Doctor 021

IMMUNOLOGY

Sheet no. 8

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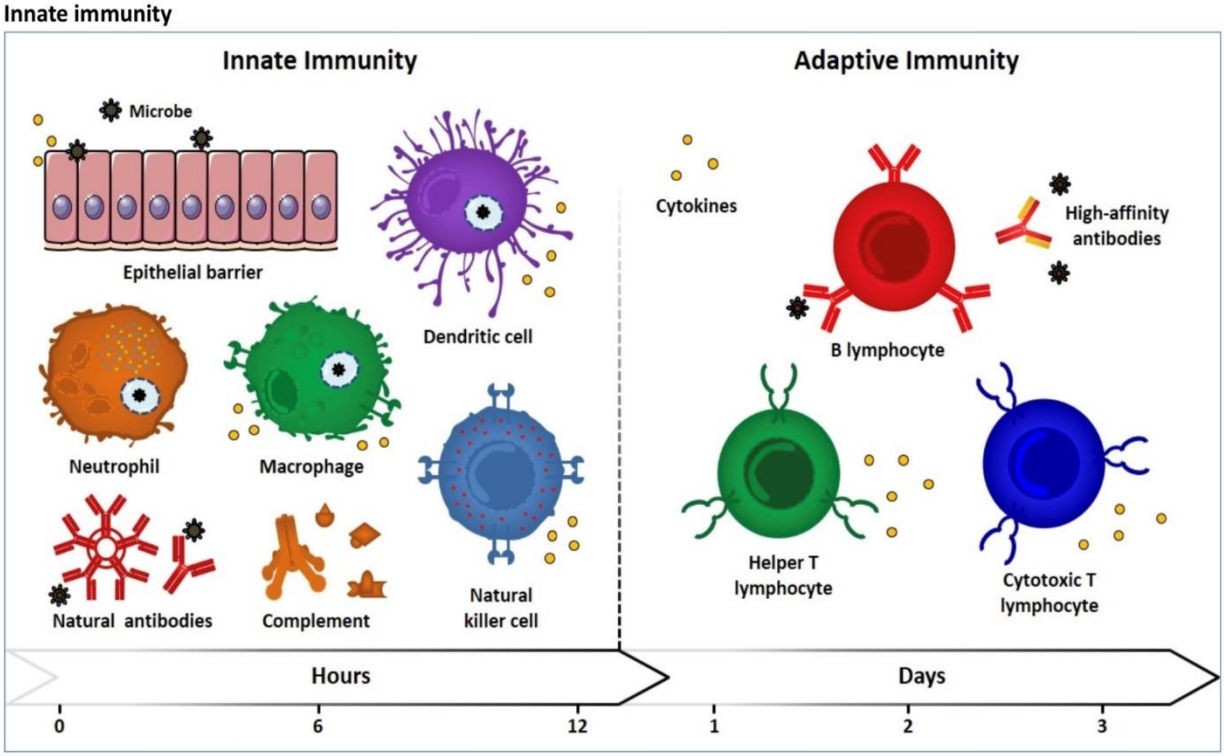
INNATE IMMUNITY

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

• 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.

Most pathogen will come throw the mucosal epithelial barriers, some go directly to the blood.

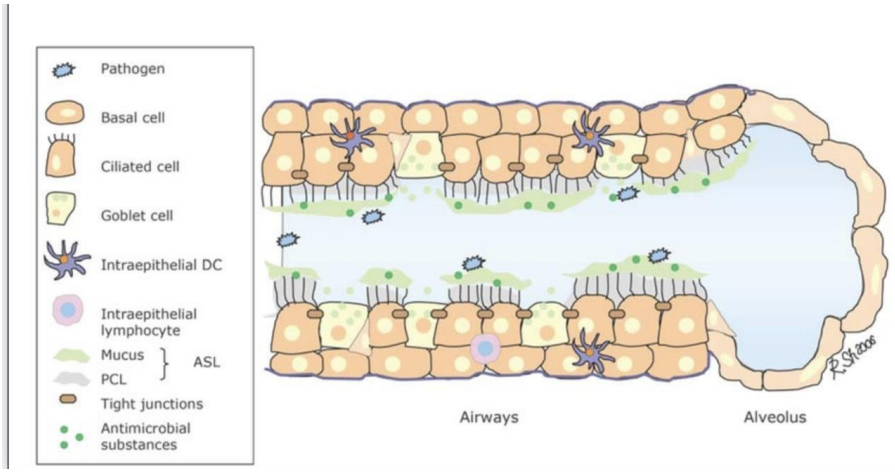
epithelial barriers

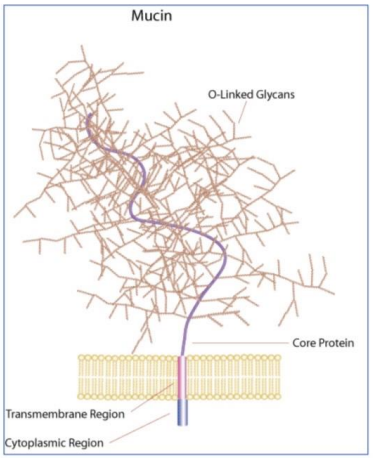
* Mucus

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.

Several properties that makes it inhospitable to pathogens:

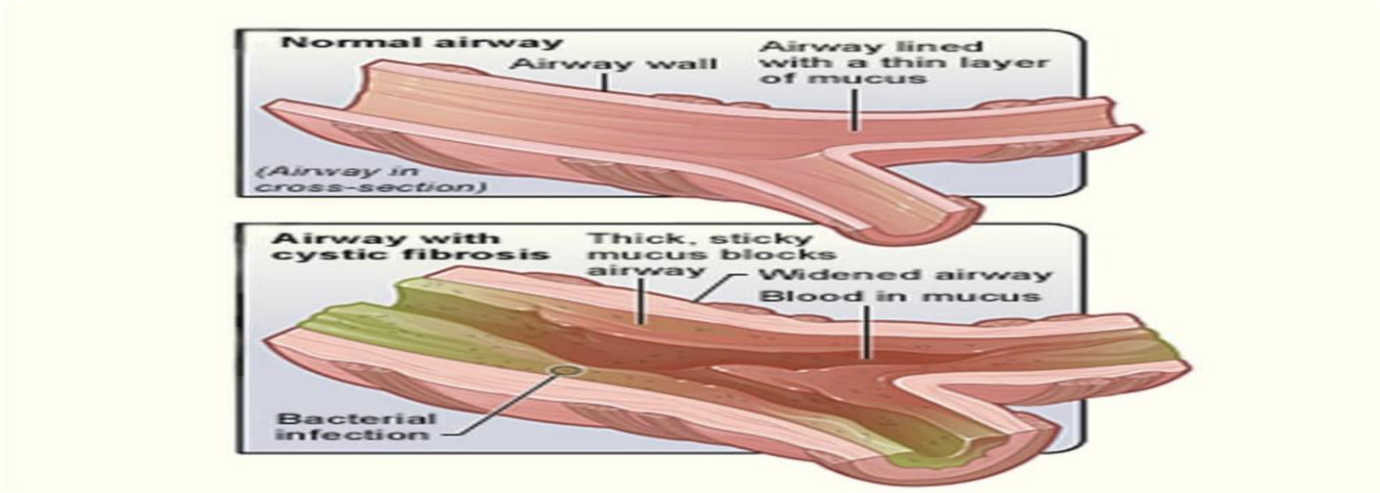
1- Its viscosity
2- Continuously moves through cilia reactions
3- the most prominent immunoglobin present in mucus is IgA
4- Presence of antimicrobial molecule (lysozymes)





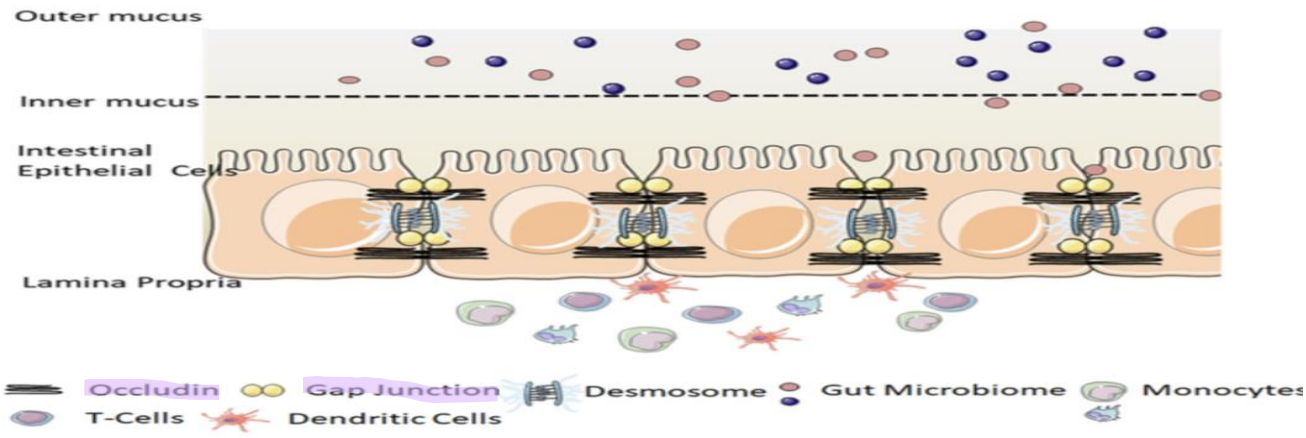
If the mucous becomes immobile it becomes suitable environments to replicate .

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. (Because increase in viscosity)



* 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**



* Epithelial cells are held together by tight junctions, which effectively form a seal against the external environment.

*Antimicrobial peptides

• 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. (Always produced by cells)

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

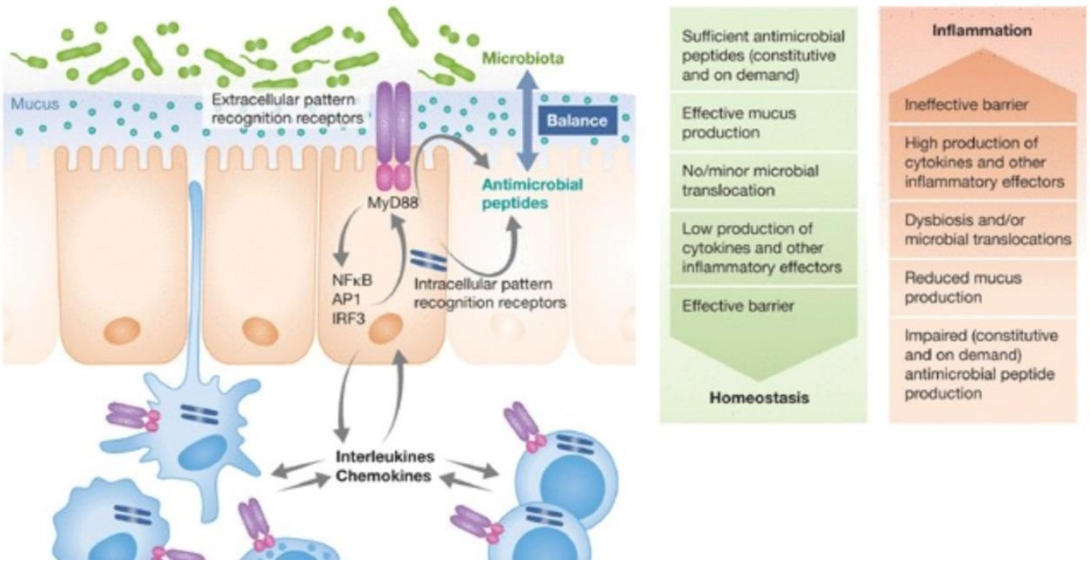
• Antimicrobial peptides possessing a net positive charge are attracted and incorporated into negatively charged bacterial membranes thus disturbing them.

Leads to formation of a pore that makes the membrane leaky and disturbing it.

immunomodulatory functions: means they can interact with immune cells leading to activation or inhibition.

*Microbiota

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

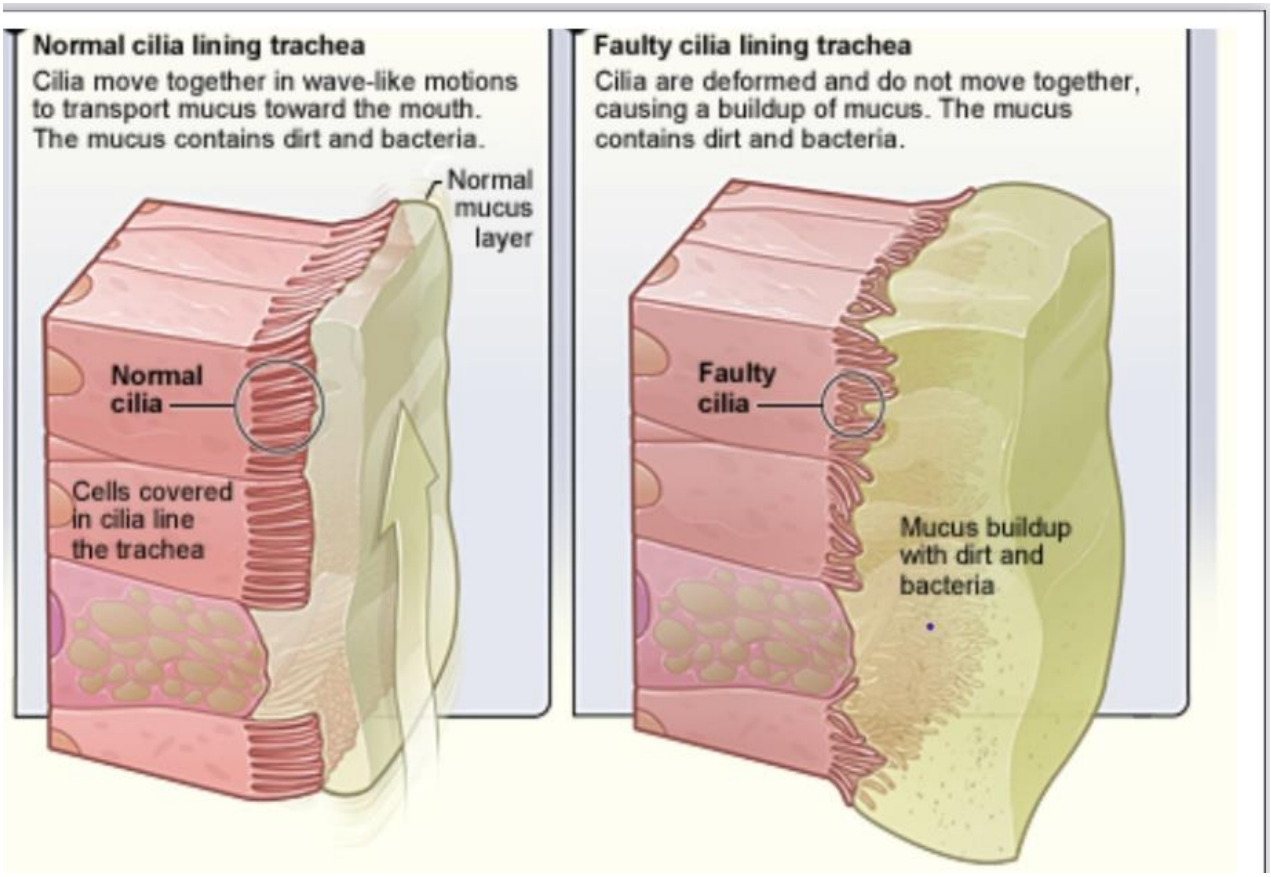


1- Essential for the integrity of the epithelial barrier
2- Help in modulation of immune response
3- Activation of immune system
4- Necessary for the maturation of immune system (slow level)
5- Reduce the possibility of pathogens (environment suitable for microbiota and not suitable for pathogens)

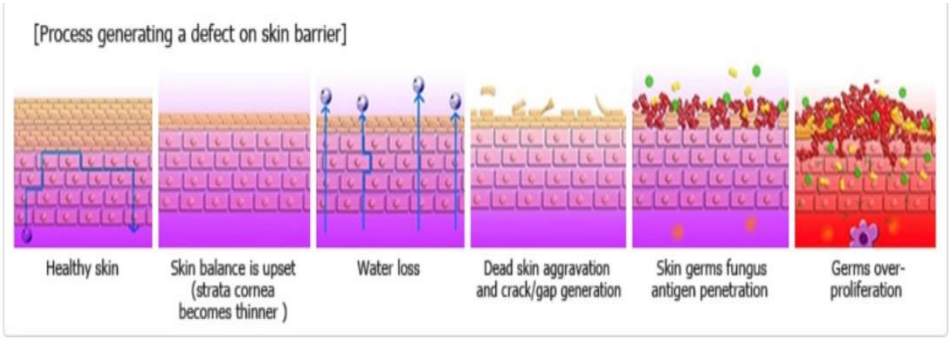
Microbiota plays an important role in innate immune response against infections, widely distributed in epithelial barriers and reducing the probability for infectious organisms to colonize there, when these commensal microorganisms are killed by antibiotics, pathogens frequently replace them and cause diseases.

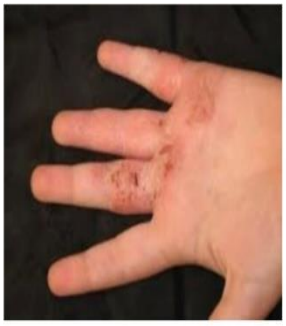
-infections related to interrupted epithelial barrier:

• 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.**





- Inflammation on the skin
- Chang microbiota
- Susceptible epithelial barrier
- recurrent infections (mainly by staphylococci aureus)

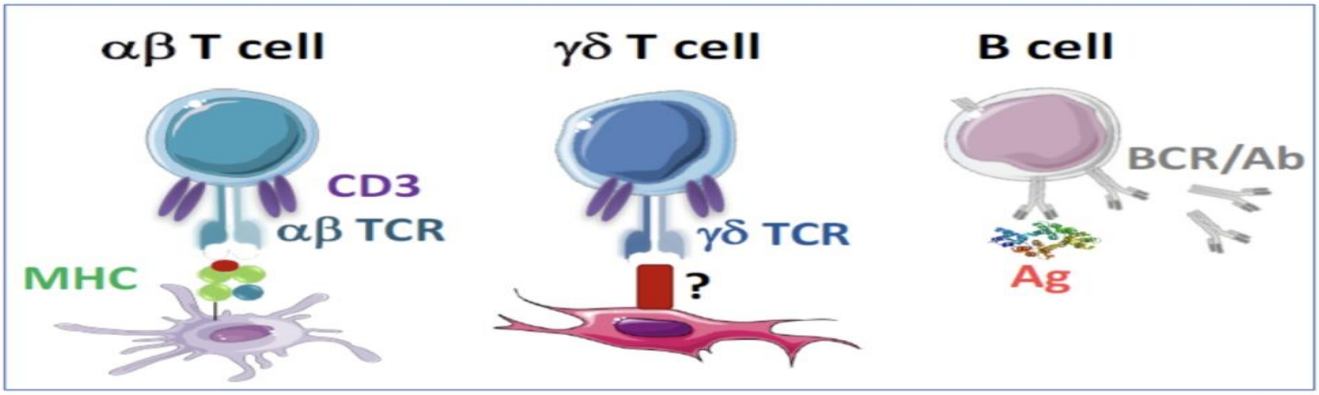
Abstract Go to:

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.

* Intraepithelial T lymphocytes

- **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 γ δ 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.**



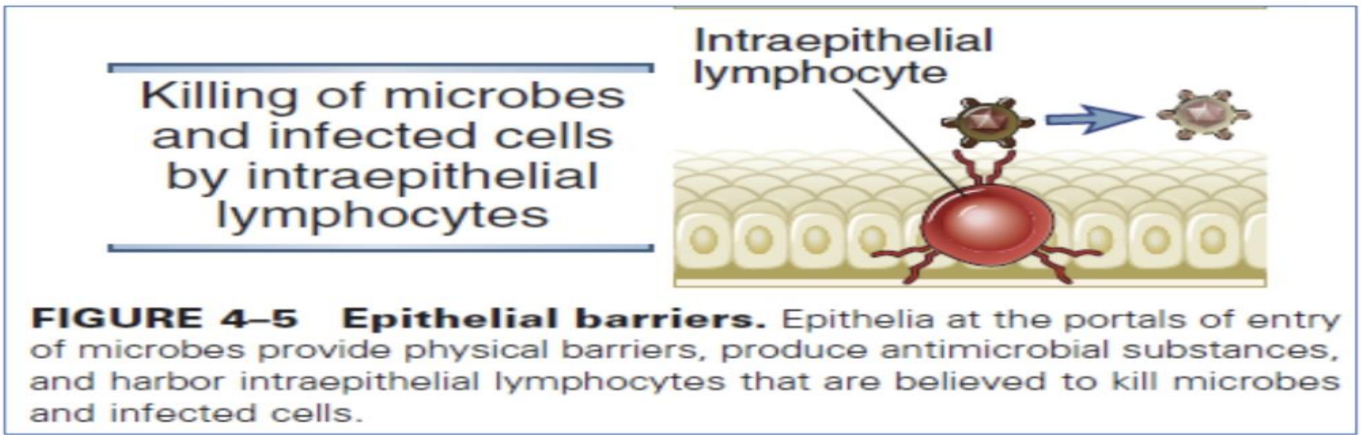


FIGURE 4–5 Epithelial barriers. Epithelia at the portals of entry of microbes provide physical barriers, produce antimicrobial substances, and harbor intraepithelial lymphocytes that are believed to kill microbes and infected cells.

Barrier epithelia contain certain types of lymphocytes that are not a component of the adaptive immune system because they have a limited specificity , including intraepithelial T lymphocytes, that recognize and respond to commonly encountered microbes.

Leukocyte Migration into Tissues:

• 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 sites 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.

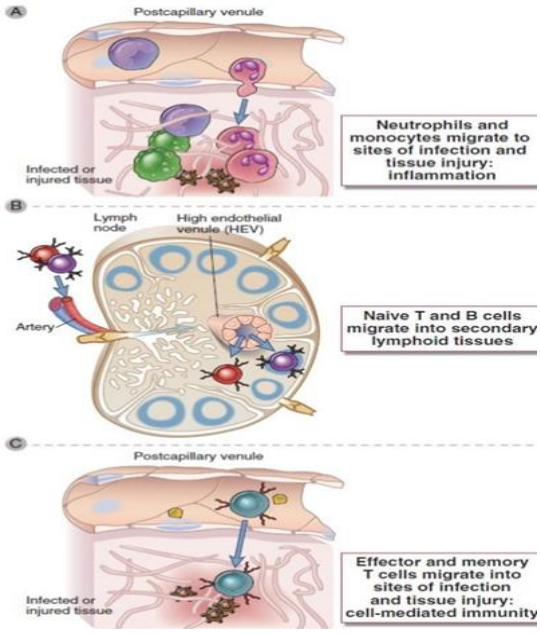
• Endothelial cells at sites of infection and tissue injury are also activated, mostly in response to cytokines secreted by macrophages and other tissue cells at these sites.

• 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.



►HOW CELLS REACH TO THE SITE OF INFECTION?

- Selectins are produced on the surface of endothelial cells by the action of cytokines, they need to upregulate of selectins on the endothelial cells.
- The endothelial cells near the site of infection are ready now to slowdown leukocytes through their expression of P-selectin and E-selectin.
- The leukocyte that pass by the area will have to slow down because their ligands will bind to those selctins, causing the leukocyte to slowdown and start rolling.
- Now it's rolling in a tissue where a lot of chemokines are produced, these chemokines work after slowdown and rolling leukocytes, by the action of chemokines; the integrins will change from a low affinity conformation to a high affinity conformation such as LFA-1 (this integrin is

important, and mutation in this integrin will lead to abnormal homing to the site of infection, it's a type of immune deficiency).

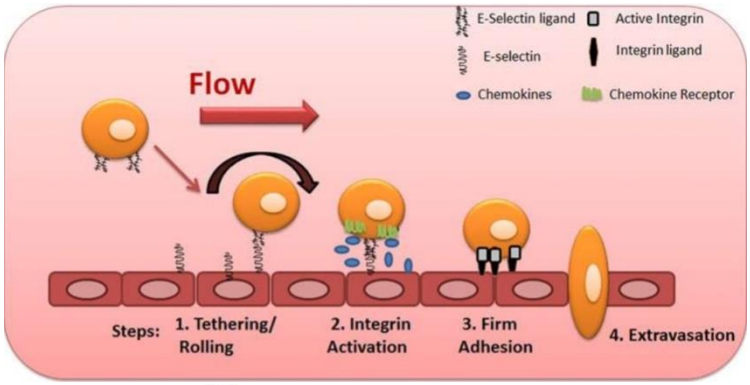
- Then the integrin will bind strongly to the (ICAM), the attachment is quite strong.
- There is no more rolling, it attaches strongly and then undergoes (diapedesis) or transmigration, and then it goes to the tissue to follow the chemokine gradient.

This video is in doctor slides, watch it for more understanding:

https://youtu.be/B9Qi7we0Ynk

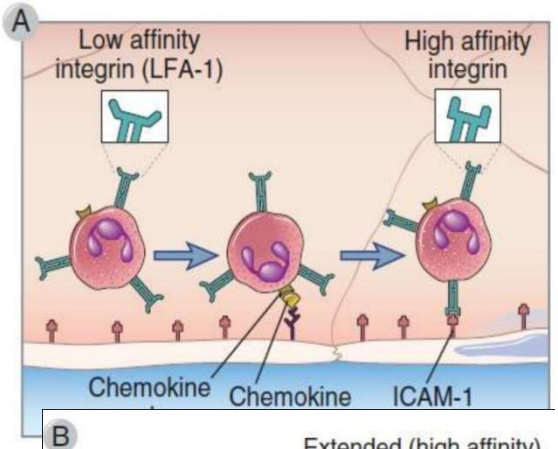
ADHESION MOLECULES:

• 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.



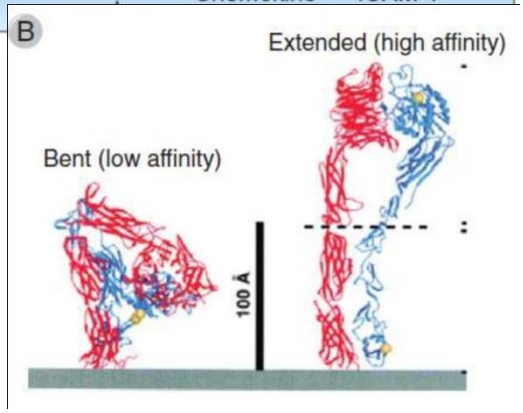
• The ligands on leukocytes that bind to E-selectin and P-selectin on endothelial cells are complex sialylated carbohydrate.

• 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.

CHEMOKINES:

(Chemoattractant cytokines)

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-kD to 12-kD polypeptides.

(They are smaller than antibodies and growth factors).

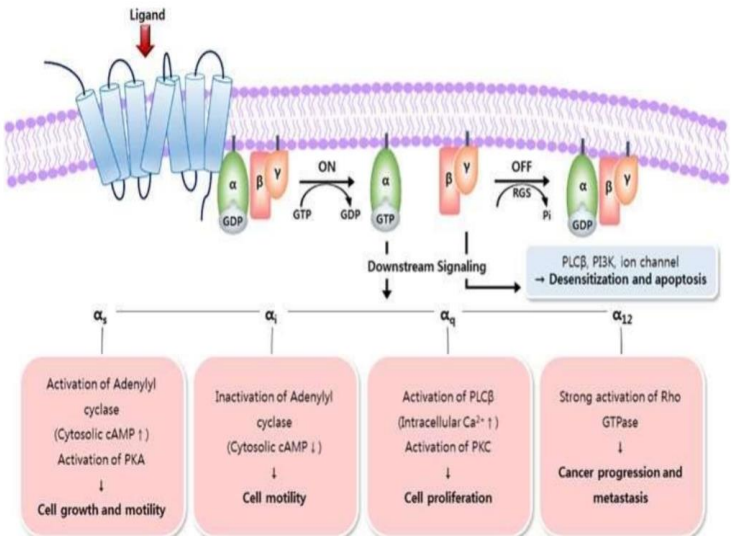
• The two major families are:

1. the CC chemokines; in which the cysteine residues are adjacent.

2. 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).

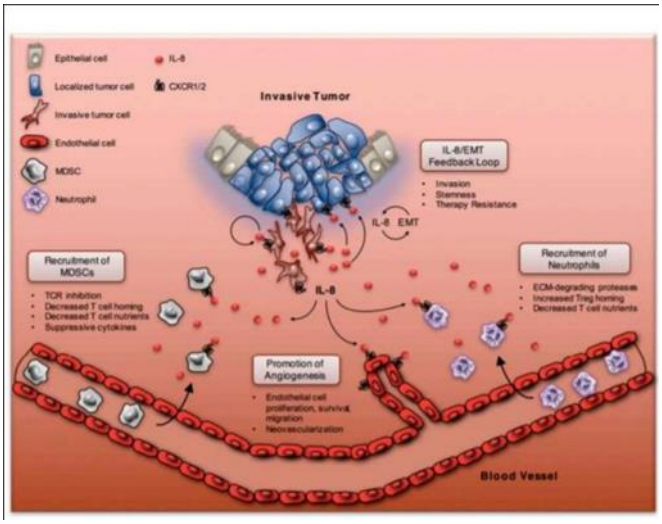
• The receptors for chemokines belong to the seven transmembrane, guanosine triphosphate(GTP)–binding (G) protein–coupled receptor (GPCR) superfamily.



activation of GPCR not only leads to migration of leukocytes, it also stimulate cell proliferation or apoptosis, this depends on the intensity of the signal and receptor that has been activated.

• 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 protumoral 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.

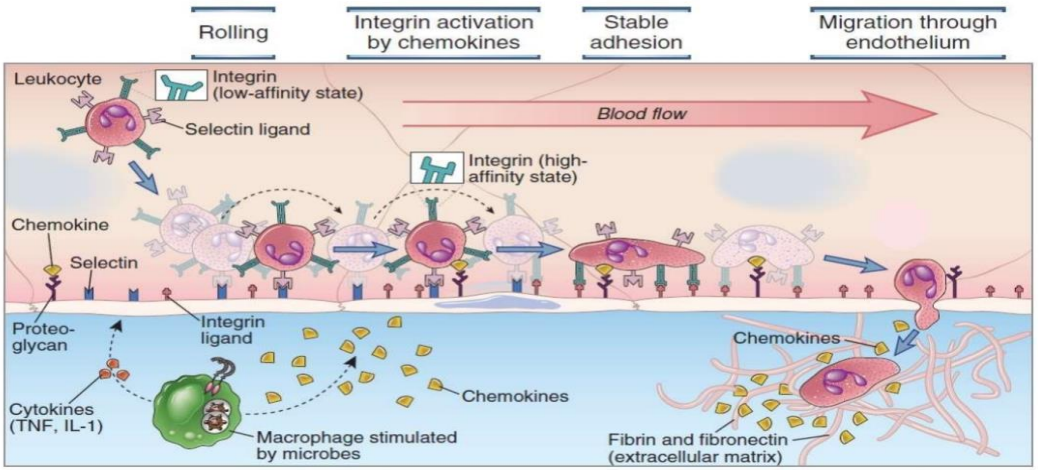


SUMMARY:

• 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.

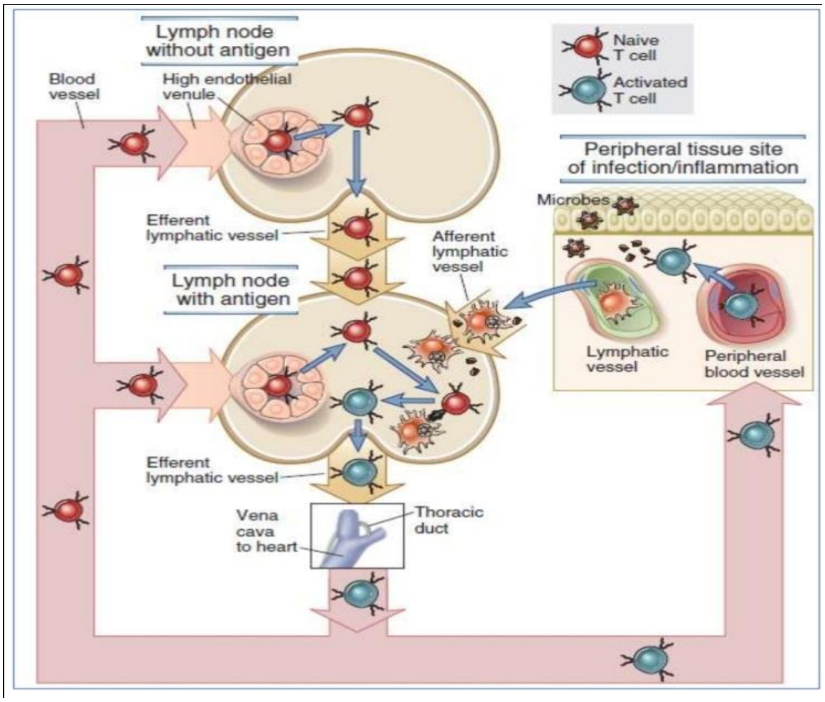
• Chemokines bind to specific chemokine receptors on the surface of the rolling leukocytes, resulting in increased avidity of binding of leukocyte integrins to their ligands on the endothelial surface. leukocytes attach firmly to the endothelium, their cytoskeleton is reorganized, and they spread out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



• 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.



Good luck