation

A Cell intrinsic inhibitory signaling



Signal block ⇒
**inhibition of T cell
activation**

B Blocking and removing B7 on APC



**Reduced B7
costimulation** ⇒
**inhibition of T cell
activation**

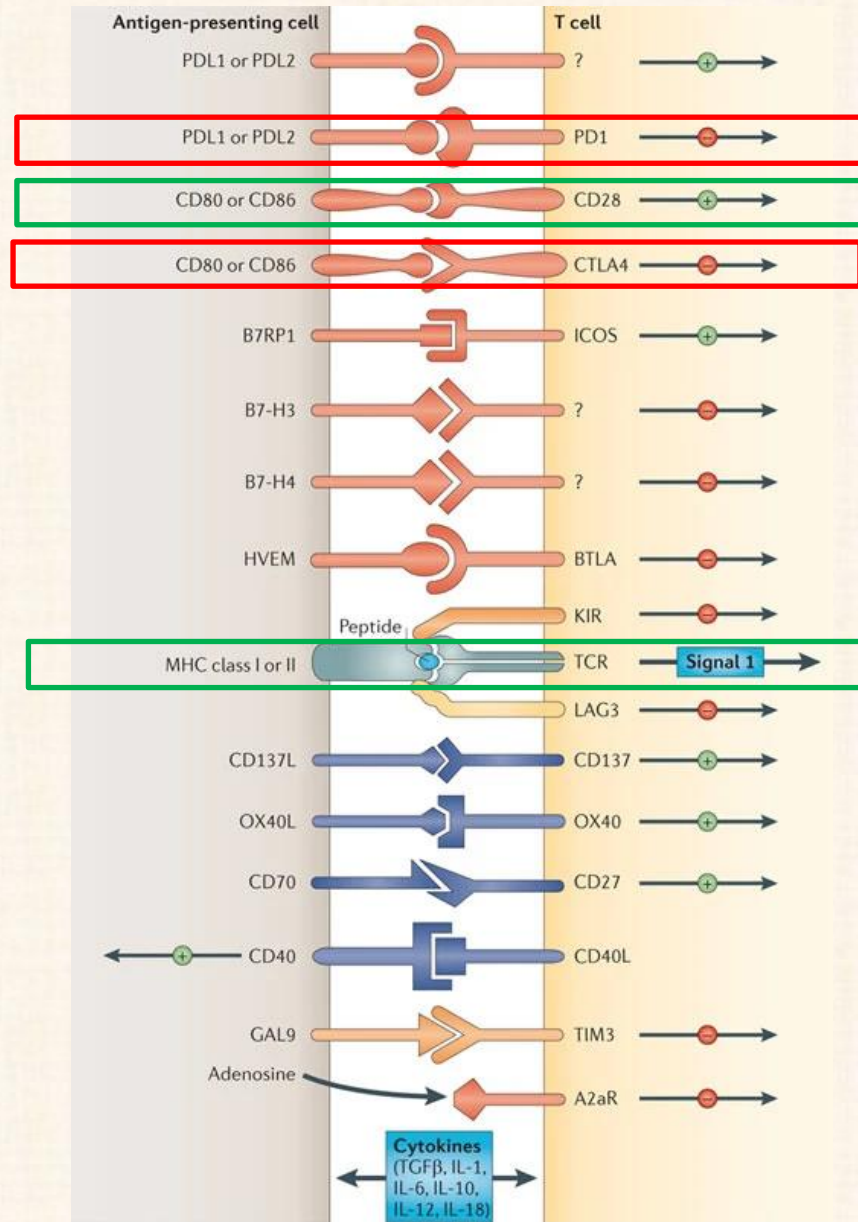
CD28: constitutively expressed on T cells
CTLA-4: expressed after activation
higher affinity towards B7

Fig 15-6

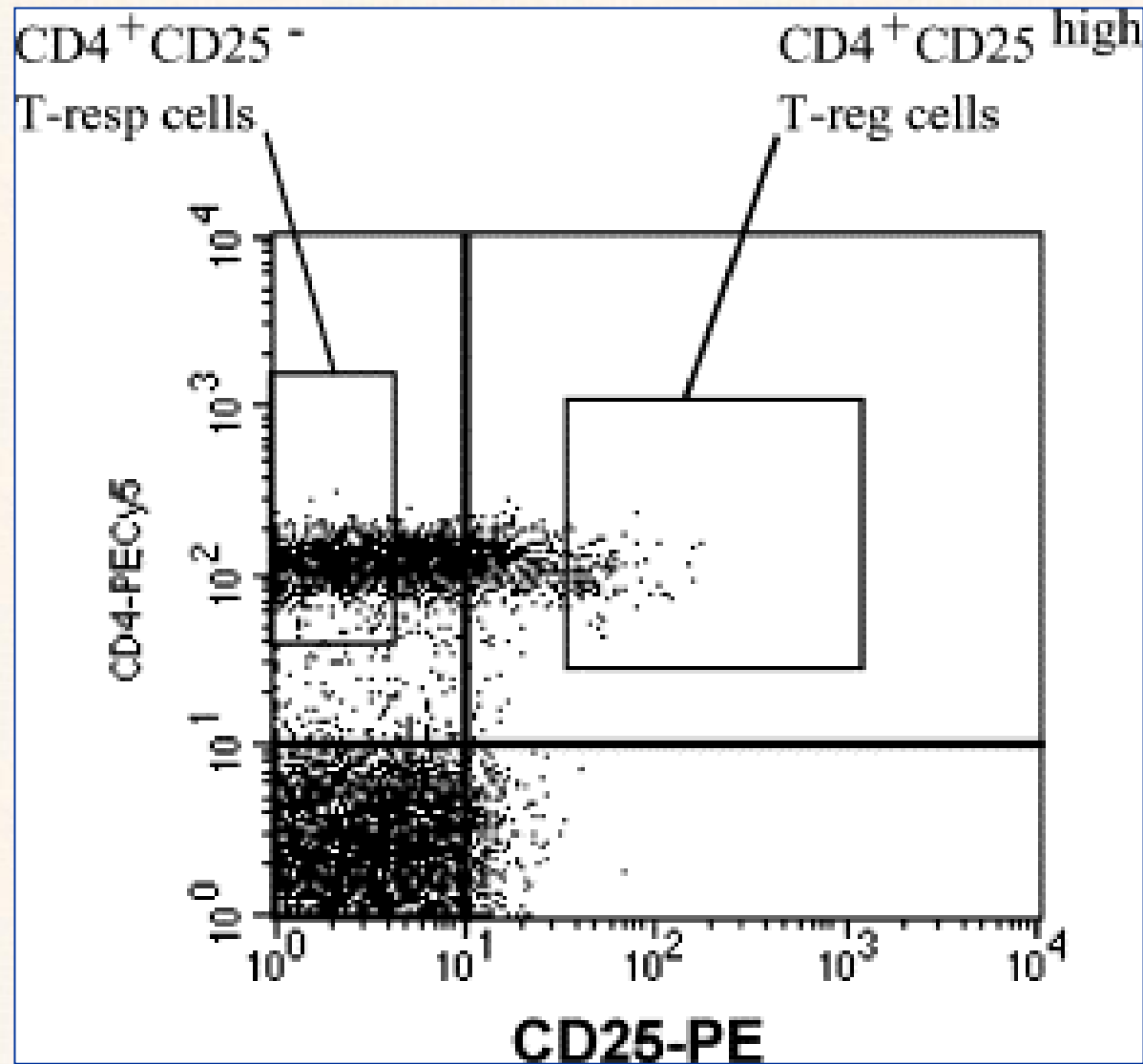
2. Need for costimulation: Immune checkpoints

Antigen presenting cell

T cell



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



3. Main functions of regulatory T cells

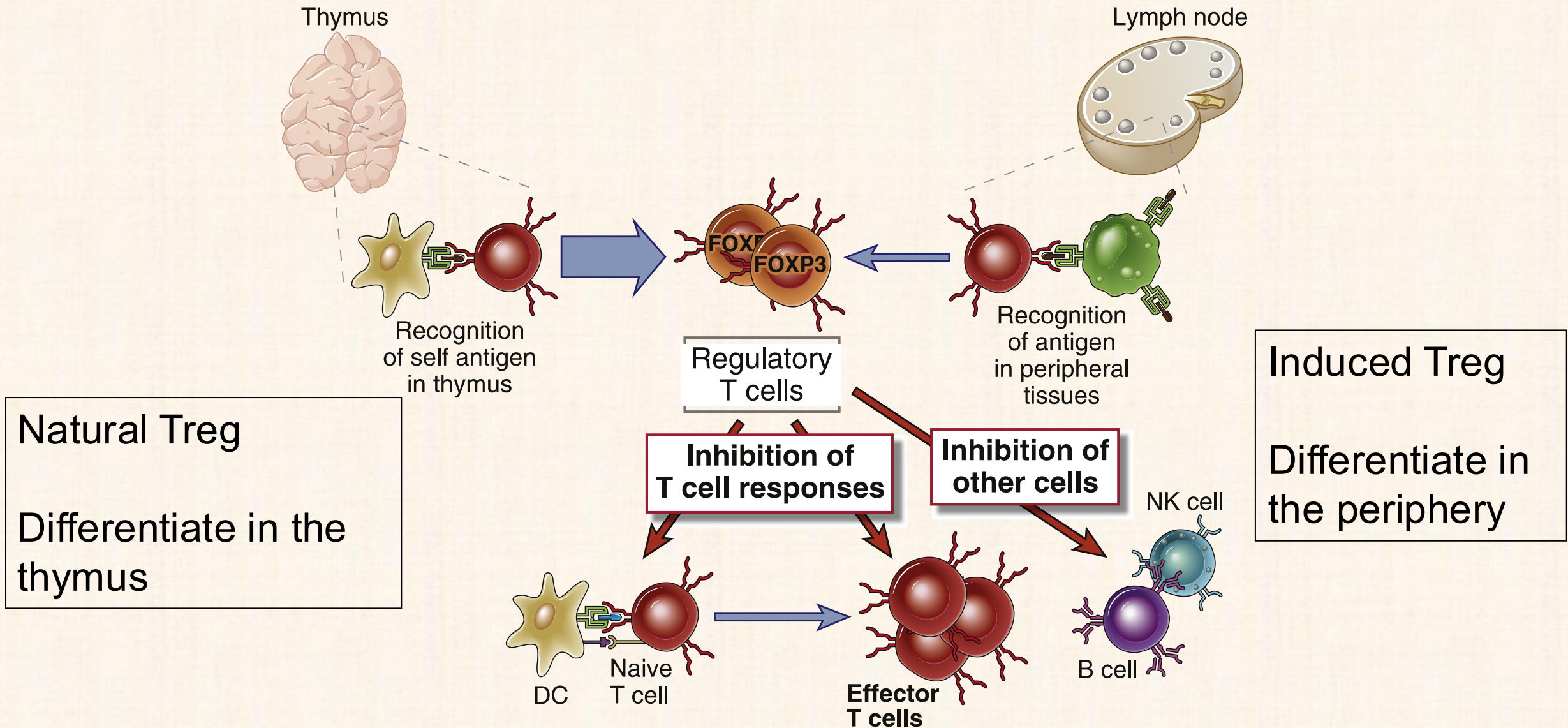
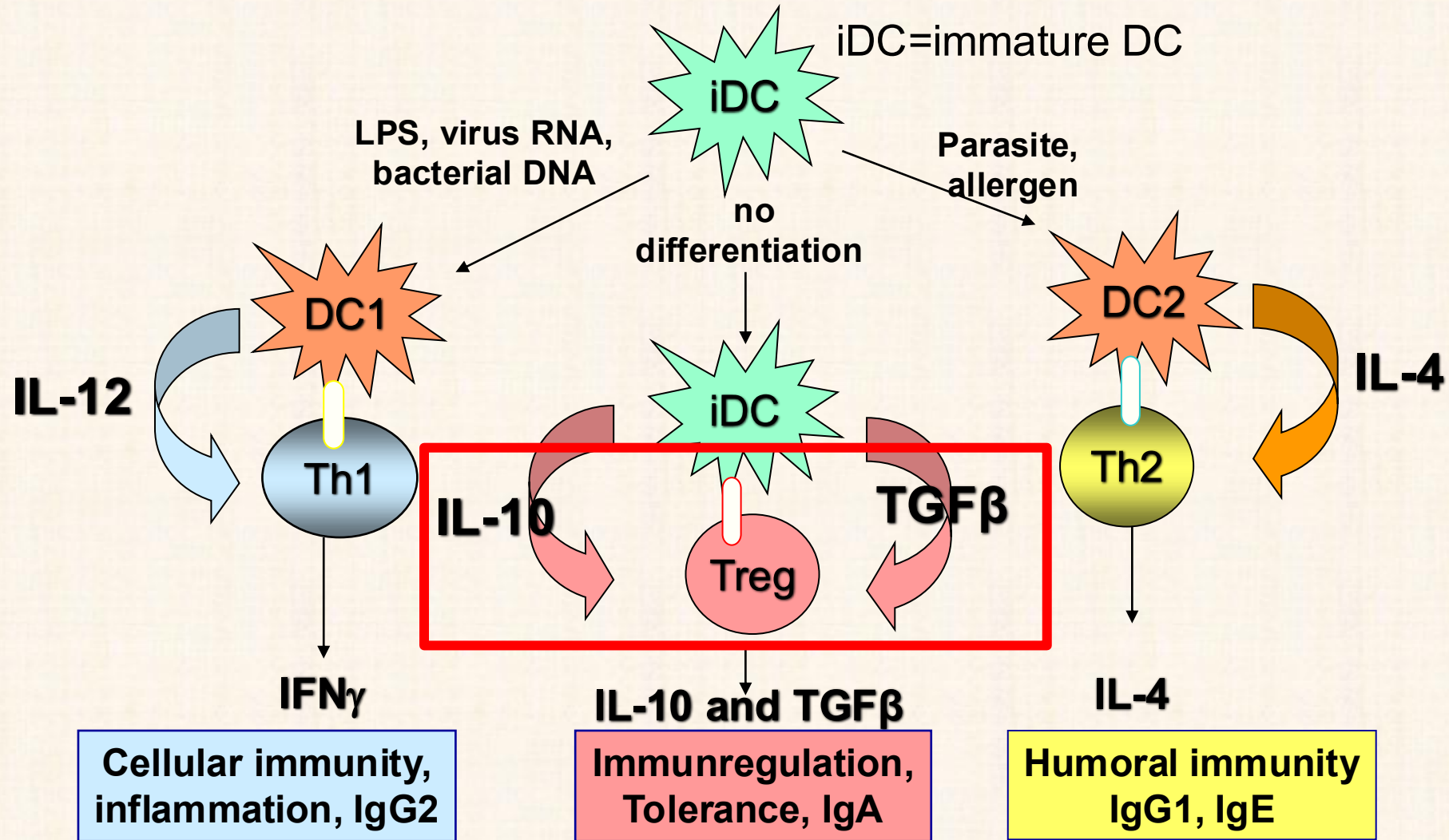
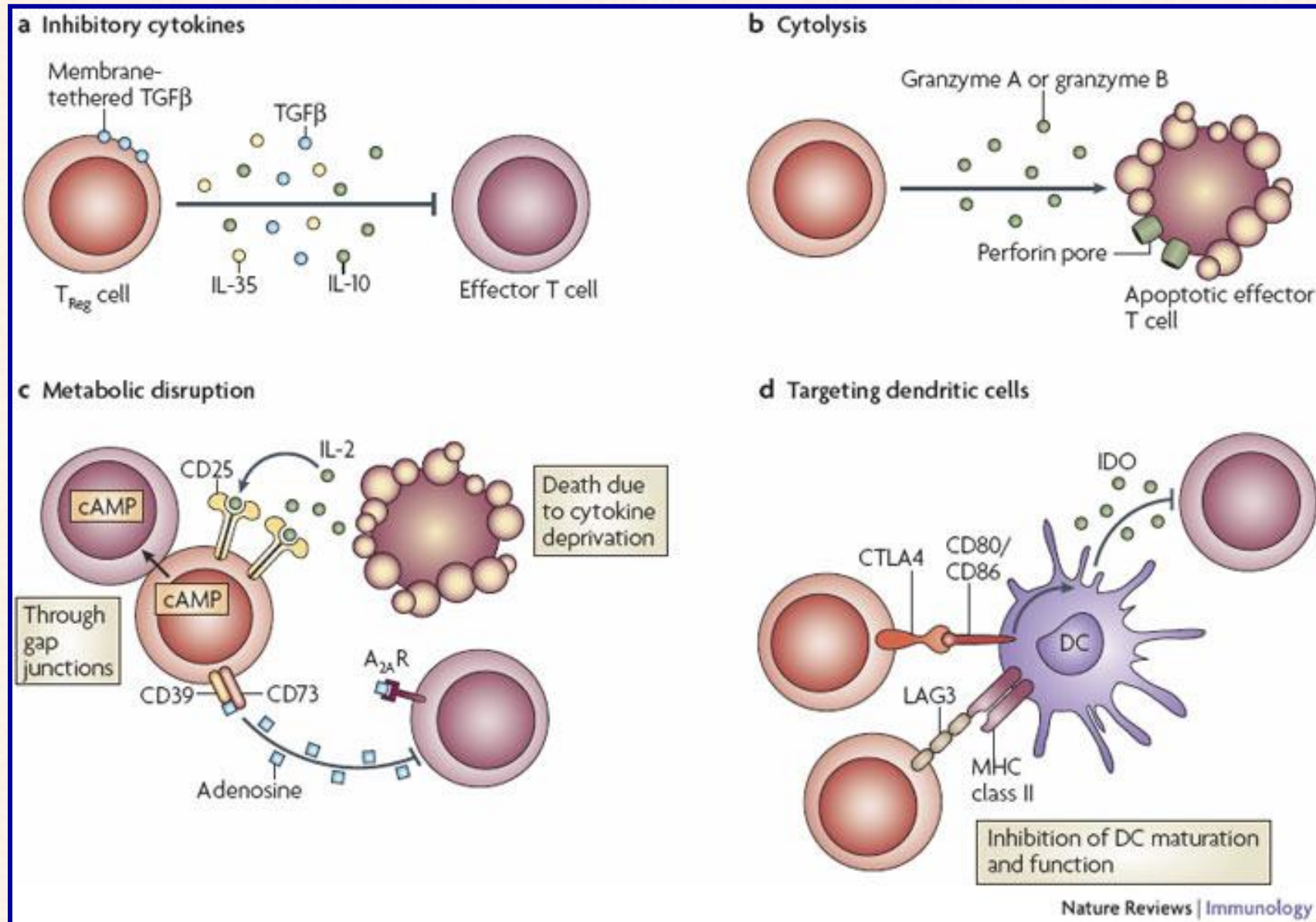


Fig 15-7

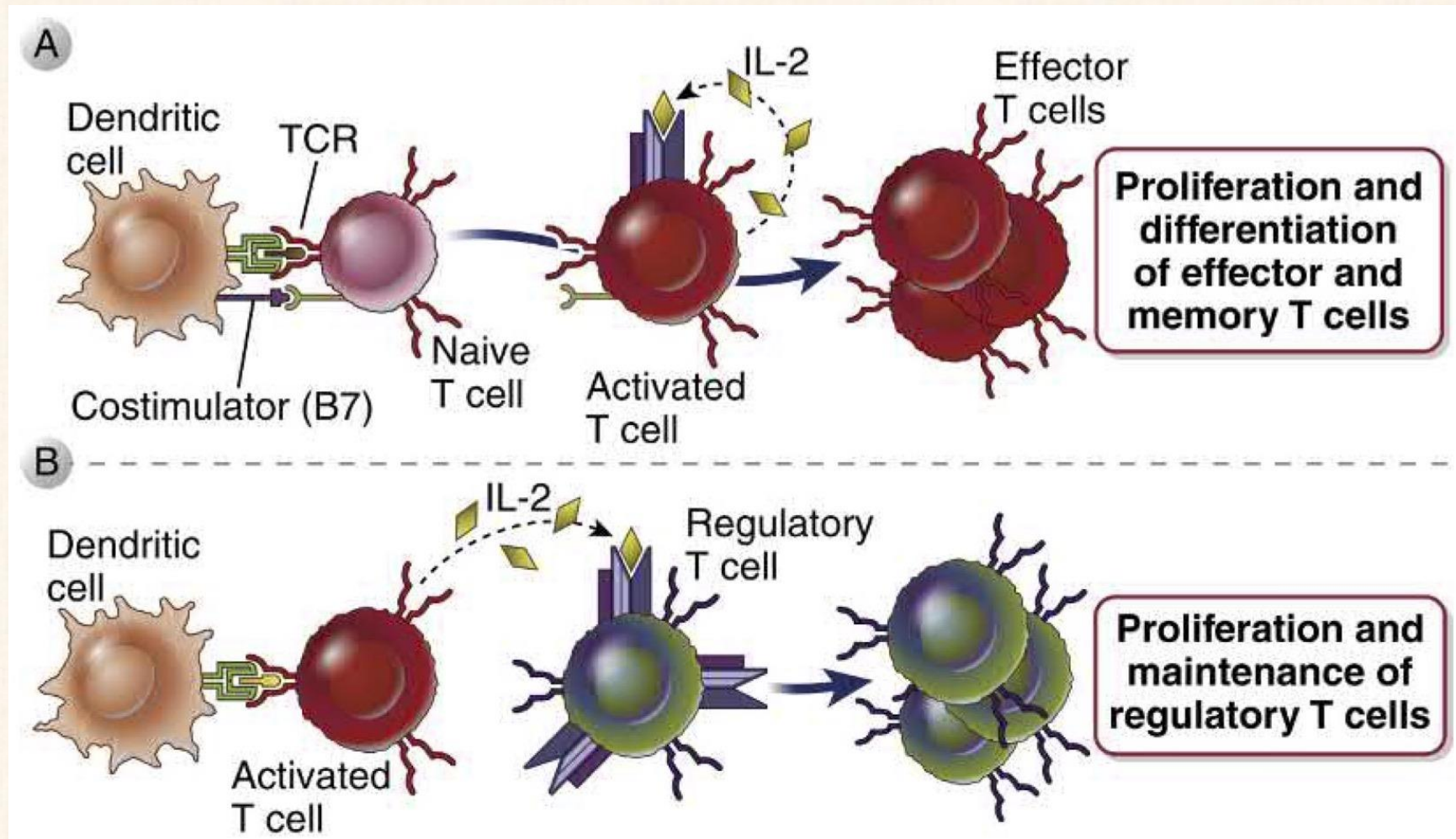
3. Development of induced T_{reg} cells



3. T_{reg} suppression mechanisms



3. T_{reg} suppression mechanisms: IL-2 consumption



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

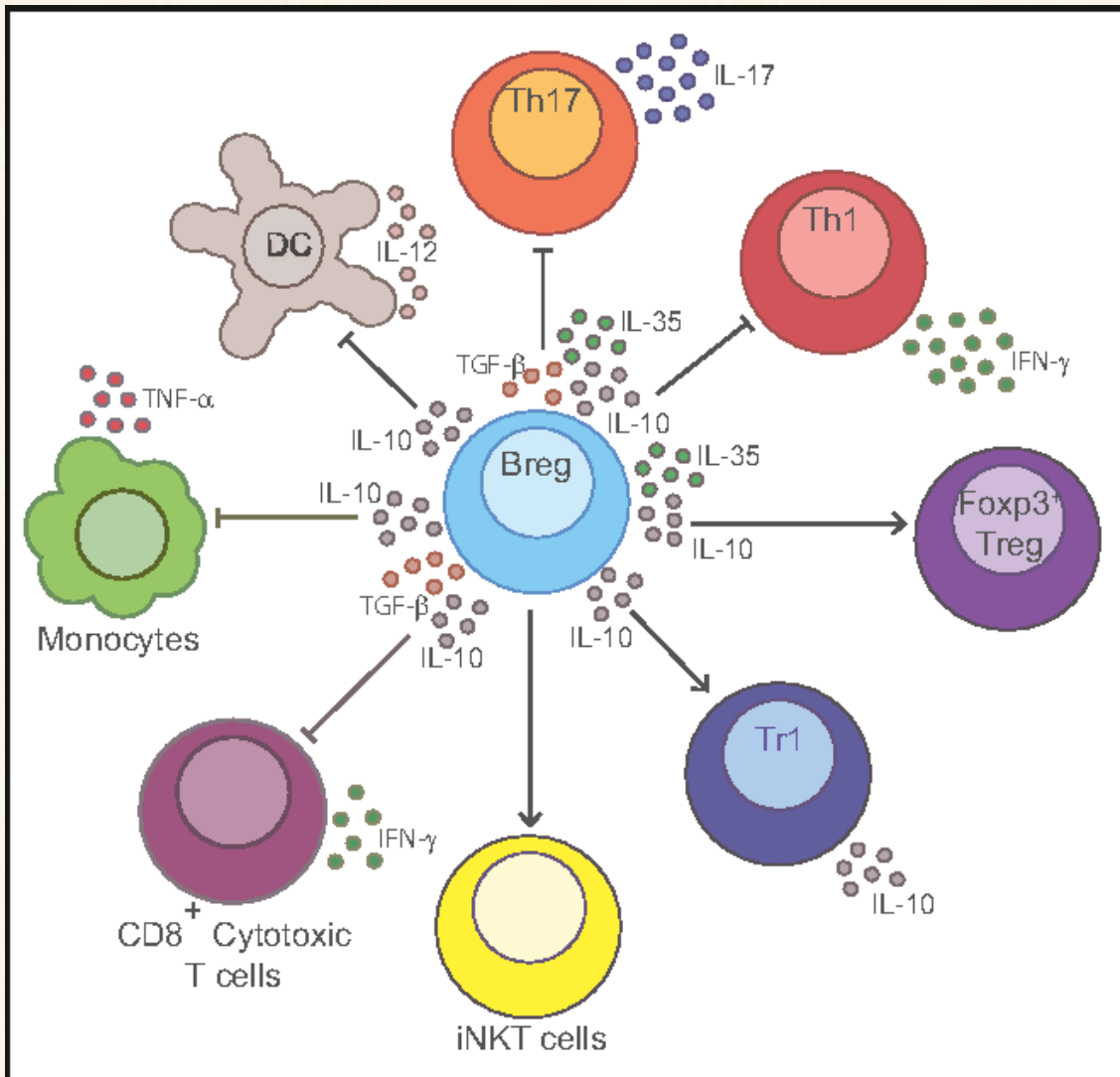
Regulatory B cells (B_{reg})

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



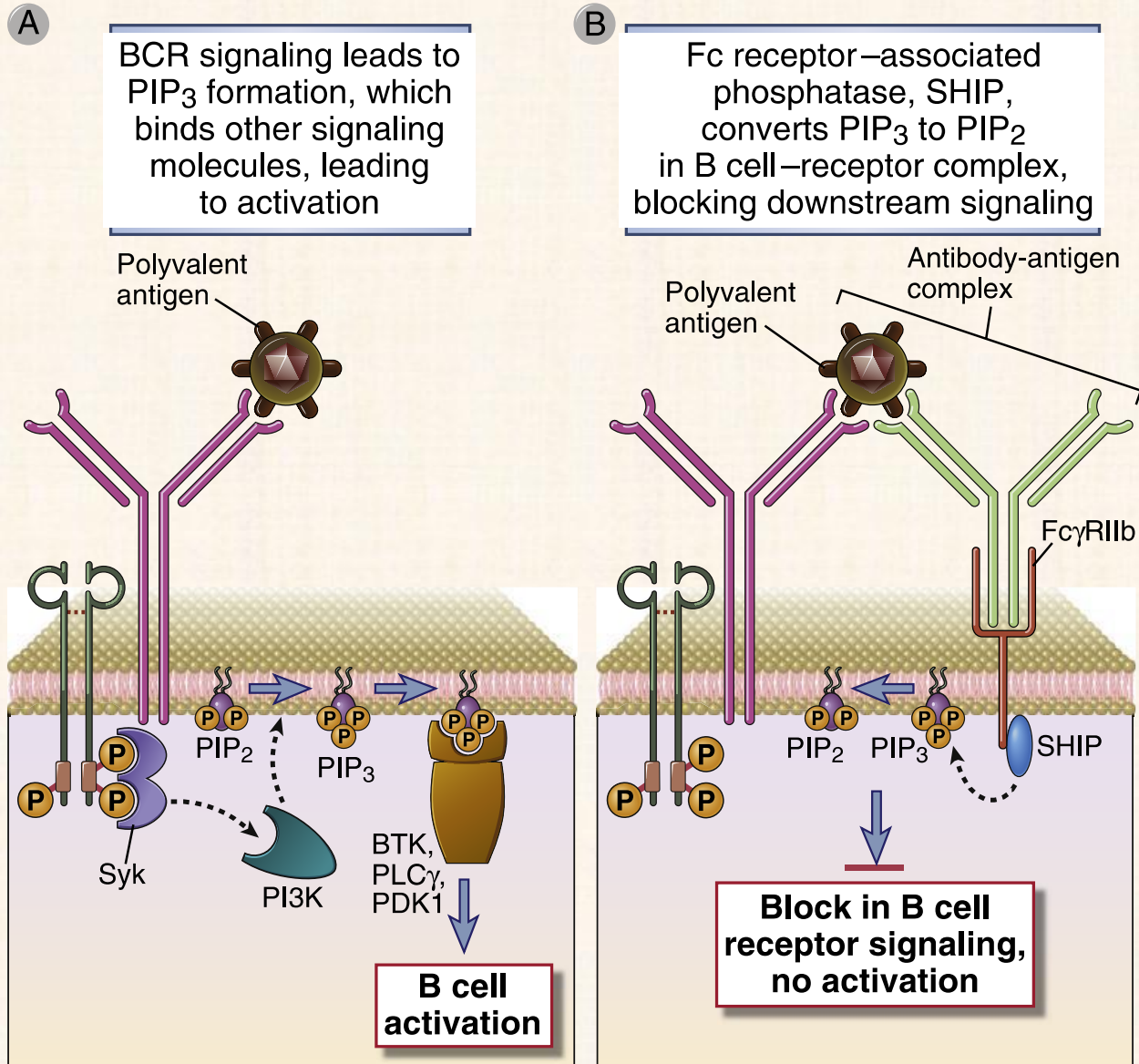
B_{reg} cells produce **IL-10**, IL-35, and TGF- β

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



Fc γ RIIb: inhibitory FcR (contains ITIM!)

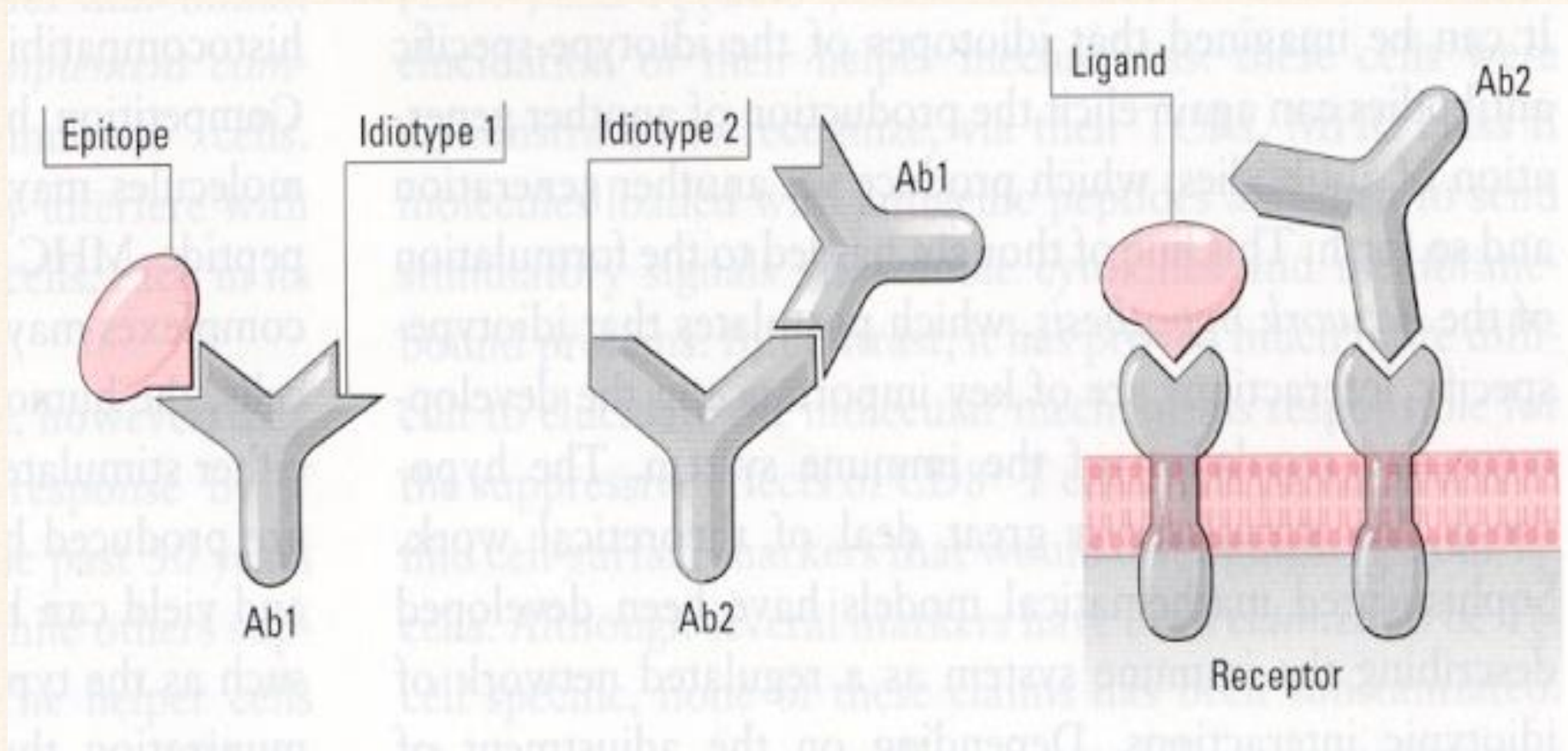
Simultaneous binding of antigen + IgG leads to B cell inhibition

Fig 12-21

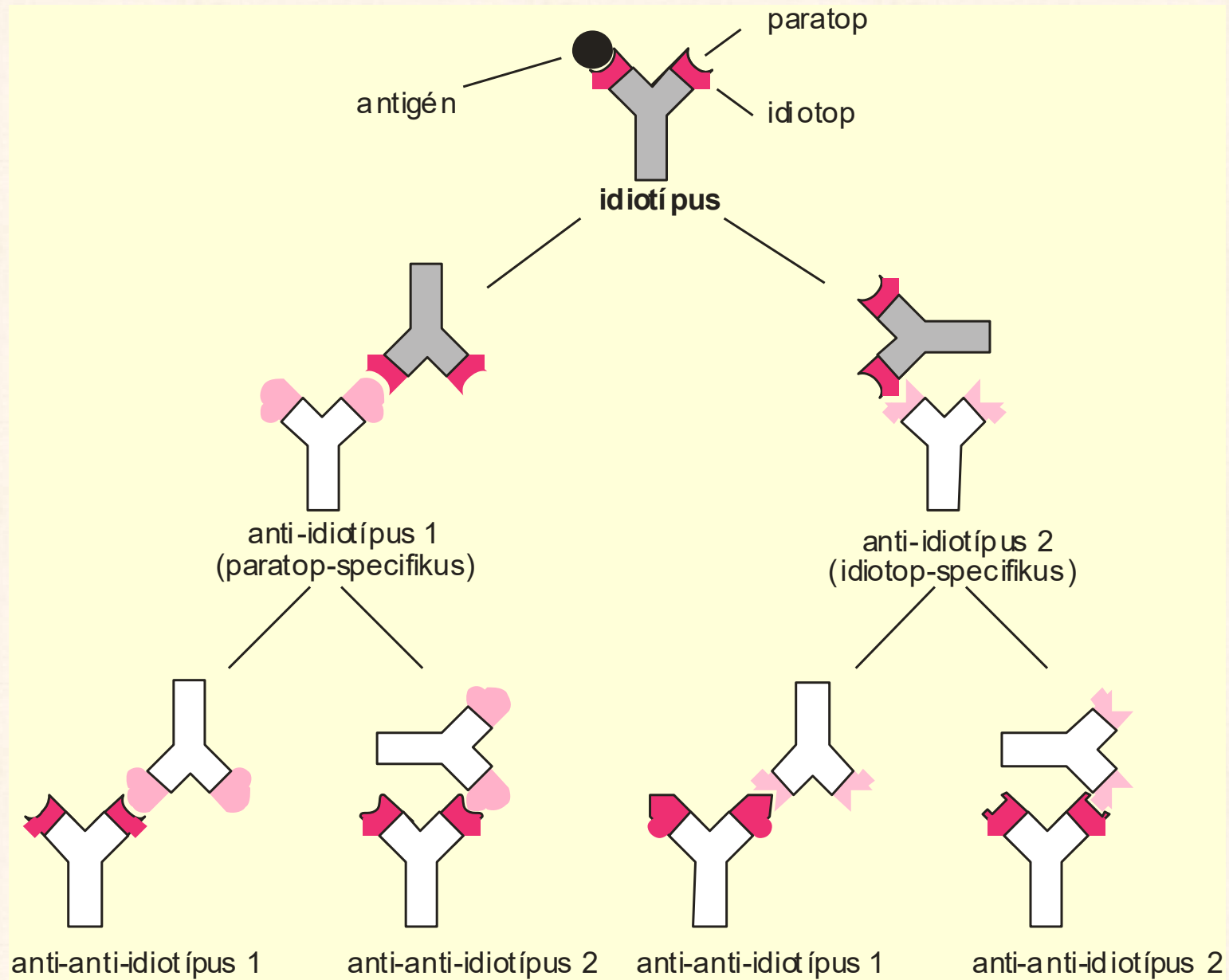
4. Anti-idiotypic antibodies

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-idiotypic network



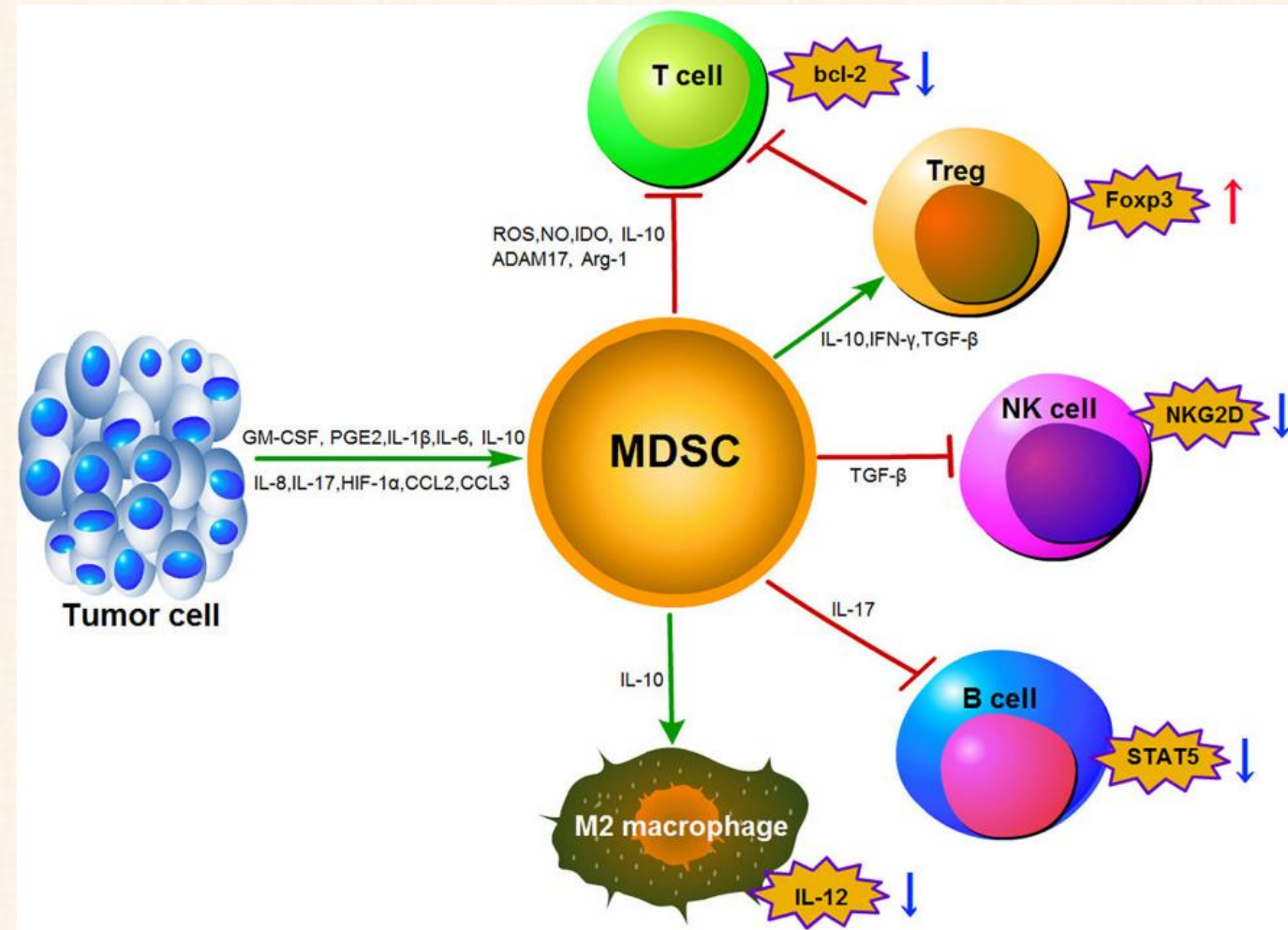
4. Functions of the anti-idiotypic network

Suppression of B and T cells

Functional memory formation

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

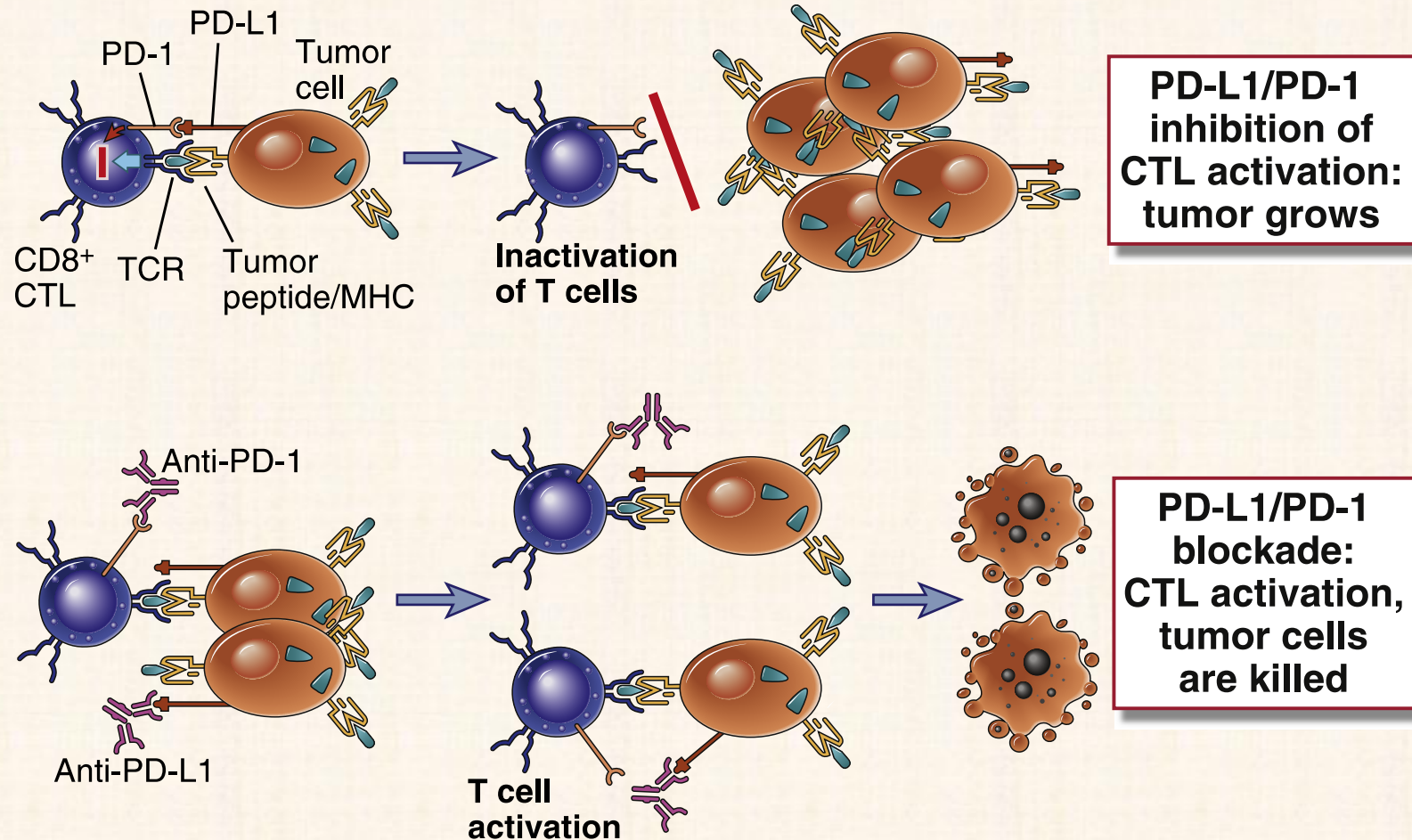
+1a: Pathological suppression: Myeloid Derived Suppressor Cells (MDSCs)



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*)