Basic Immunology

18th lecture:
Regional immunity
MALT and SALT

Zoltán Kellermayer

Regional immunity

Systemic immunity

- Lymph nodes, spleen

Local immunity

- MALT = mucosa associated lymphoid tissues
  - Gastrointestinal tract
  - Respiratory tract
  - Urogenital tract
- Cutaneous immune system

Mucosa associated lymphoid tissues

Intestine

Large surface (>200m^2)

Huge amount of harmless (and important!) foreign material: food and microbes

Small amount of pathogens

Delicate balance between tolerance and attack

Intestinal lymphoid tissues

"Programmed lymphoid tissues:" PP (+mLN)

Peyer's patch/
colonic patch

Mesenteric
lymph node
regional lymph node!

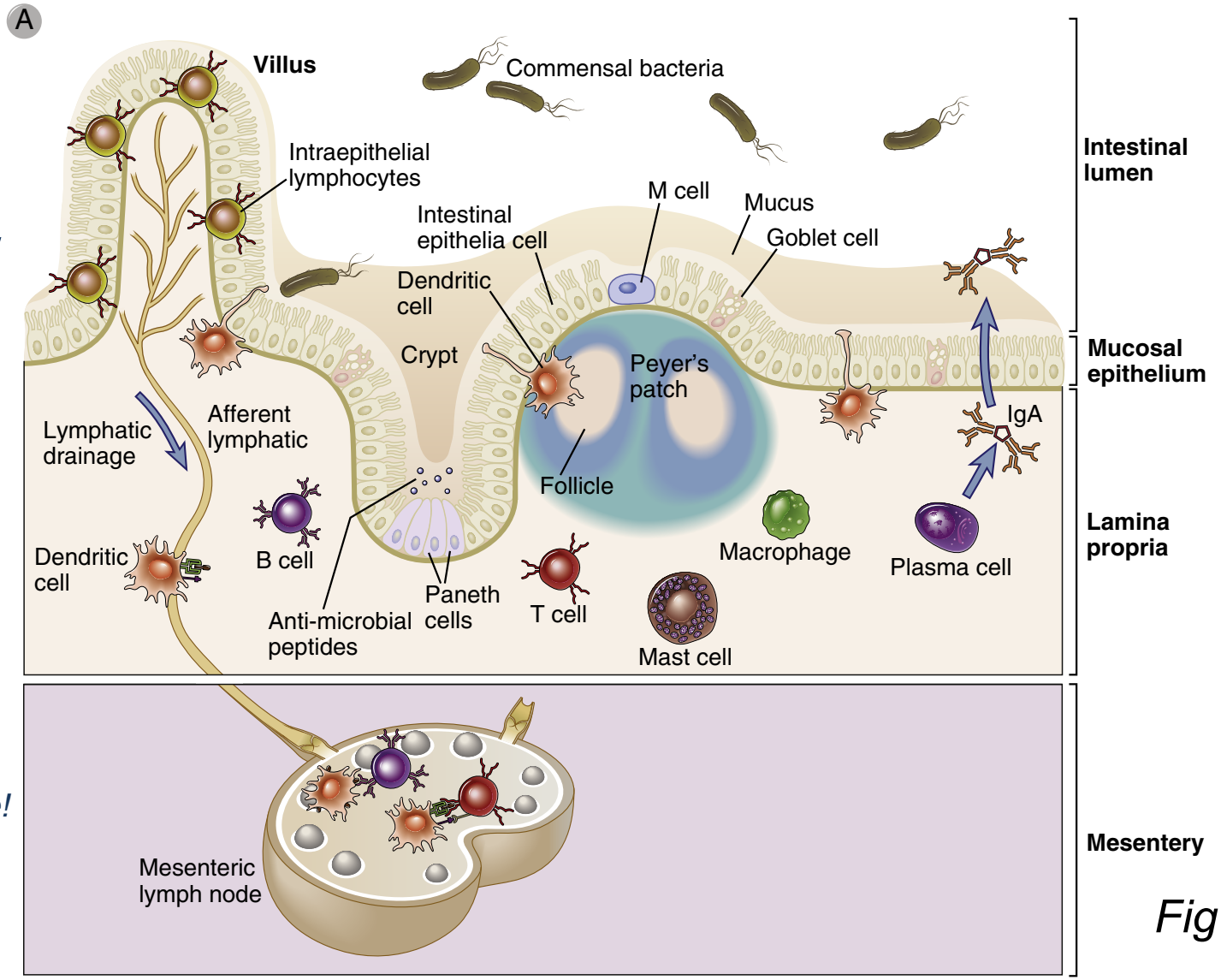


Fig 14-1

Intestinal lymphoid tissues

SILT: Solitary Intestinal lymphoid tissues

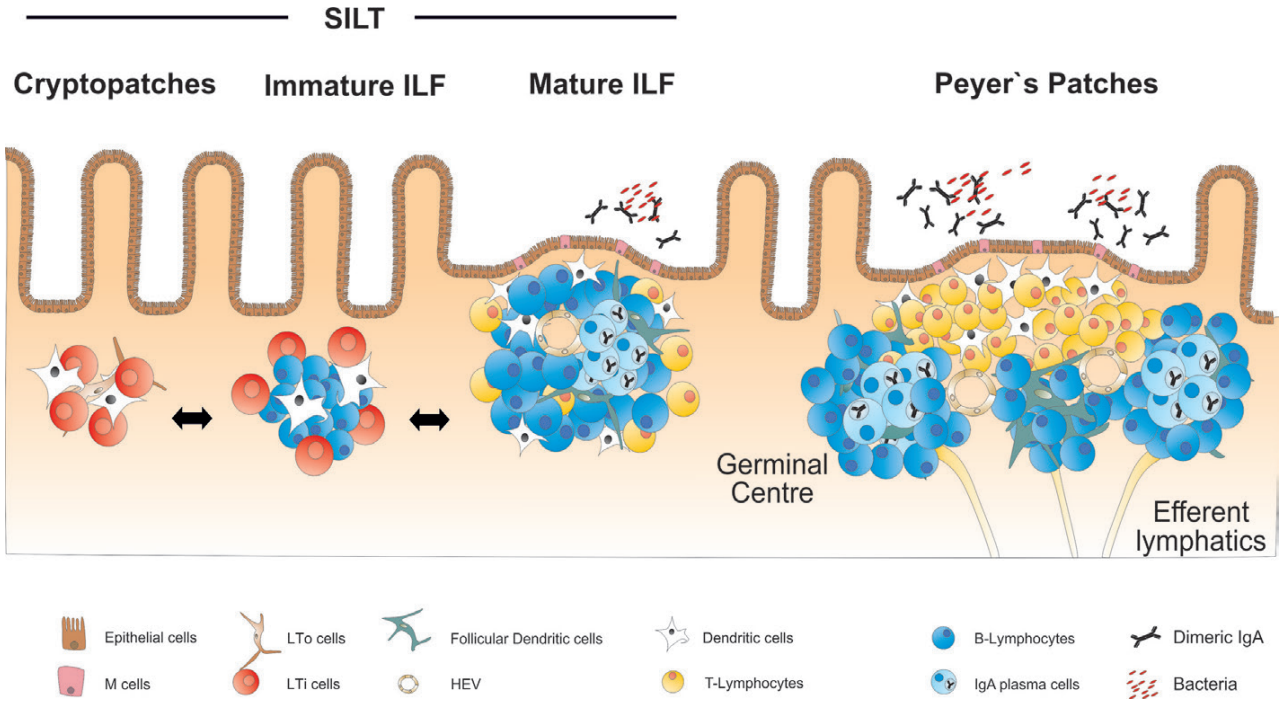


FIGURE 1 | Overview on the anatomy and structure of CP, ILF, and PP in the small intestine. SILT consists of a dynamic continuum of structures ranging from small cryptopatches (CP) to large mature isolated lymphoid follicles (ILF). CP start to develop into immature ILF by recruiting B cells. Mature ILF contain one big B cell follicle and develop germinal centers, vascular structures, and a follicle-associated epithelium. PP represent the most structured lymphoid organs in the intestine, containing several B cell follicles and distinct T and B cell areas.

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

Cells of the intestinal immune system

Epithelial cells

- Goblet cells: mucus secretion
  - mucus: inner (dense) and outer (less-dense) layer
  - antigen sampling…
- Paneth cells: anti-microbial peptide secretion
- M-cells: antigen transport

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

Epithelial cells express PRRs (TLRs, NLRs)

PRR ligation can lead either to inflammation or to tolerance

Cells of the intestinal immune system

M cell: ***transport*** of antigen from lumen to underlying cells
*(**not** antigen presentation!!)*

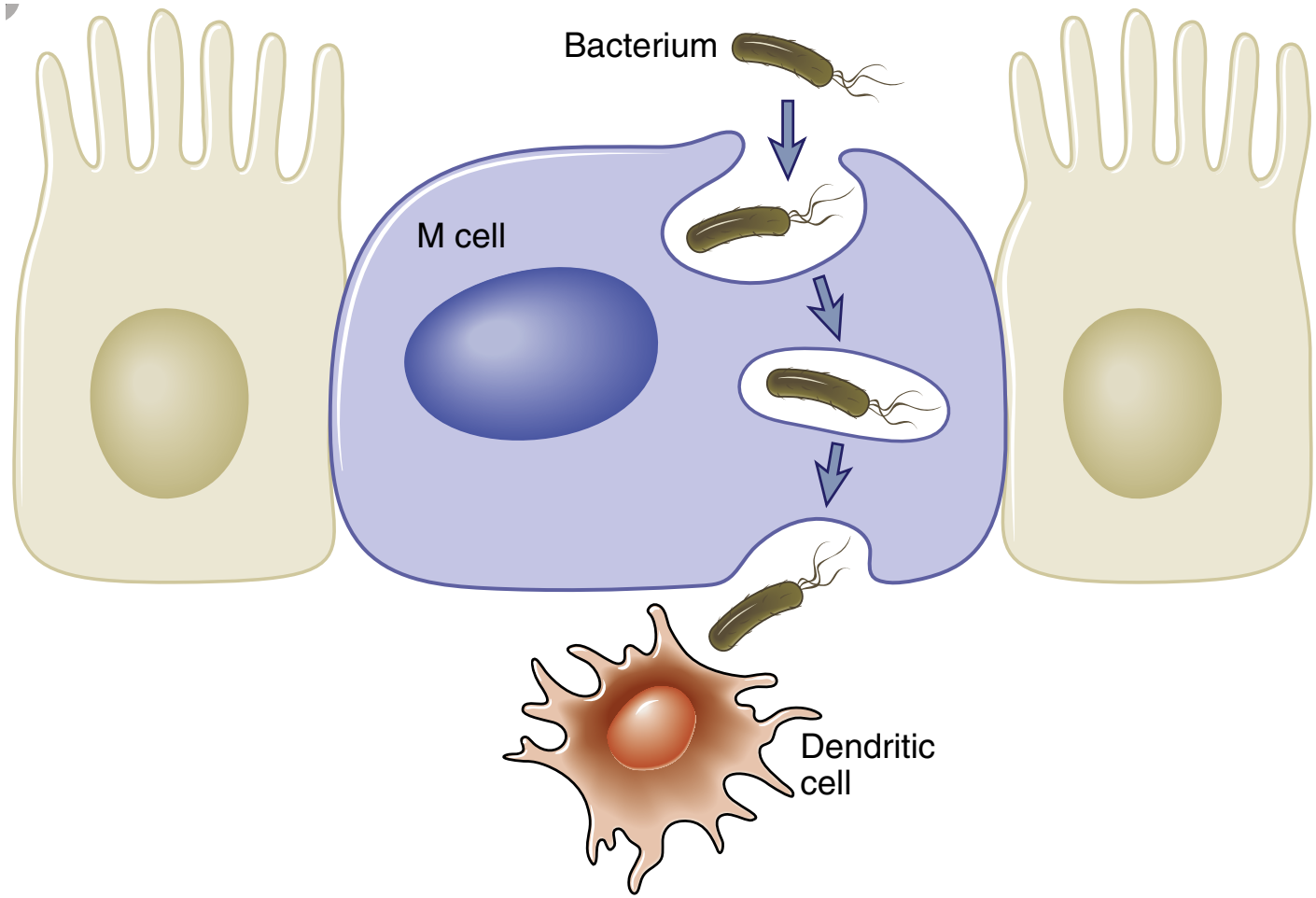


Fig 14-3

Cells of the intestinal immune system

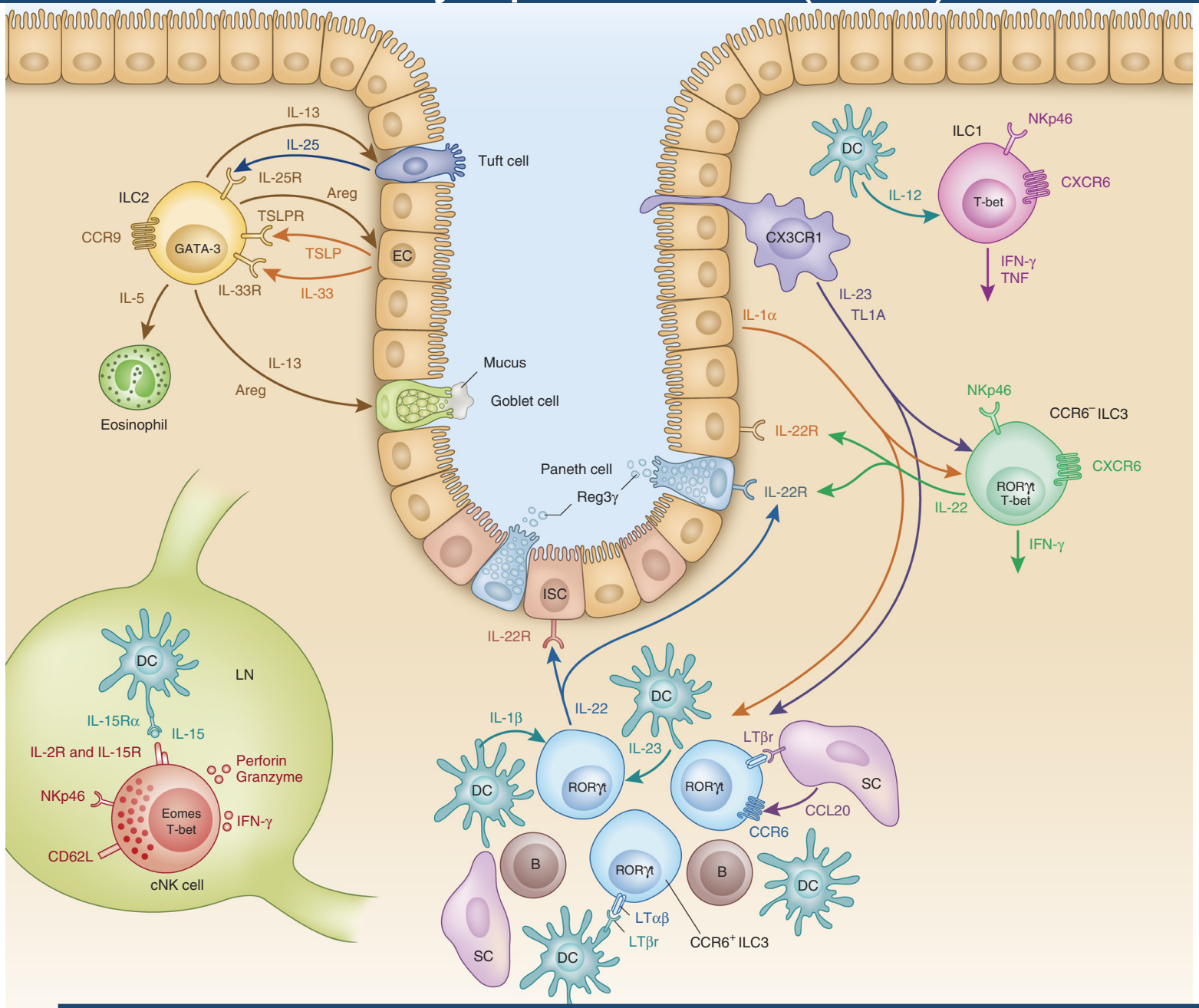
Dendritic cells, Macrophages

- 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

- *(ILC1: NKs + non-cytotoxic ILC1s)*
- *(ILC2: immune response against helminths, allergy)*
- ILC3: LTi, mucosal healing, inflammation

Innate lymphoid cells (ILCs)



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

Homing to mucosal lymphoid tissues

Endothelium	Leukocyte
MAdCAM-1	α4β7
CCL25	CCR9

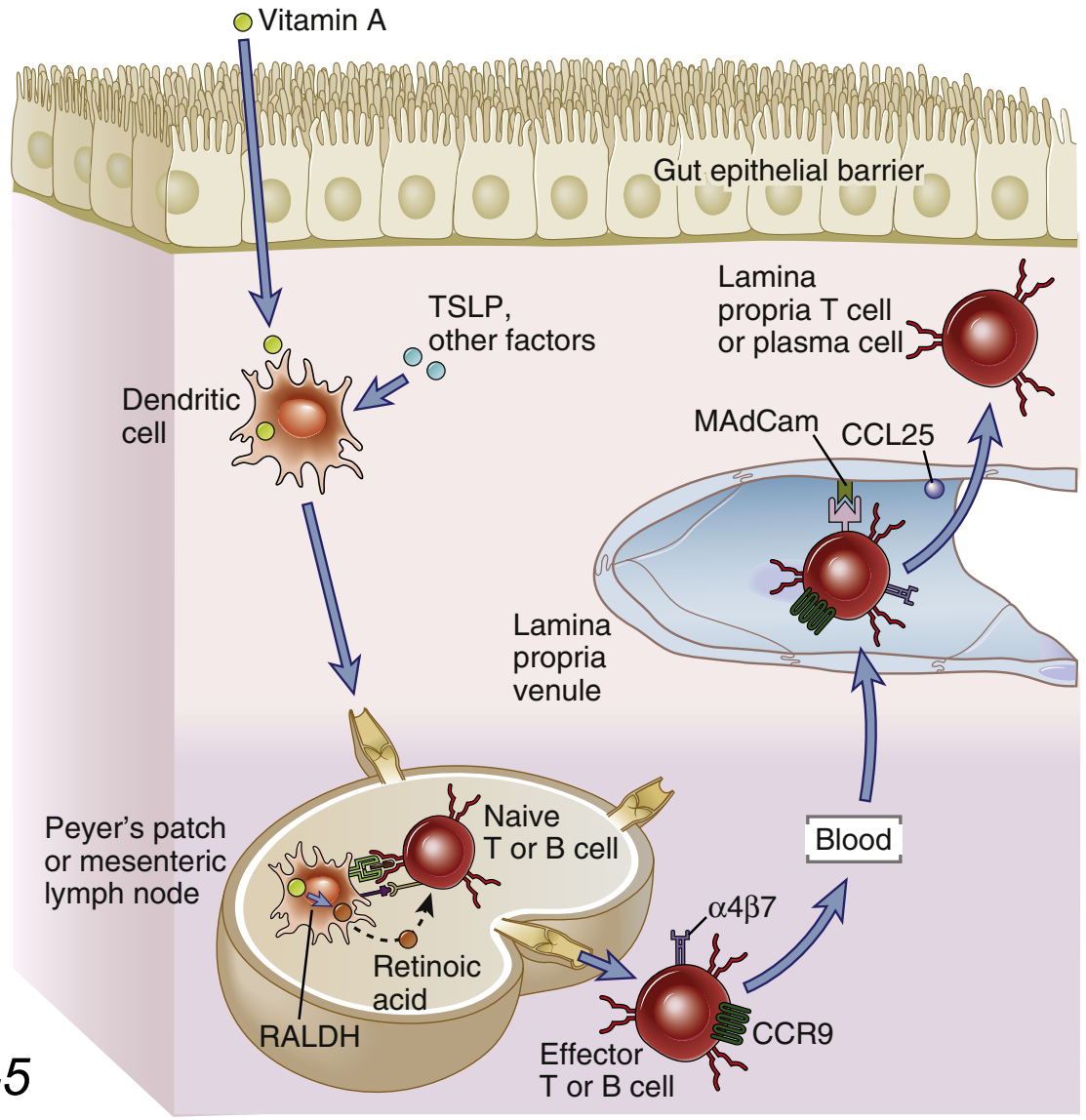


Fig 14-5

Intestinal humoral response

IgA$^+$ B cells!!!!

(some IgM, IgG…)

Isotype switch: both T-dependent, but also T-independent (!)

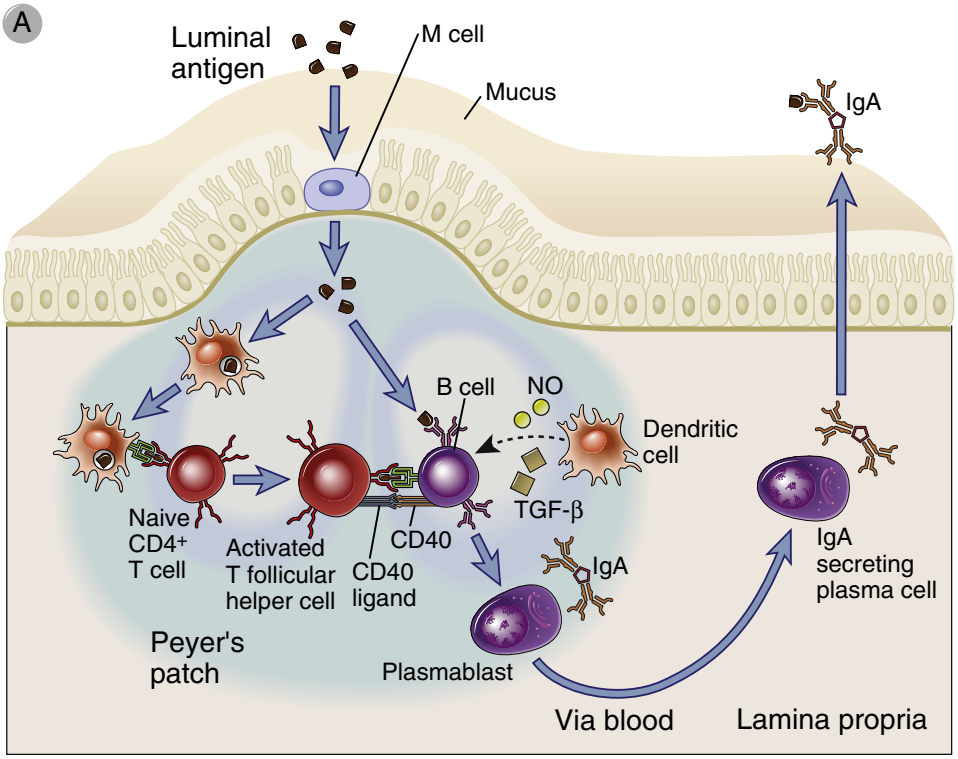
Large amounts of TGFβ

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

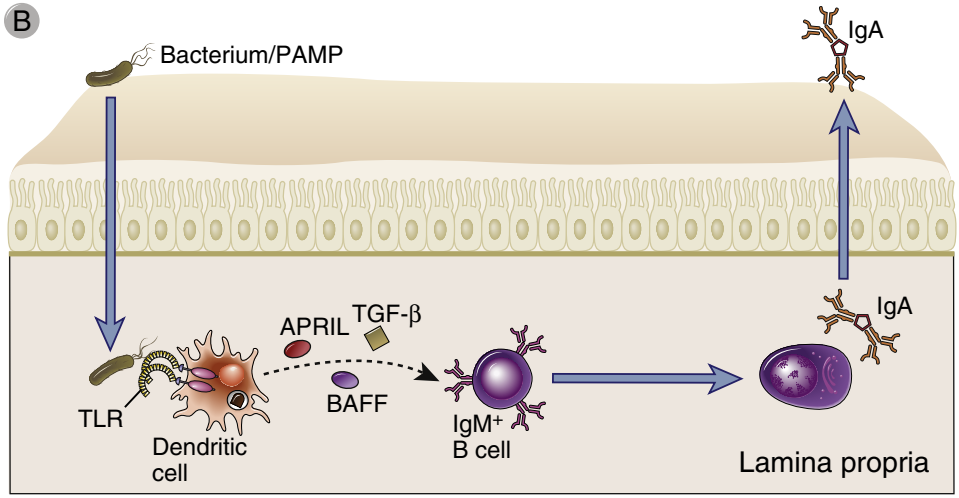
Within lymphoid follicles (PP, ILF) and dispersed throughout the lamina propria

IgA: dimer, transported across the epithelium via *poly-Ig receptor* (=transcytosis)

Intestinal humoral response



T-dependent IgA production



T-independent IgA production

Fig 14-7

Intestinal humoral response

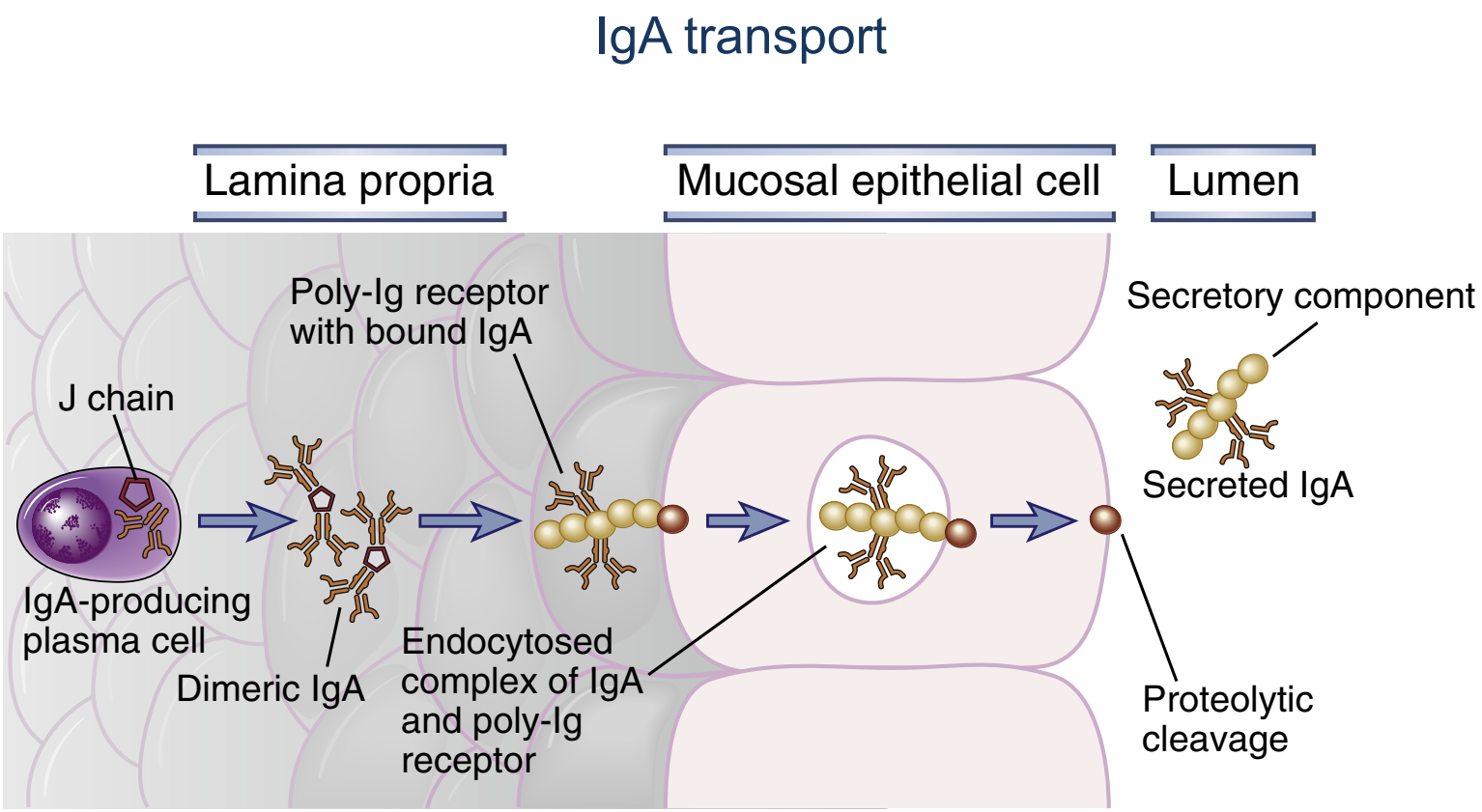


Fig 14-8

Intestinal T-cell response

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

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)

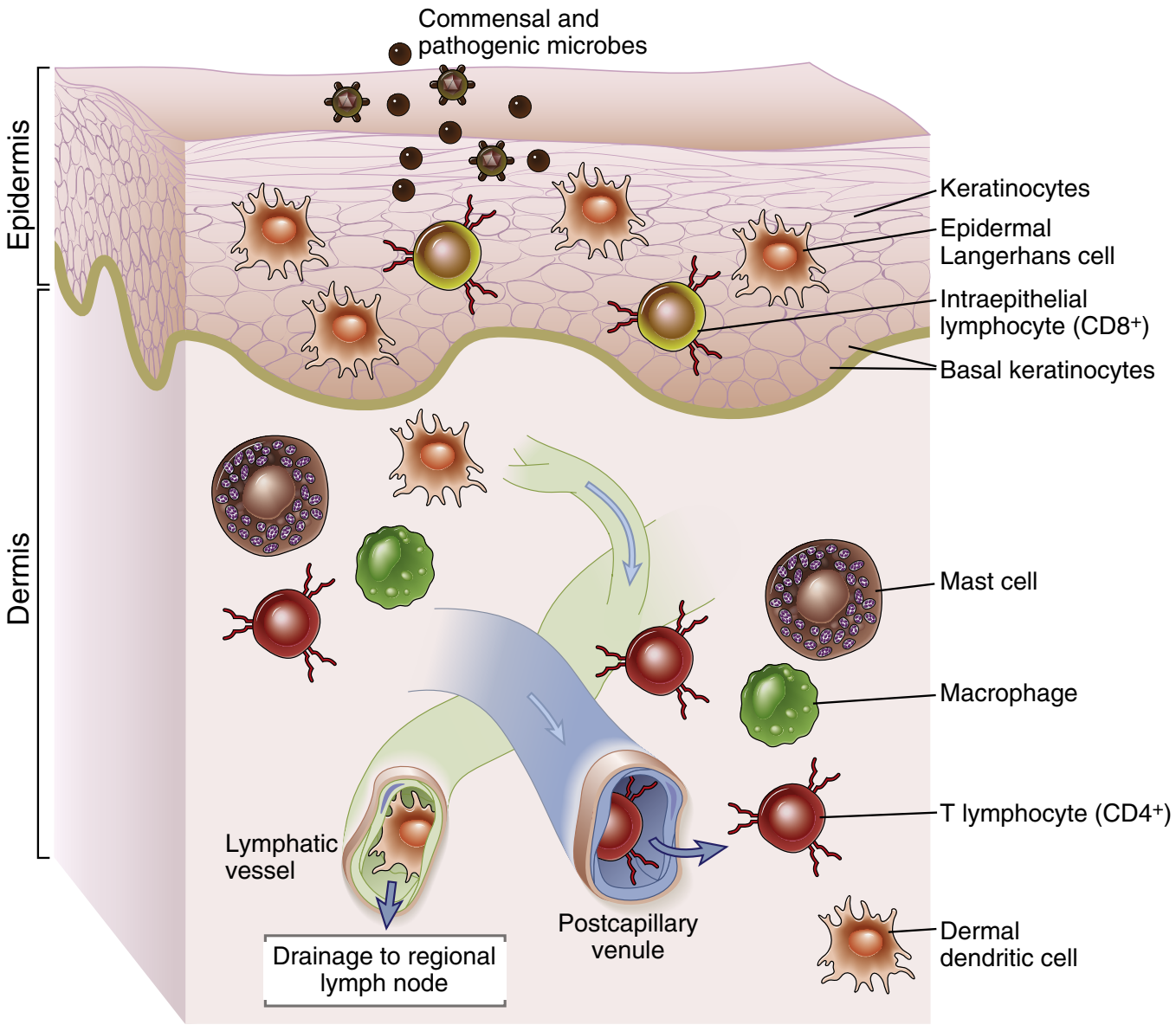
Example:

Clostridium difficile infection: usually caused by alteration of normal flora by antibiotic use

- Treatment: fecal transplantation (bacterial flora from healthy donors)

Cutaneous immune system

Cutaneous immune system



$2m^2$
Physical barrier
Sunburns
Microbes
Traumas

Fig 14-9

Cells of the cutaneous immune system

Keratinocytes

- Physical barrier
- Cytokines: TNFα, IL-1, IL-6 (inflammation); IL-10 (regulation)
- Chemokines: CCL27
- Anti-microbial peptides: defensins, cathelicidins
- Activation: through PRRs (TLRs, NLRs)

Dendritic cells

- 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})

Homing to the skin

Endothelium	Leukocyte
E-selectin	CLA
CCL27	CCR10

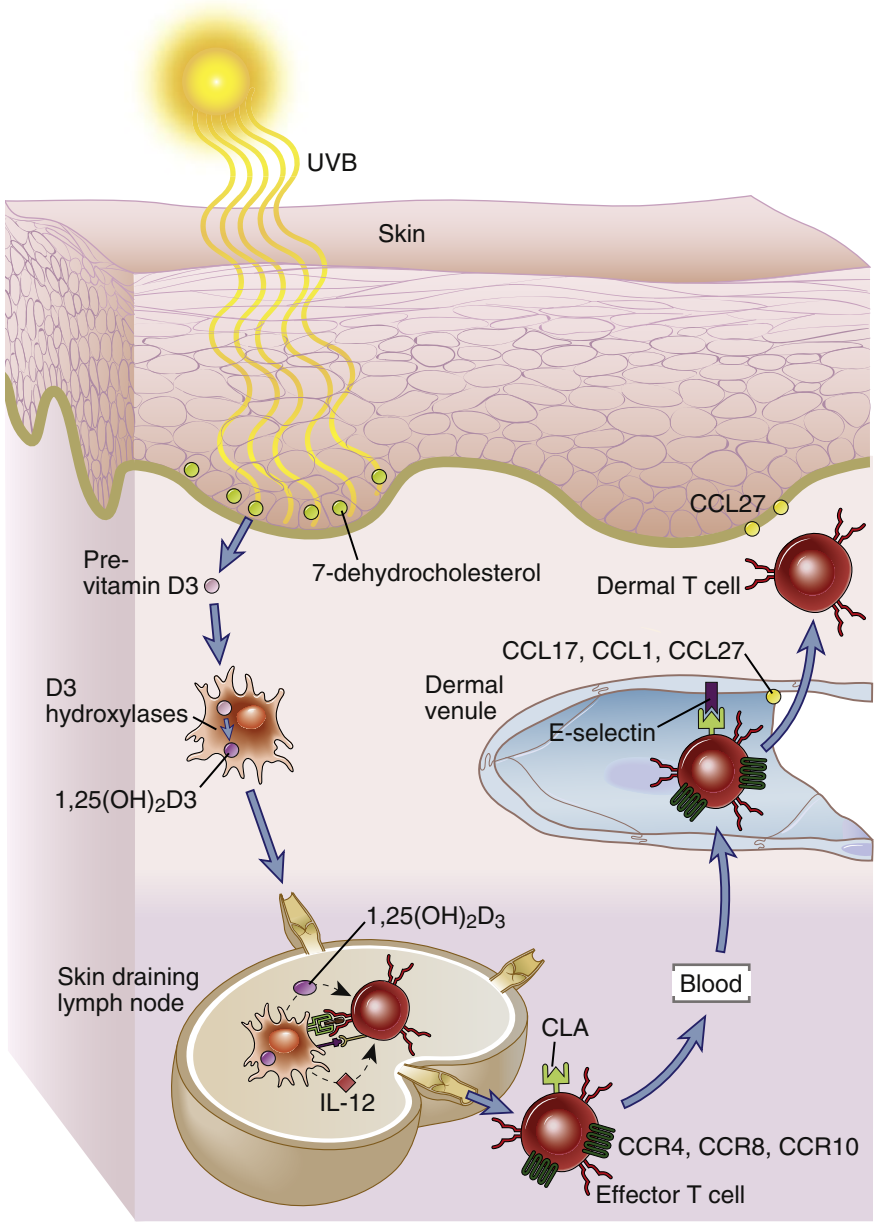


Fig 14-10