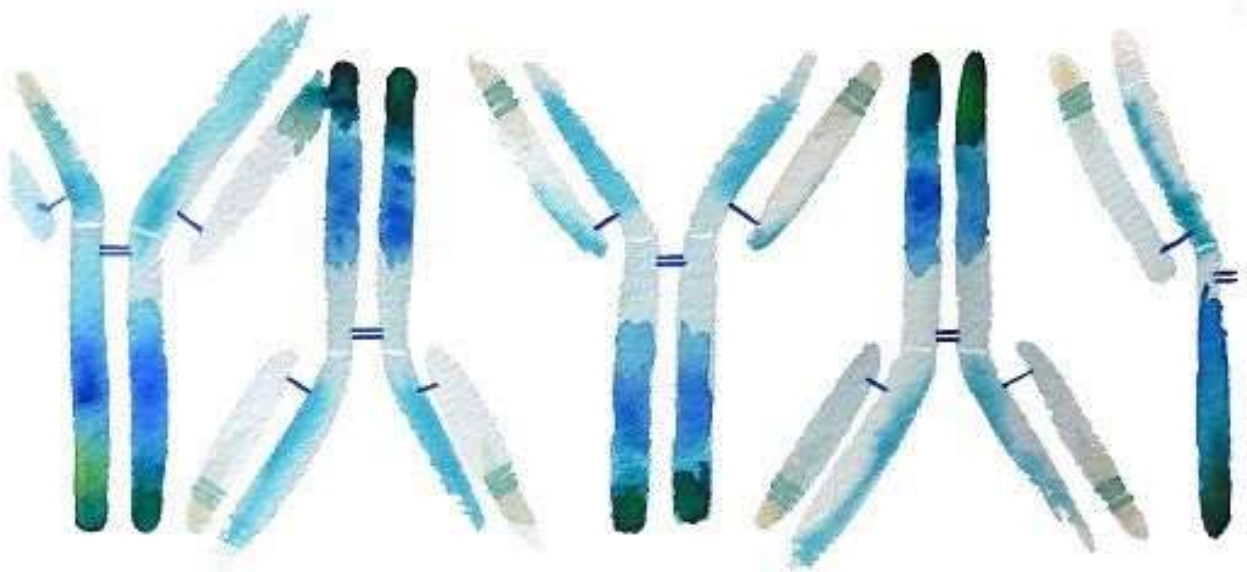
Medical Immunology



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M.D. Ph.D.

Lecture 8

Innate immunity

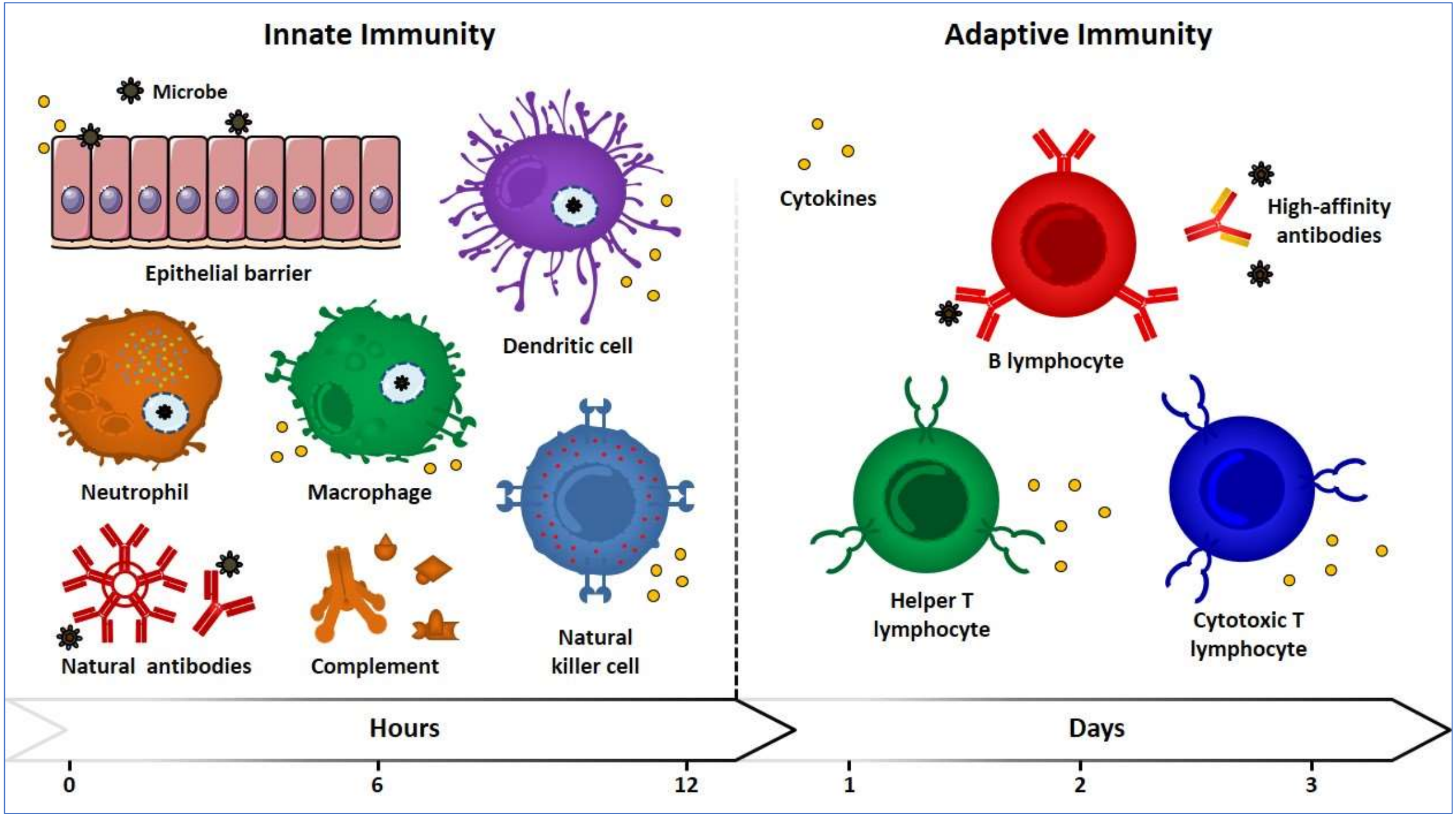
- The innate immune system is the phylogenically oldest component of the human immune system. Although it is ancient, the innate immune system is highly complex and consists of barriers to infection (epithelia of skin, gastrointestinal, respiratory, genitourinary tracts), antimicrobial peptides and proteins, humoral components (i.e. complement and opsonins) and cellular components (i.e. neutrophils, monocytes/macrophages, dendritic cells, and innate lymphoid cells)

- In the coming 2-3 lectures we will discuss components of the immune system and how the response to a pathogen takes place.

- Main topics:

Epithelial barriers of innate immunity
Migration of leukocytes into tissue

Innate immunity



Innate immunity

Table 1

Innate immune system components

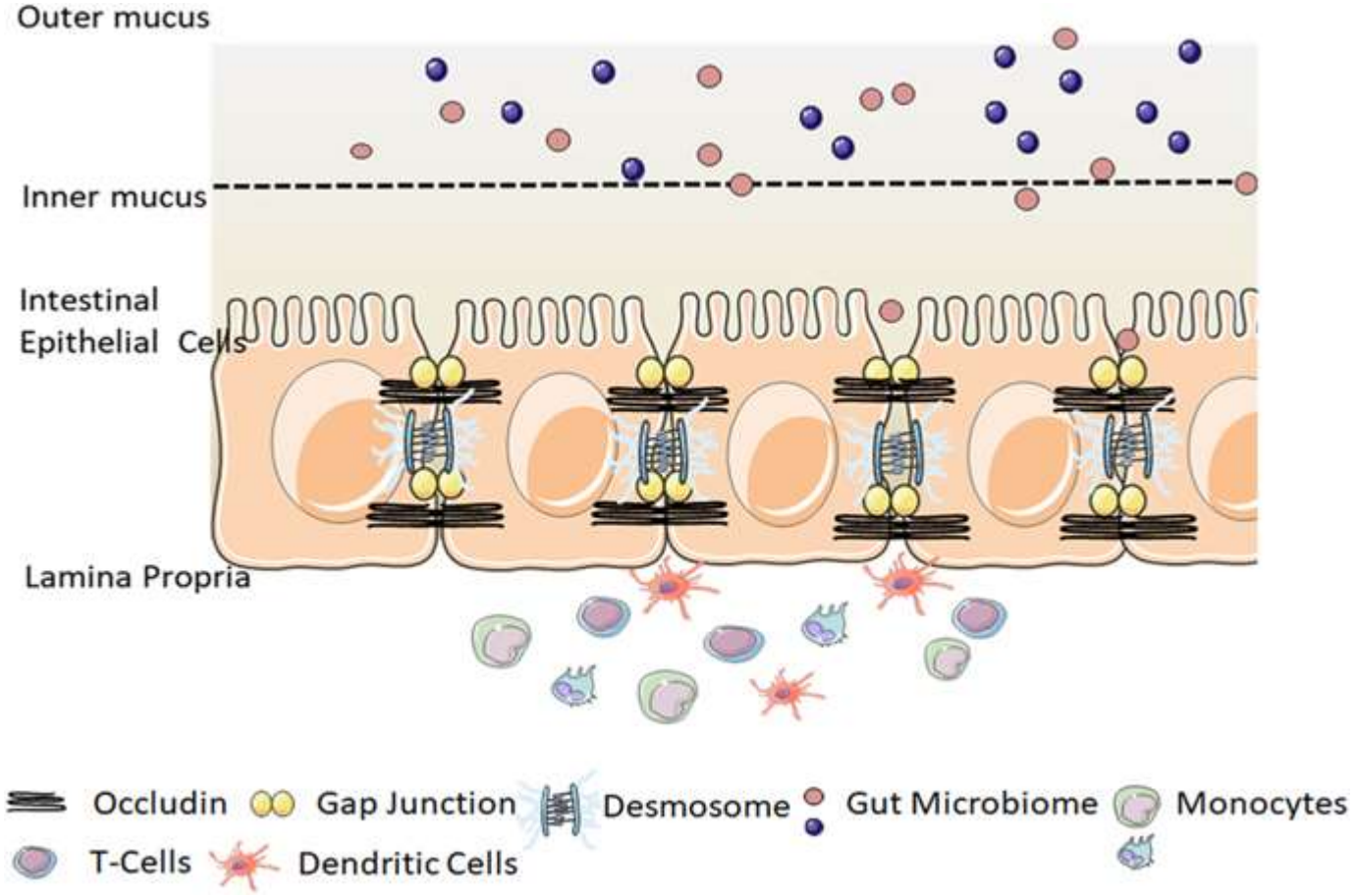
Natural barriers	Cells	Pattern-recognition receptors	Cytokines	Natural antimicrobial products
Skin, mucosal epithelia	Neutrophils, macrophages/dendritic cells, natural killer cells, natural killer T cells, γδ T cells, B1 lymphocytes	Mannose-banding lectins, Toll-like receptors, ...	IL-1, IL-6, IL-8, IL-12, IL-15, IL-18, G-CSF, M-CSF, GM-CSF, TNF-α, IFN-γ, ...	Defensins, lactoferrin, lysozyme, natural antibodies, complement, reactive oxygen species

IFN interferon; IL interleukin; *G-CSF* granulocyte colony-stimulating factor; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *M-CSF* macrophage colony-stimulating factor; *TNF* tumor necrosis factor

Innate immunity / epithelial barriers/ tight junctions

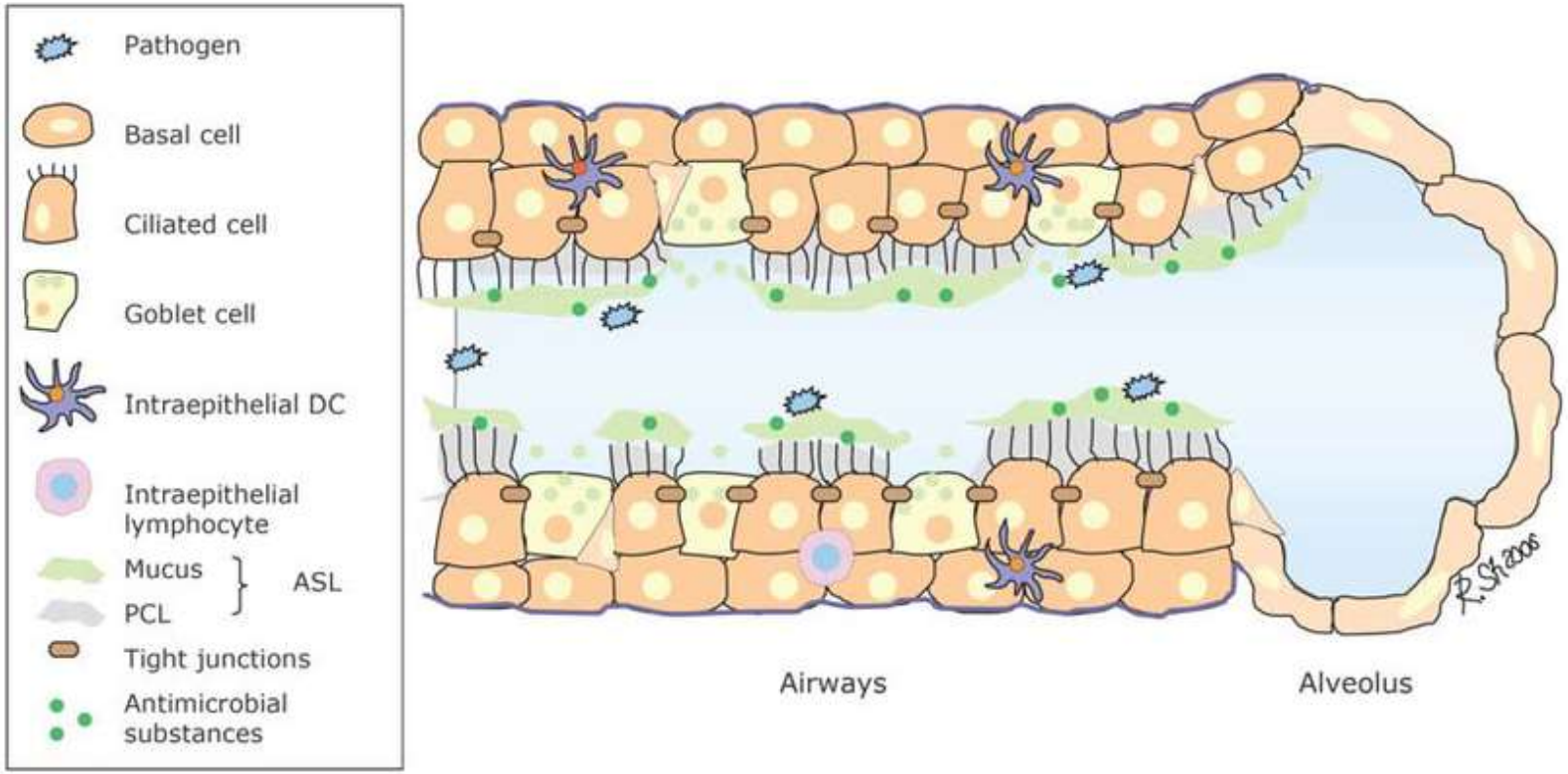
- Intact epithelial surfaces (in the skin and the mucosal surfaces of the gastrointestinal, respiratory, and genitourinary) form **physical barriers** between microbes in the external environment and host tissue.

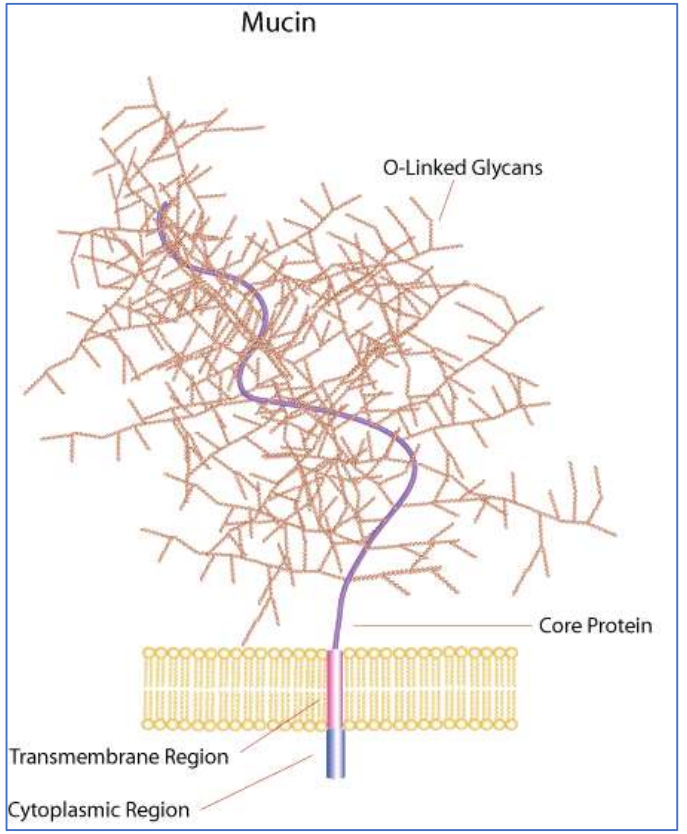
- **Tight junctions** are crucial for the maintenance of barrier integrity



Innate immunity / epithelial barriers/ mucus

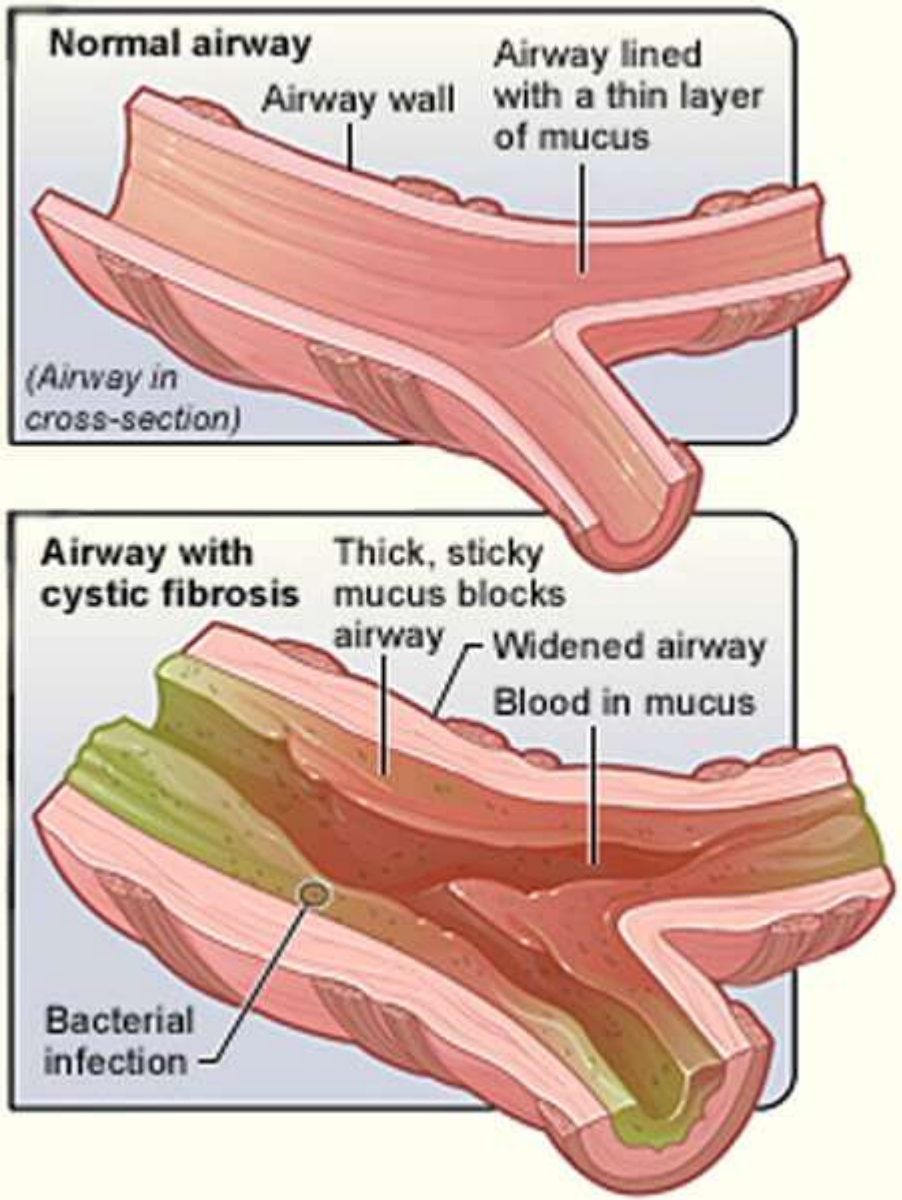
Mucus, a viscous secretion containing inorganic salts, antimicrobial enzymes (such as **lysozymes***), **immunoglobulins**, and glycoproteins such as lactoferrin and mucins. Mucus **physically impairs microbial invasion** and facilitates microbe removal by **ciliary action** in the bronchial tree and **peristalsis** in the gut. *Lysozyme is a **naturally occurring enzyme** found in bodily secretions such as tears, saliva, and milk. It functions as an antimicrobial agent by cleaving the peptidoglycan component of bacterial cell walls





Innate immunity / epithelial barriers/ mucus

In cyctic fibrosis (CF) Defective CFTR protein impacts the function of several organs and **alters the consistency of mucosal secretions**. The latter of these effects probably plays an important role in the **defective resistance of CF patients to many pathogens**.

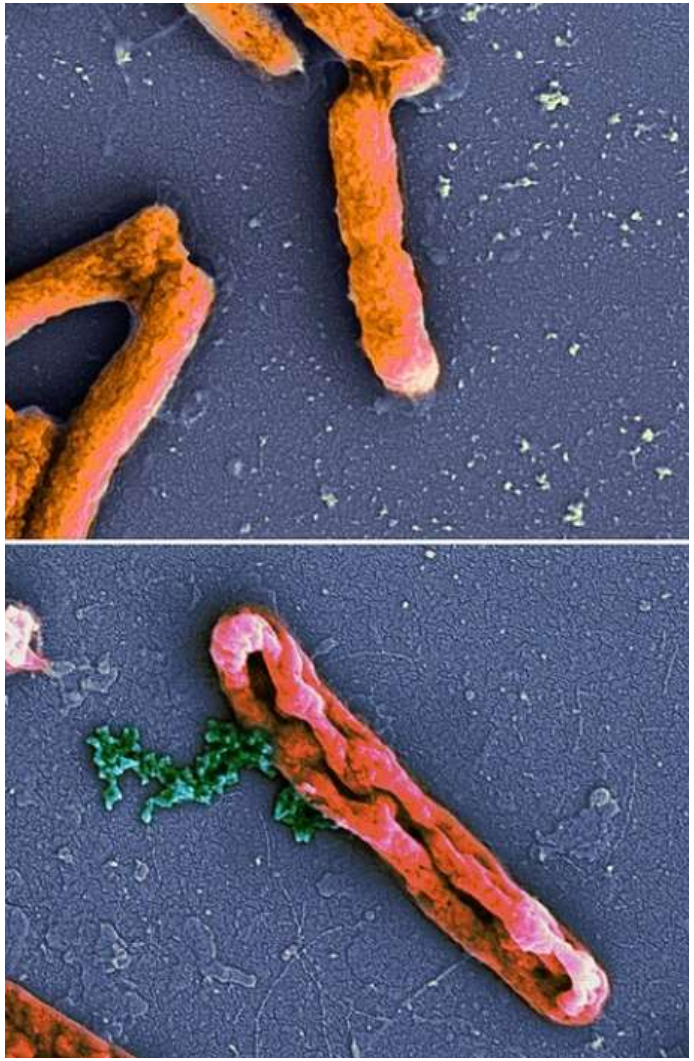


- **Antimicrobial peptides (AMPs),** also called host defense peptides (**HDPs**) are part of the innate immune response found among all classes of life.

- **Defensins** are **small cationic peptides**, produced by epithelial cells of mucosal surfaces and by granule-containing leukocytes, including neutrophils, natural killer cells, and cytotoxic T lymphocytes.

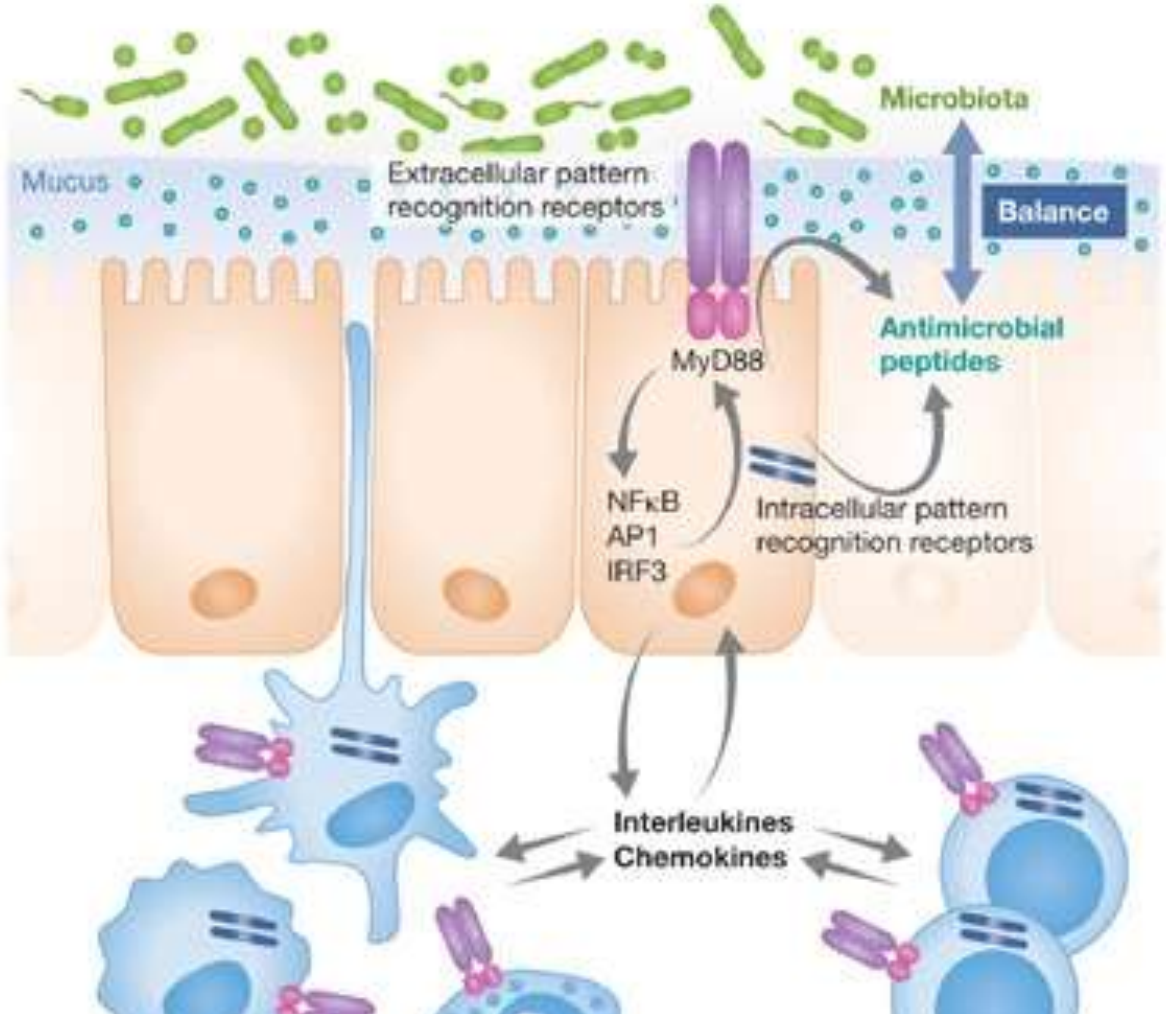
- **Cathelicidins** are produced by neutrophils and various barrier epithelia, after cleavage they have **bactericidal** and **immunomodulatory functions**.

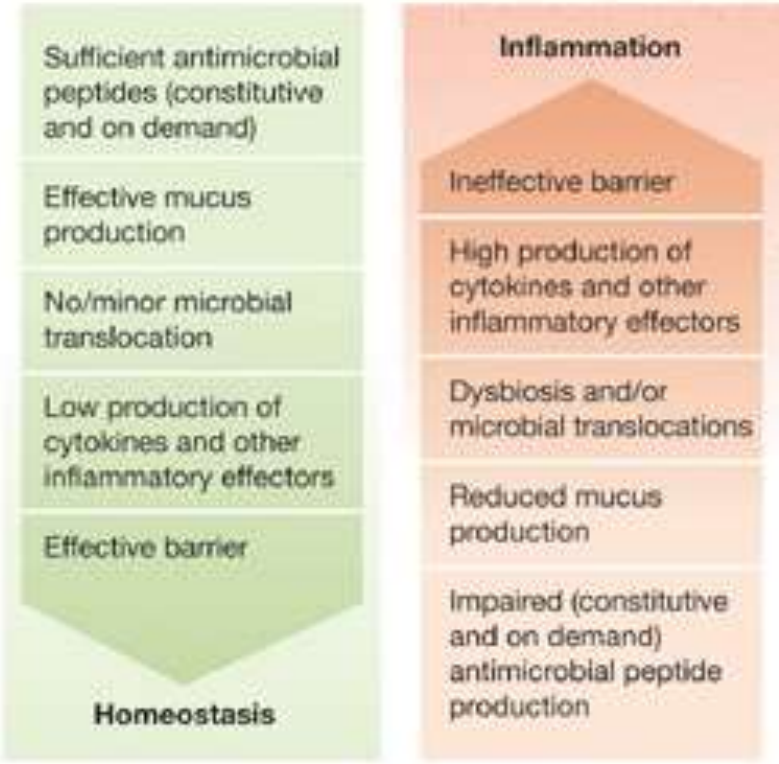
- Antimicrobial peptides possessing a net positive charge are attracted and **incorporated** into negatively charged **bacterial membranes** thus disturbing them.



BELOW: Disrupted cell membranes and leakage of bacterial chromosome (green) in the treated group.

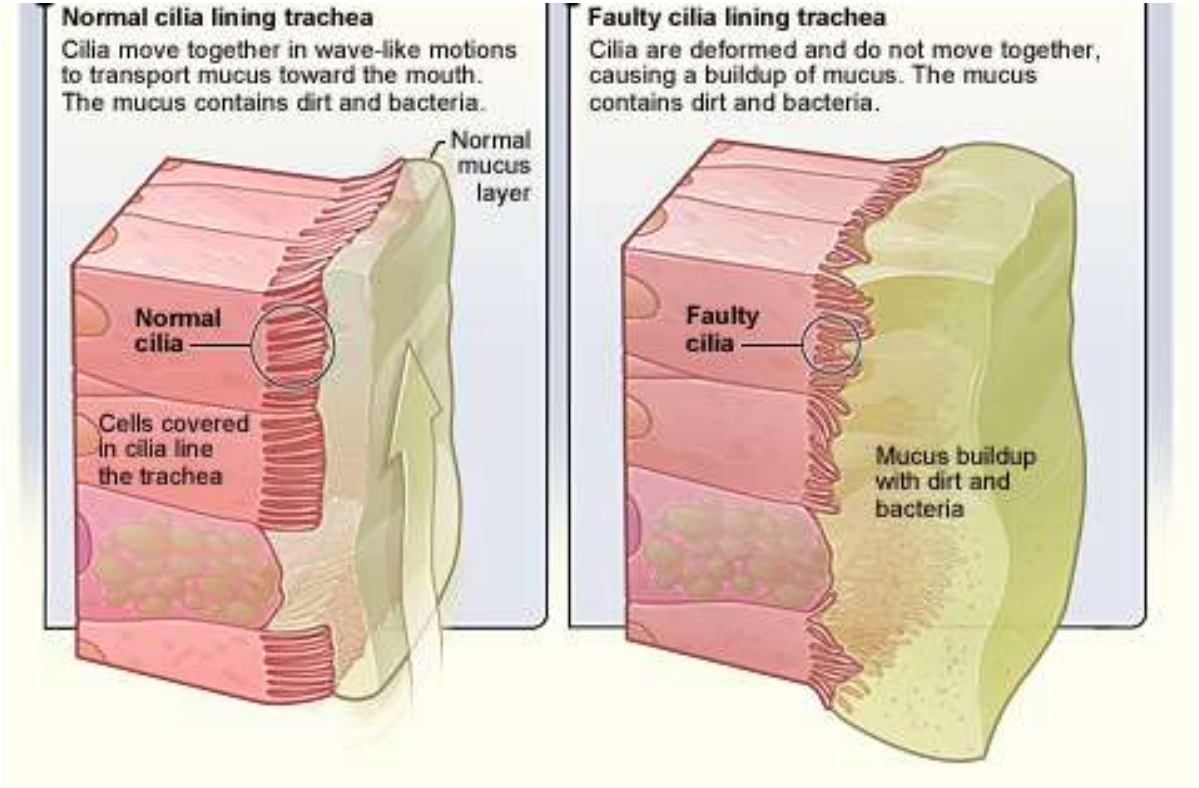
- The gut **microbiota** is key to the efficient development and maintenance of the intestinal barrier.



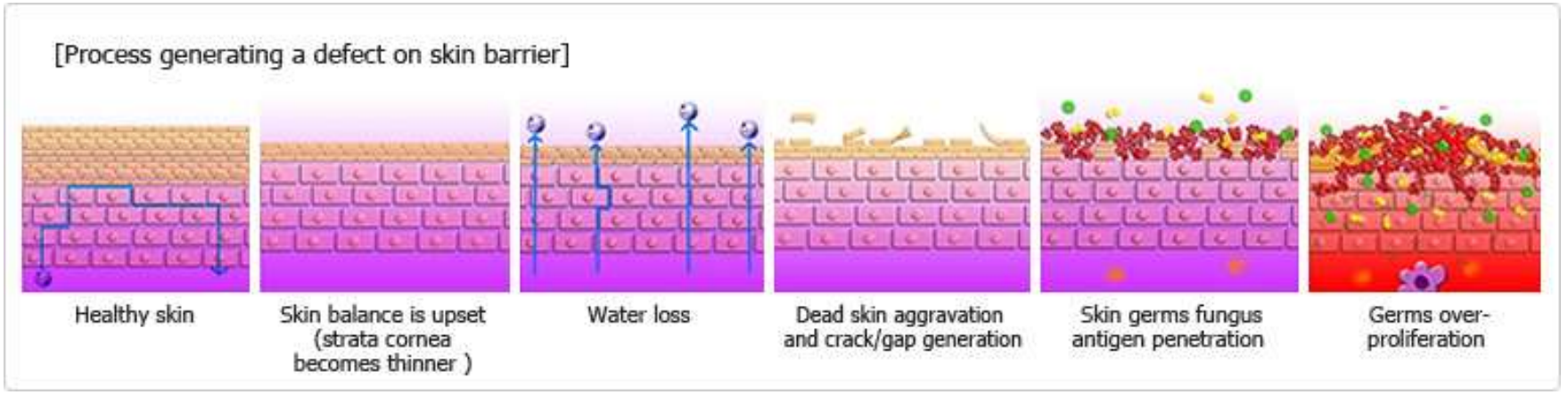


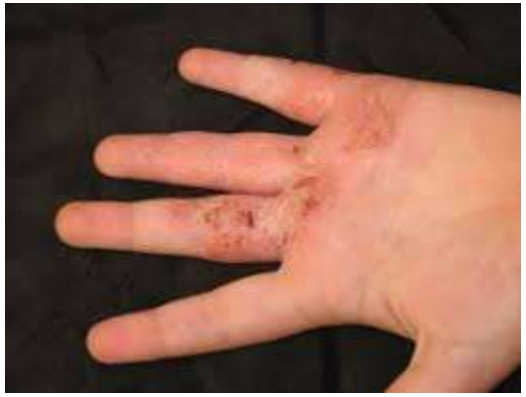
Innate immunity / epithelial barriers

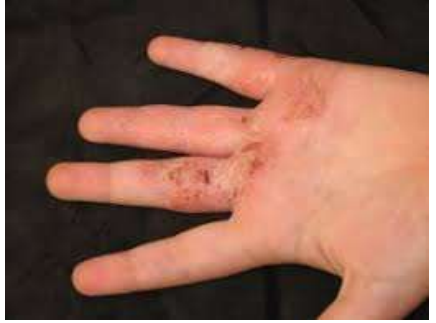
- **primary ciliary dyskinesia**, an inherited disorder that leads to impaired mucociliary clearance,and repeated **chest infections.**



- In **eczema** a defective skin barrier leads to recurrent infections.







- In **eczema** a defective skin barrier leads to recurrent infections.

Abstract

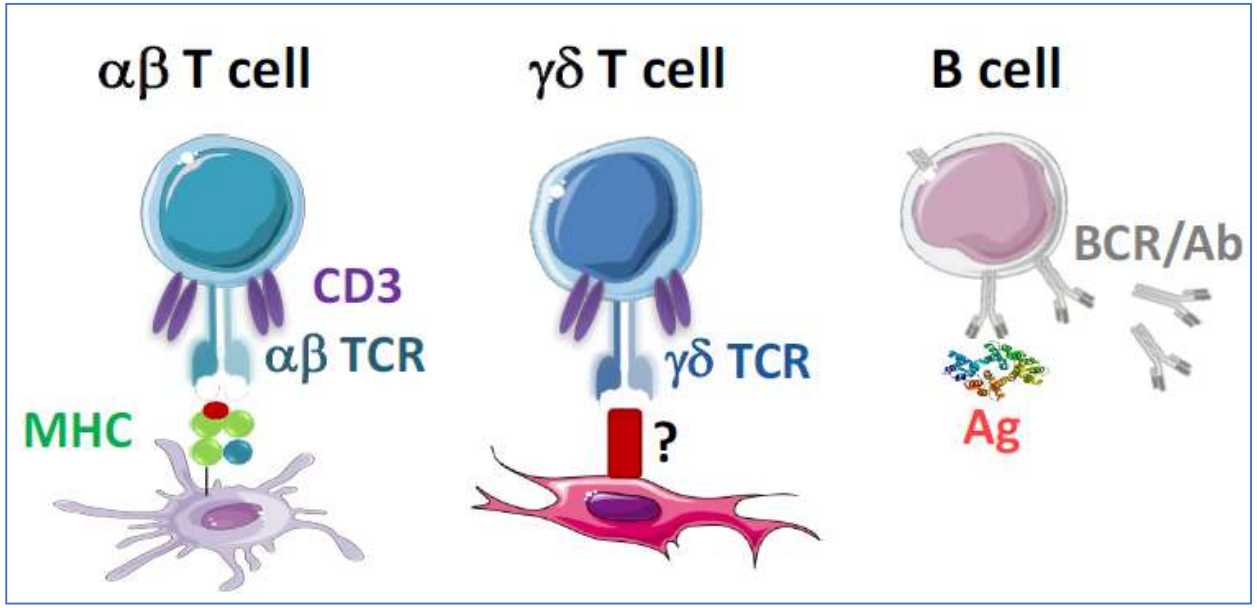
Go to:

Question A 10-year-old boy with atopic dermatitis (AD) came for consultation with an exacerbation. He suffered from pruritus and multiple erythematous skin lesions, identified as inflamed but not infected. Because skin colonization with *Staphylococcus aureus* is very common in AD and can worsen the skin condition, is it reasonable to add topical antibiotic treatment to the anti-inflammatory treatment in this case?

Answer Skin colonization with *S aureus* is prevalent in children and adults with AD, and can aggravate skin inflammation. Although topical combination creams with steroids and antibiotics are widely used for AD flare-ups, their superiority over anti-inflammatory treatment alone is not well established. Antibiotic treatment, whether systemic or topical, should be reserved for cases in which explicit signs of infection are present.

- Barrier epithelia contain certain types of lymphocytes, including **intraepithelial T lymphocytes**, that recognize and respond to commonly encountered microbes, Most of them do not express CD4 nor CD8 and differentiate in the thymus.

- T cells in epithelia express a form of antigen receptor called the **γδ receptor** that may recognize peptide and nonpeptide antigens. A common characteristic of these T cells is the **limited diversity** of their antigen receptors compared with most T cells in the adaptive immune system. And **do not depend on MHC** presentation.



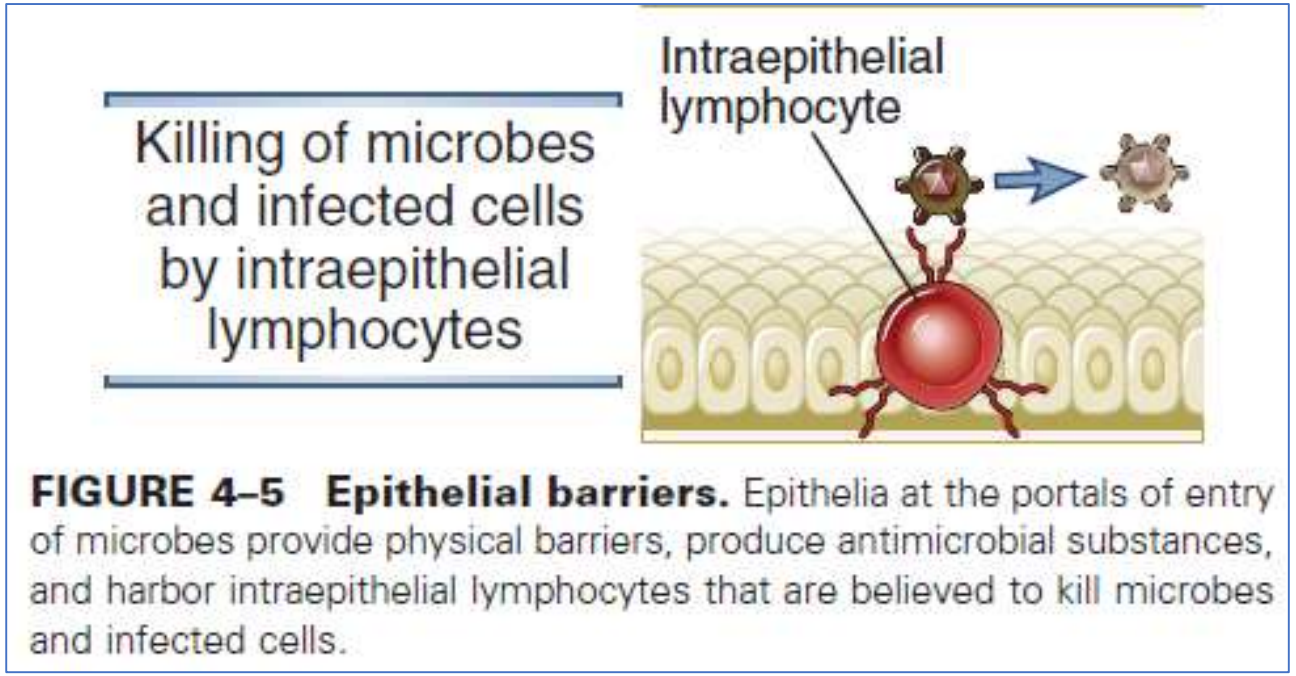


FIGURE 4–5 Epithelial barriers. Epithelia at the portals of entry of microbes provide physical barriers, produce antimicrobial substances, and harbor intraepithelial lymphocytes that are believed to kill microbes and infected cells.

- Major immune cellular components move through the blood, into tissues (leukocyte homing/ recruitment), and often back into the blood again.

- Example: Delivery of leukocytes **from their sites of maturation** (bone marrow or thymus) **to injured tissue** (or **secondary lymphoid organs** where they encounter antigens and differentiate into effector lymphocytes and are delivered into sights of infection).

- Leukocytes that have not been activated by external stimuli (i.e. considered to be in a resting state), normally located in the circulation and lymphoid organs.

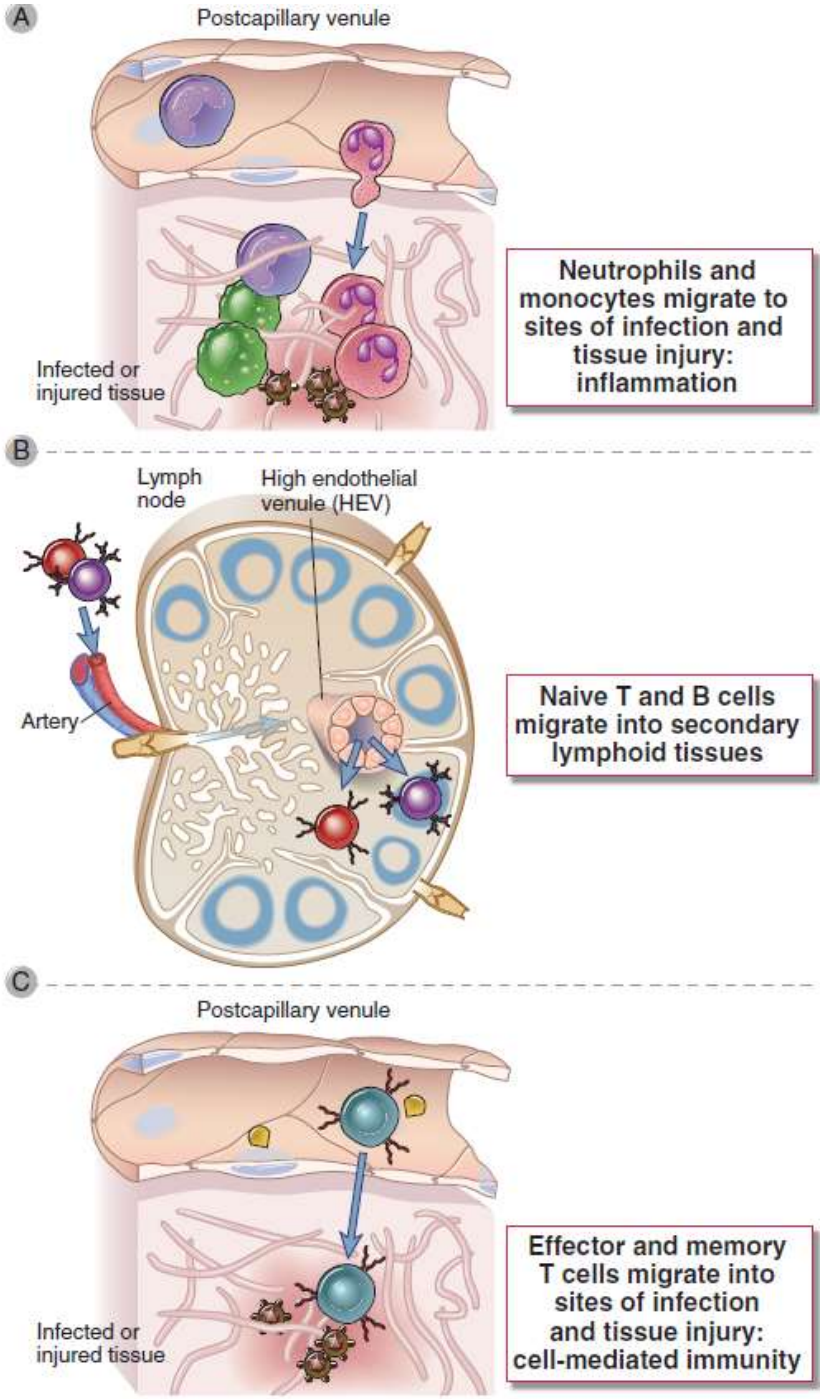
- Endothelial cells at sites of infection and tissue injury are also activated, mostly in response to cytokines secreted by macrophages and other tissue cells at these sites.

- The recruitment of leukocytes and plasma proteins from the blood to sites of infection and tissue injury is called **inflammation**.

- Leukocyte recruitment from the blood into tissues depends first on adhesion of the leukocytes to the endothelial lining of postcapillary venules and then movement through the endothelium and underlying basement membrane into the extravascular tissue.

- This **adhesion** is mediated by two classes of molecules, called **selectins** and **integrins**, and their **ligands**.

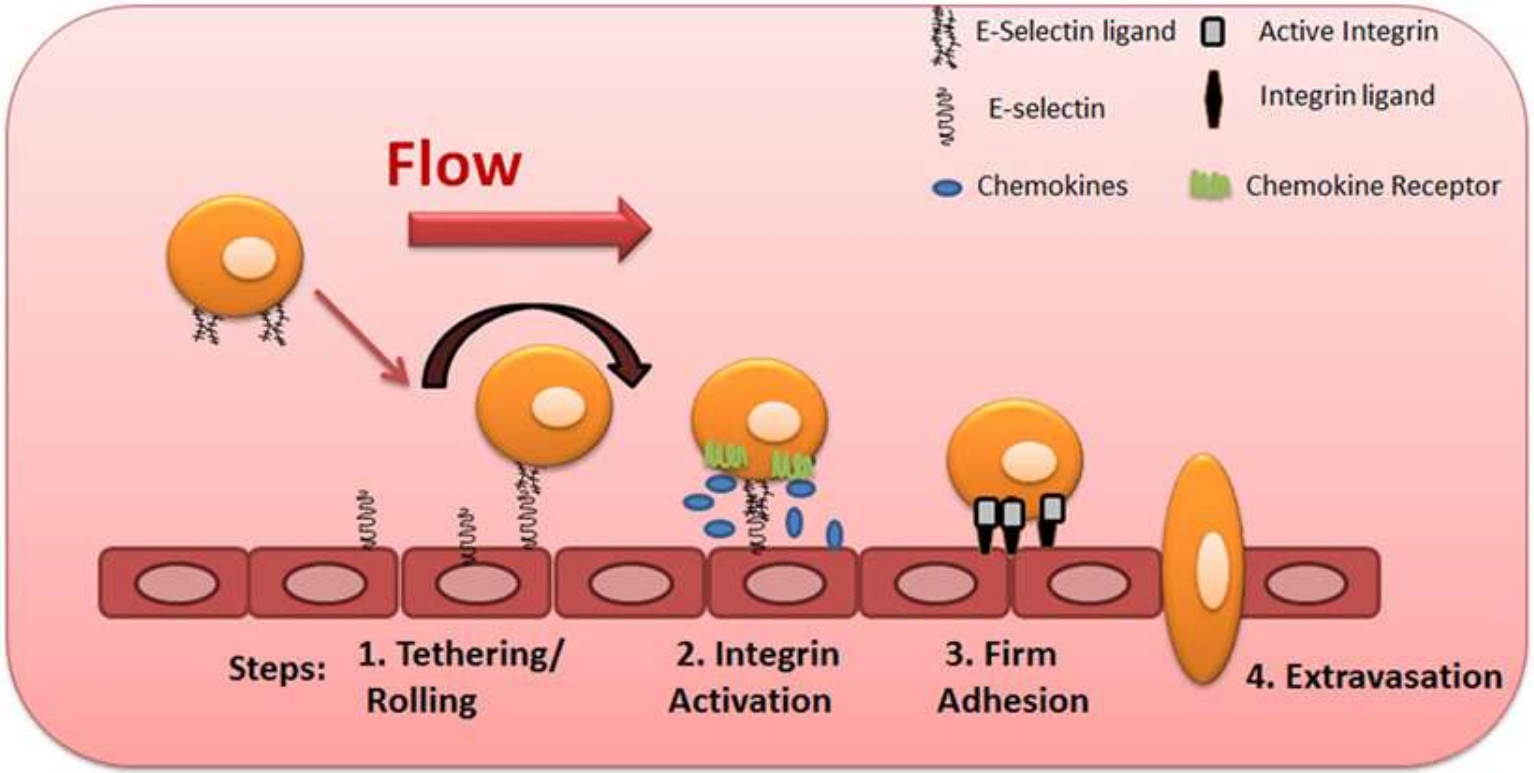
- The leukocytes **home** into tissue following signals from different **chemokines**.



Leukocyte Migration into Tissues/ adhesion molecules

- **Selectins** are **plasma membrane carbohydrate-binding adhesion molecules** that mediate an initial step of **low affinity adhesion** of circulating leukocytes to endothelial cells lining postcapillary venules. Expressed within 1 to 2 hours in response to the cytokines IL-1 and TNF.

- The ligands on leukocytes that bind to **E-selectin** and **P-selectin** on endothelial cells are **complex sialylated carbohydrate**



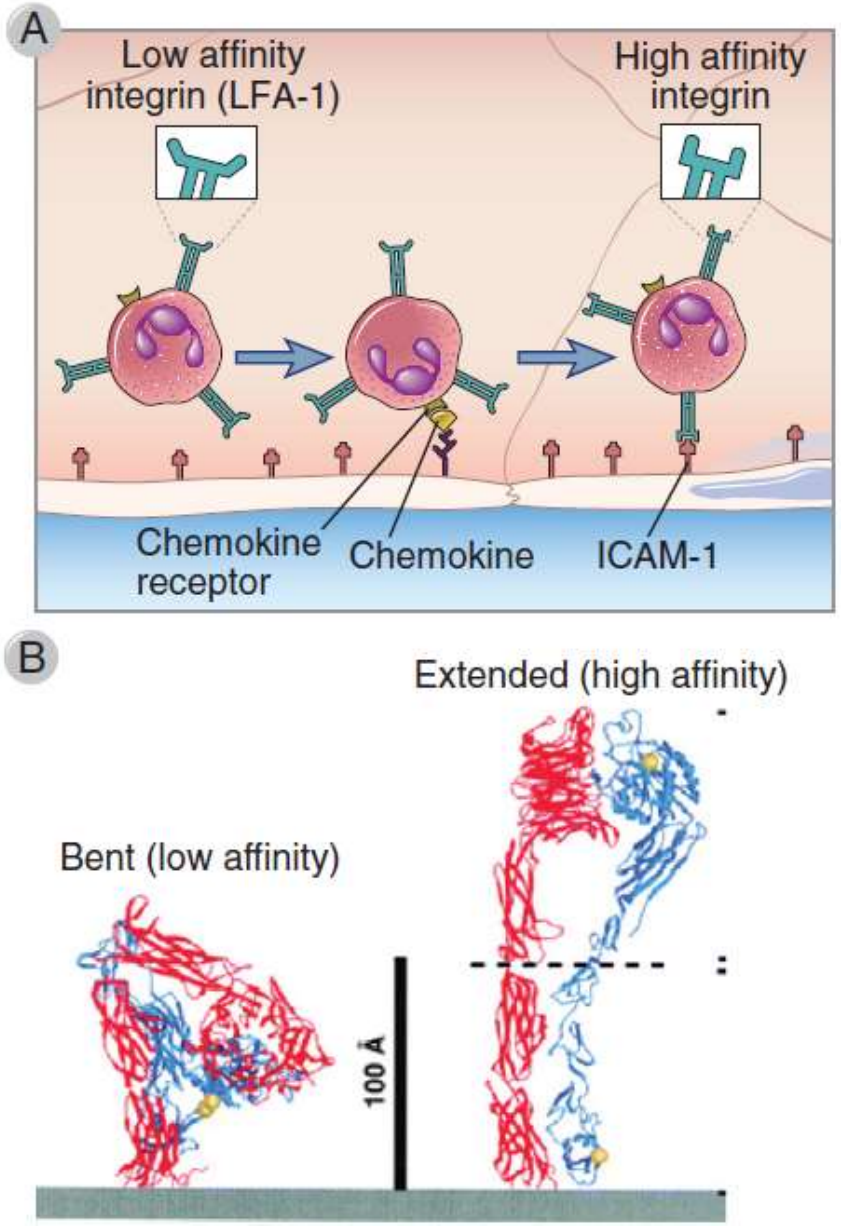
Leukocyte Migration into Tissues/ adhesion molecules

- **Integrins** are heterodimeric **cell surface proteins** that **mediate adhesion** of cells to other cells or to extracellular matrix, through specific binding interactions with various **ligands**.

- **Integrins** respond to intracellular signals by rapidly **increasing their affinity** for their ligands.

- An important integrin is called **LFA-1** (leukocyte function-associated antigen 1) expressed on leukocytes and it's ligand (intercellular adhesion molecule) **ICAM-1**.

- **Chemokines** also induce membrane clustering of integrins leading to **increased avidity of integrin interactions** with ligands on the endothelial cells, and therefore tighter binding of the leukocytes to the endothelium.



Leukocyte Migration into Tissues/ Chemokines

- Chemokines are a large family of structurally homologous cytokines that **stimulate leukocyte movement** and **regulate the migration** of leukocytes from the blood to tissues.

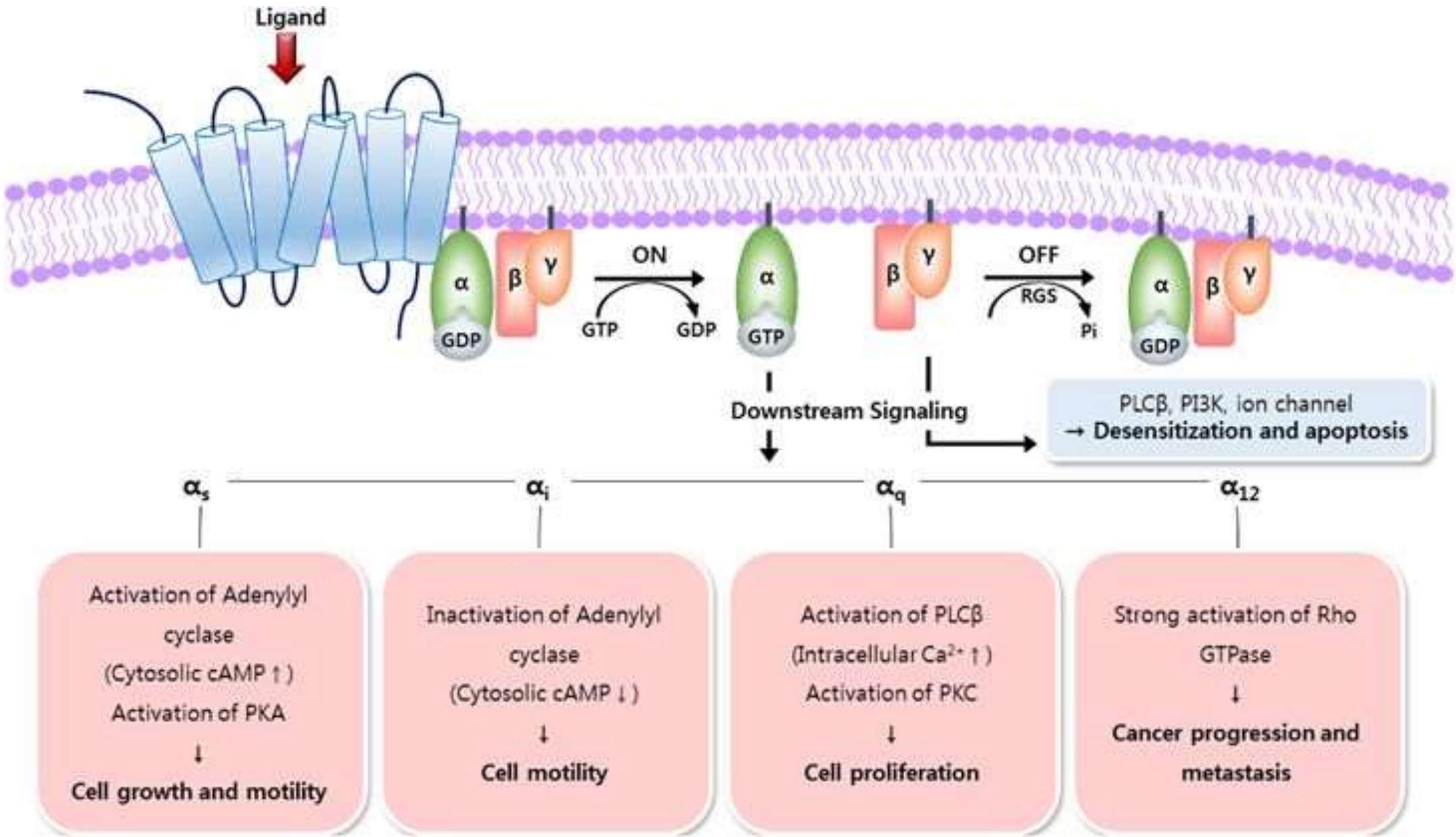
- There are about 50 human chemokines, all of which are 8- to 12-kD polypeptides.

- The two major families are the **CC** chemokines, in which the **cysteine residues are adjacent**, and the **CXC** family, in which these **residues are separated by one amino acid**

- The chemokines of the CC and CXC subfamilies are produced by **leukocytes** and by **several types of tissue cells**, such as endothelial cells, epithelial cells, and fibroblasts.

- The receptors for chemokines belong to the seven transmembrane, guanosine triphosphate (GTP)–binding (G) protein–coupled receptor (**GPCR**) superfamily

Leukocyte Migration into Tissues/ Chemokines



Leukocyte Migration into Tissues/ Chemokines

- **Interleukin-8 (CXCL8)** was originally described as a chemokine whose main function is the attraction of a polymorphonuclear inflammatory leukocyte infiltrate acting on **CXCR1/2.**

- Recently, it has been found that tumors very frequently co-opt the production of this chemokine, which in this malignant context exerts different pro-tumoral functions. Reportedly, these include angiogenesis, survival signaling for cancer stem cells and attraction of myeloid cells endowed with the ability to immunosuppress and locally provide growth factors.

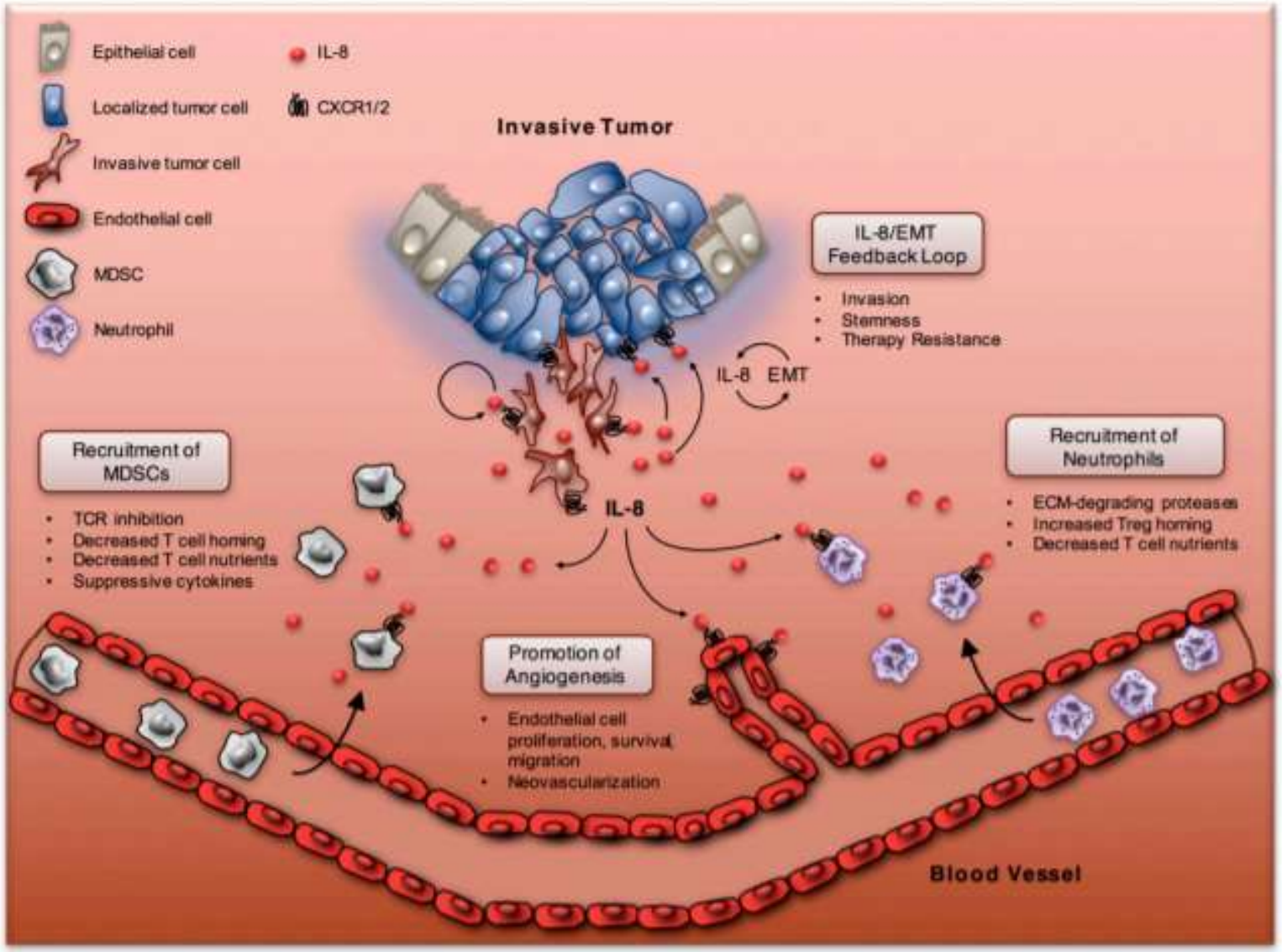
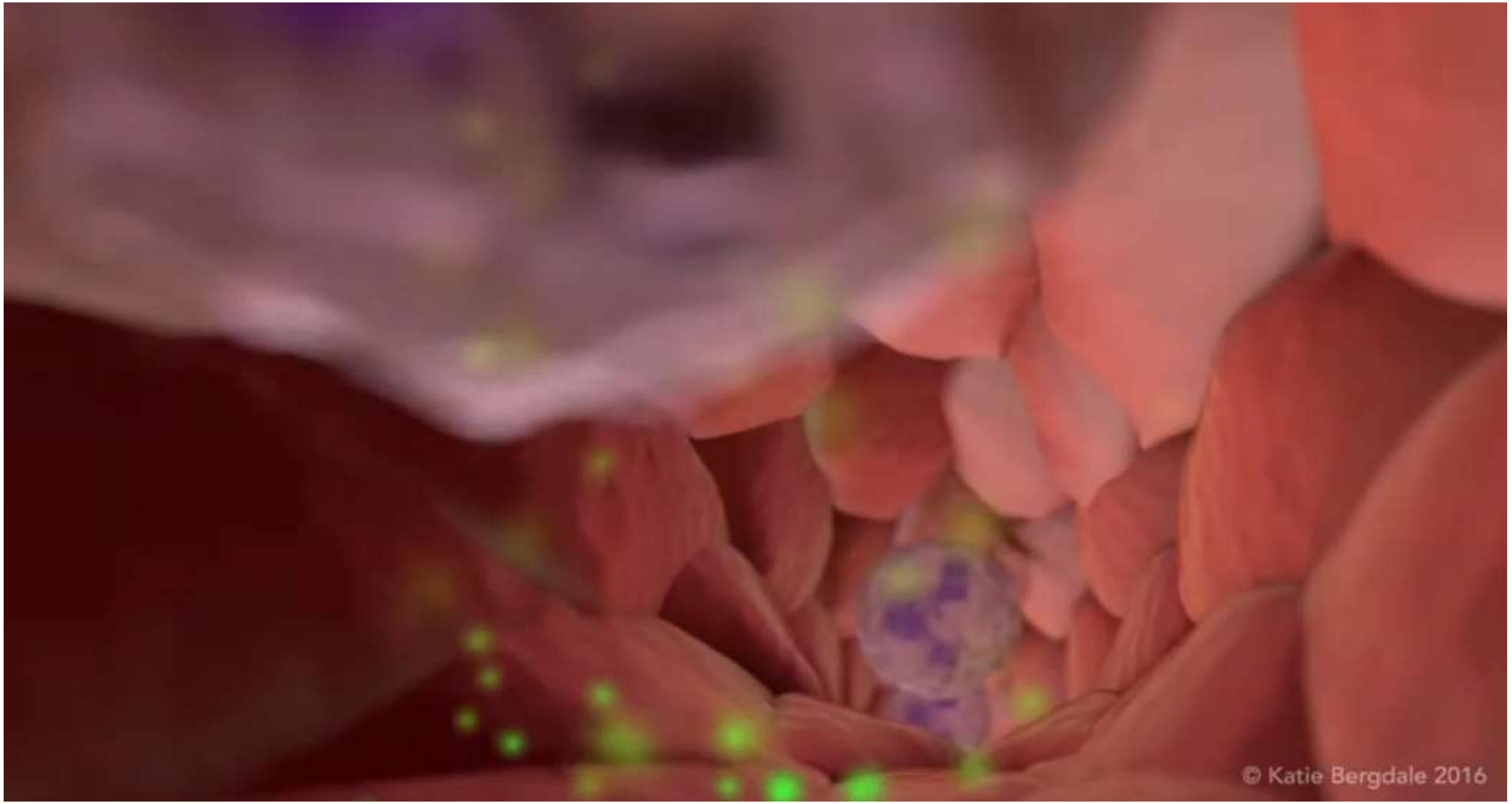


Figure 1. Effects of IL-8 on the tumor and microenvironment. Depiction of IL-8 promoting autocrine and paracrine tumor cell EMT, enhancing angiogenesis, and remodeling the tumor microenvironment through attraction of neutrophils and myeloid-derived suppressor cells (MDSCs).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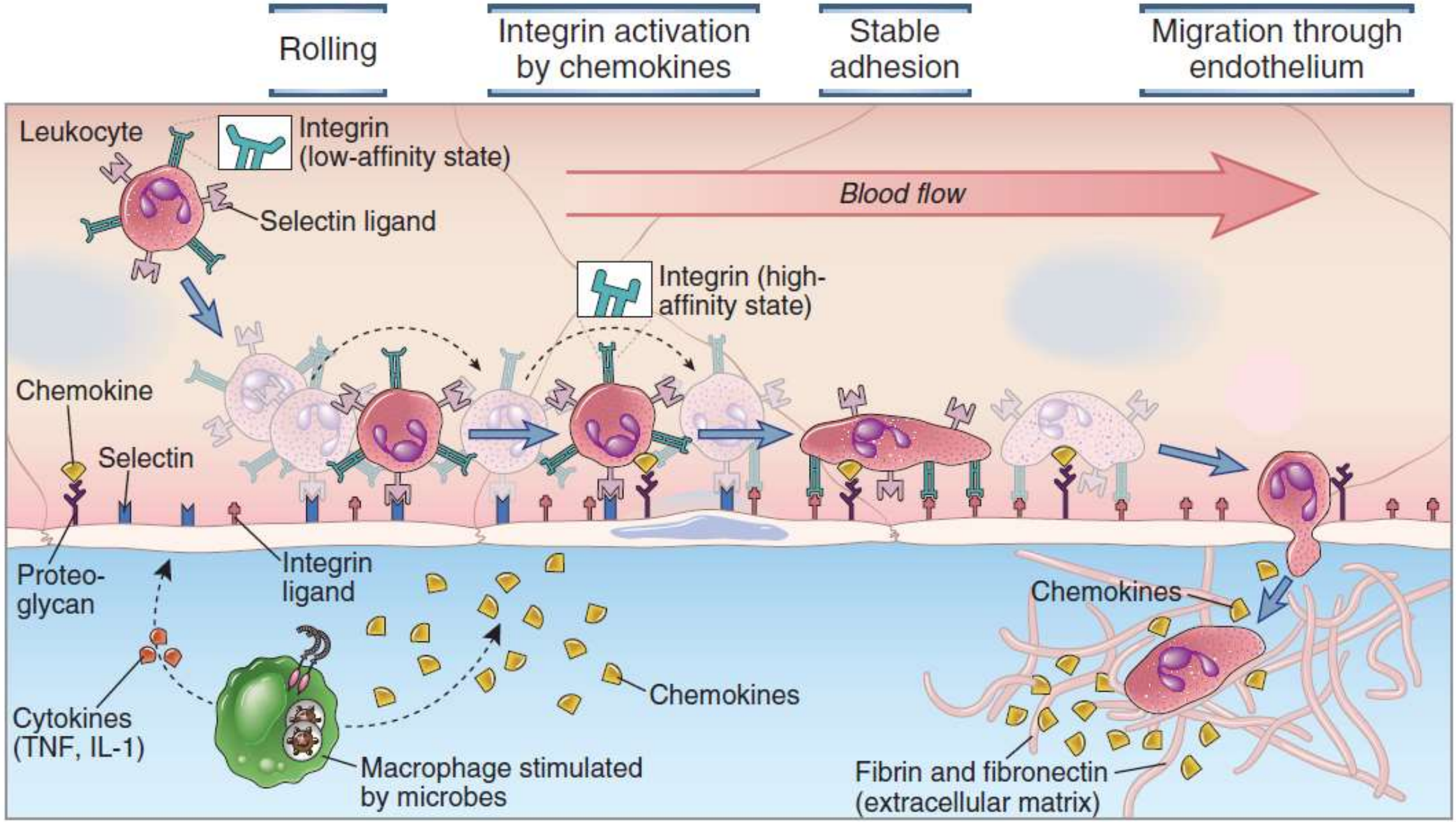
Leukocyte Migration into Tissues/ summary

- In response to microbes and cytokines produced by encounter with microbes, endothelial cells lining postcapillary venules at the site of infection **rapidly increase** surface expression of **selectins**. **Slowing down** leukocytes.

- **Chemokines** bind to specific chemokine receptors on the surface of the rolling leukocytes, resulting in increased avidity of binding of leukocyte **integrins** to their ligands on the endothelial surface. leukocytes attach firmly to the endothelium, their cytoskeleton is reorganized, and they spread out on the endothelial surface.

- Leukocytes **transmigrate** between the borders of endothelial cells, a process called **paracellular transmigration**, to reach extravascular tissues. Paracellular transmigration depends on leukocyte integrins and their ligands on the endothelial cells

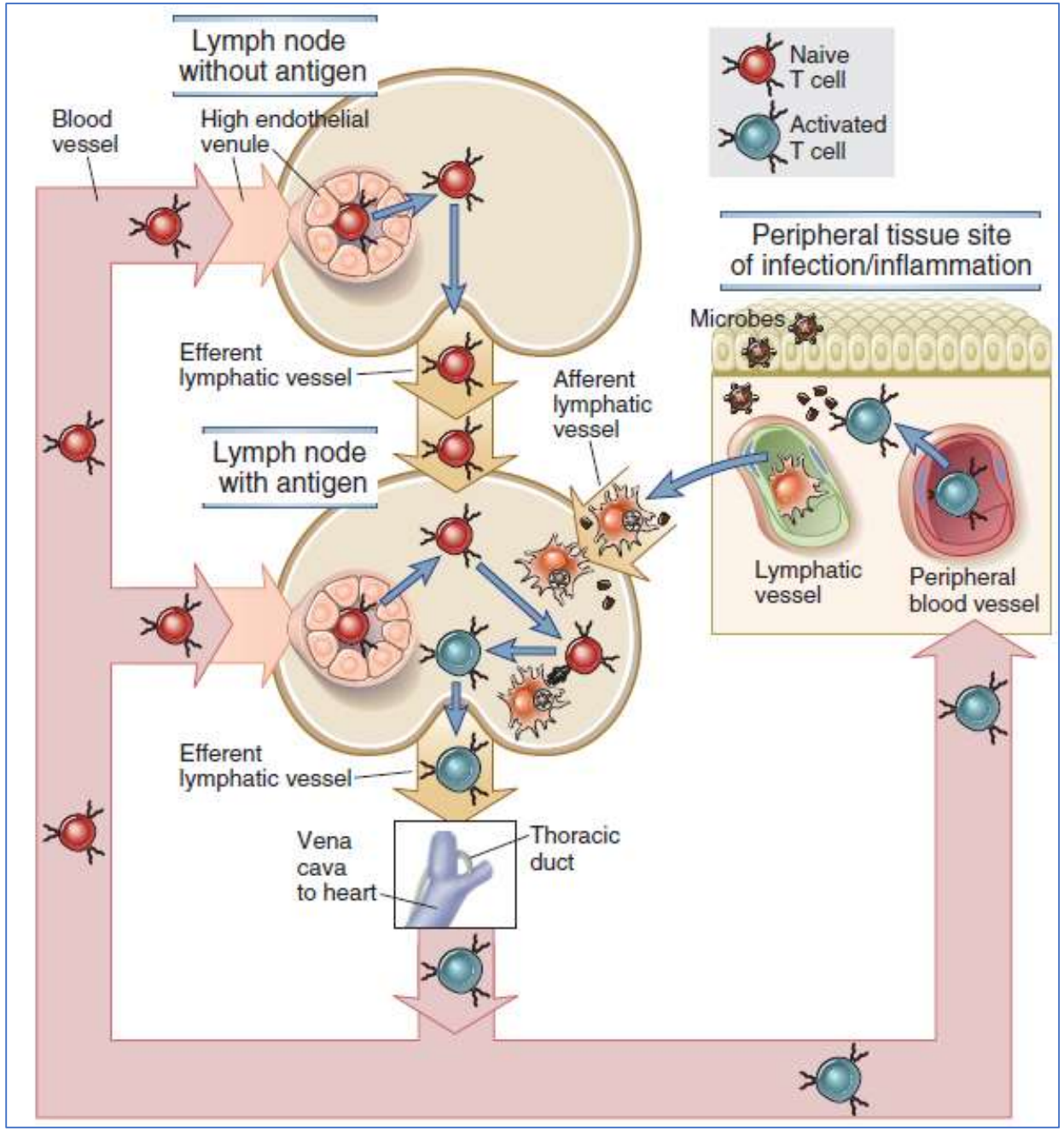
Leukocyte Migration into Tissues/ summary



Leukocyte Migration into Tissues/ summary

- Each lymphocyte goes through one node once a day on average. Peripheral tissue inflammation, which usually accompanies infections, causes a significant increase of blood flow into lymph nodes and consequently an increase in T cell influx into lymph nodes draining the site of inflammation.

- Naive B cells use the same basic mechanisms as do naïve T cells to home to secondary lymphoid tissues throughout the body, which enhances their likelihood of responding to microbial antigens in different sites.



Further reading:

- Cellular and Molecular Immunology. 7th Edition.

Chapter 3. Leukocyte Migration into Tissues

Chapter 4. Innate immunity