Basic Immunology

Suppression of the immune response
Suppressor mechanisms of immune functions

19th lecture
April 10th, 2024
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

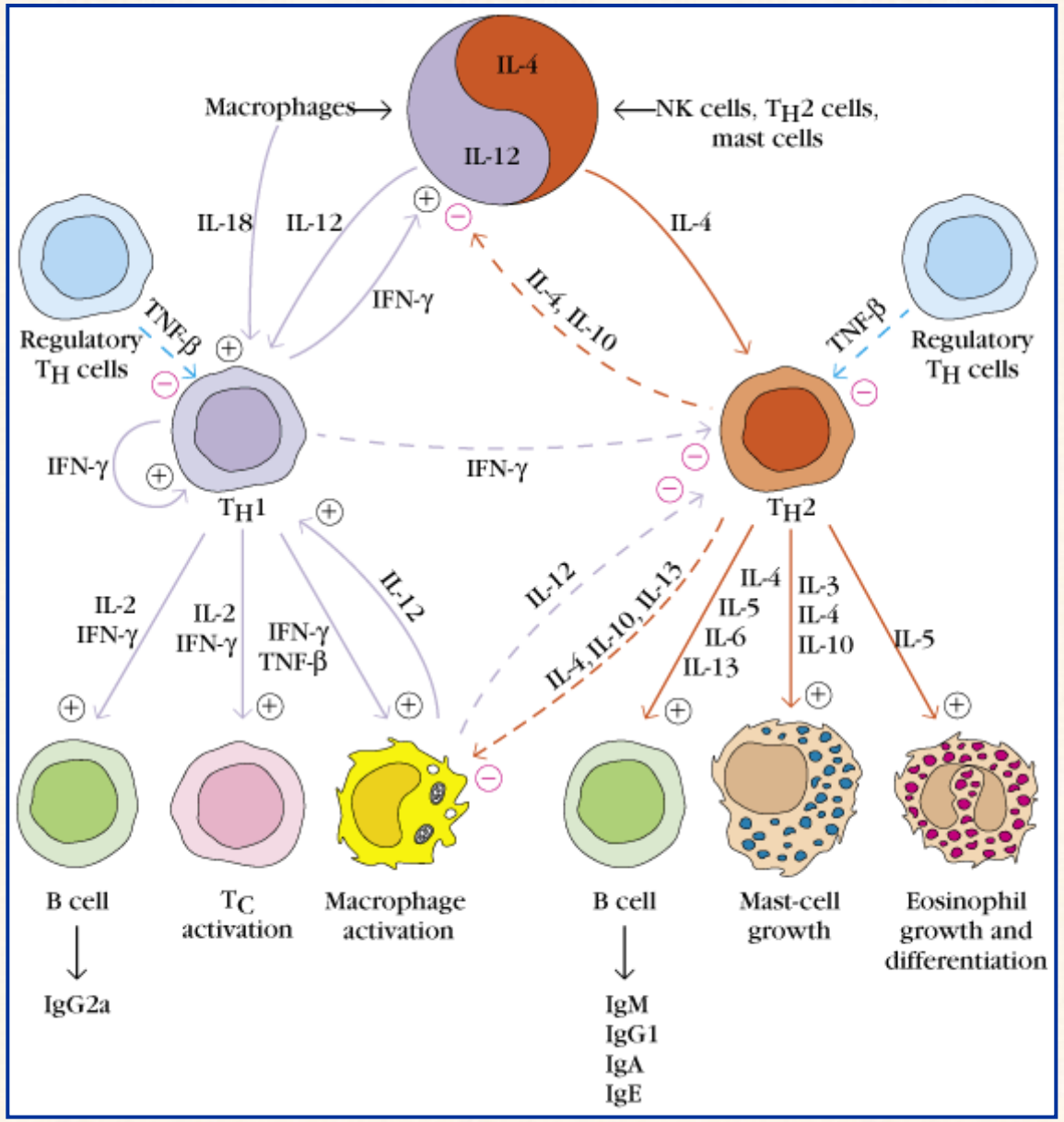
Activates T and B cells

Antigen nature, dose, location influence the immune response

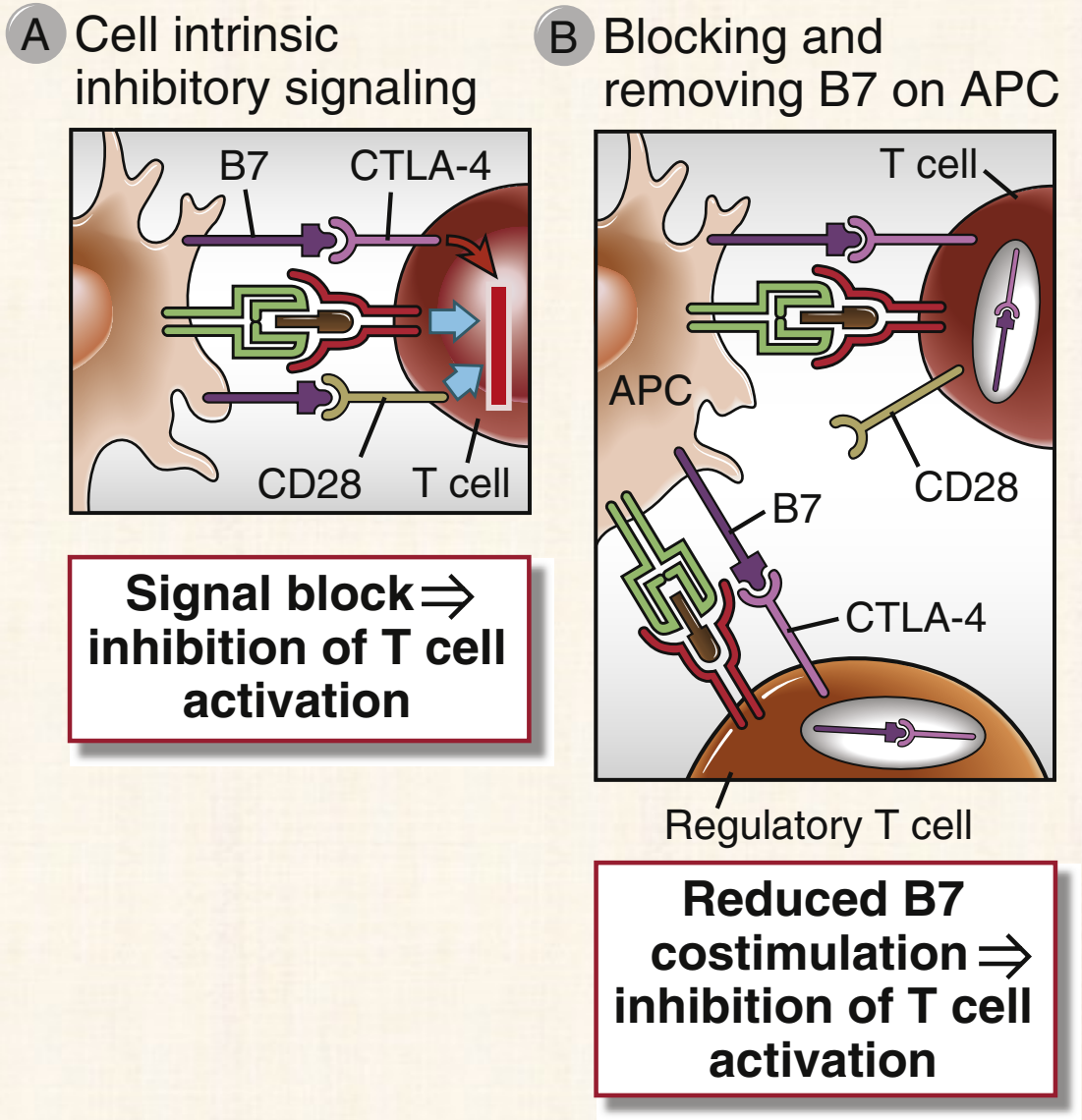
T_H1 vs T_H2

Withdrawal/elimination of the antigen stops further activation

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



2. Need for costimulation

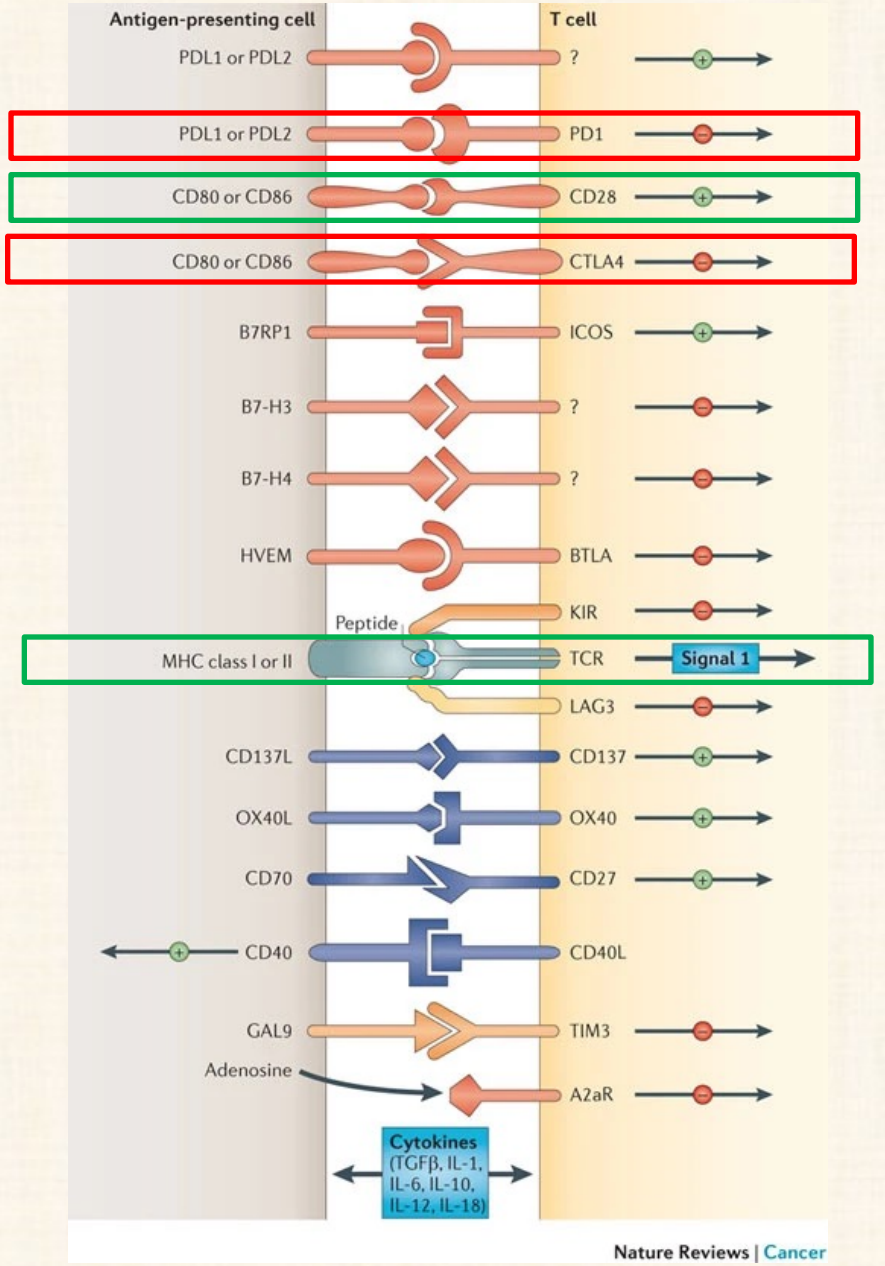


CD28: constitutively expressed on T cells
CTLA-4: expressed after activation
higher affinity towards B7

Fig 15-6

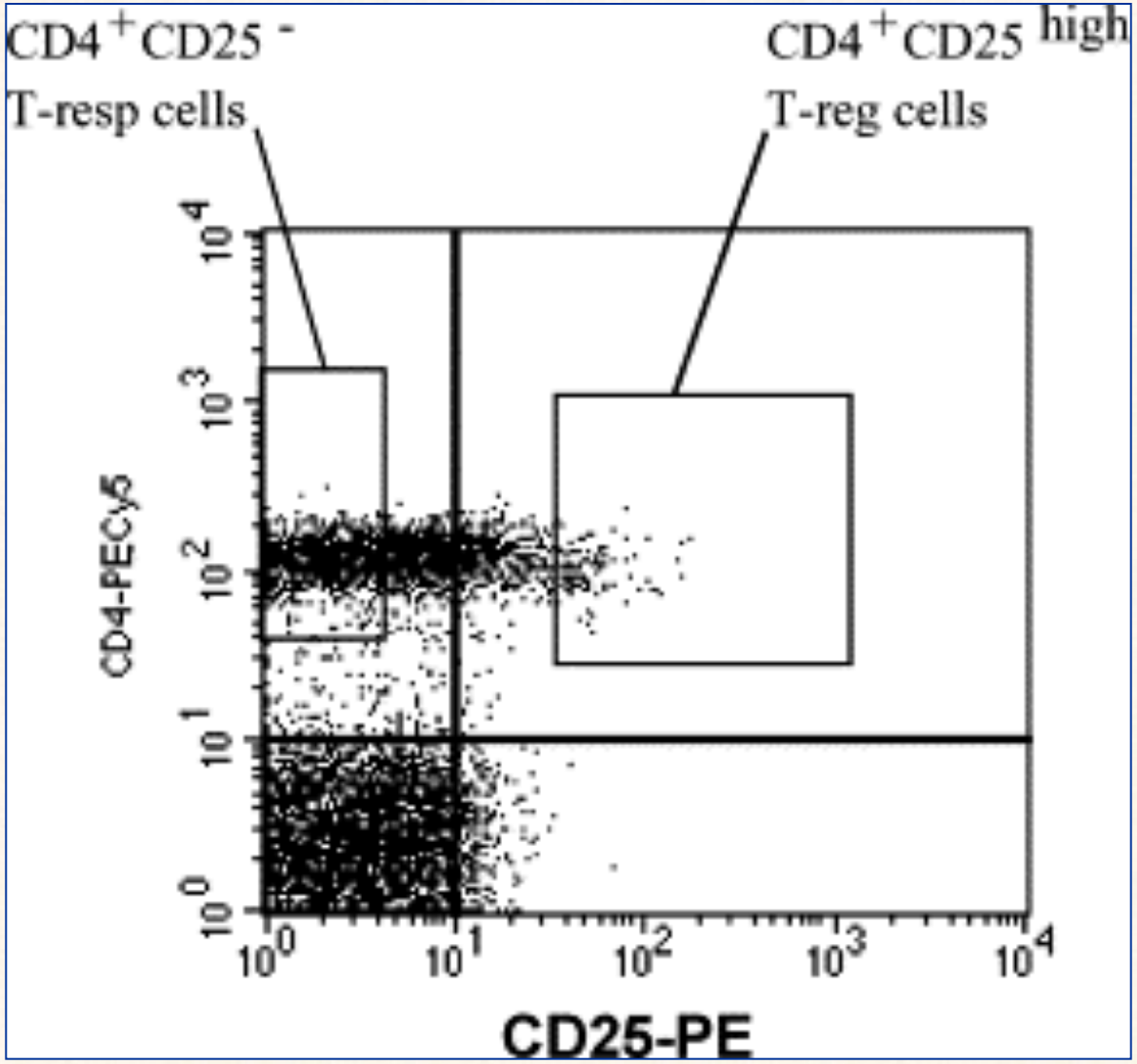
2. Need for costimulation: Immune checkpoints

Antigen presenting cell

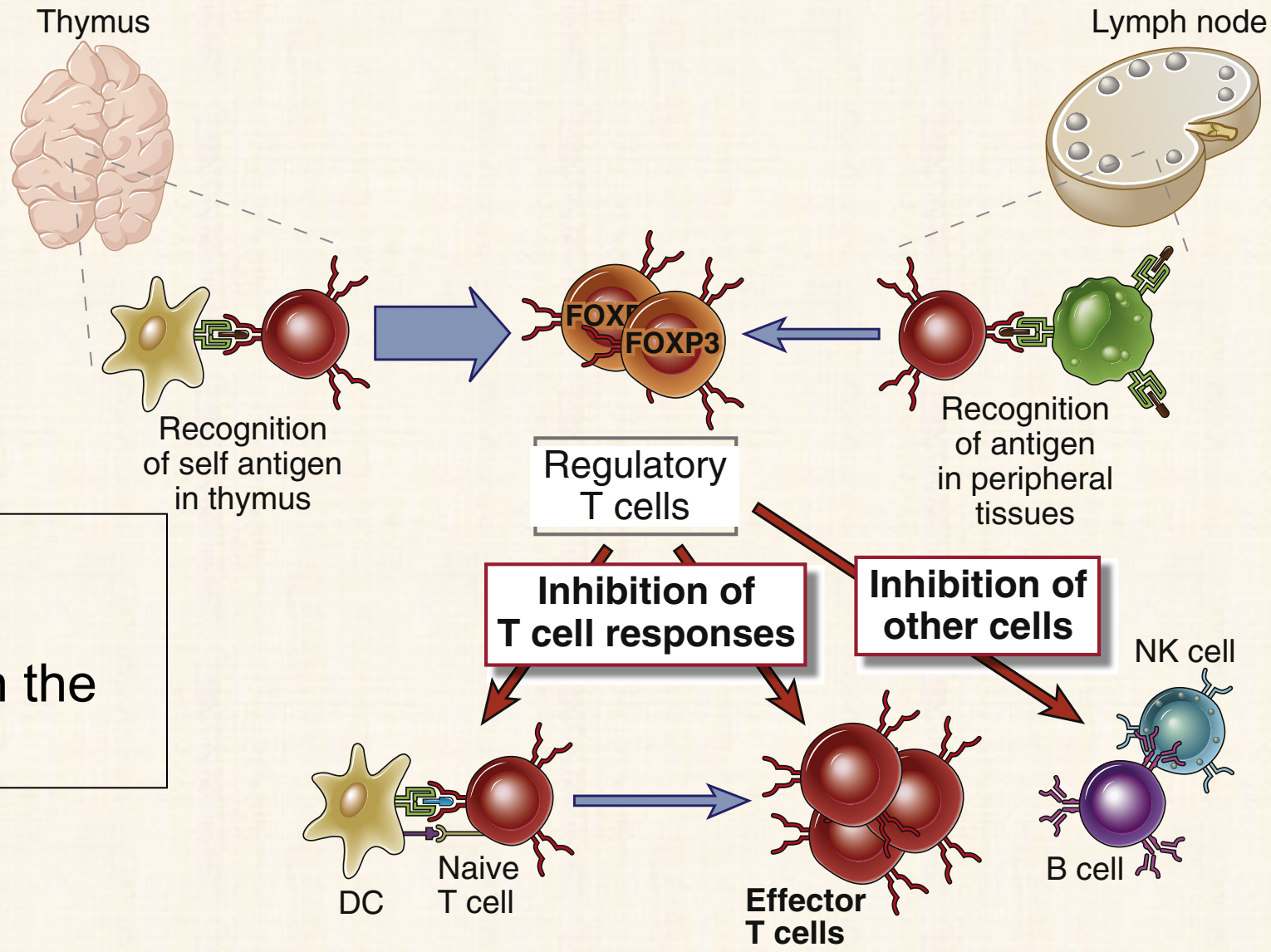


T cell

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



3. Main functions of regulatory T cells



Natural Treg

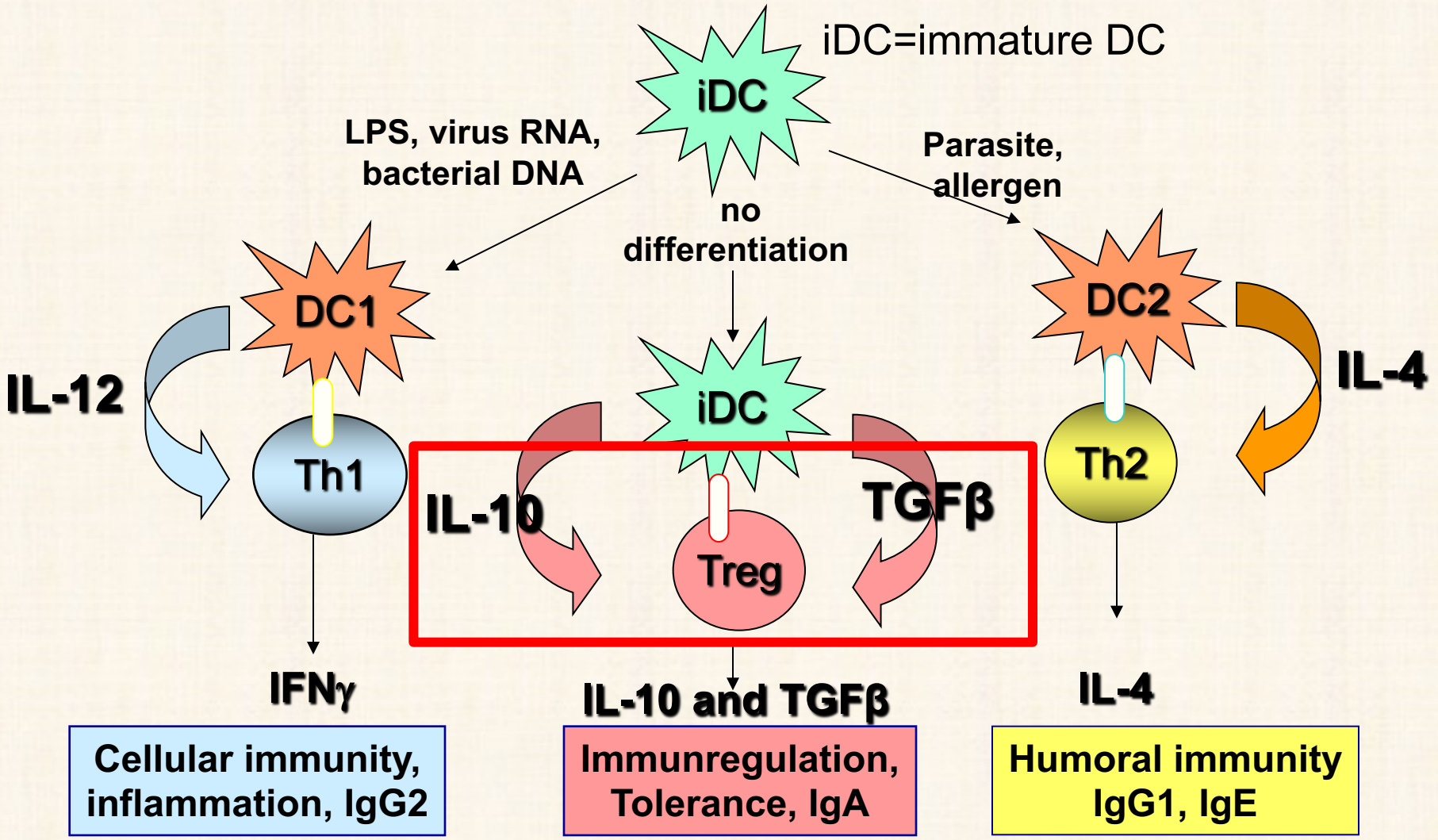
Differentiate in the thymus

Induced Treg

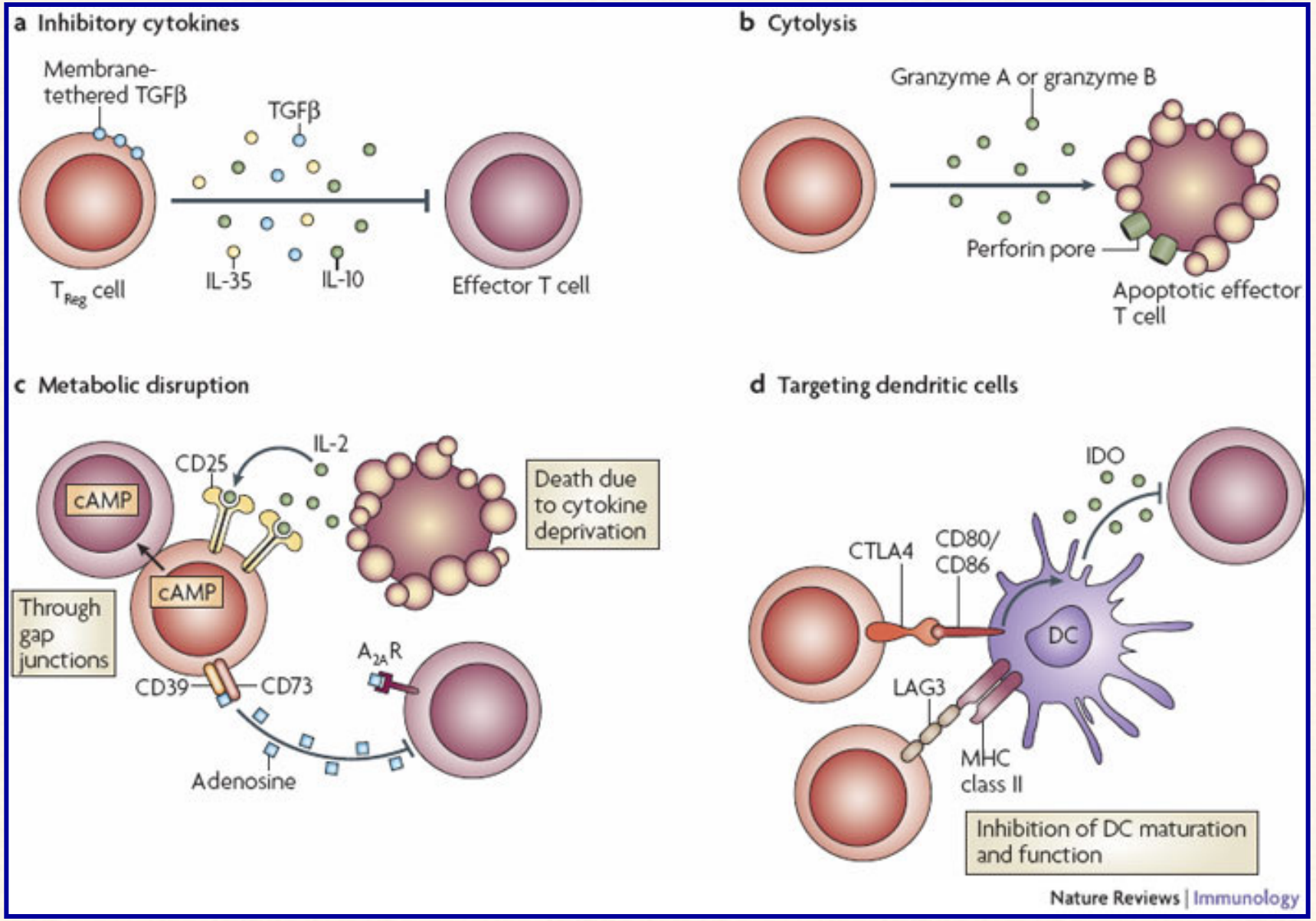
Differentiate in the periphery

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

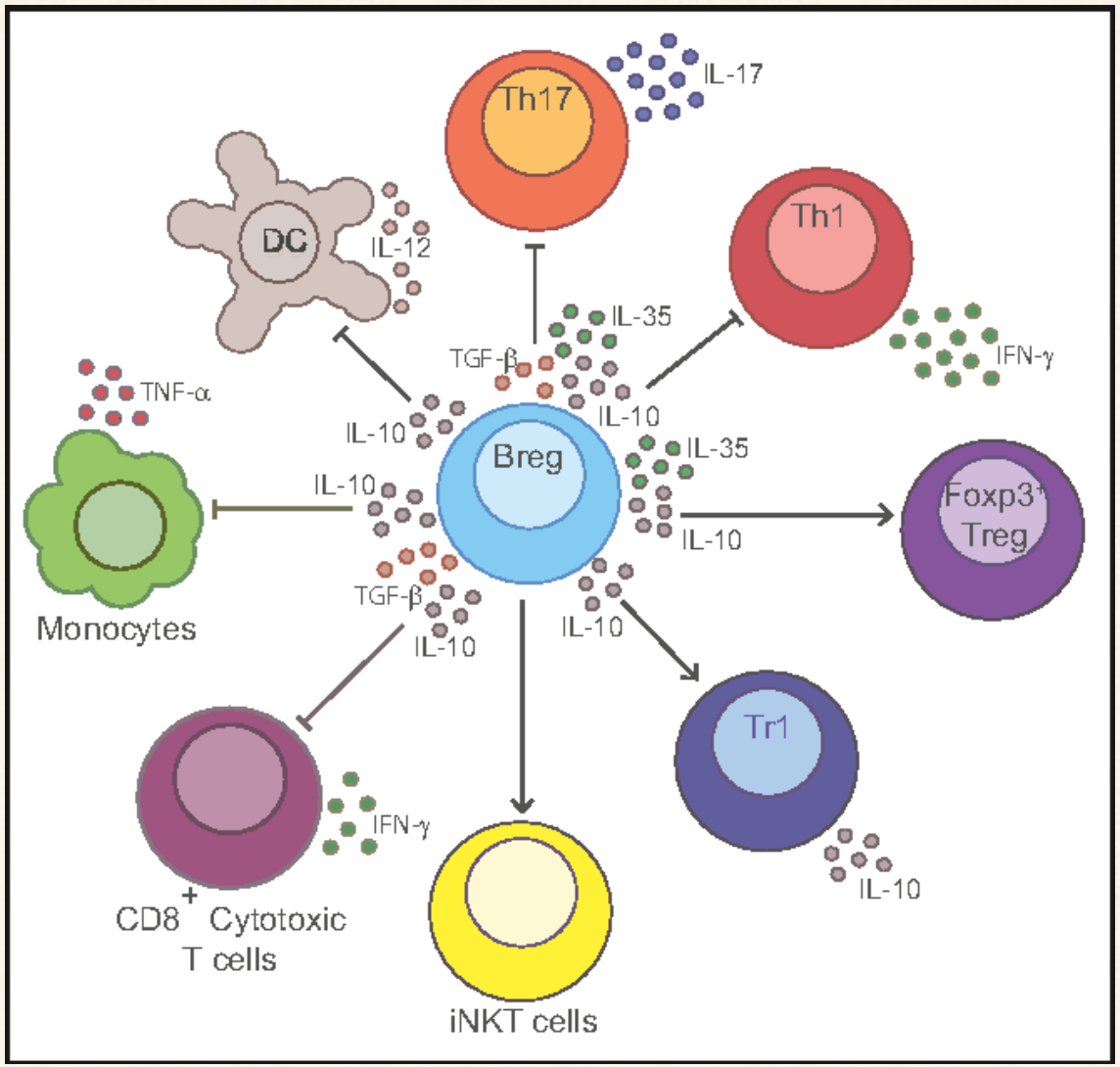
Regulatory B cells (B_{reg})

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



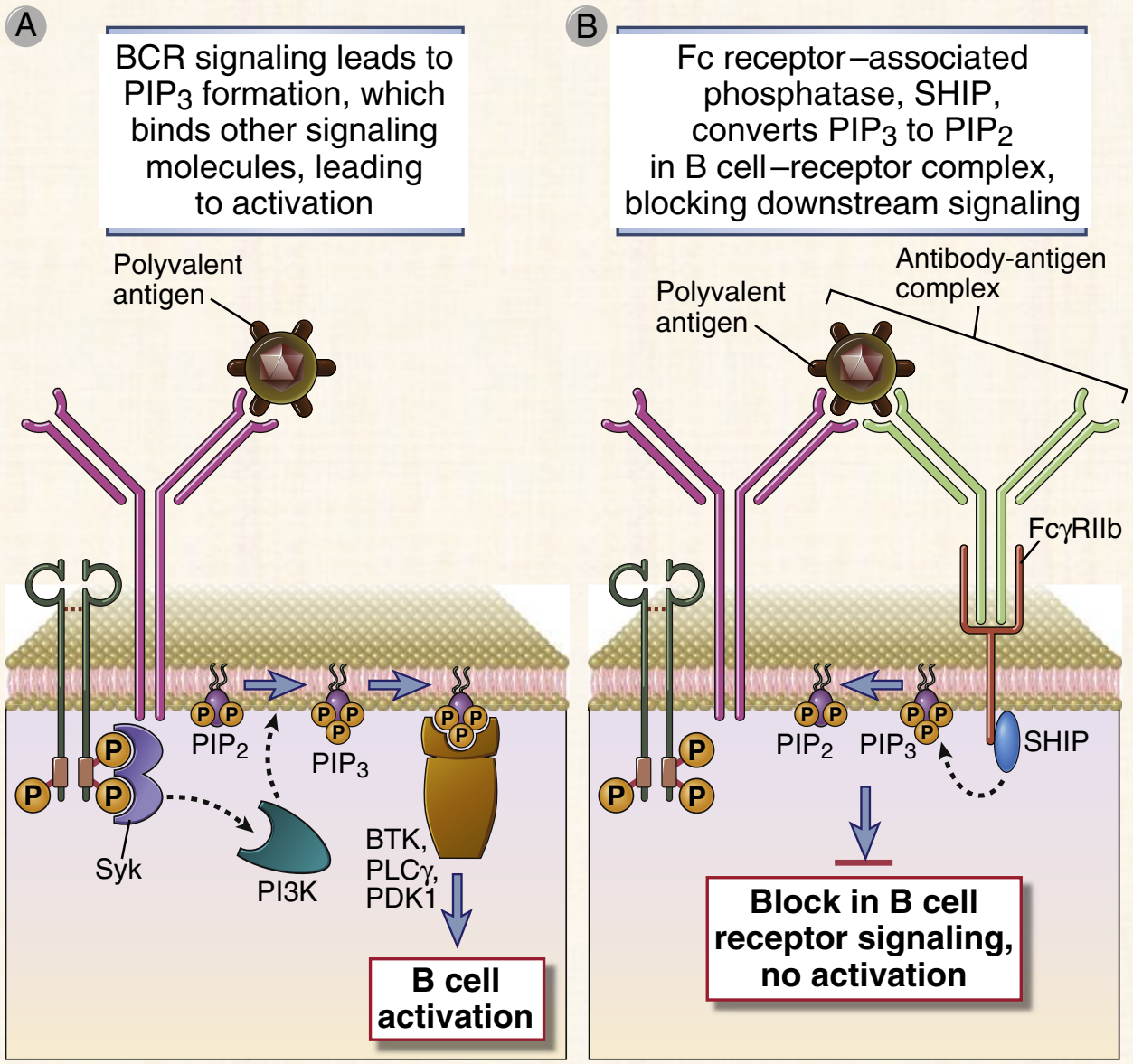
B_{reg} cells produce **IL-10**, IL-35, and TGF-β

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!

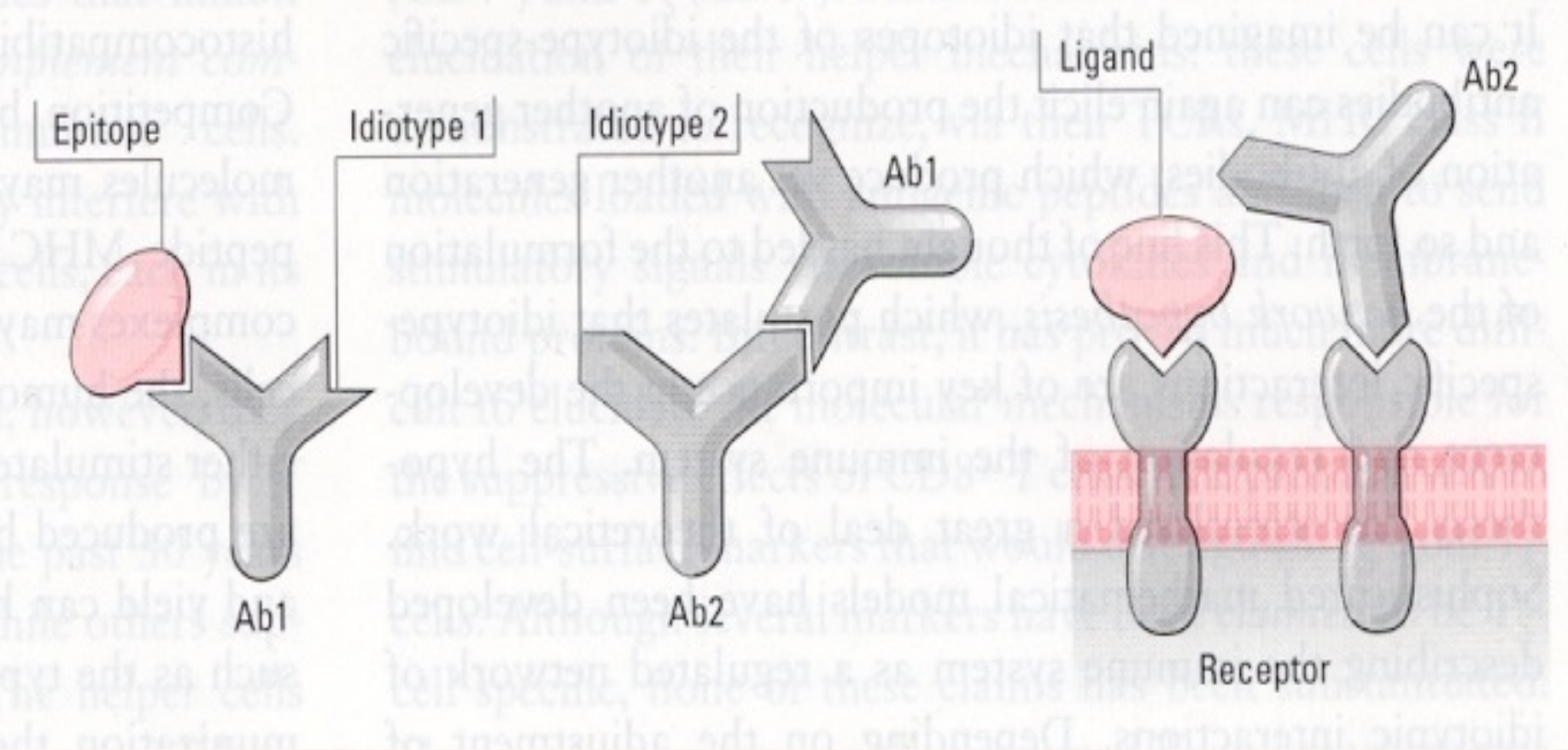
Simultaneous binding of antigen + IgG leads to B cell inhibition

Fig 12-21

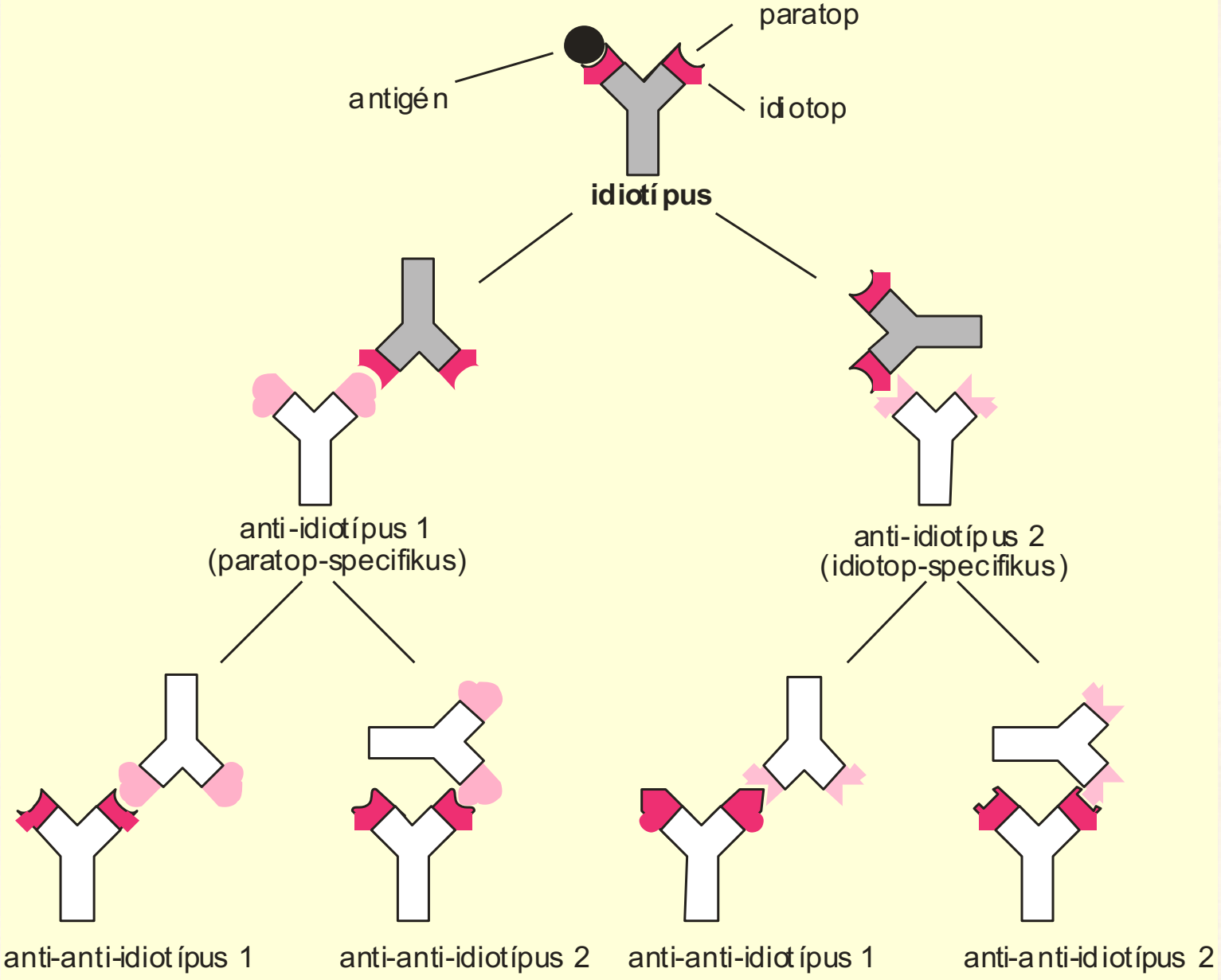
4. Anti-idiotype antibodies

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



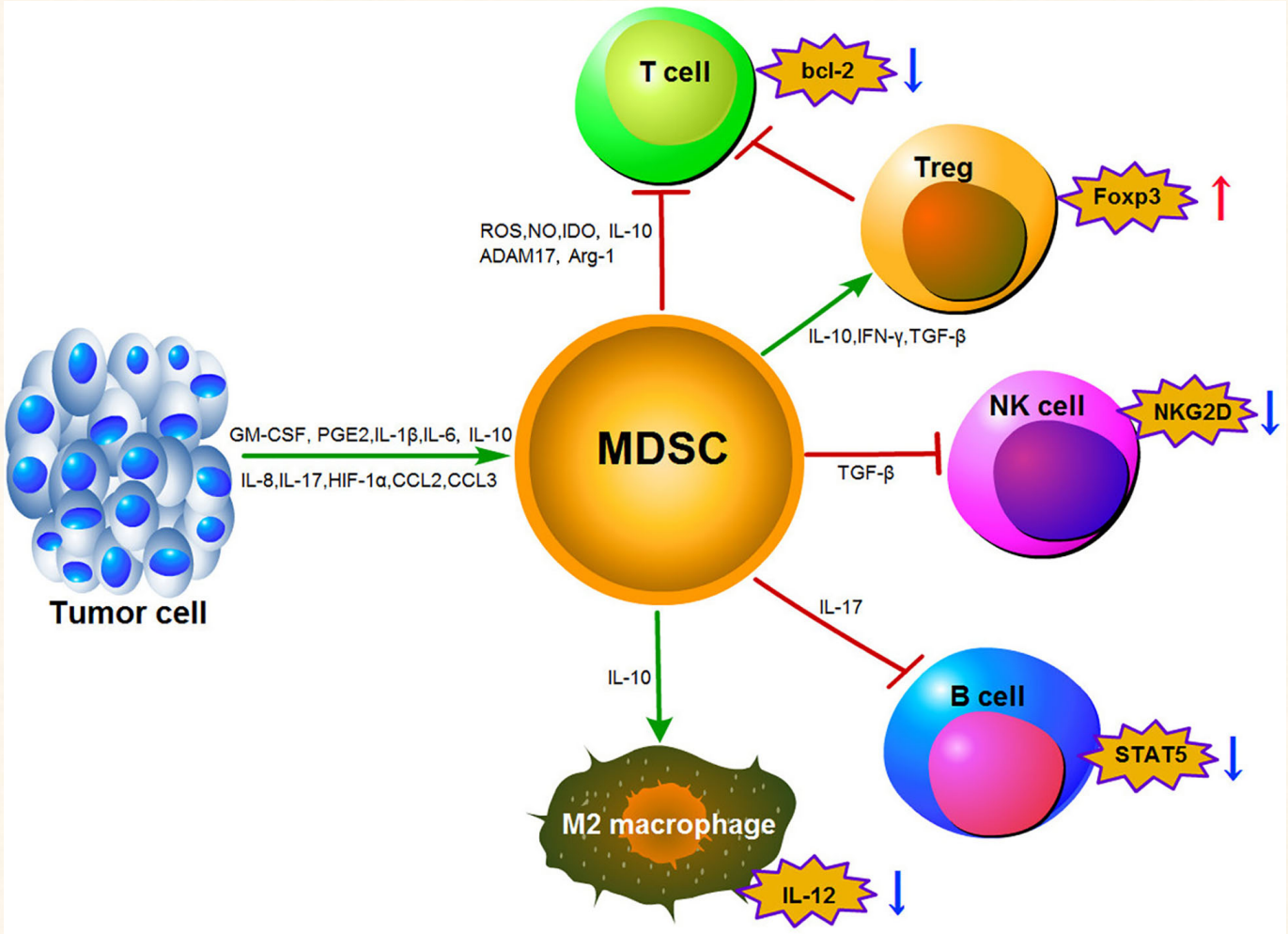
4. Functions of the anti-idiotype network

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)

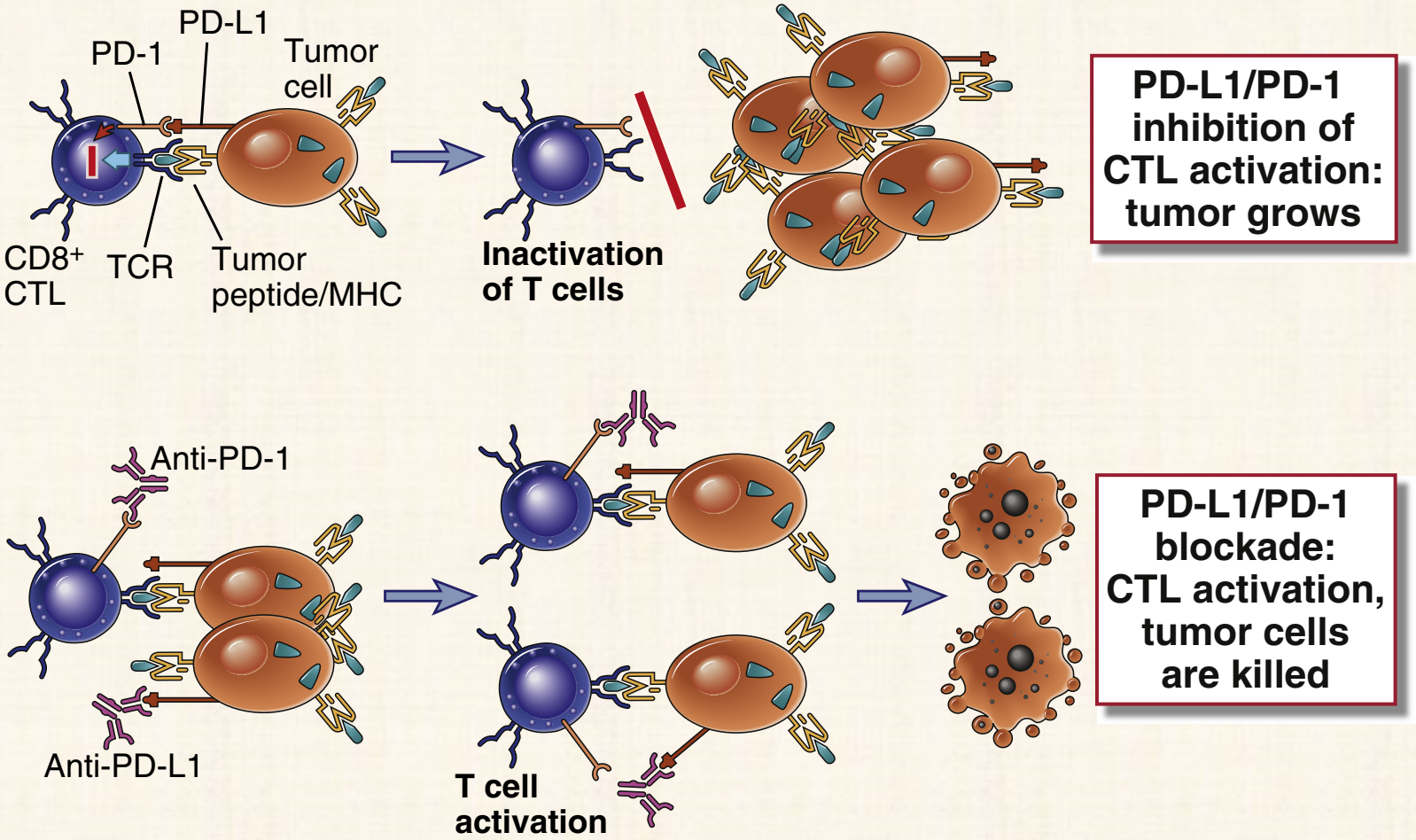


Yin K et al 2020. Front. Oncol. 10:610104. doi: 10.3389/fonc.2020.610104

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

Mucosa and skin associated immune system

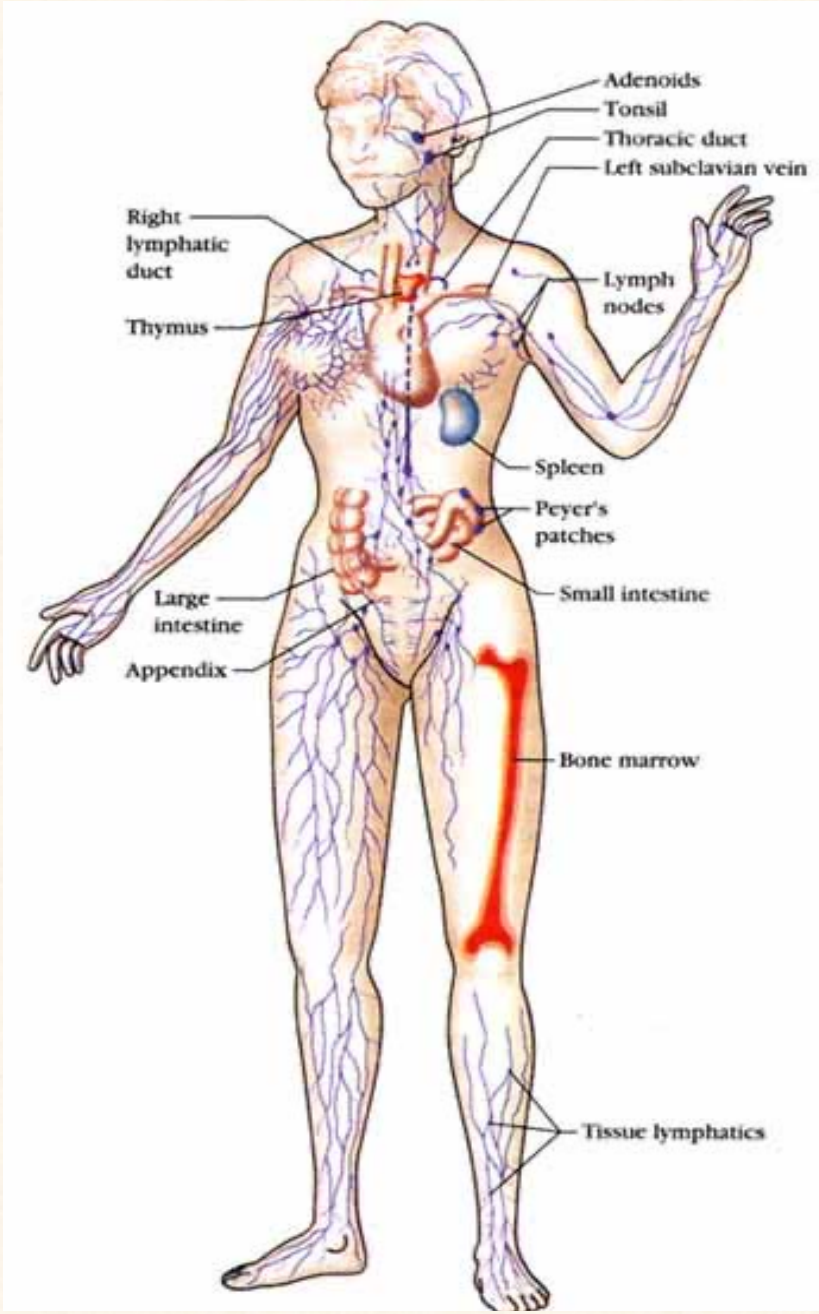
20th lecture
April 10th, 2024
Zoltán Kellermayer

Regional immune system

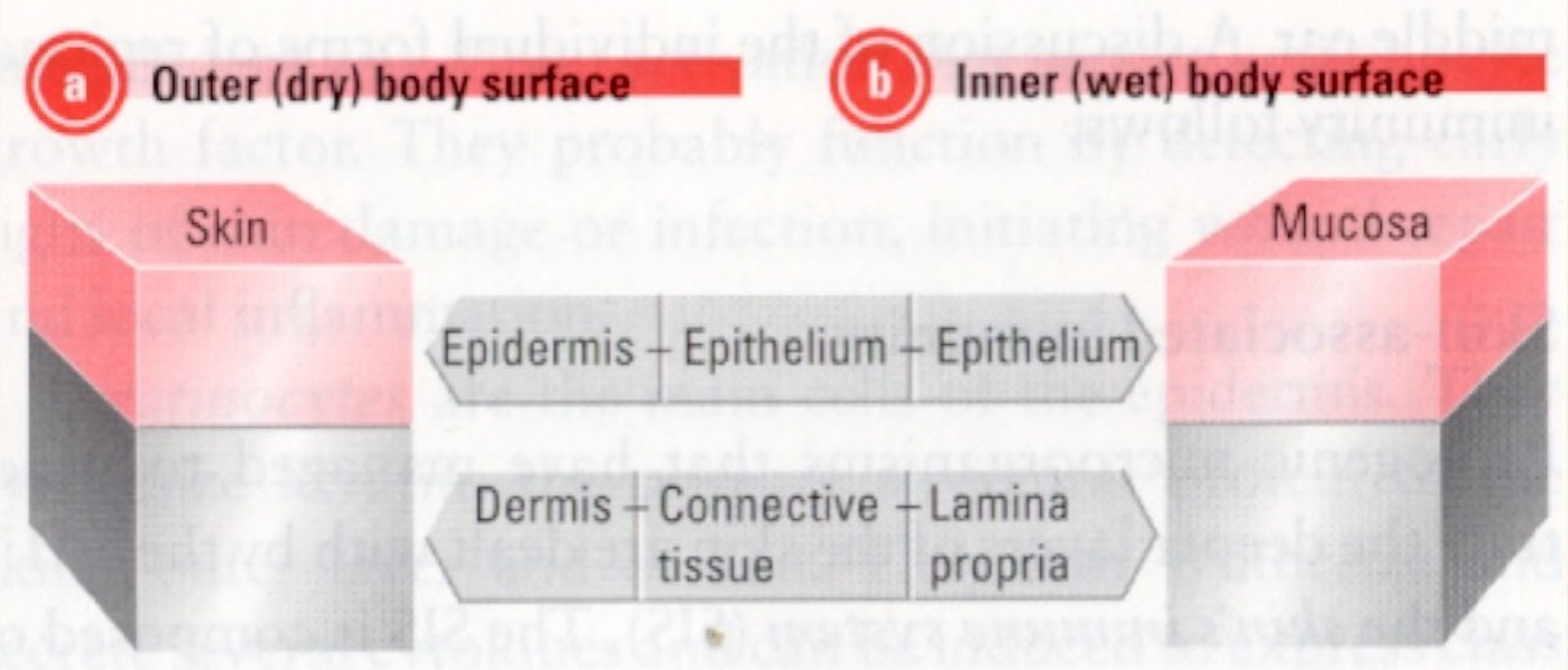
The collection of *immune cells* and *molecules* with specialized functions at a particular anatomic location

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})

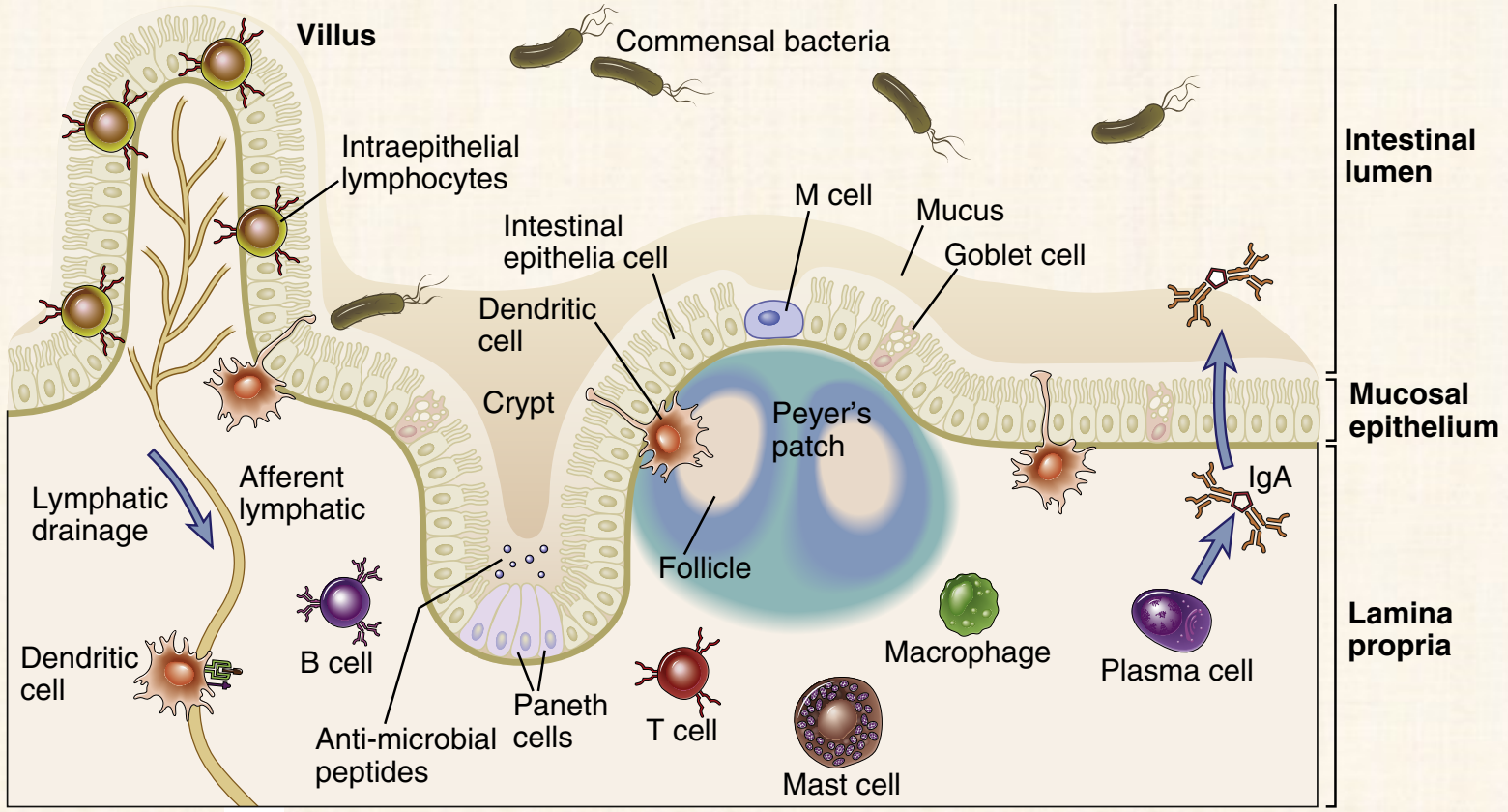
Huge amount of microbes: 10^{14}

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

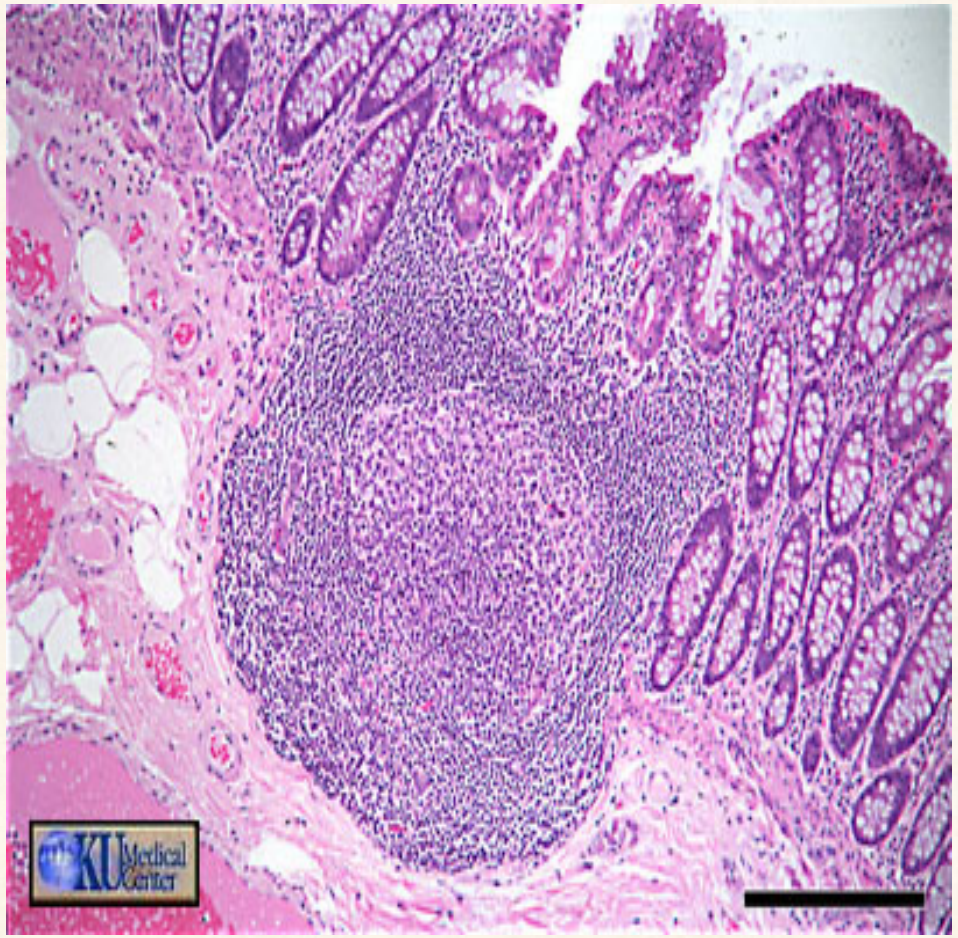
Cryptopatch - isolated lymphoid follicle spectrum

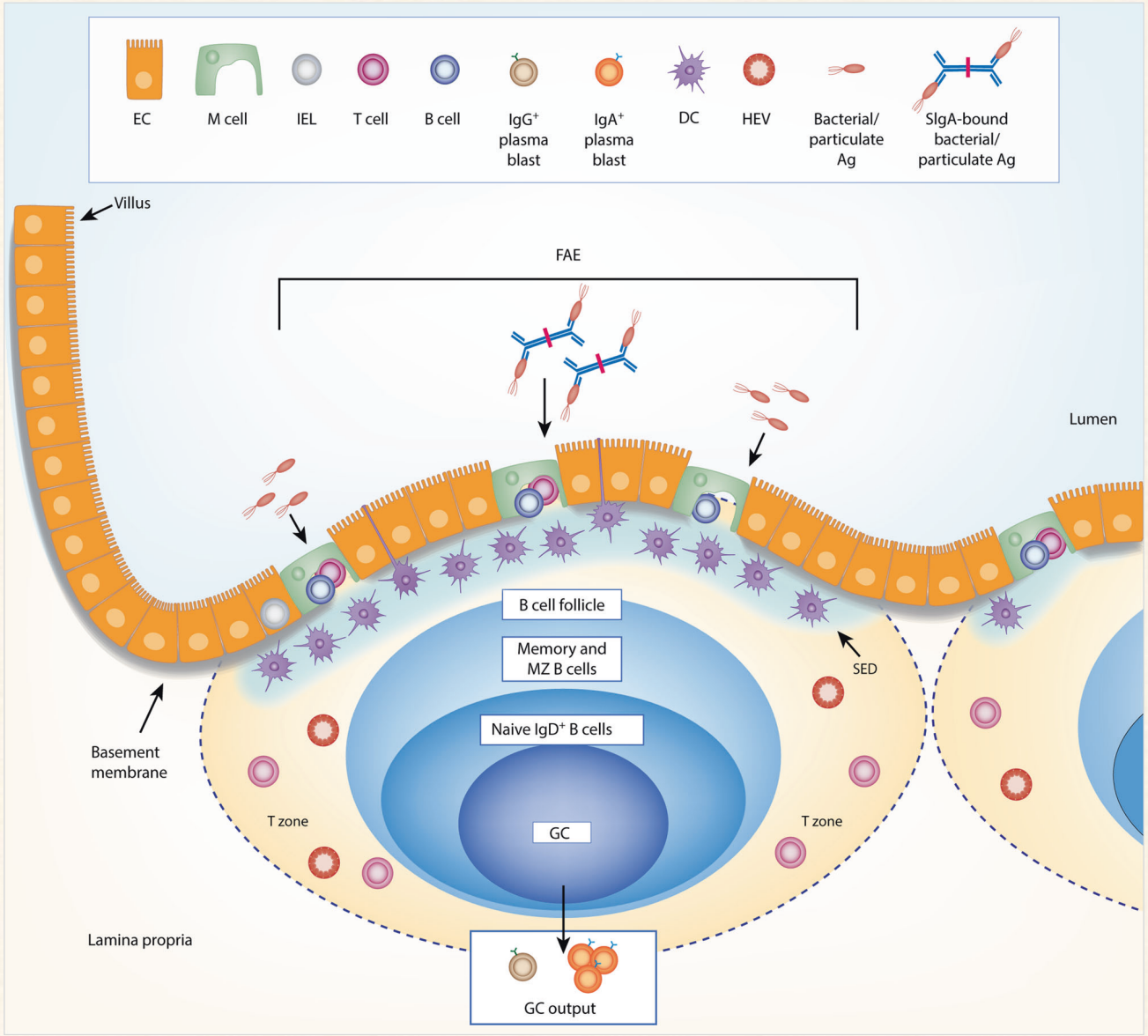
Diffuse MALT (D-MALT)

Effector tissue

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

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

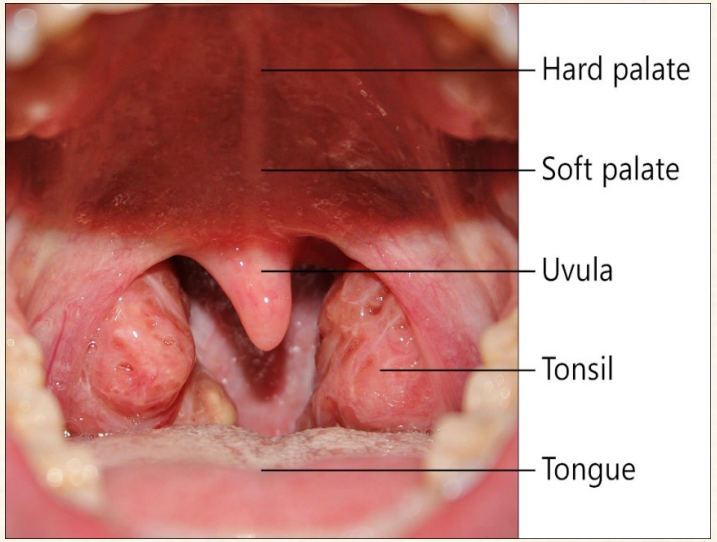


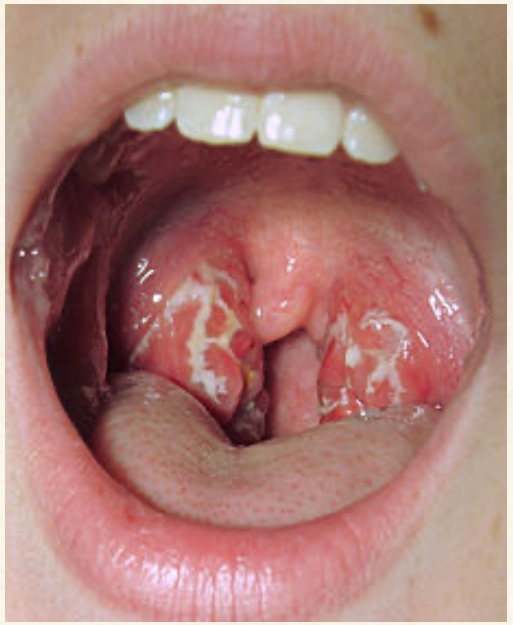


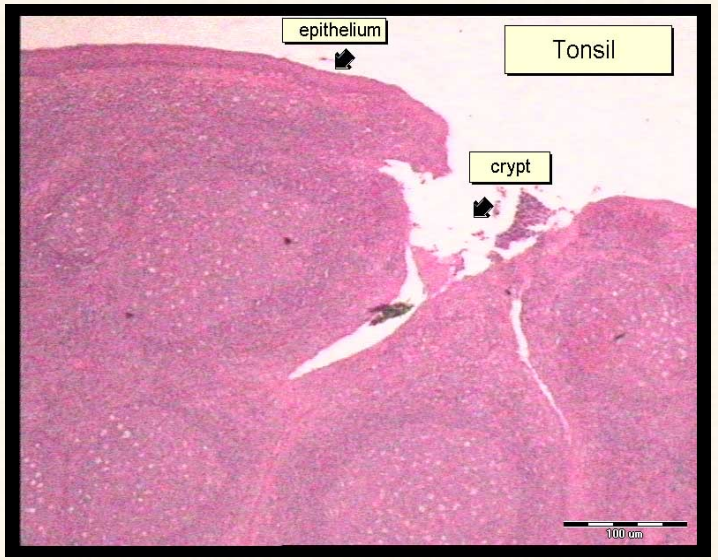
SED: Subepithelial dome
FAE: Follicle associated epithelium

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

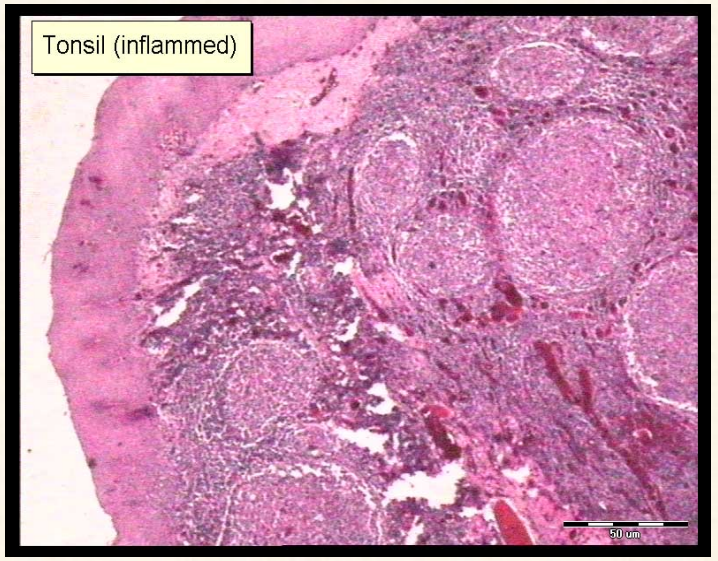
Programmed lymphoid tissues in the gastrointestinal tract: tonsils





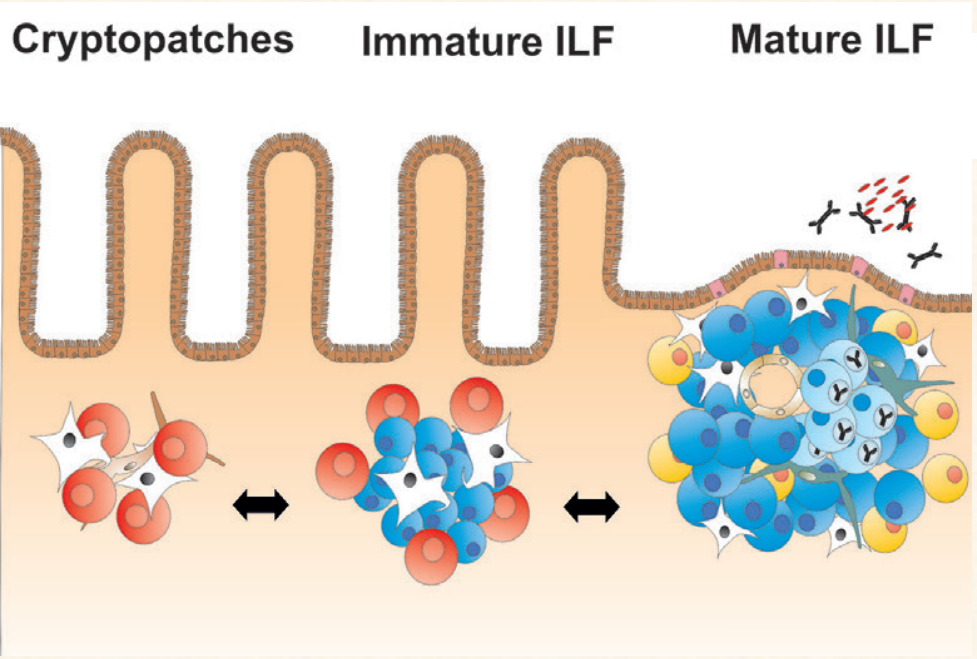


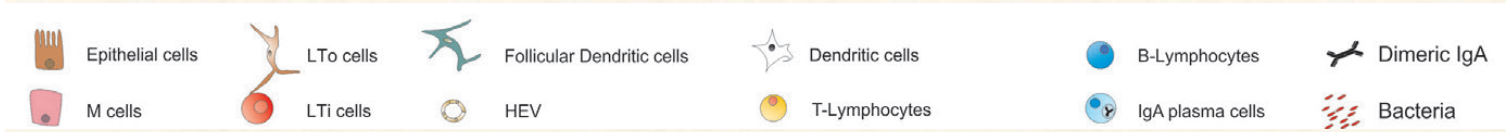
Normal tonsil



Inflamed tonsil

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

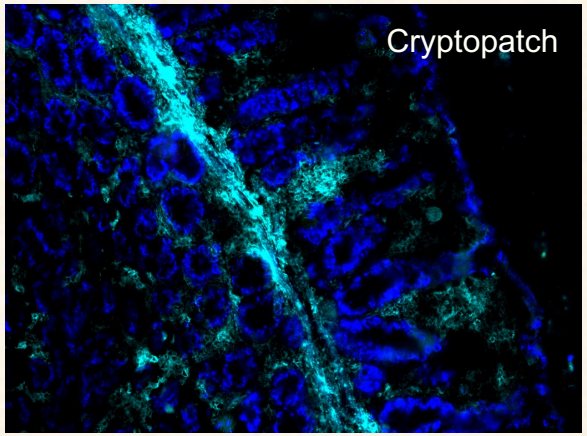


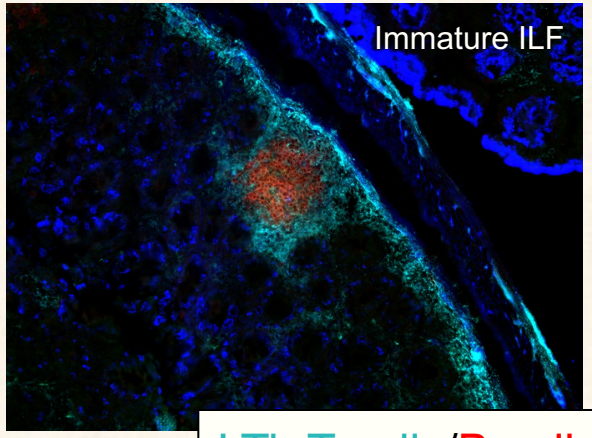


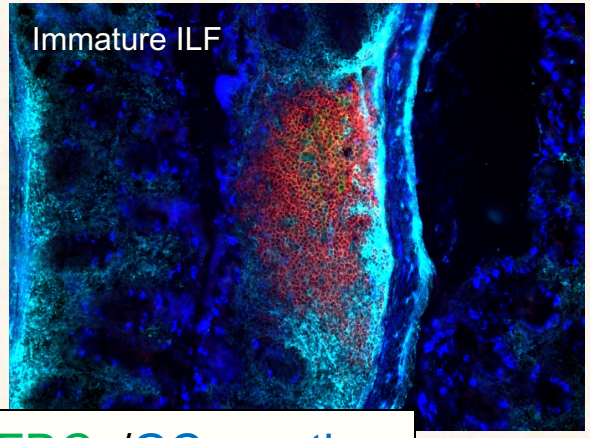
Buettner M and Lochner M (2016) Development and function of secondary and tertiary lymphoid organs in the small intestine and the colon. Front Immunol.

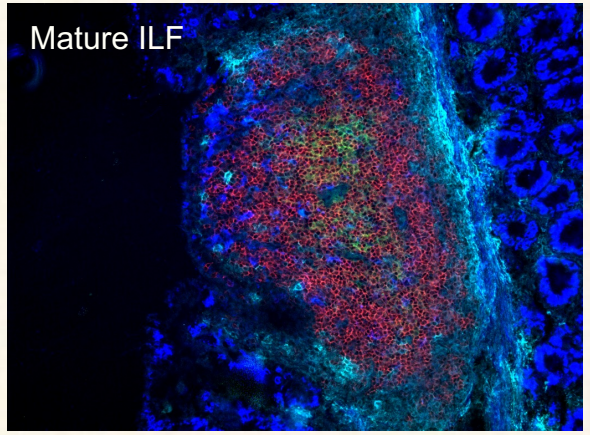
ILF: Isolated lymphoid follicle
LTi: Lymphoid tissue inducer cell

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

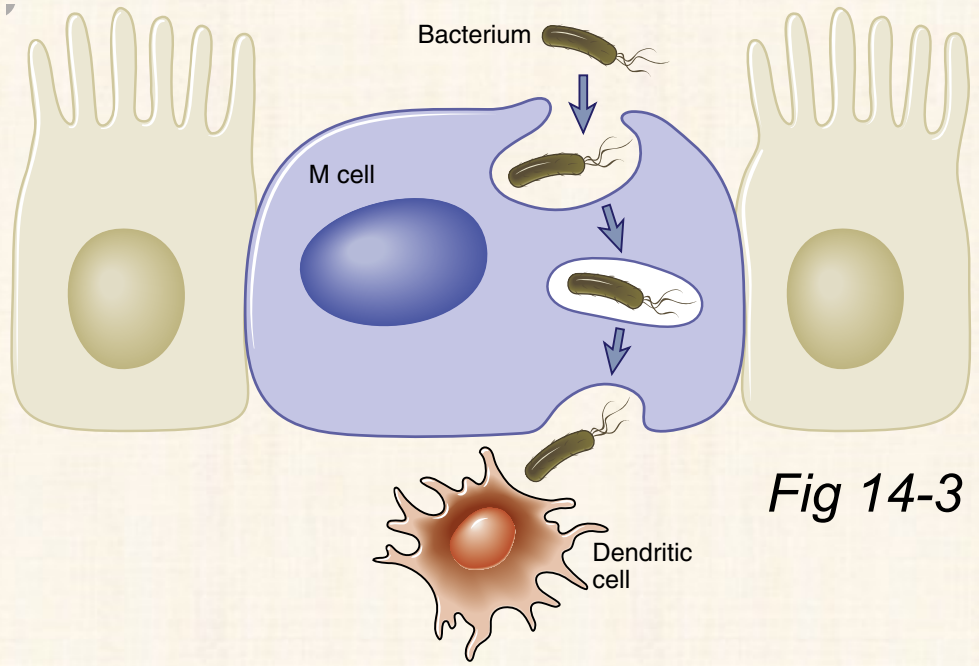
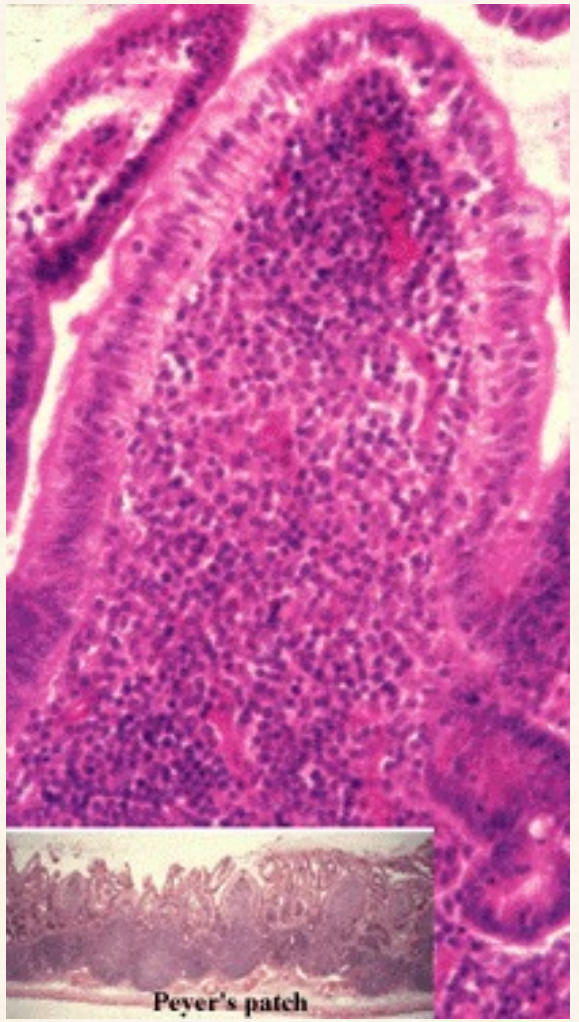
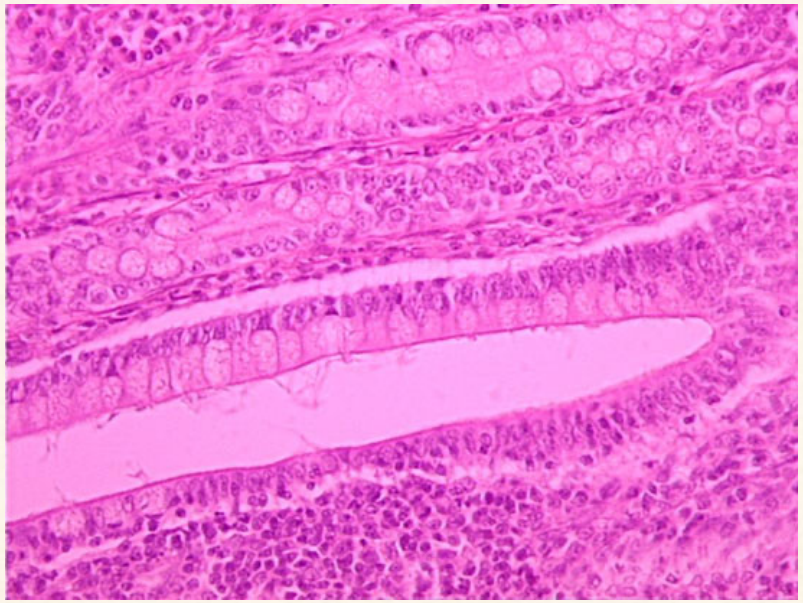


Fig 14-3

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

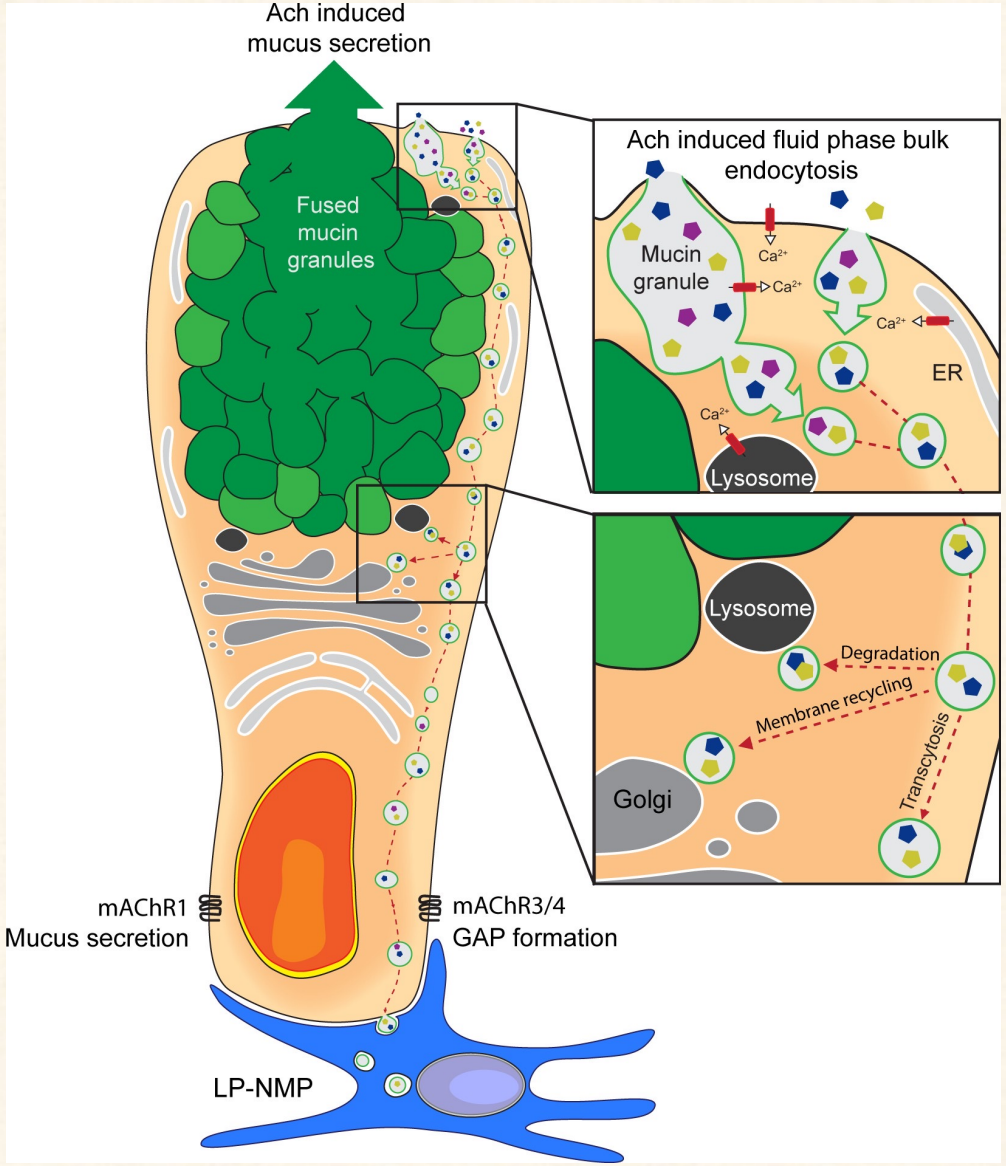




M cell region

(Not antigen presentation!)

Goblet cells: not only mucus secretion…



Gustafsson et al. eLife 2021;0:e67292. DOI: https://doi.org/10.7554/eLife.67292

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, 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)

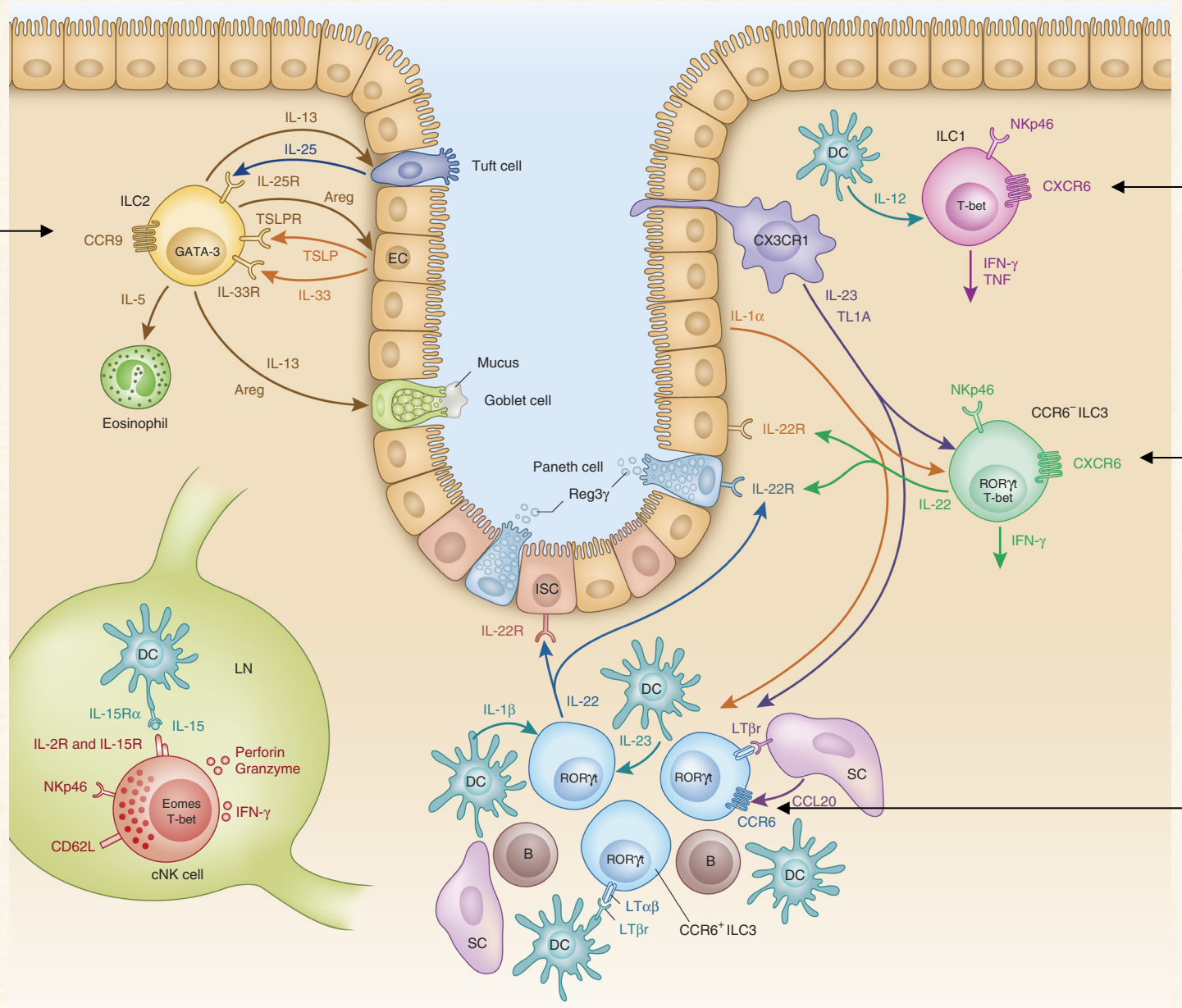
Innate lymphoid cells (ILCs)

ILC2

ILC1

ILC3

ILC3

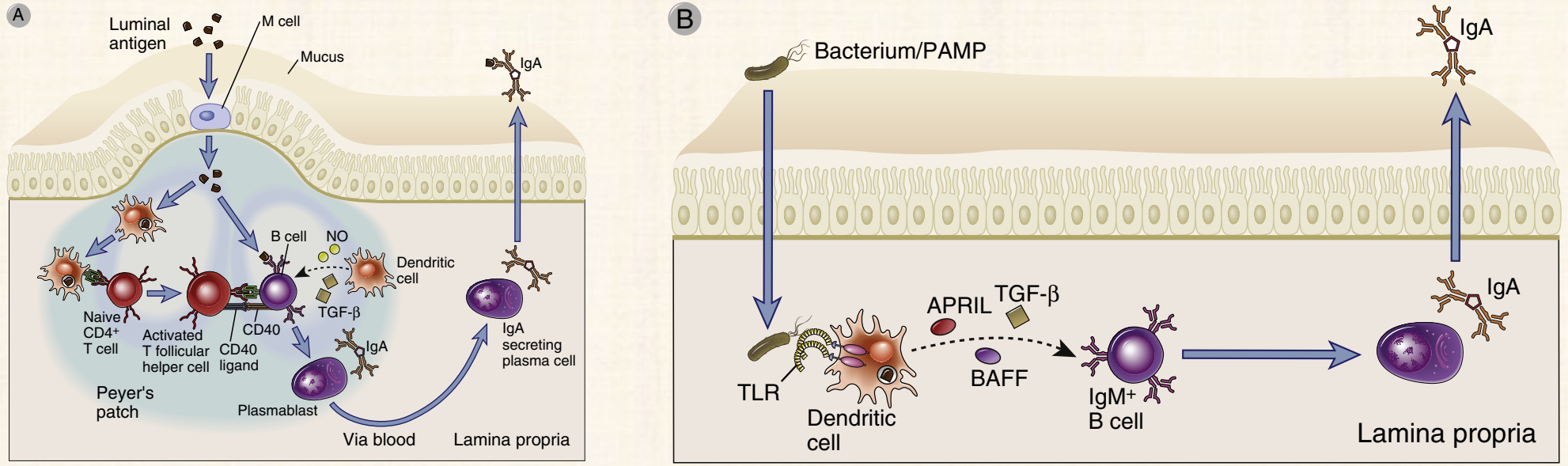


Klose CSN and Artis D (2016) Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nature Immunology

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

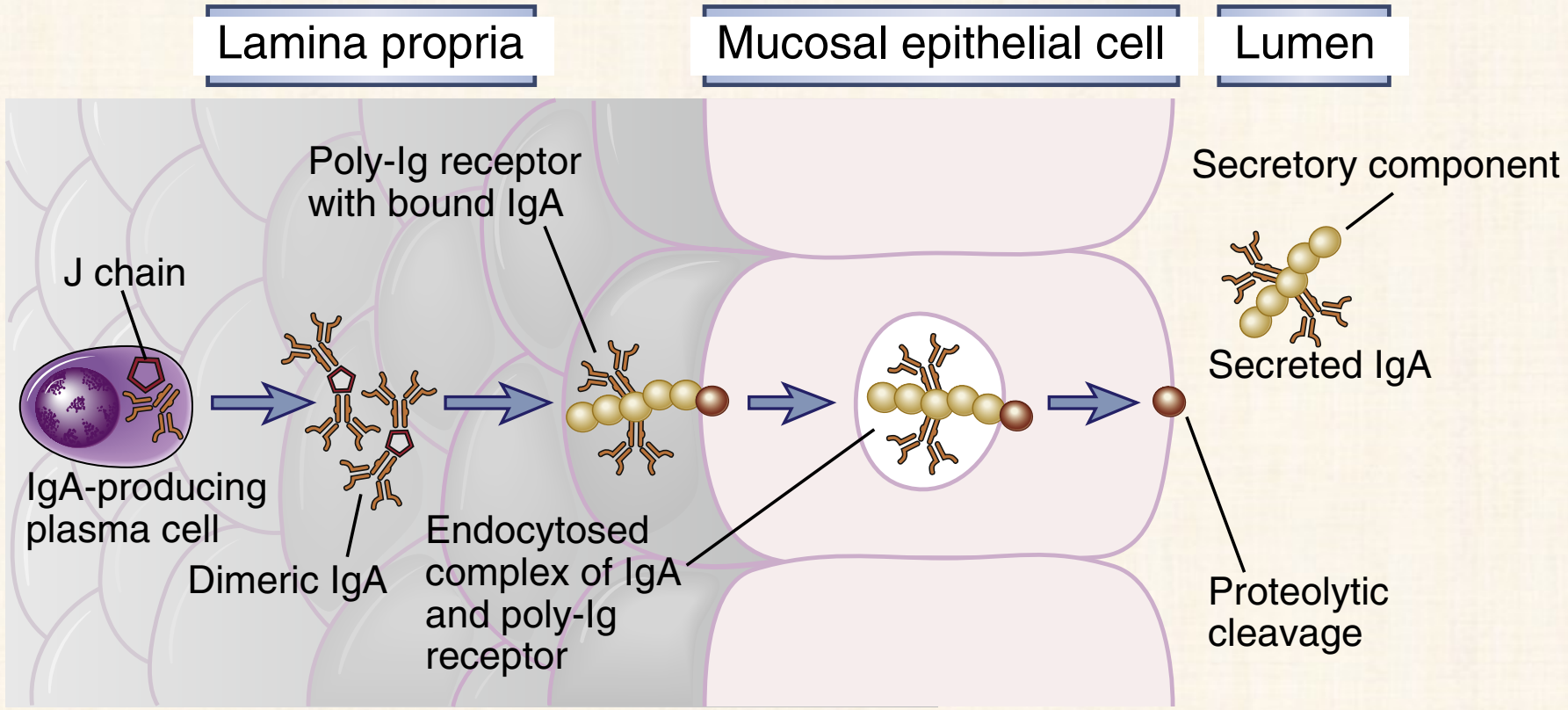


Fig 14-8

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

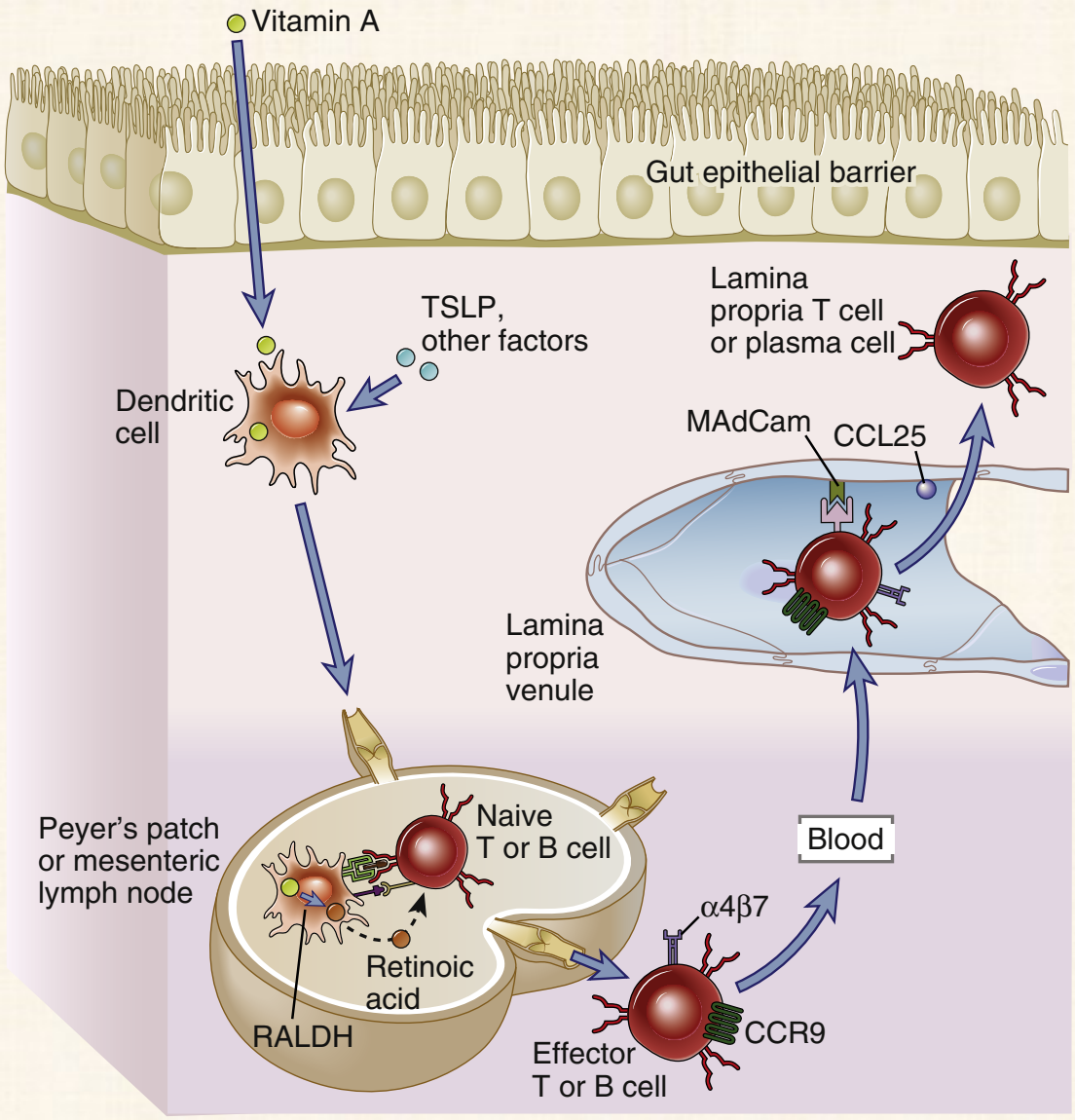


Fig 14-5

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:

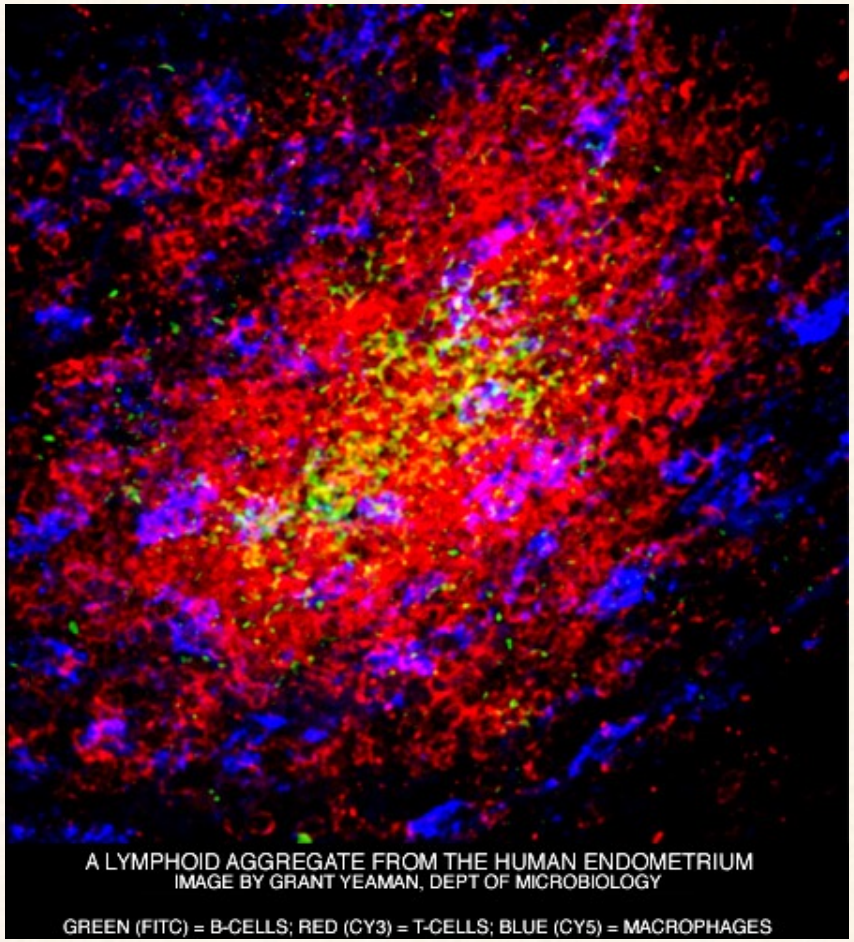
- epithelial barrier, mucus and antimicrobial factors
- lymphoid tissues beneath the epithelium
- antigen sampling
- secretory IgA as prevention

Airways

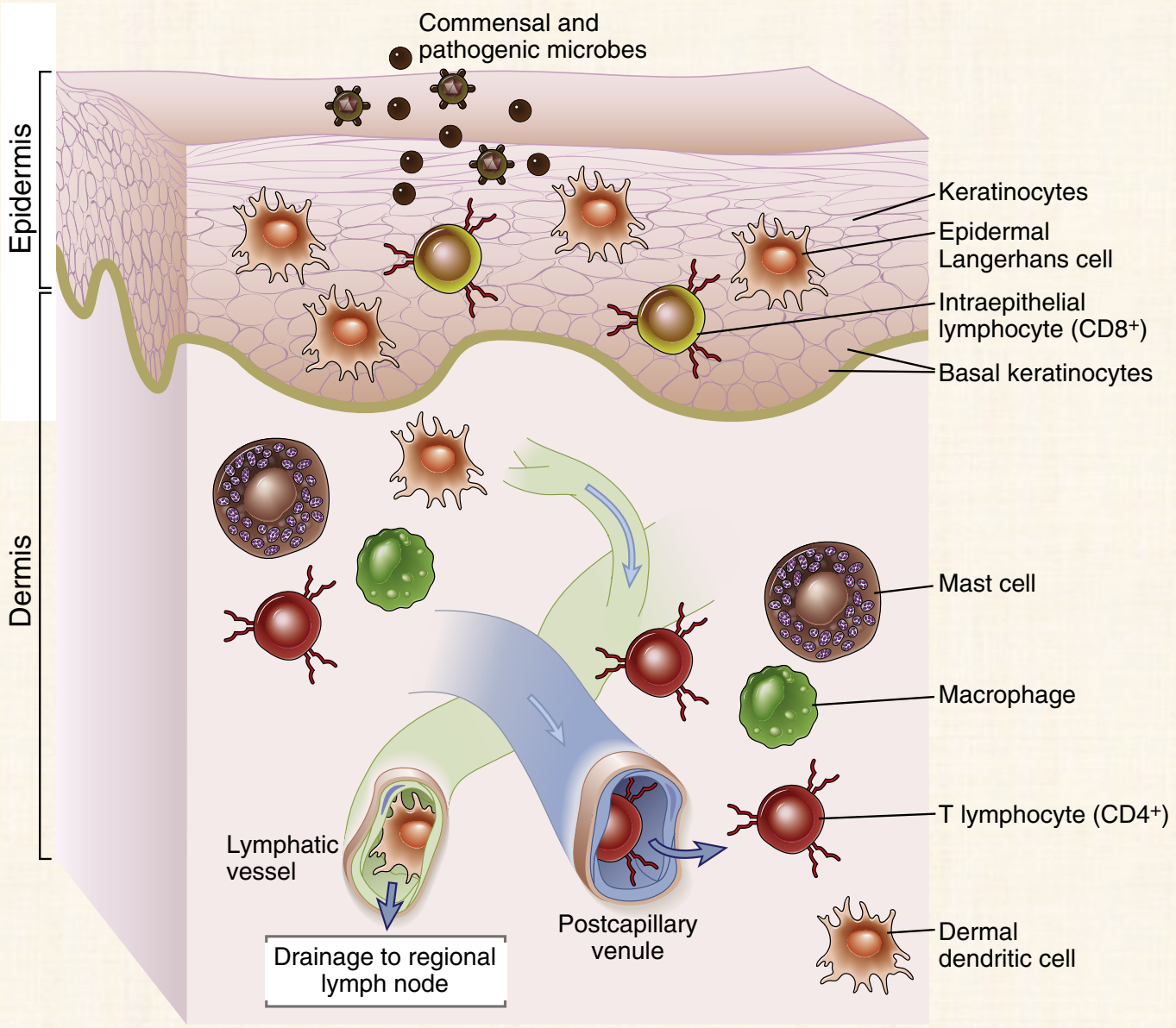
- Innate: surfactant protein; alveolar macrophages
- Adaptive: IgA, IgE (allergic reactions)

Genitourinary tract

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



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

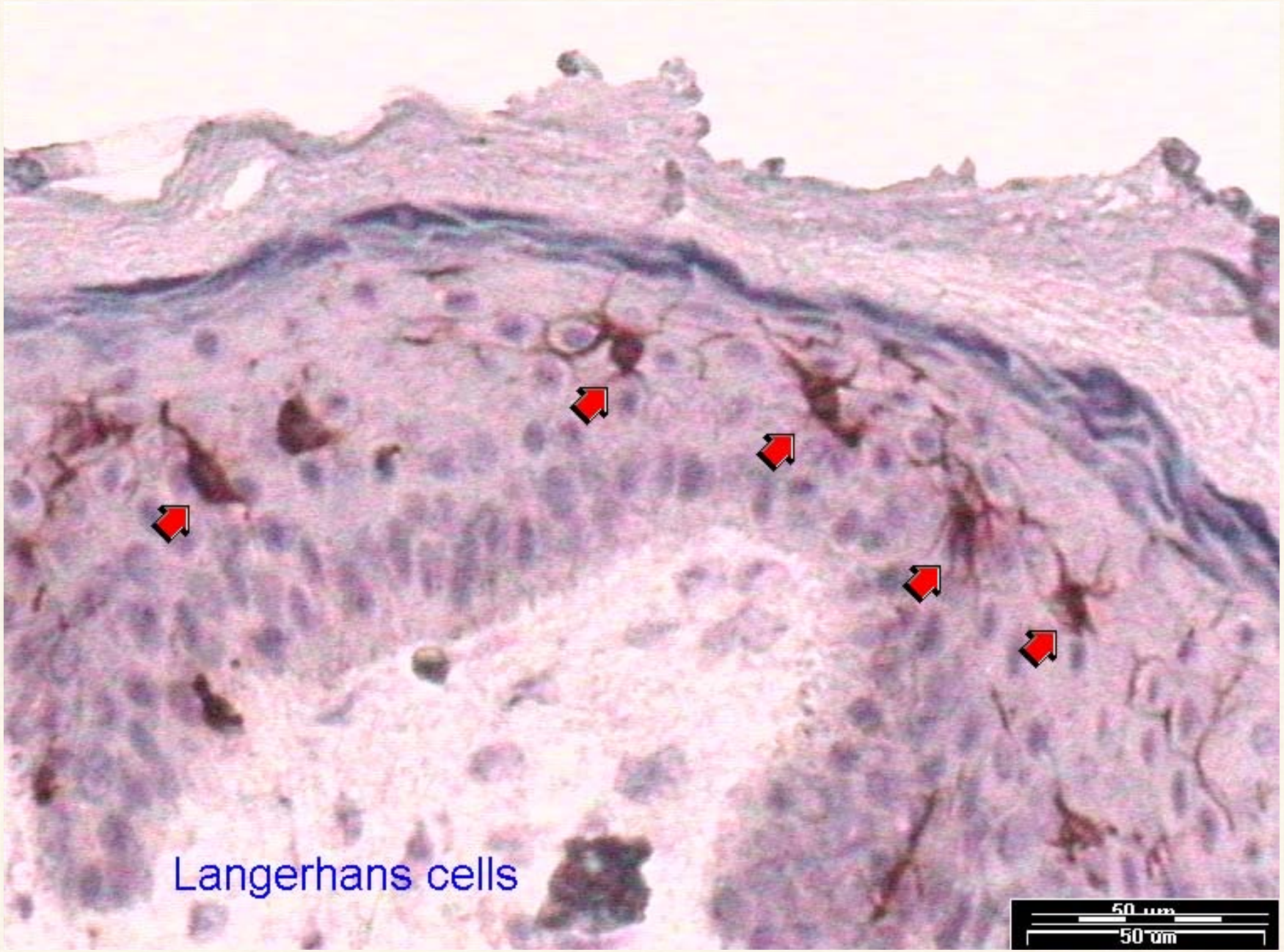
- Physical barrier
- Cytokines: TNF, IL-1, IL-6, IL-18, IL-25, IL-33 (inflammation); IL-10 (regulation)
- Chemokines: CCL27
- Growth factors: PDGF, FGF, GM-CSF
- Anti-microbial peptides: defensins, cathelicidins
- Activation: through PRRs (TLRs, NLRs)

Dendritic cells, macrophages

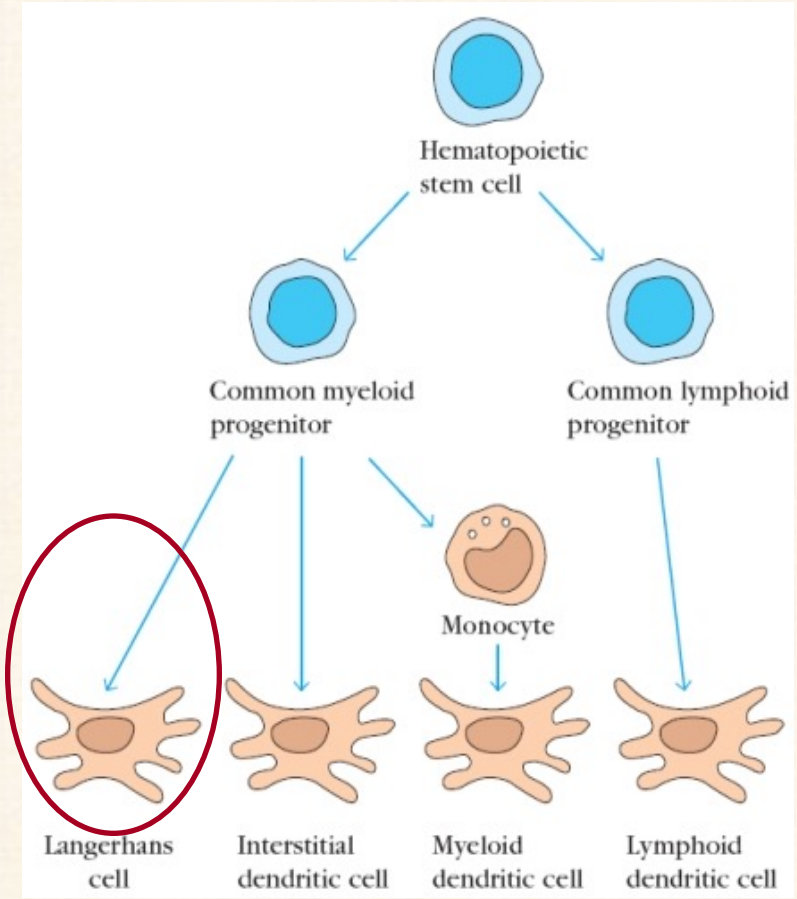
- Mainly Langerhans cells
- Migrate to regional lymph nodes following phagocytosis of antigens
- Present antigens to T cells, imprint skin-homing properties

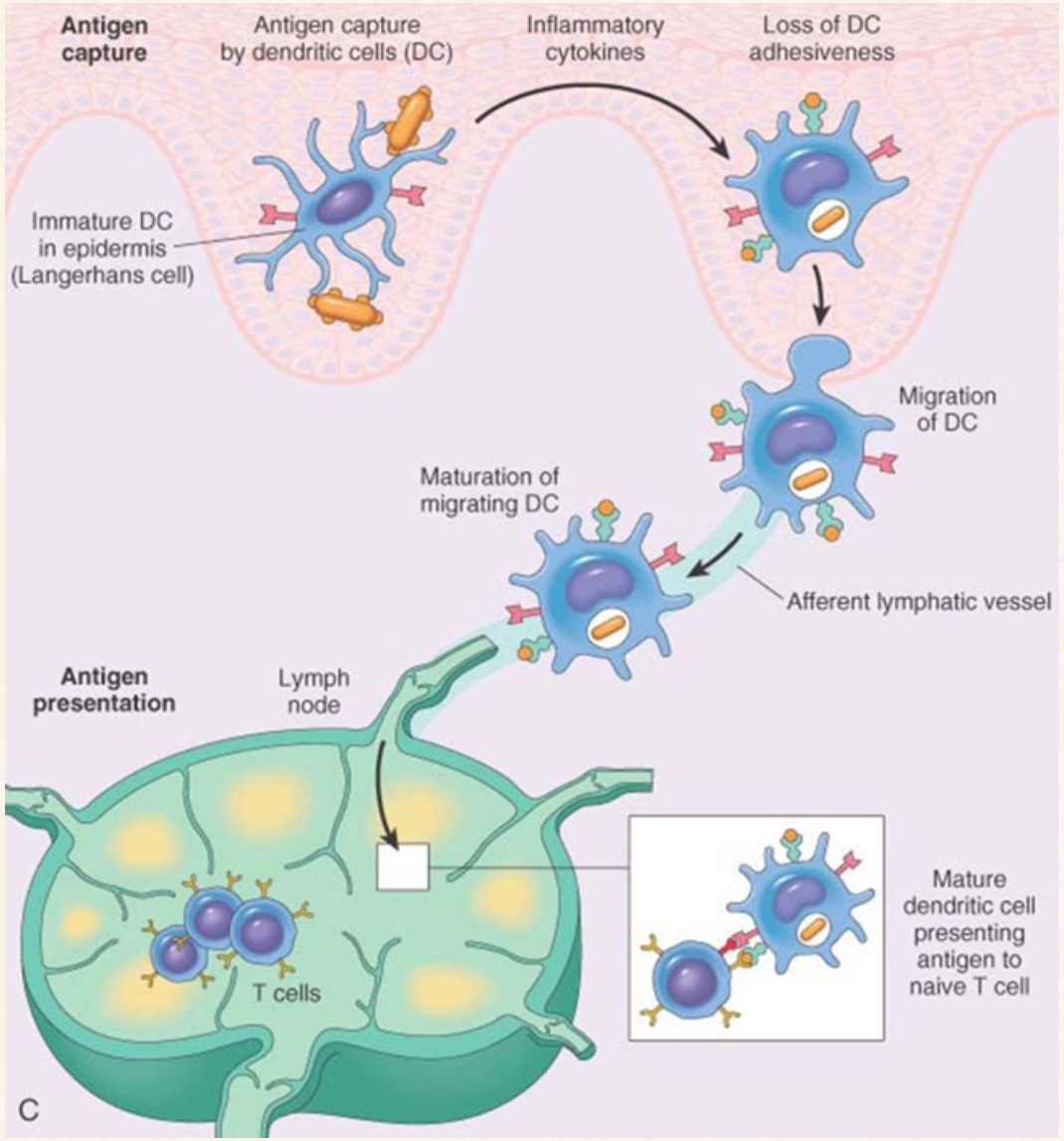
T cells

- Intraepidermal: mainly $CD8^+$ or γδ T cells
- Dermal: $CD4^+$ (T_H1, T_H2, T_H17, T_{reg}), mostly memory T cells


Langerhans cells
50 um
50 um

Dendritic cells





Homing to the skin

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

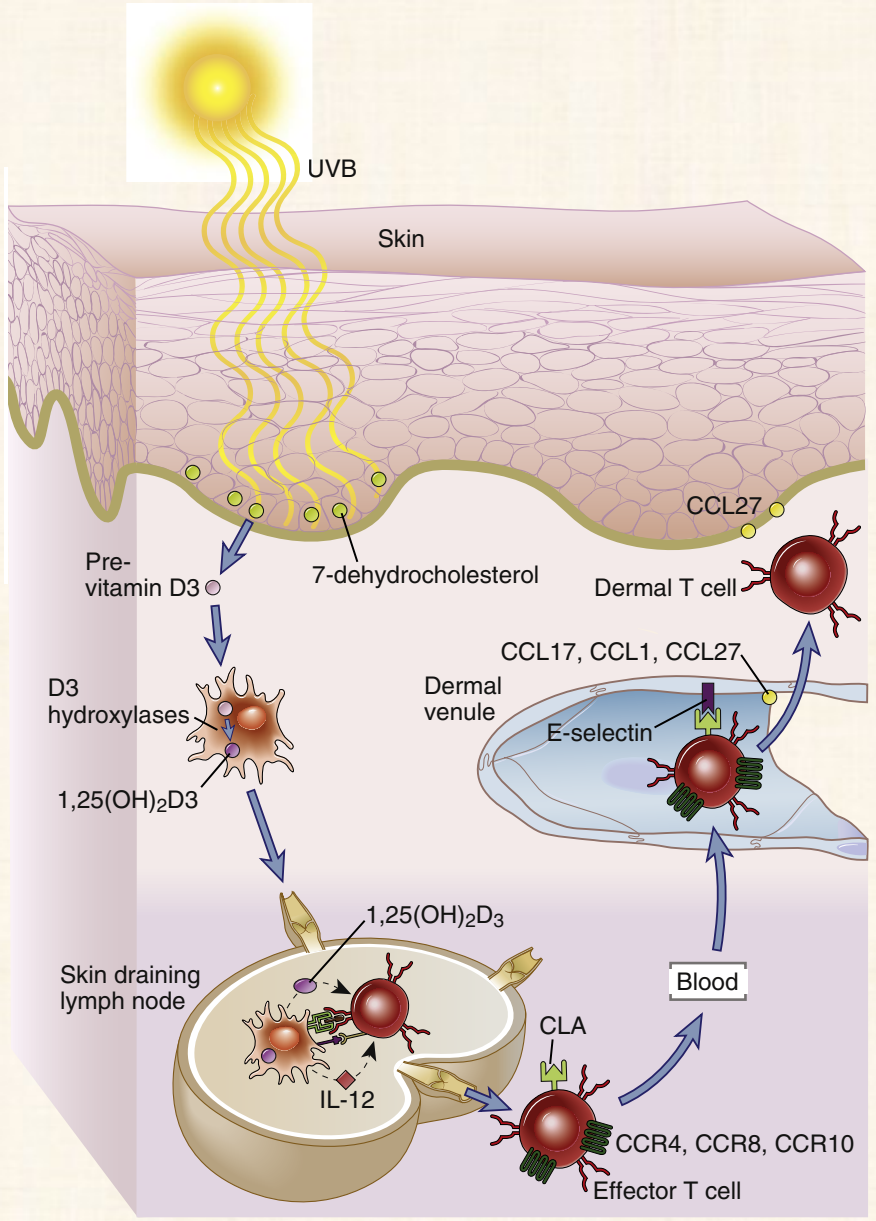


Fig 14-9

Dichotomy of the immune systems