# Basic Immunology

## Suppression of the immune response
## *Suppressor mechanisms of immune functions*

19th lecture
April 10th, 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

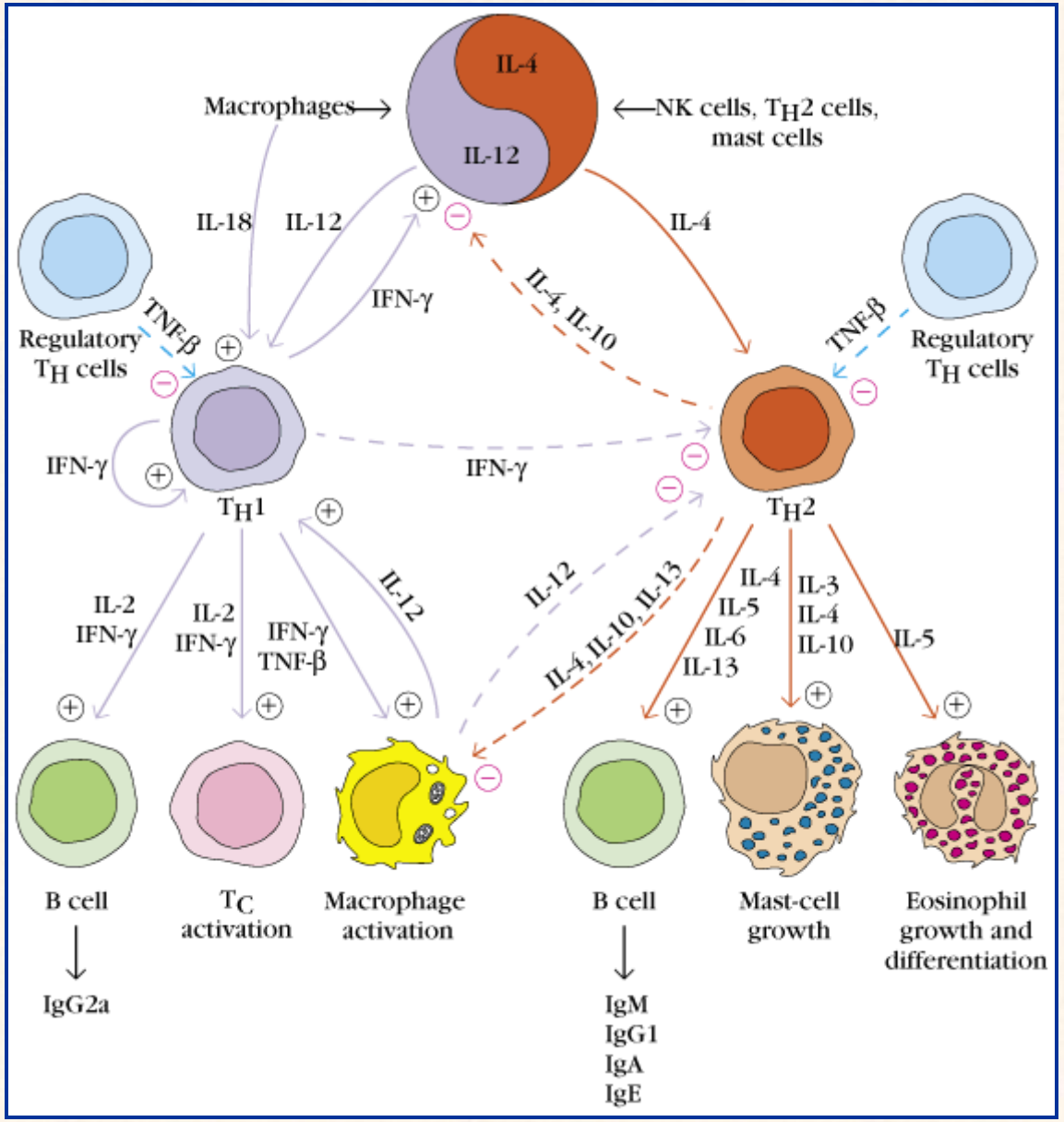
Activates T and B cells

Antigen nature, dose, location influence the immune response

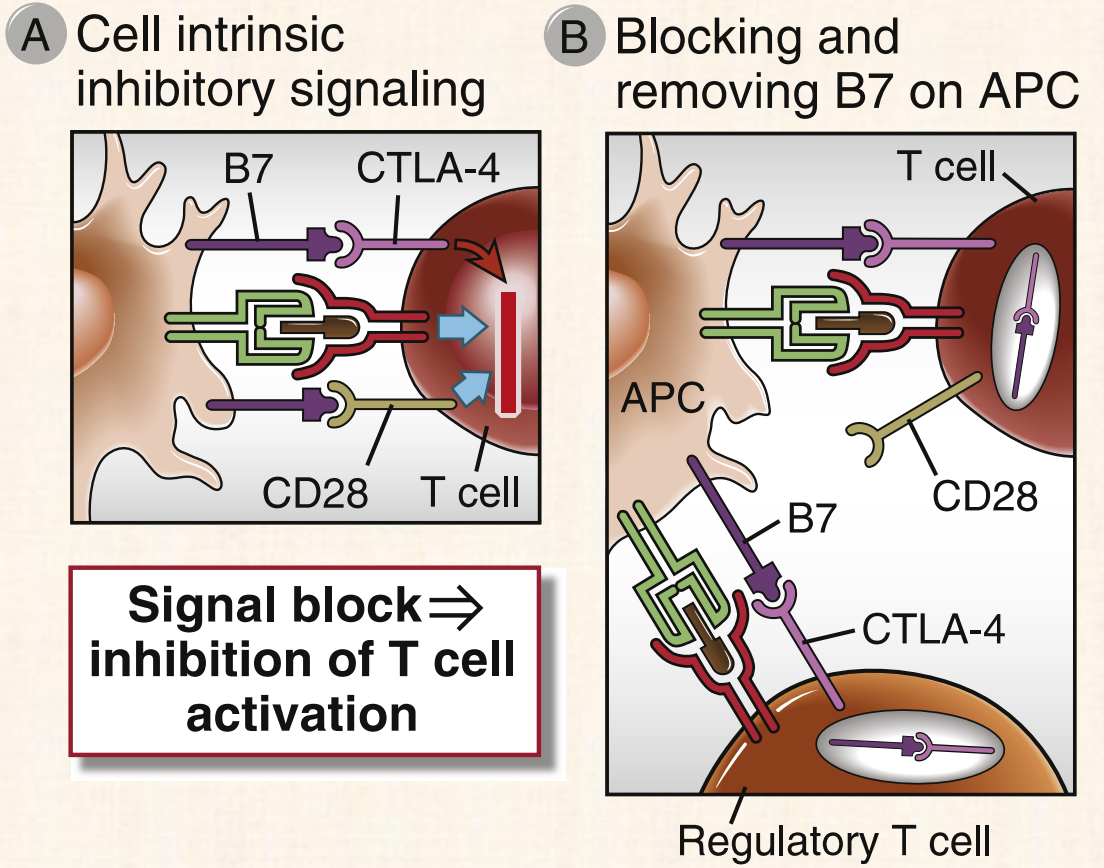
$T_H1$ vs $T_H2$

Withdrawal/elimination of the antigen stops further activation

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



# 2. Need for costimulation

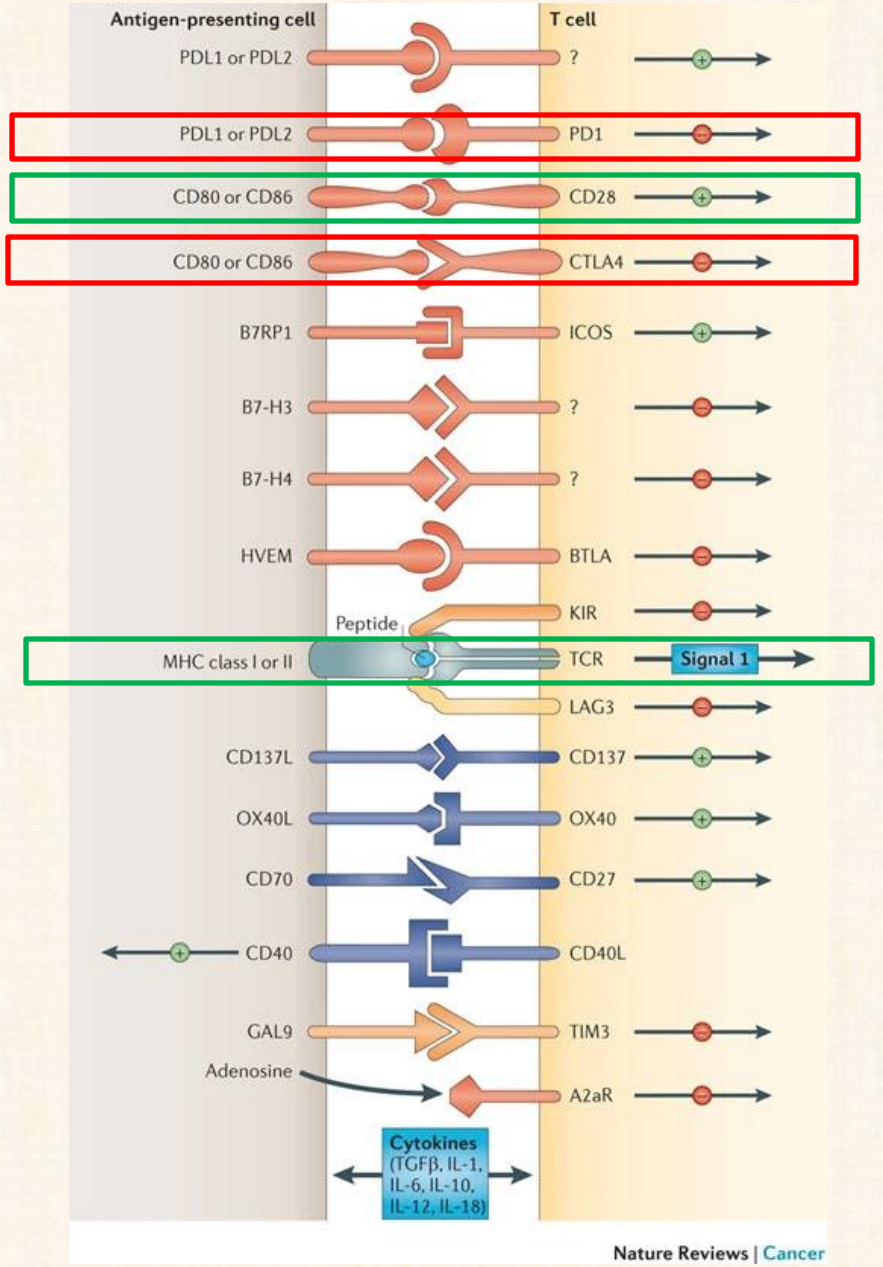



CD28: constitutively expressed on T cells
CTLA-4: expressed after activation
higher affinity towards B7

*Fig 15-6*

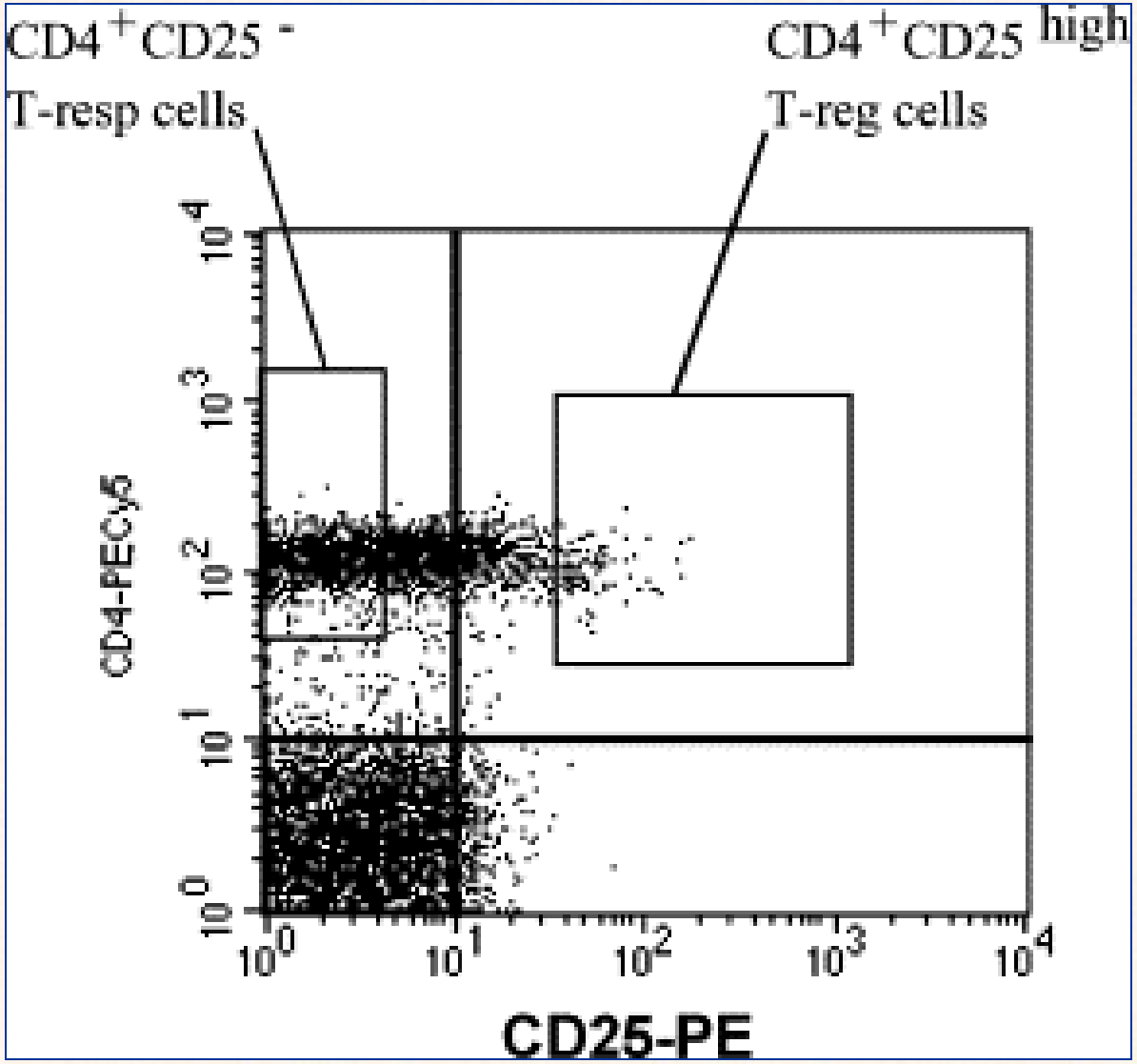
# 2. Need for costimulation: Immune checkpoints

Antigen presenting cell

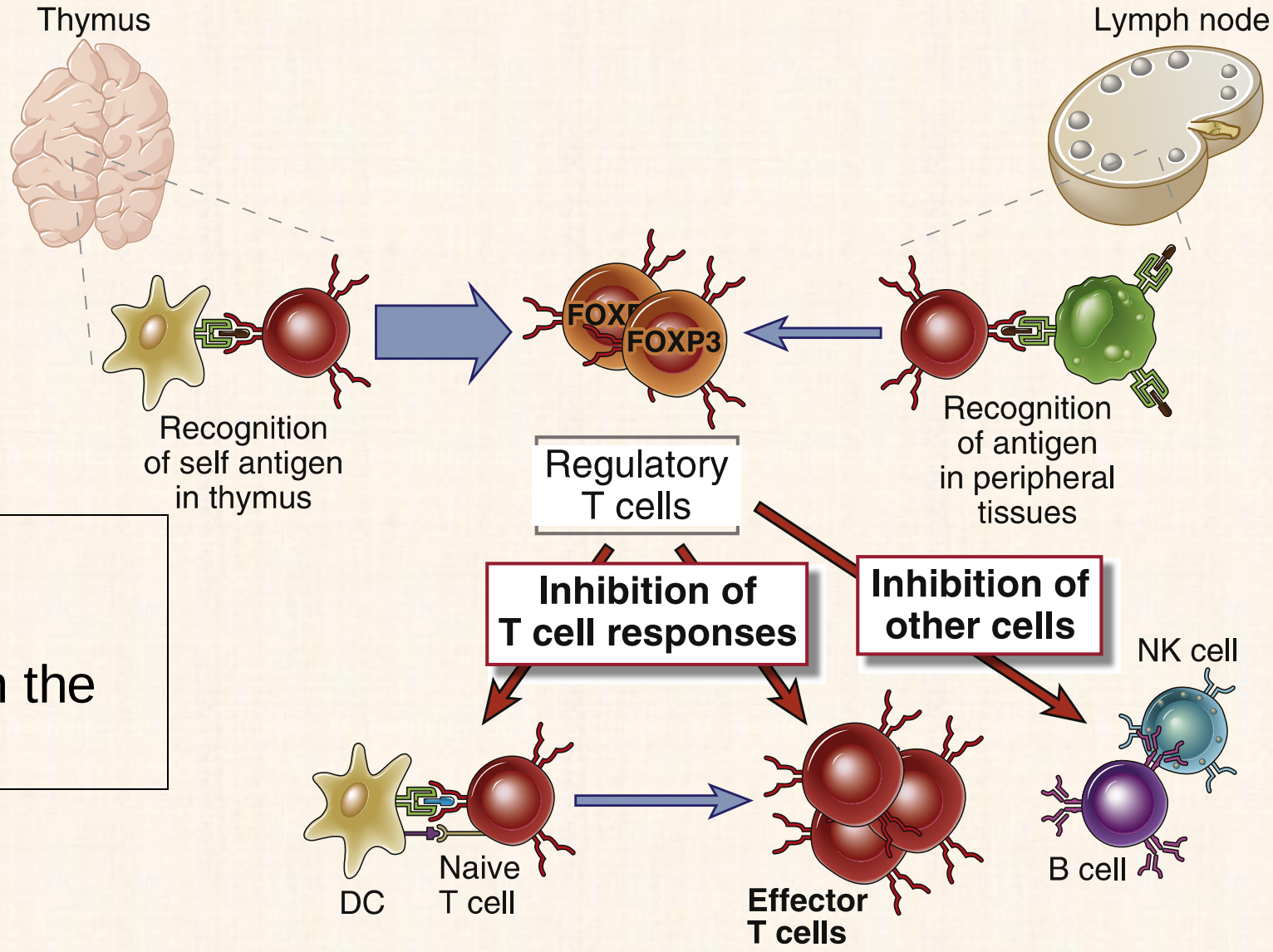



T cell

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



# 3. Main functions of regulatory T cells




Natural Treg

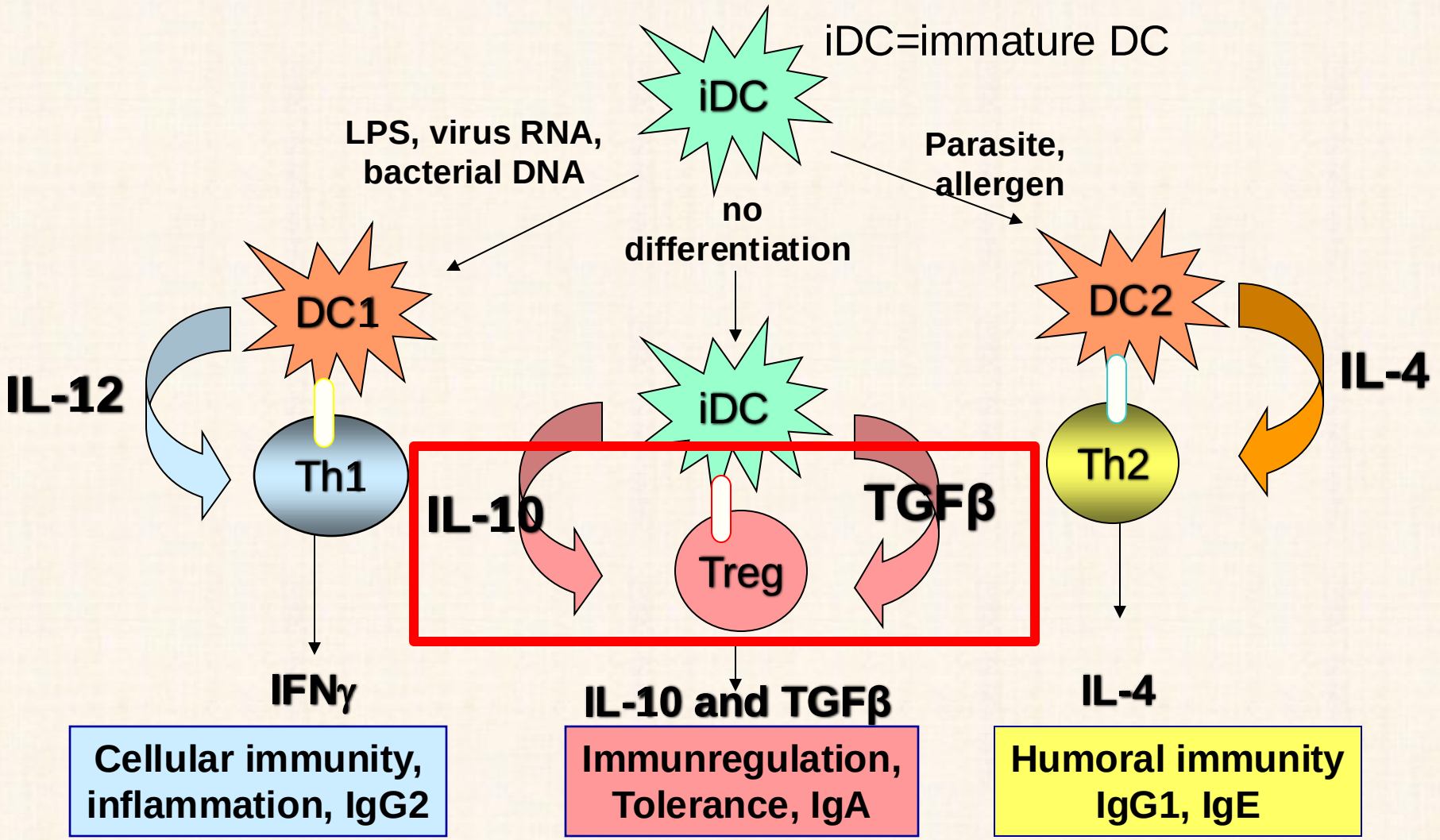
Differentiate in the thymus

Induced Treg

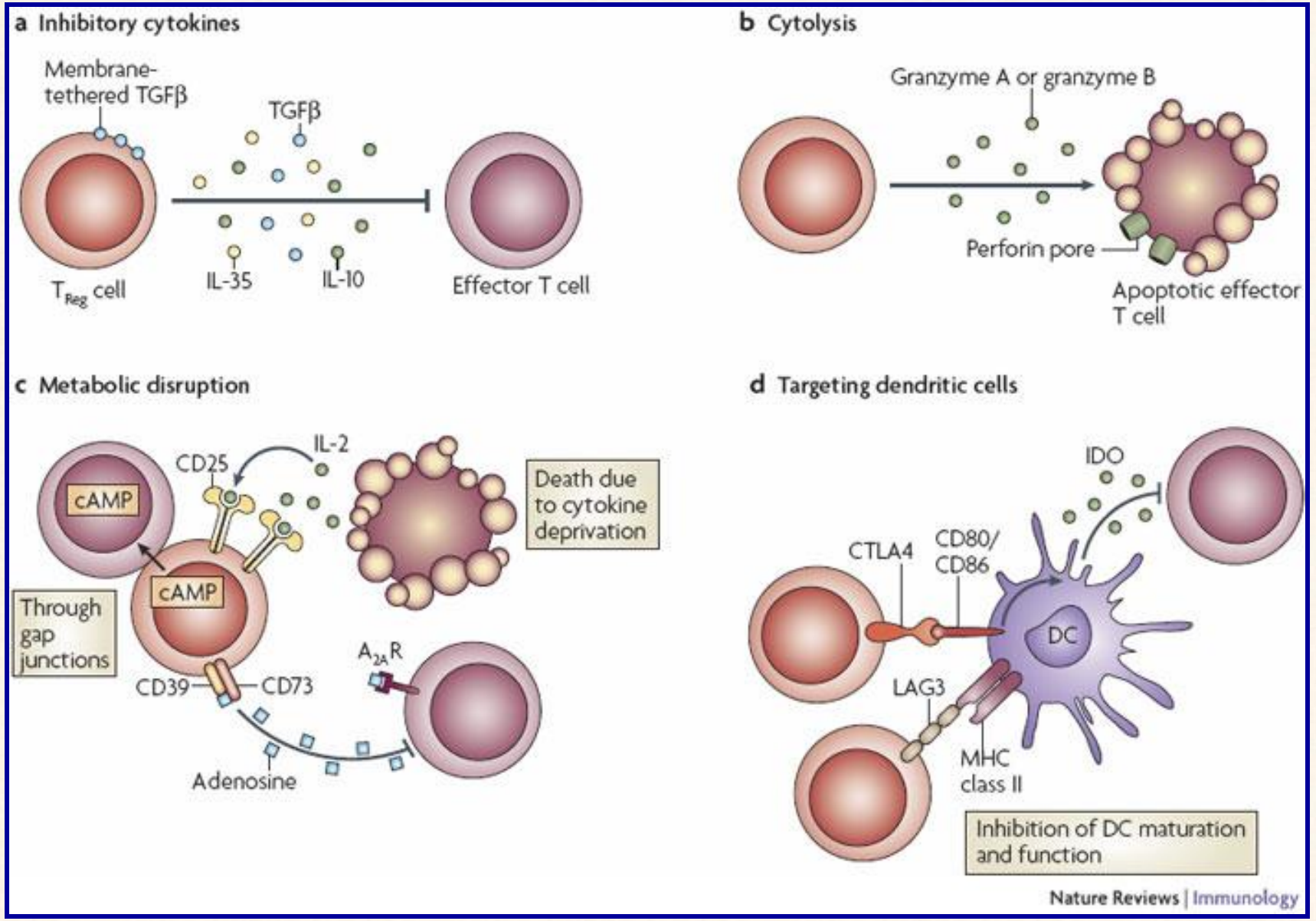
Differentiate in the periphery

*Fig 15-7*

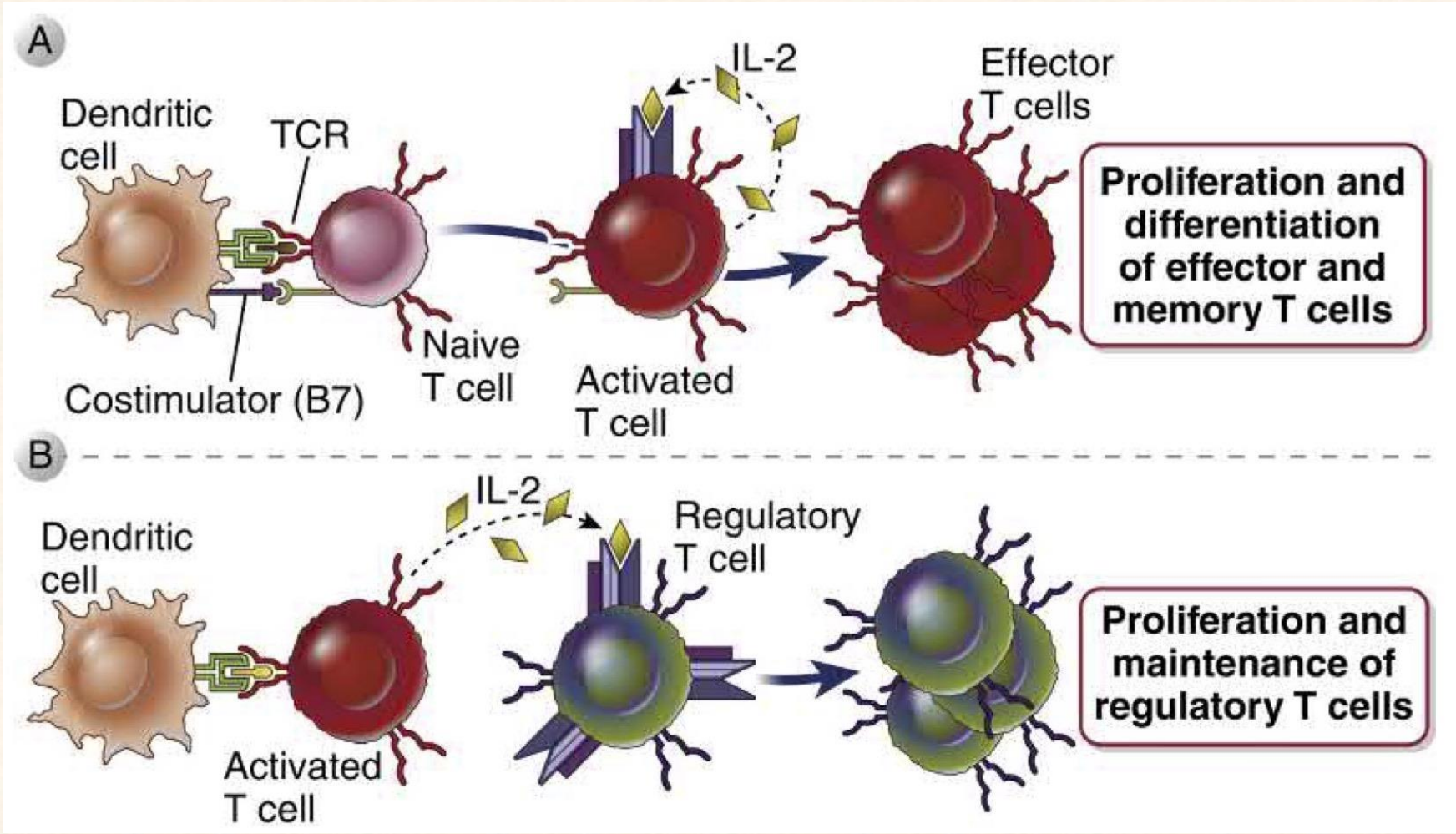
# 3. Development of induced $T_{reg}$ cells



# 3. $T_{reg}$ suppression mechanisms



# 3. $T_{reg}$ 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
  - *$IL\text{-}10^{-/-}$ mice: colitis*
- Blocking costimulation via CTLA-4
- IL-2 “consumption” via IL-2Rα (CD25, high-affinity IL-2R)
- cytolysis

# 4. B cell suppression

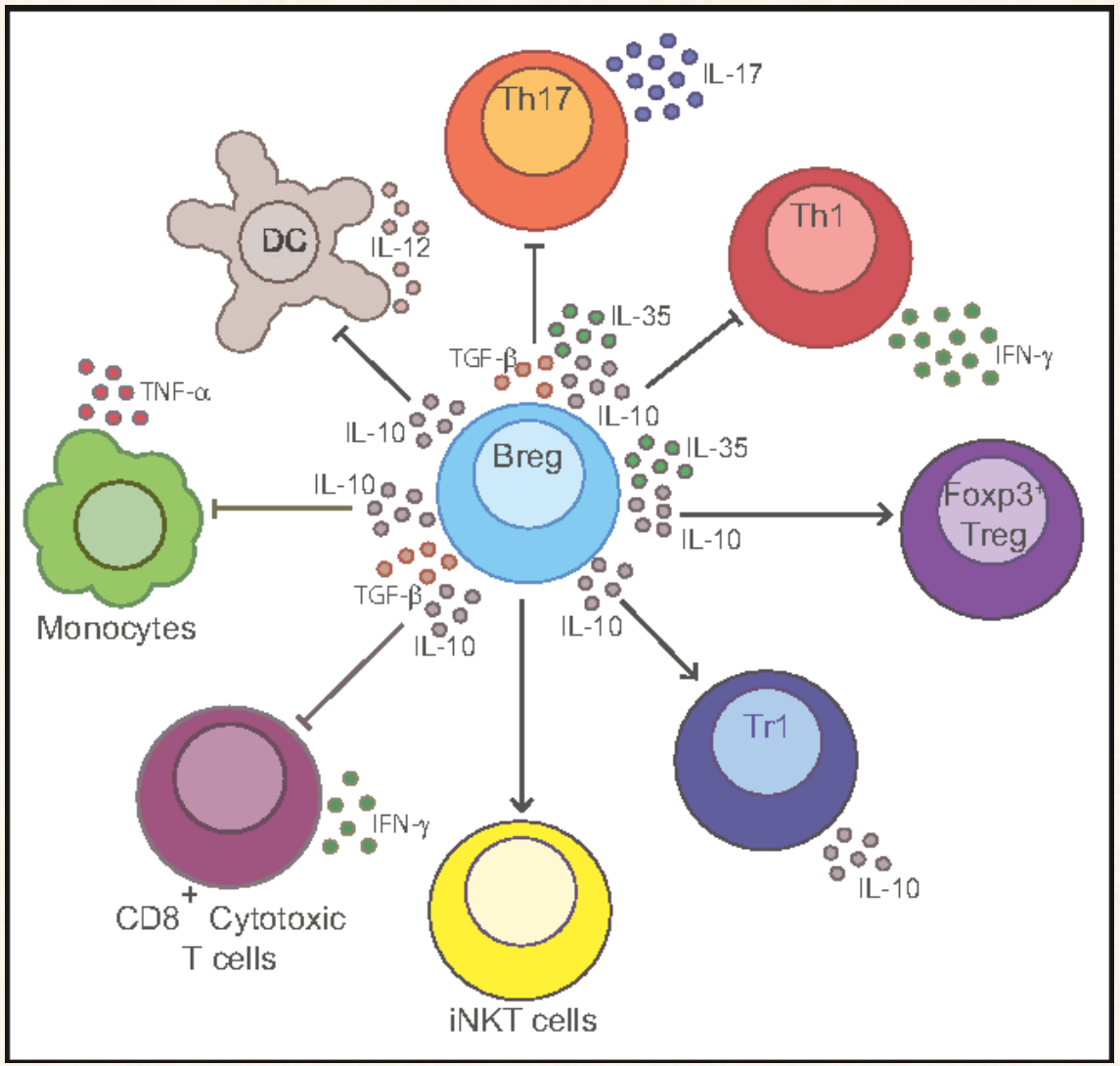
Regulatory B cells ($B_{reg}$)

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



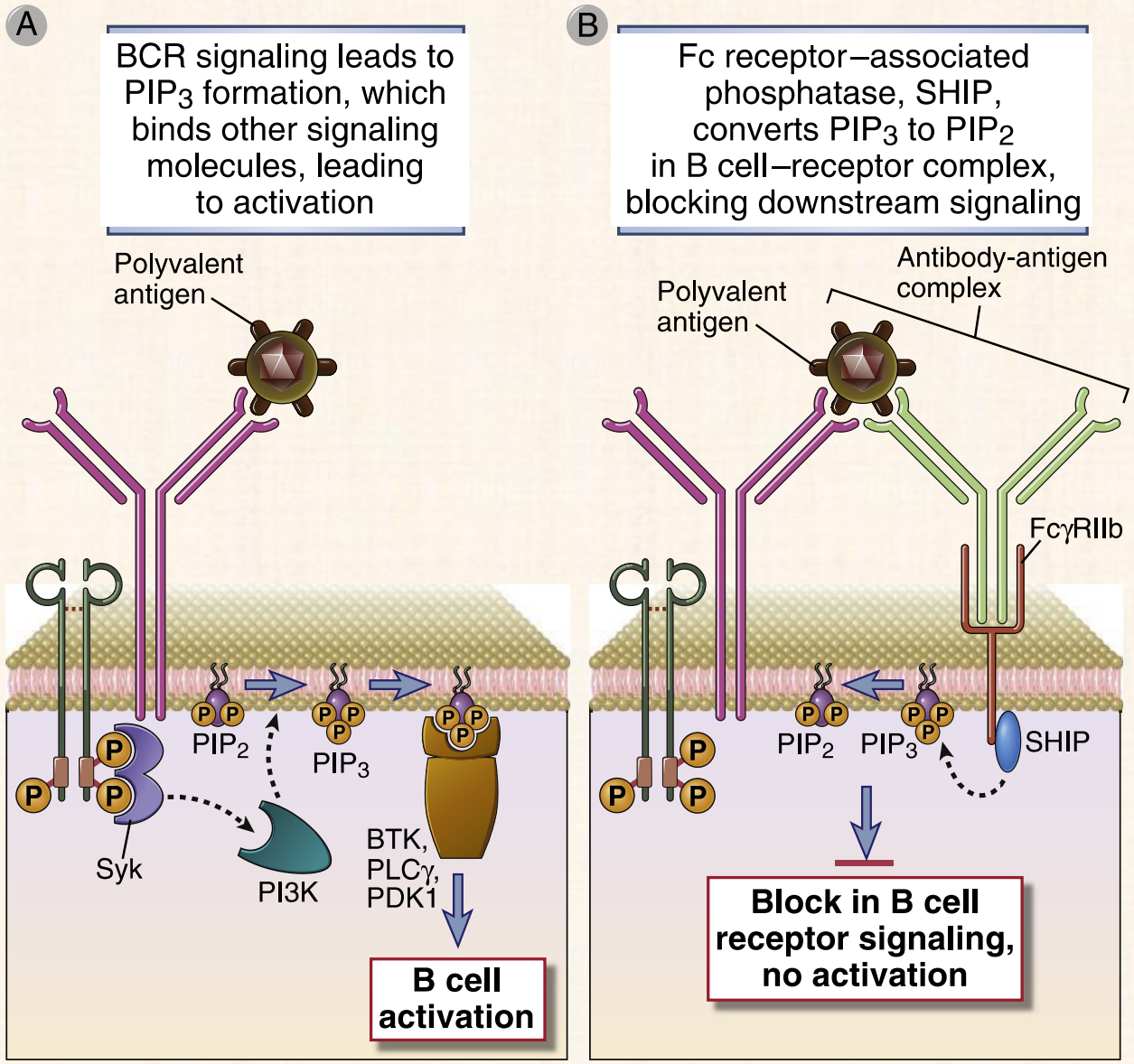

$B_{reg}$ cells produce **IL-10**, IL-35, and TGF-β

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!)

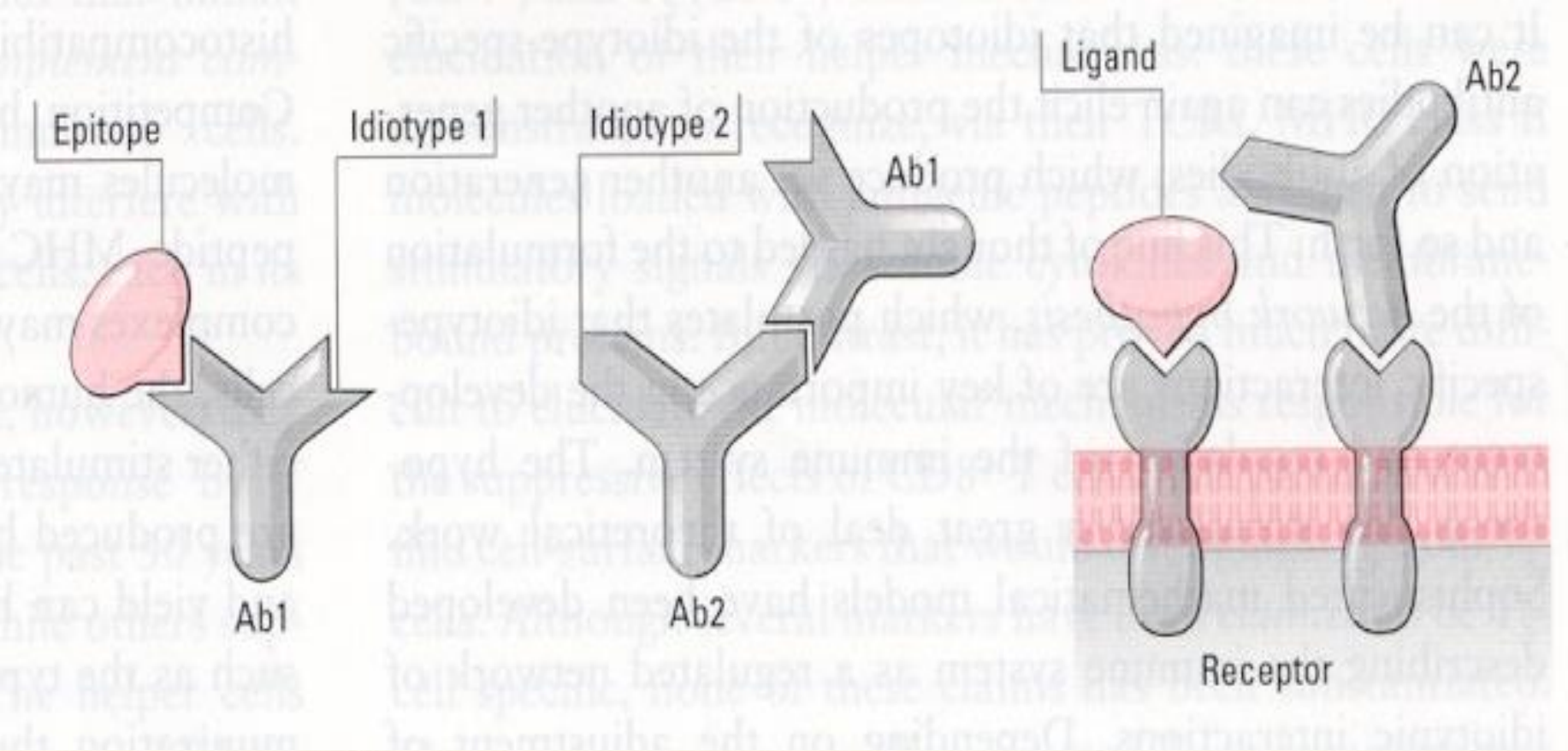
Simultaneous binding of antigen + IgG leads to B cell inhibition

*Fig 12-21*

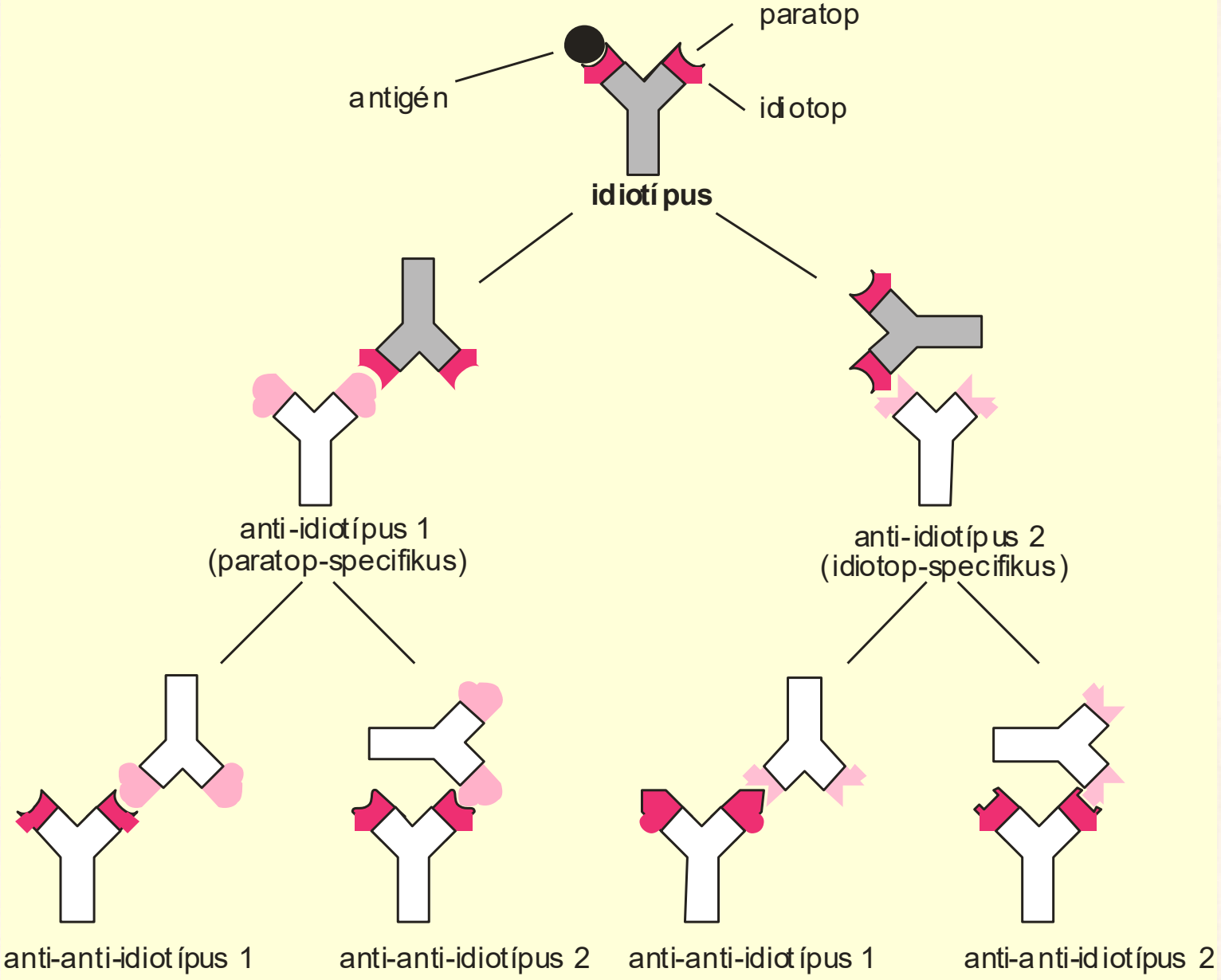
# 4. Anti-idiotype antibodies

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



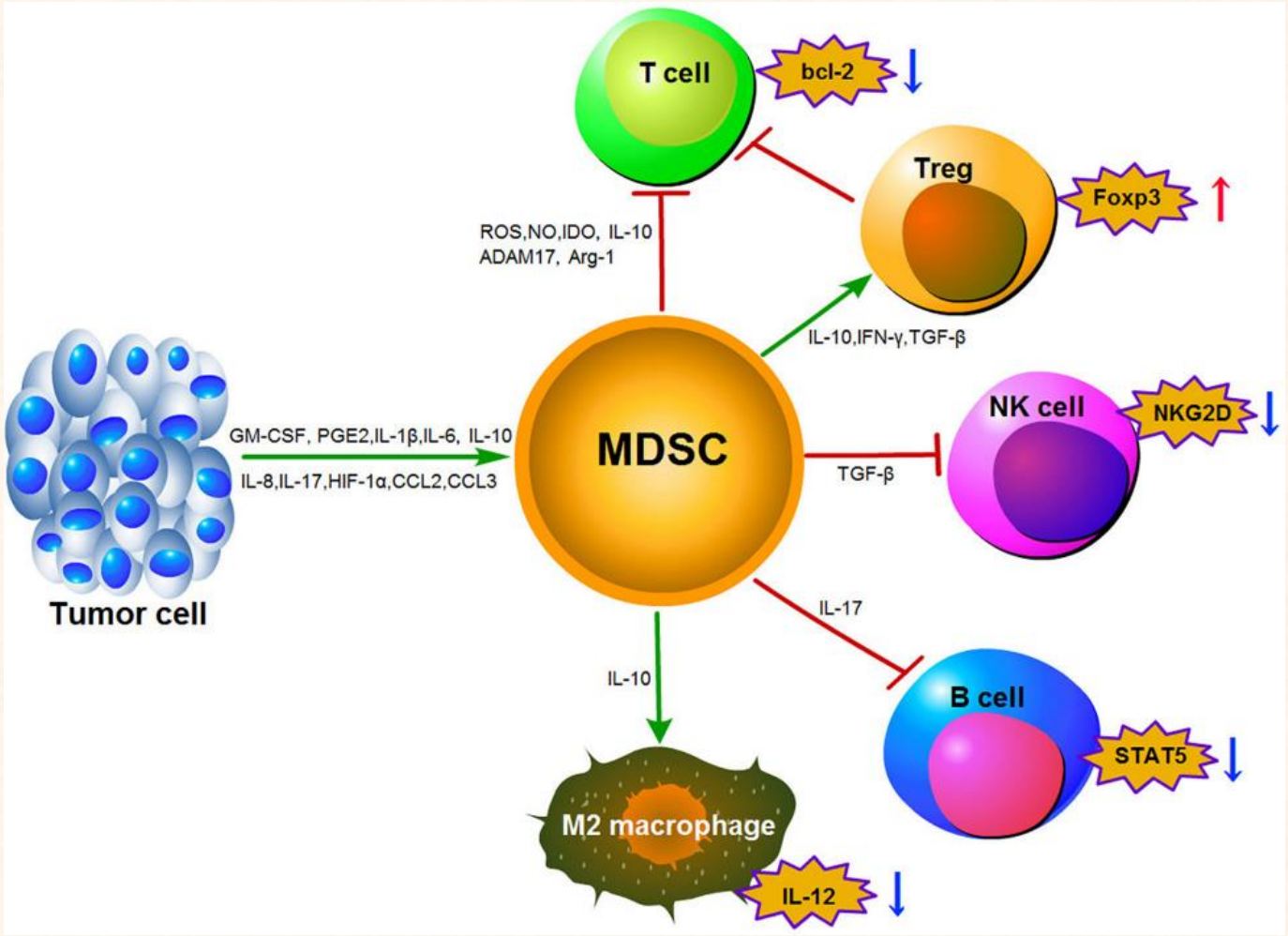
# 4. Functions of the anti-idiotype network

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)

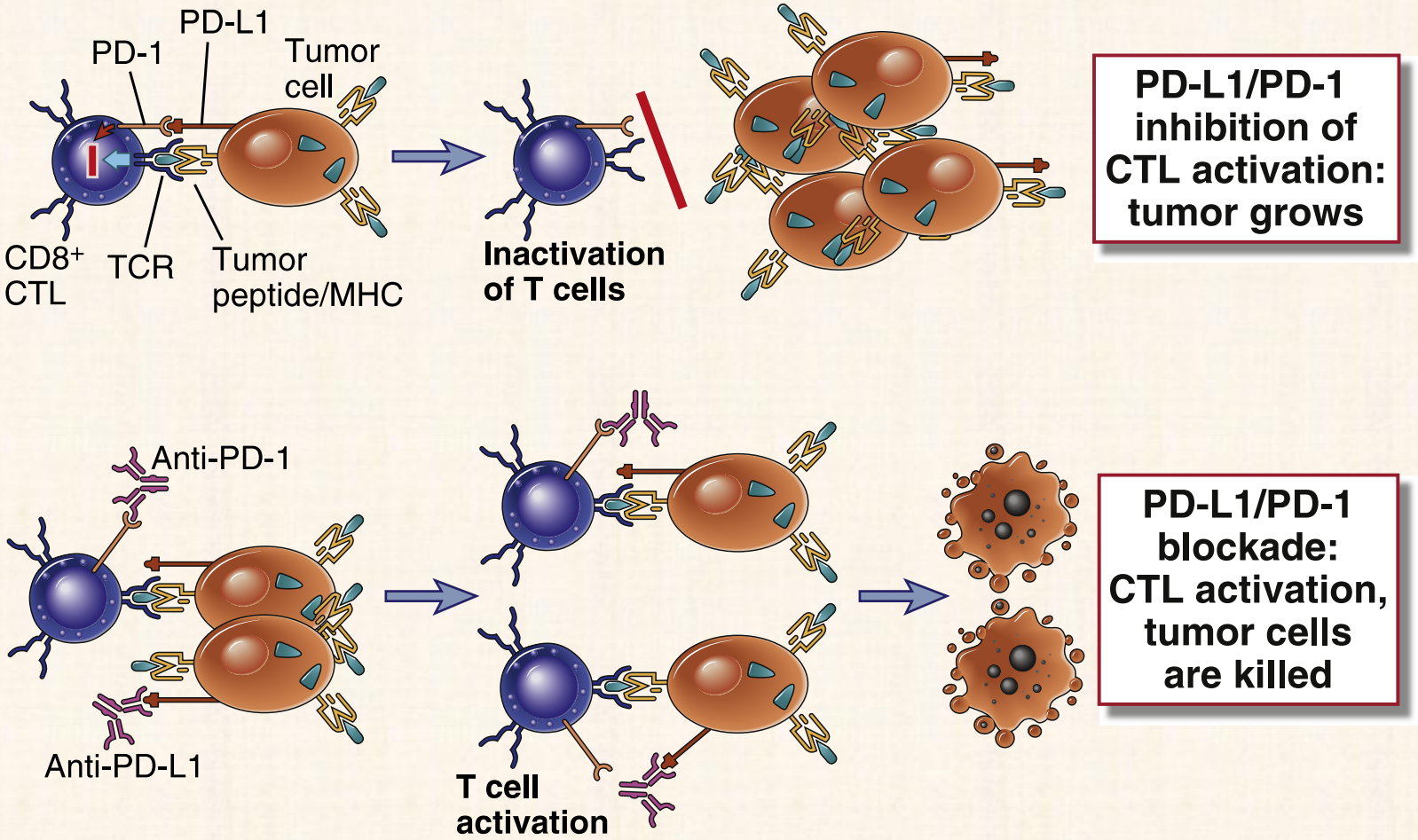



*Yin K et al 2020. Front. Oncol. 10:610104. doi: 10.3389/fonc.2020.610104*

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*

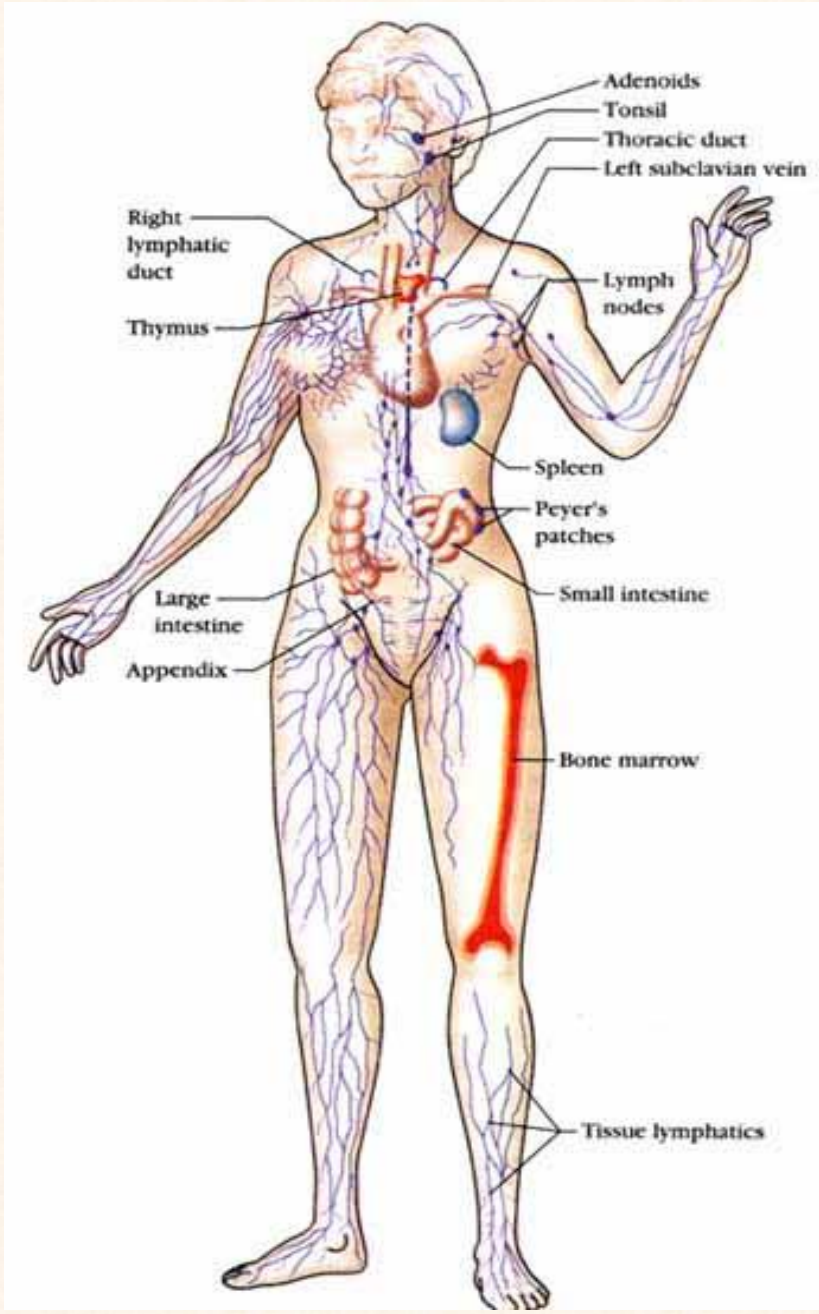
20th lecture
April 10th, 2025
Zoltán Kellermayer

**Regional immune system**

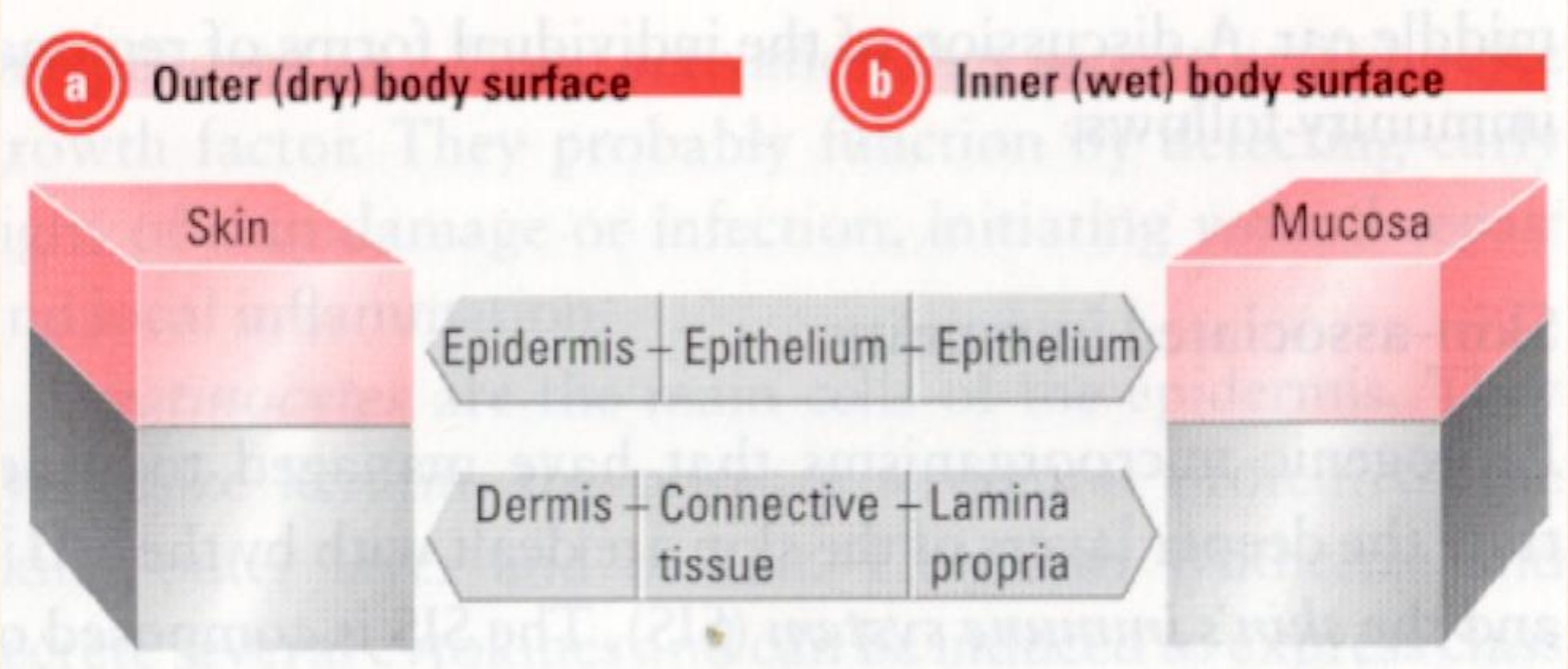
The collection of *immune cells* and *molecules* with specialized functions at a particular anatomic location

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: $10^{10}$)

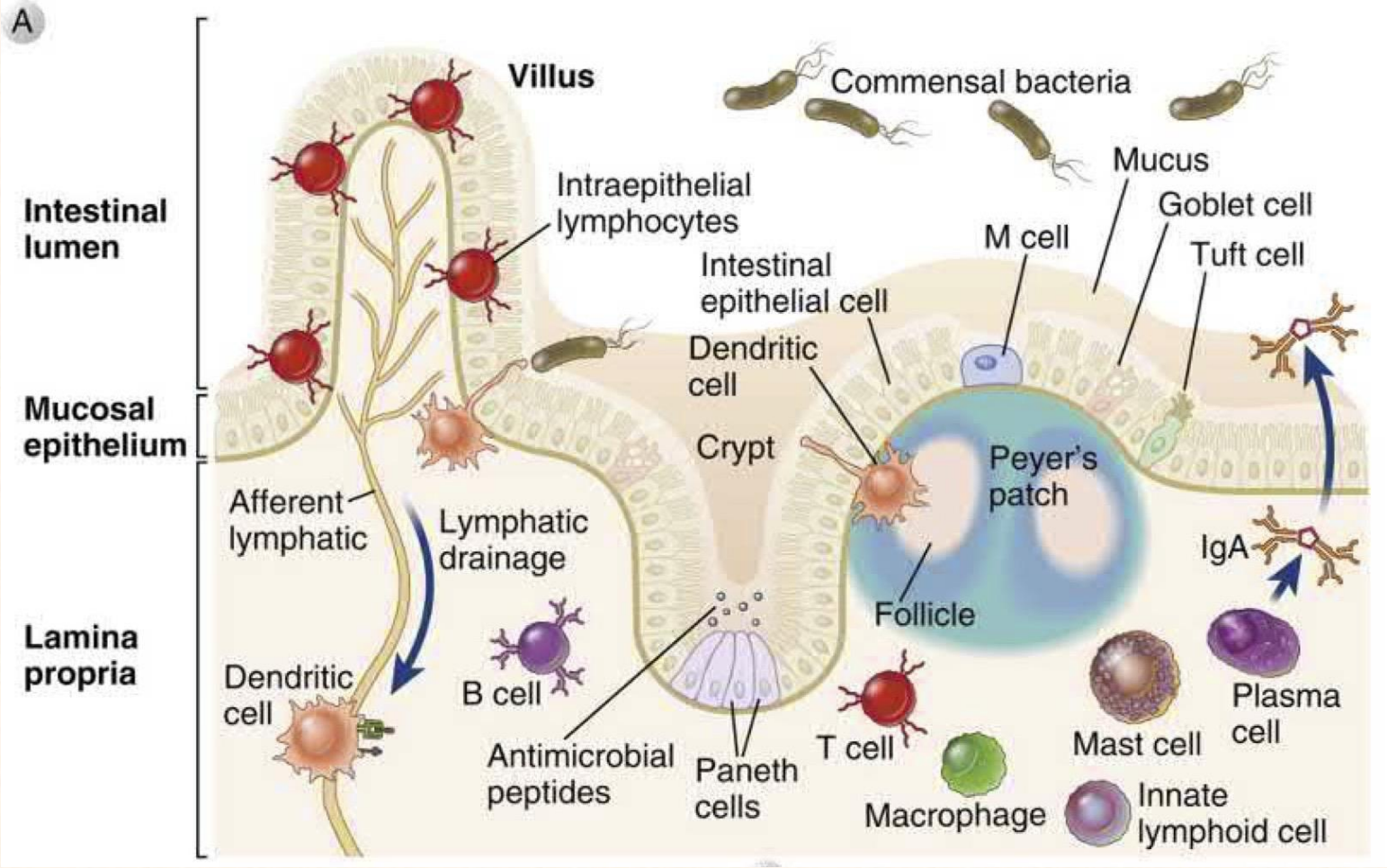
Huge amount of microbes: $10^{14}$

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**

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

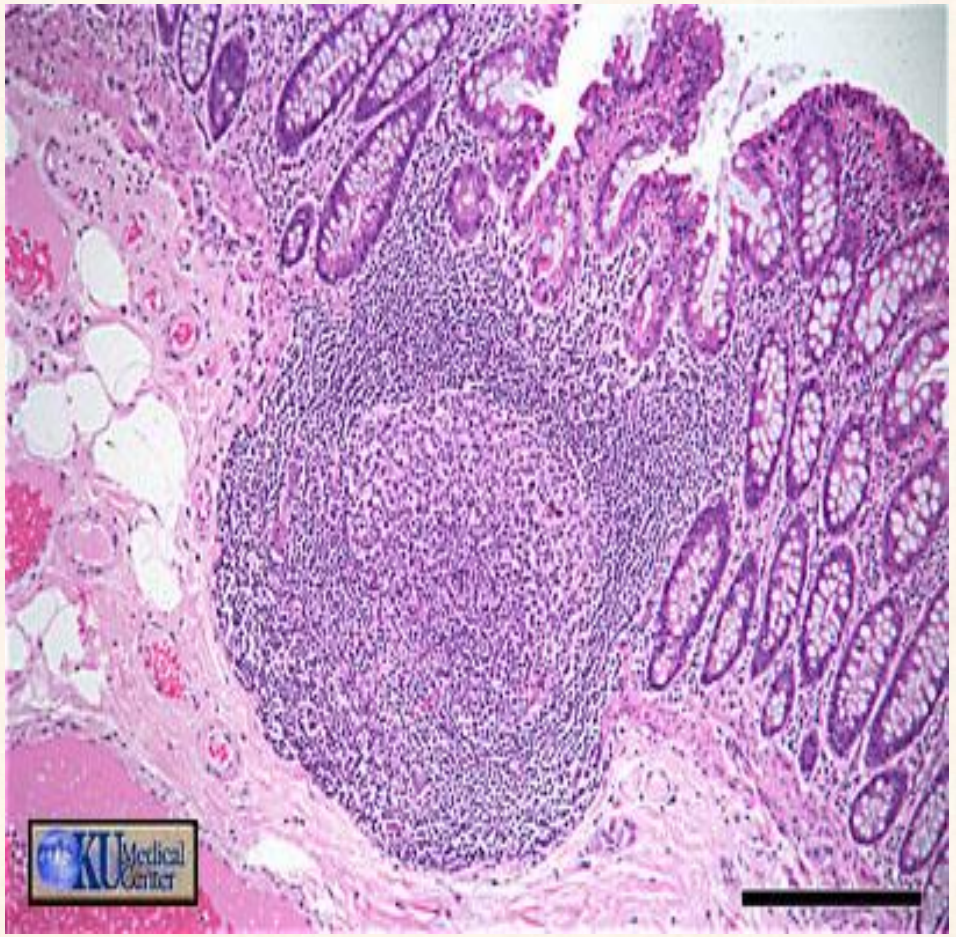
Cryptopatch - isolated lymphoid follicle spectrum

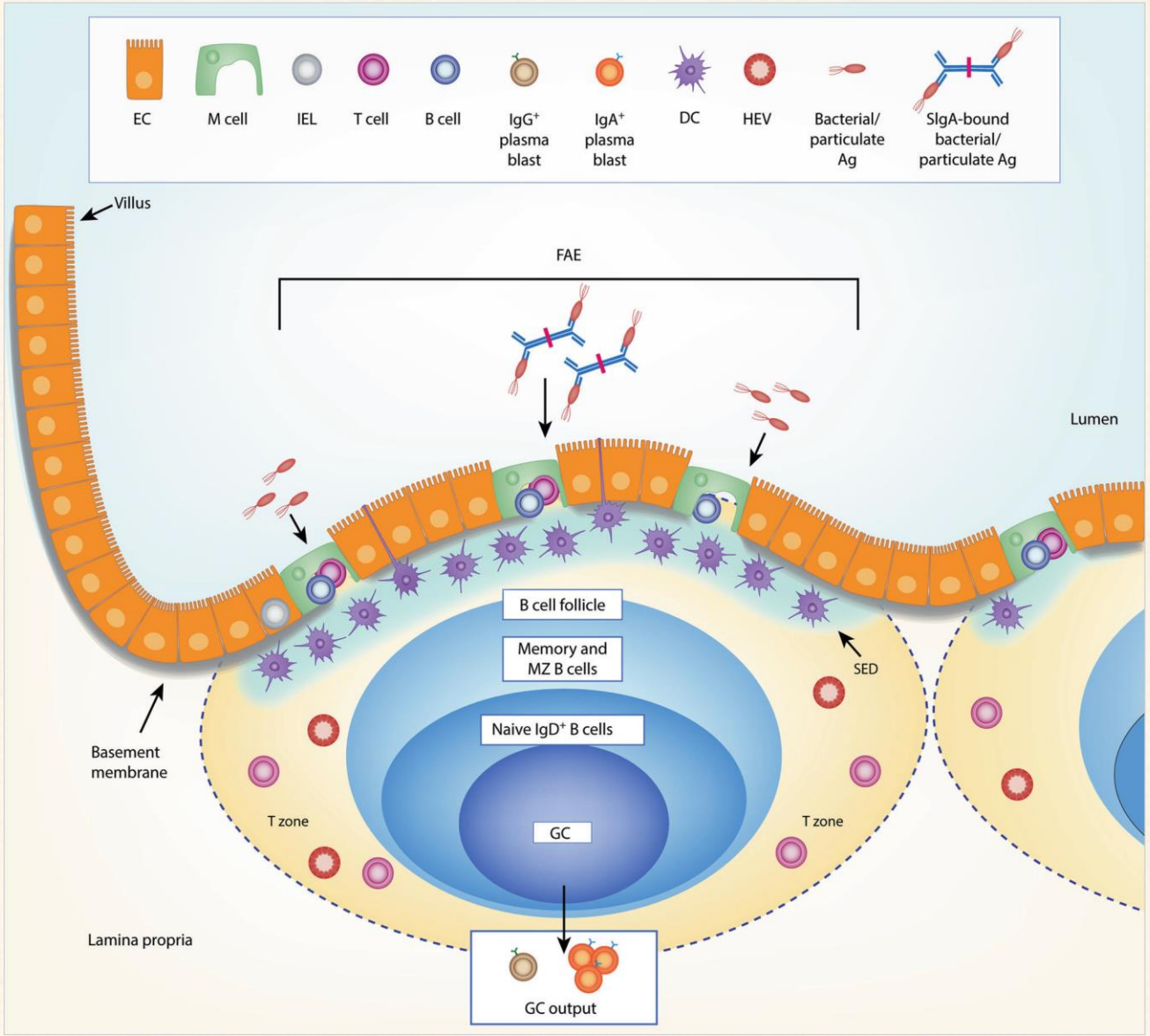
**Diffuse MALT (D-MALT)**

Effector tissue

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

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

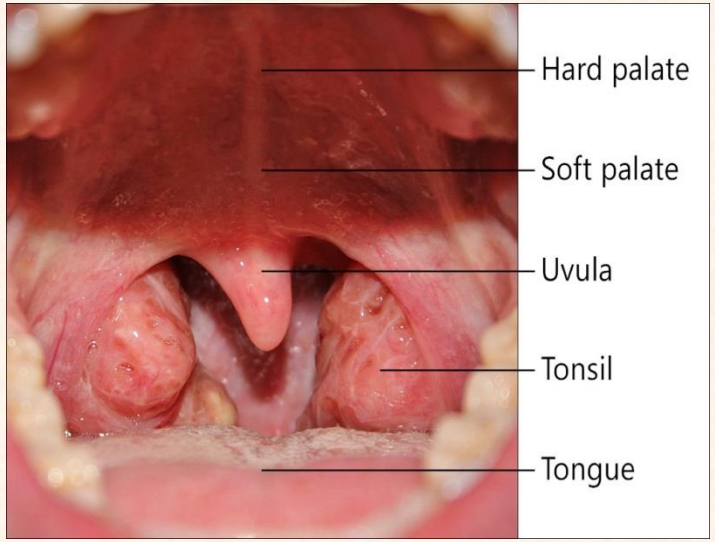


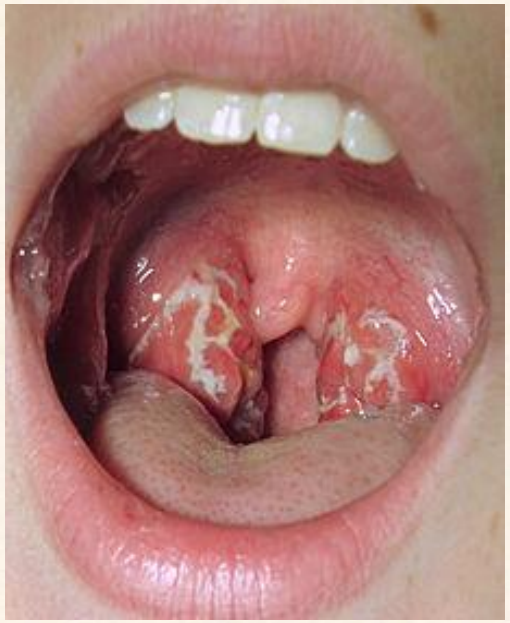



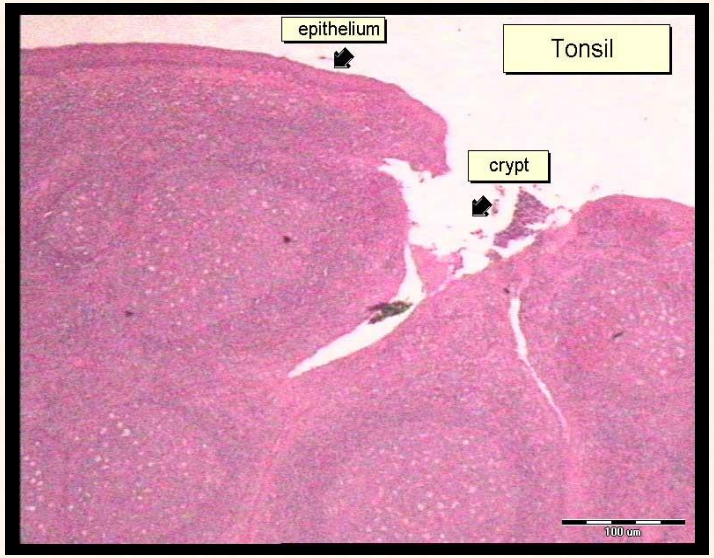

SED: Subepithelial dome
FAE: Follicle associated epithelium

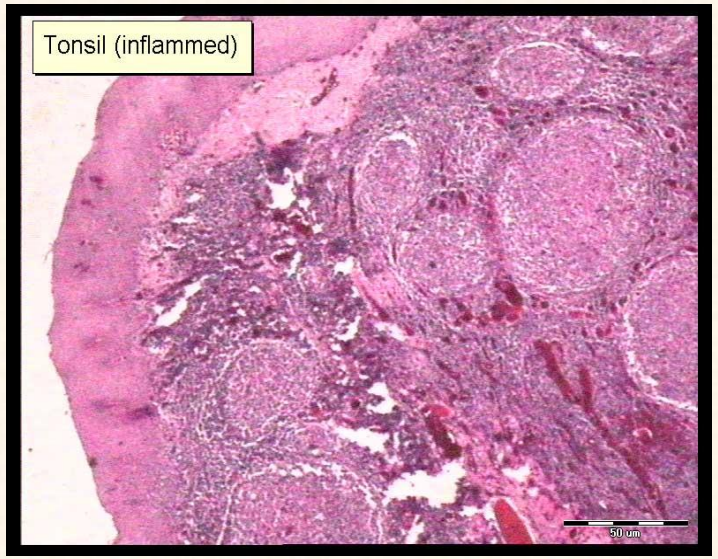
*UM Mörbe et al 2021. Mucosal Immunology 14:793-802*

# Programmed lymphoid tissues in the gastrointestinal tract: tonsils



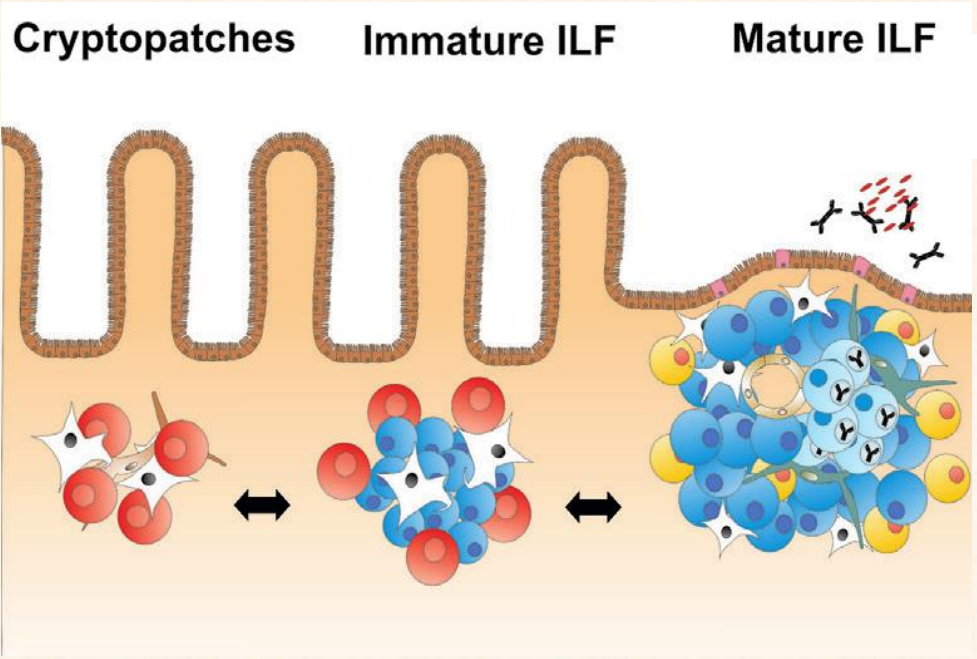



Normal tonsil

Inflamed tonsil

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

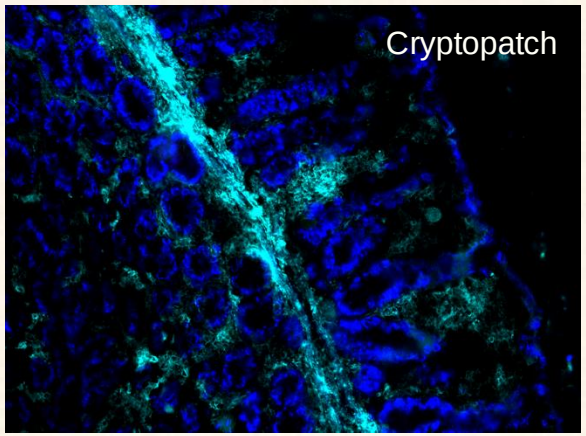


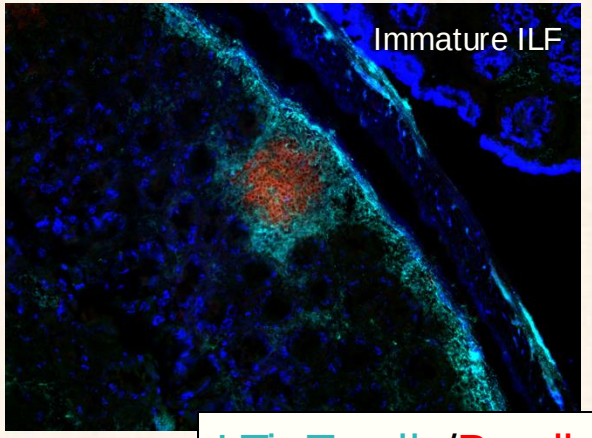


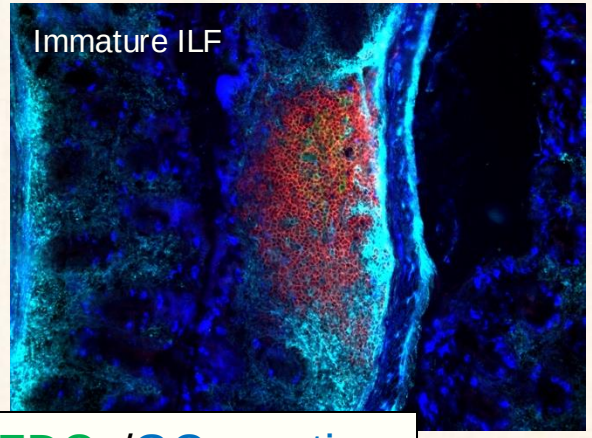
*Buettner M and Lochner M (2016) Development and function of secondary and tertiary lymphoid organs in the small intestine and the colon. Front Immunol.*

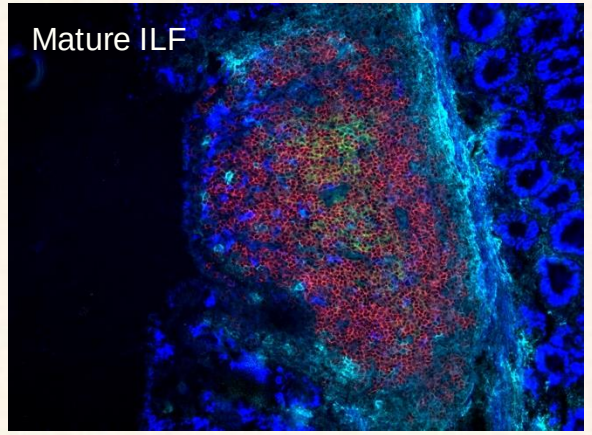
*ILF: Isolated lymphoid follicle*
*LTi: Lymphoid tissue inducer cell*

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: constant 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

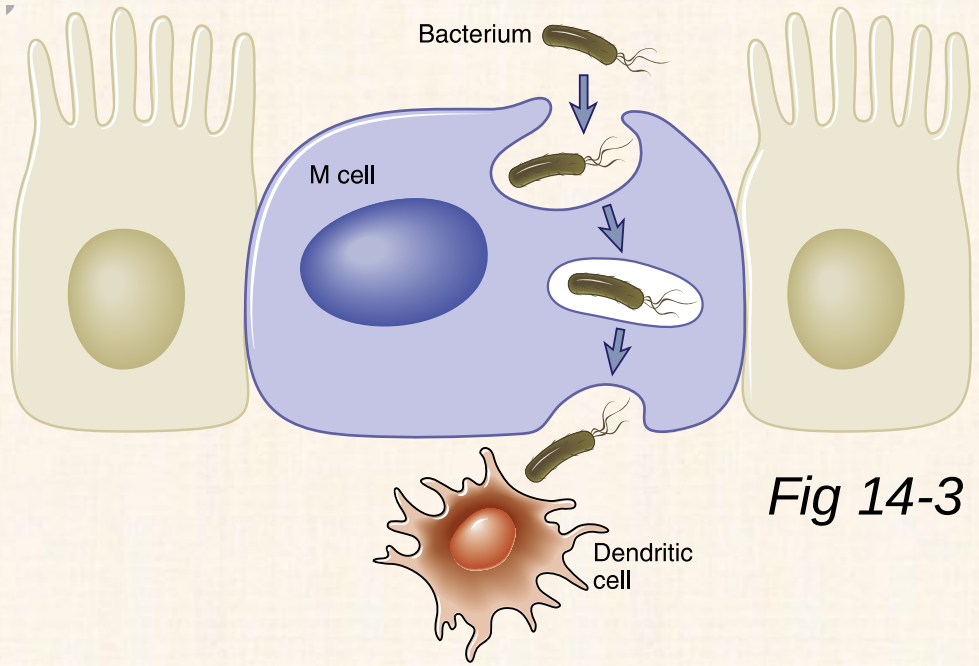
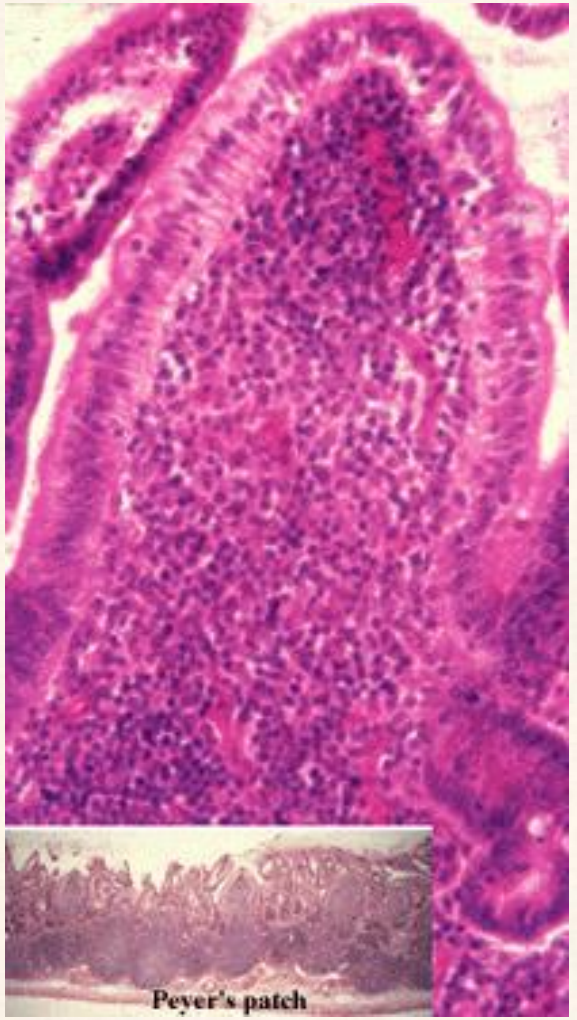
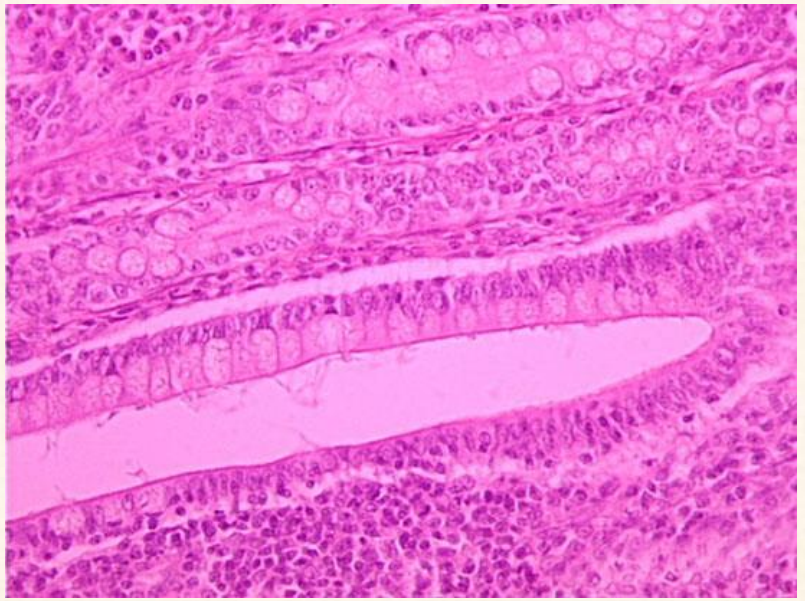



*Fig 14-3*

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

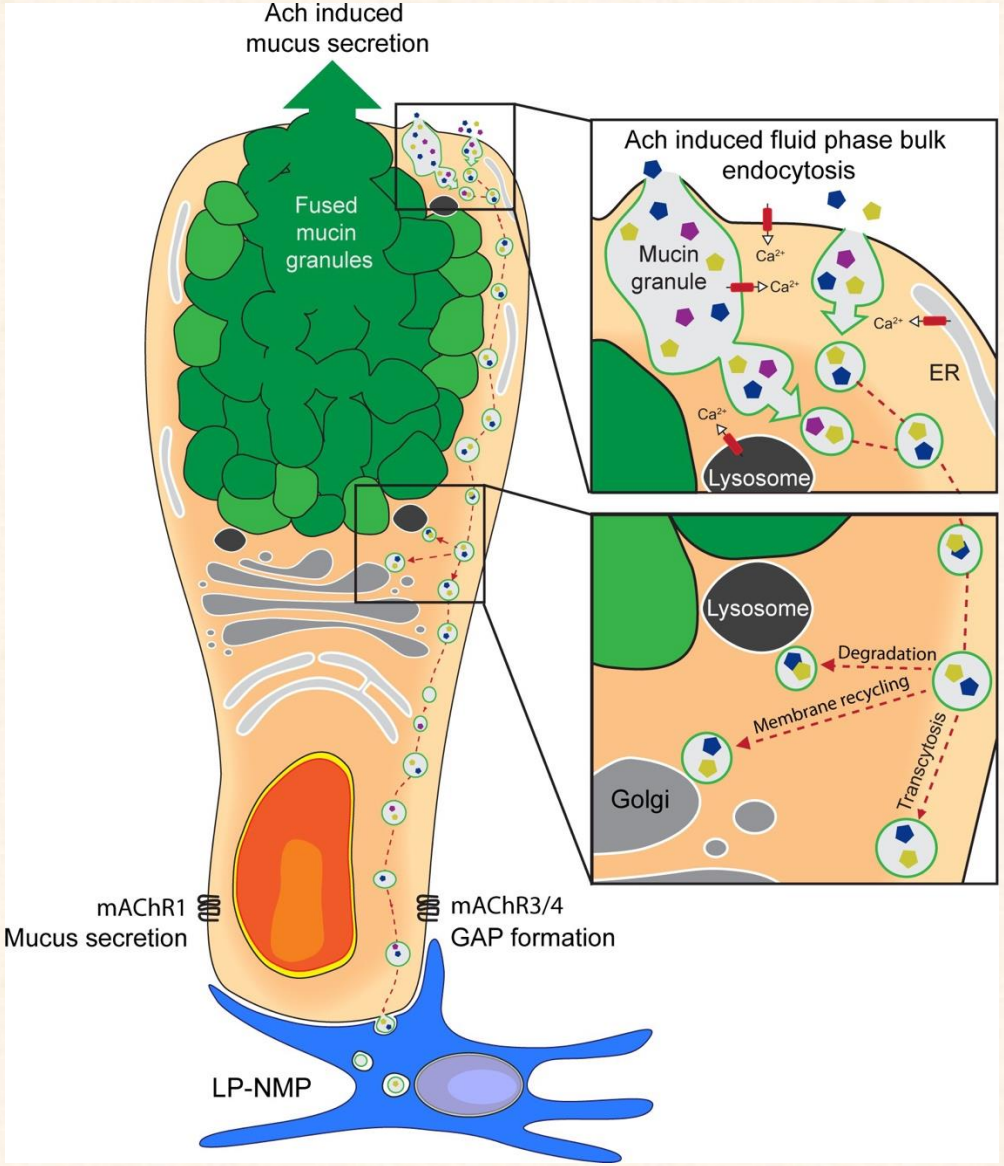



M cell region

*(Not antigen presentation!)*

# Goblet cells: not only mucus secretion…




GAP: Goblet cell associated Antigen Passages

Transport of luminal antigens to underlying mononuclear phagocytes

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

# Innate immunity of the intestinal immune system

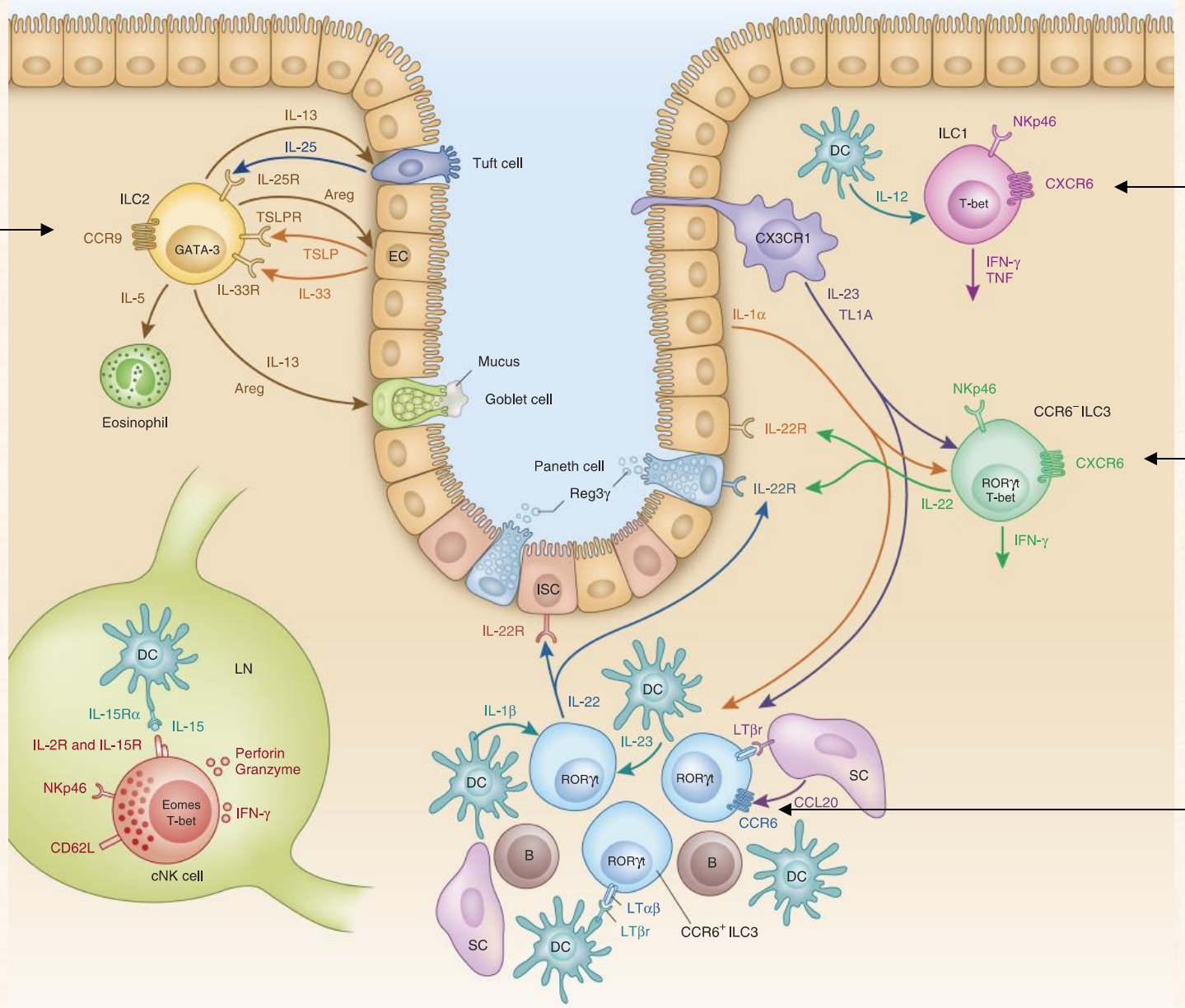
**Dendritic cells, Macrophages**

- 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)

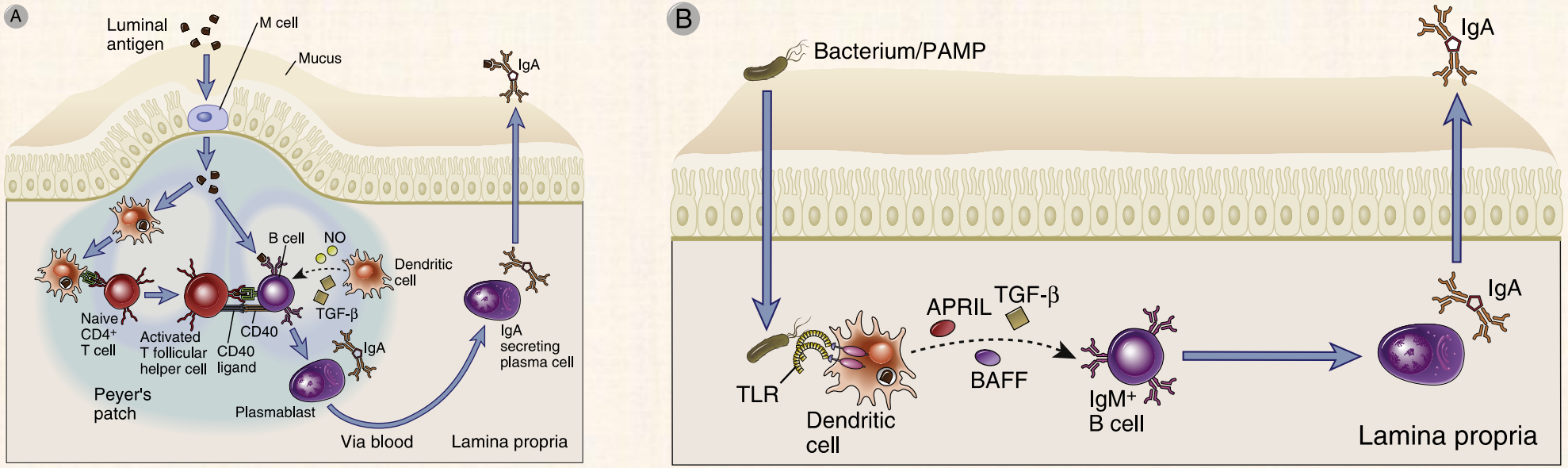



*Klose CSN and Artis D (2016) Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nature Immunology*

# 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

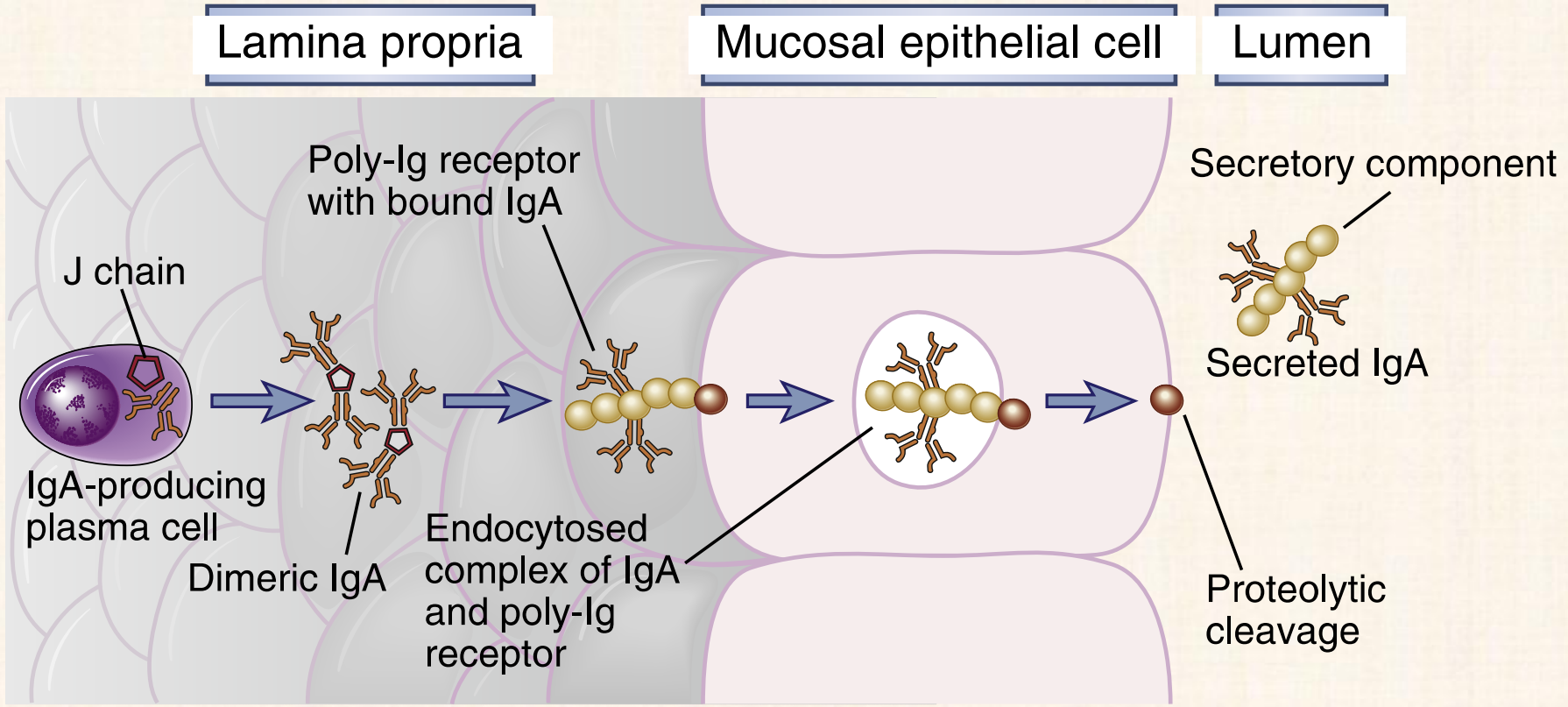



*Fig 14-8*

# 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

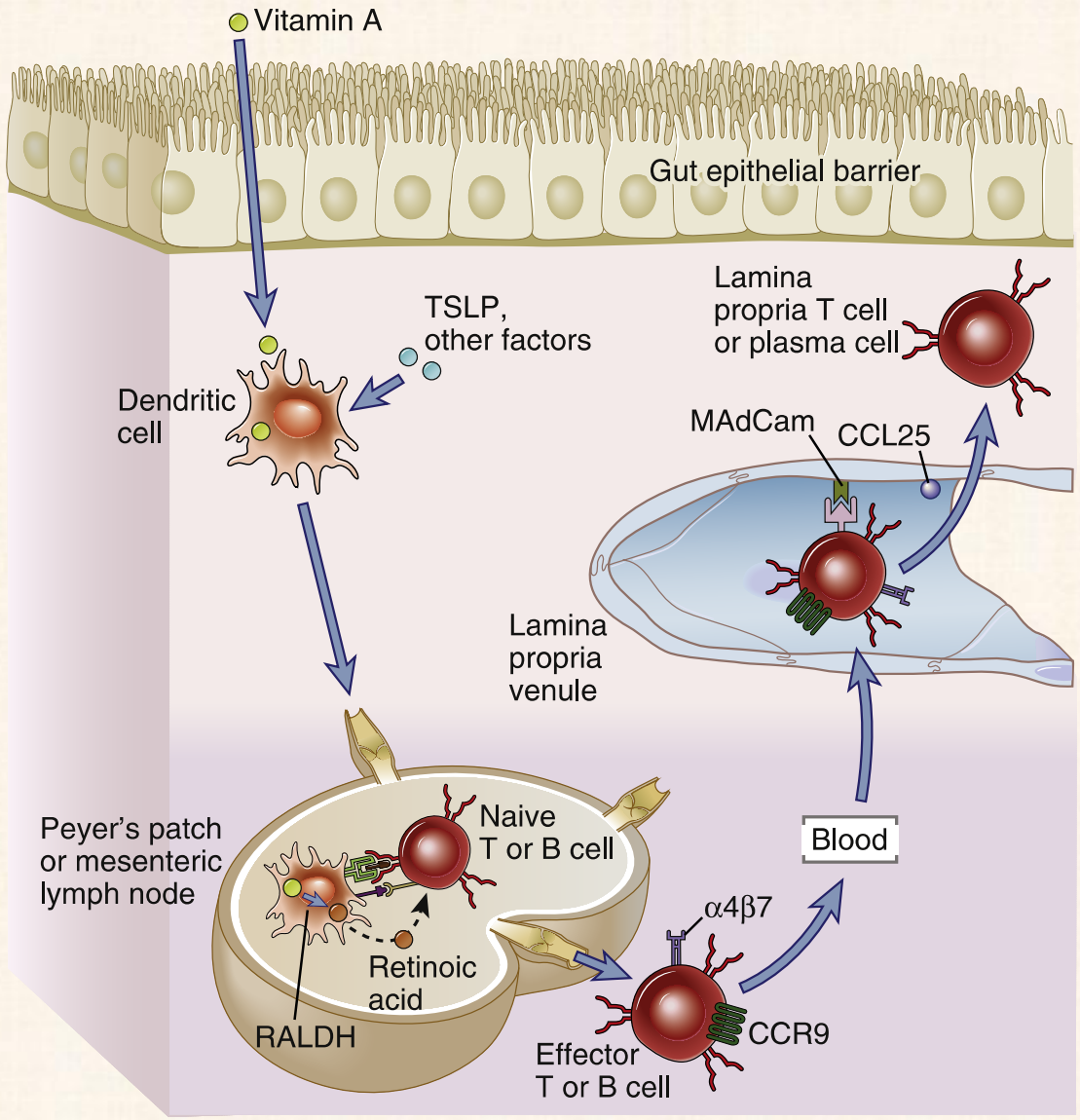



*Fig 14-5*

# 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:

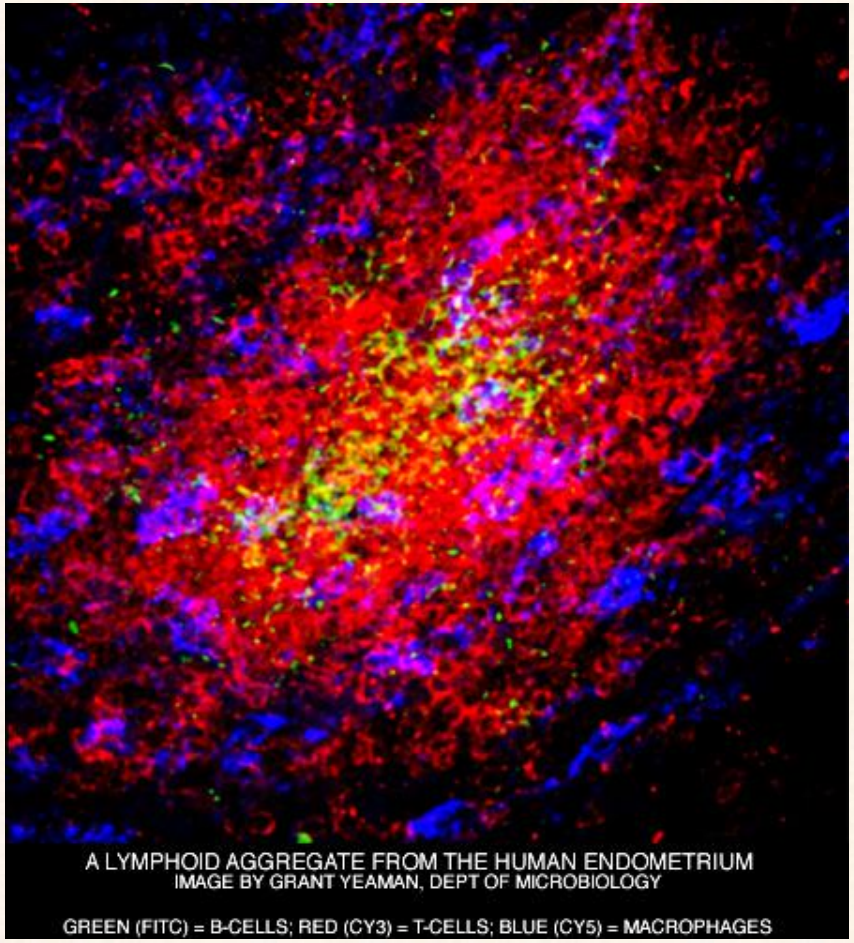
- epithelial barrier, mucus and antimicrobial factors
- lymphoid tissues beneath the epithelium
- antigen sampling
- secretory IgA as prevention

Airways

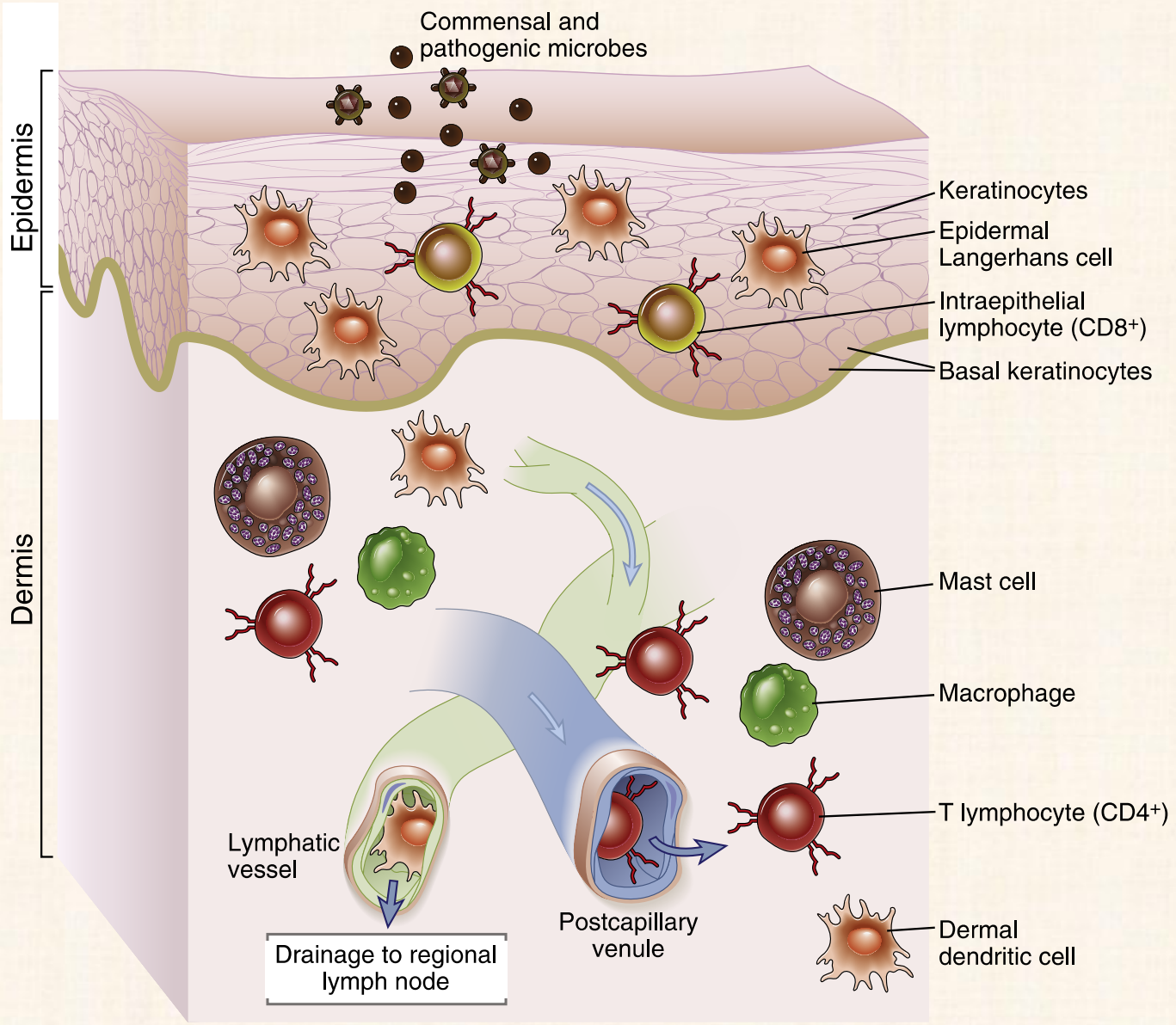
- Innate: surfactant protein; alveolar macrophages
- Adaptive: IgA, IgE (allergic reactions)

Genitourinary tract

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



# 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

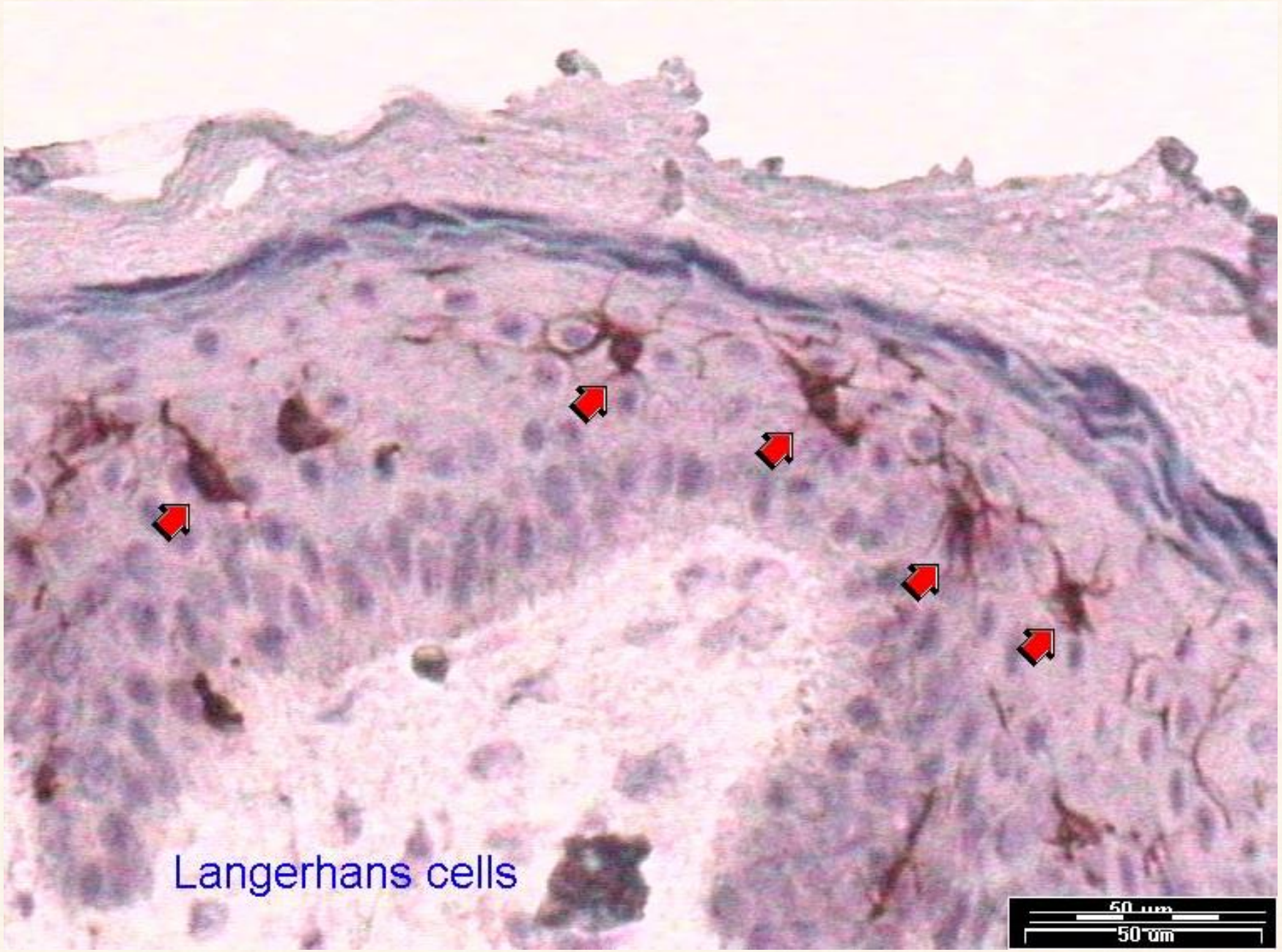
- Physical barrier
- Cytokines: TNF, IL-1, IL-6, IL-18, IL-25, IL-33 (inflammation); IL-10 (regulation)
- Chemokines: CCL27
- Growth factors: PDGF, FGF, GM-CSF
- Anti-microbial peptides: defensins, cathelicidins
- Activation: through PRRs (TLRs, NLRs)

## Dendritic cells, macrophages

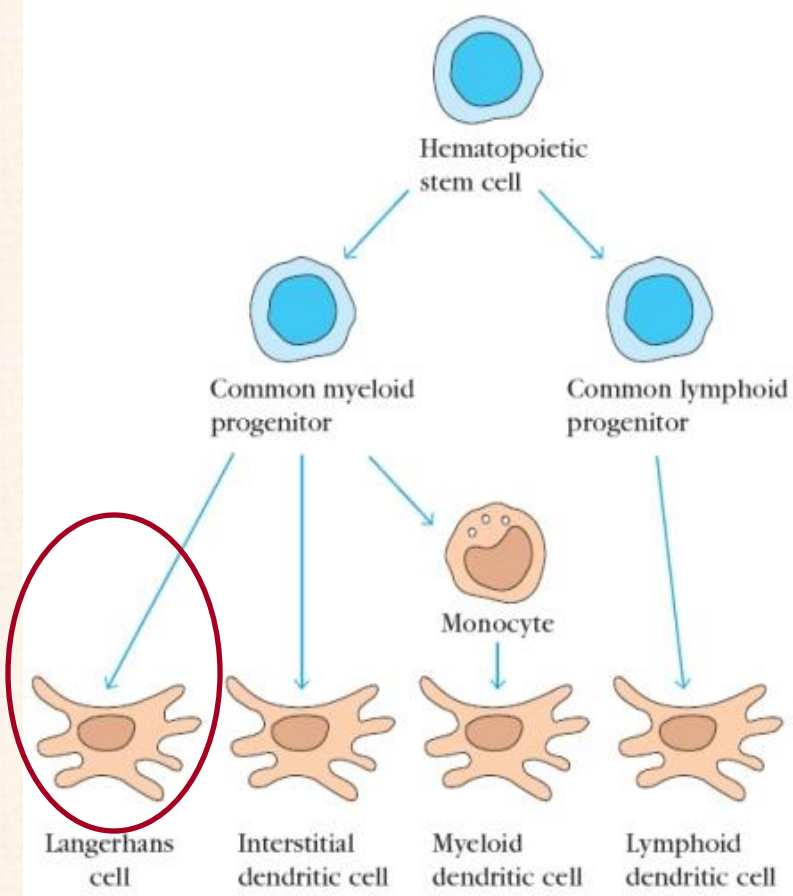
- Mainly Langerhans cells
- Migrate to regional lymph nodes following phagocytosis of antigens
- Present antigens to T cells, imprint skin-homing properties

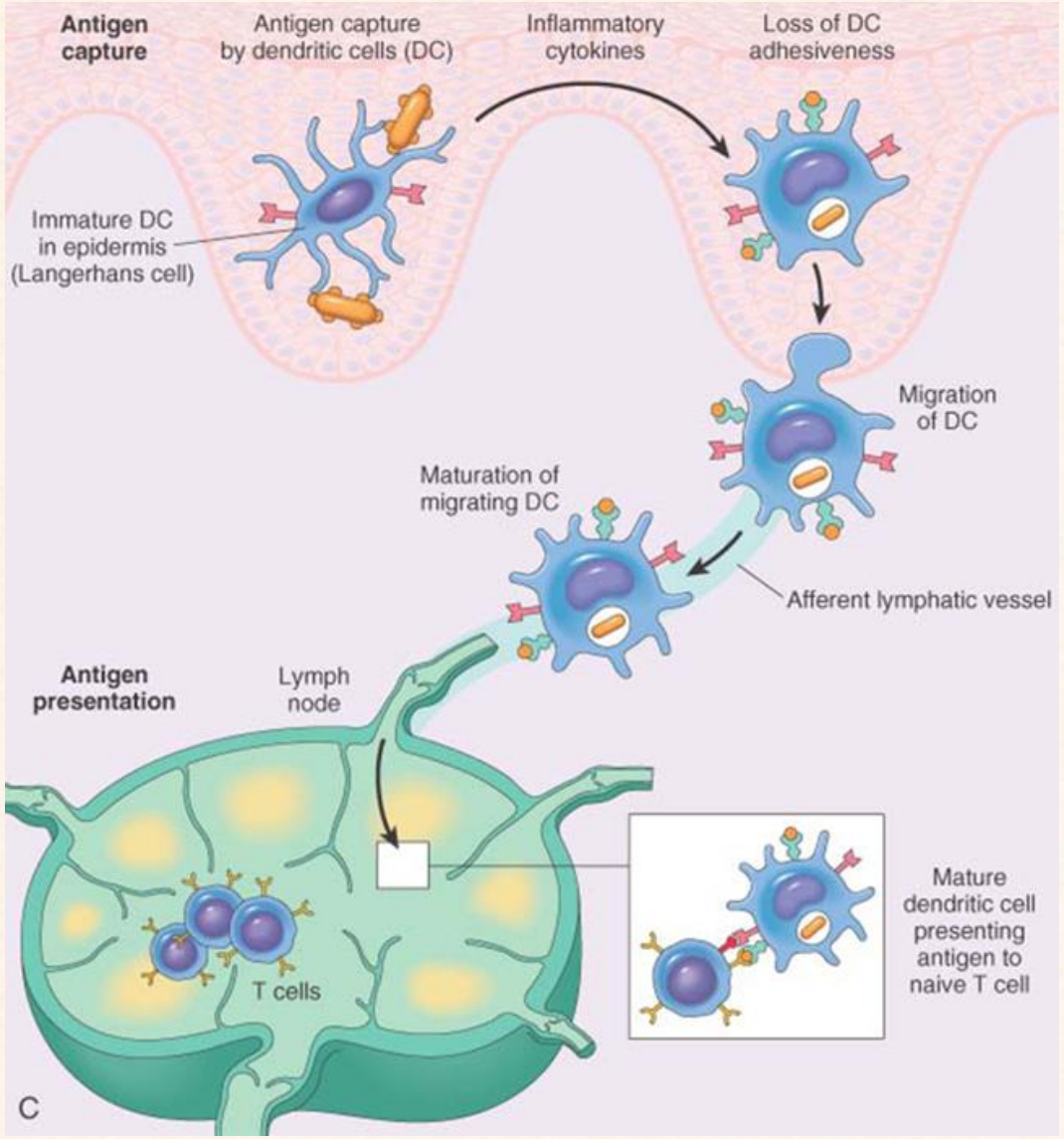
## T cells

- 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

# Dendritic cells



# Homing to the skin

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

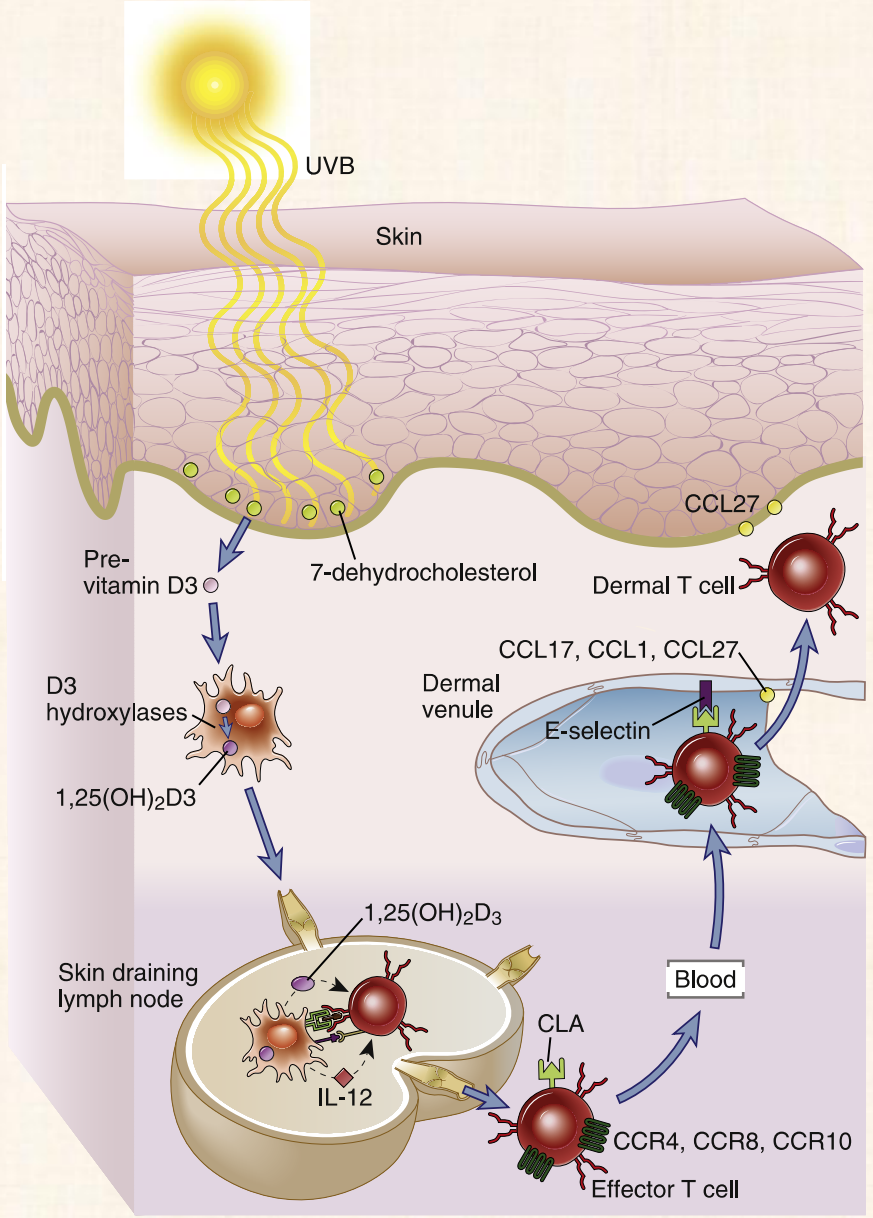



*Fig 14-9*

# Dichotomy of the immune systems