Doctor 021

PATHOLOGY

Sheet no. 2

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First step in inflammation response:

Cellular receptors: Toll-like R (TLRs); on membranes and endosomes. Recognize Pathogen Associated Molecular Patterns (PAMPs).

(their function is to recognize foreign microbes,virus or any new molecular pattern)

– Sensors of cell damage: recognize Damage Associated Molecular Patterns (DAMPs) such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins gets activated (called inflammasomes)

-Any damaged tissue such as ischemia, necrosis, burn, trauma, atherosclerosis...etc.

*Ischemia: is a condition in which the blood flow is restricted or reduced in a part of the body.

*(uric acid crystals accumulate in joints causing gout which is also recognized by sensors)(النقرس))

– Circulating proteins: complement system, mannosebinding lectins and collectins

they can also recognize damaged cells or foreign bodies

Acute inflammation :-

When the inflammatory response starts especially in acute inflammation there are several changes occur, one of the initial important steps is Acute Initial Vascular Phase of inflammation that explain multiple cardinal signs seen on the inflamed organ like(swollen , erythema, pain, tenderness, redness..etc)

↑from previous lecture

The 3 major components of acute inflammation :-

1-Blood vessel dilatation (active , initially occurs)

2-Increased vascular permeability (active & slower)

1&2 known as acute vascular phase

3-The migration of white blood cells

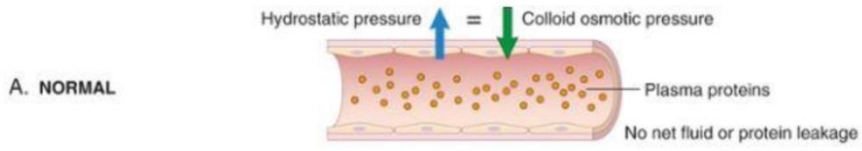
Intravascular⟶ extravascular

Summary

General Features and Causes of Inflammation

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but also may cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators that are derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five Rs: (1) recognition of the injurious agent, (2) recruitment of leukocytes, (3) removal of the agent, (4) regulation (control) of the response, and (5) resolution (repair).
- The causes of inflammation include infections, tissue necrosis, foreign bodies, trauma, and immune responses.
- Epithelial cells, tissue macrophages and dendritic cells, leukocytes, and other cell types express receptors that sense the presence of microbes and necrotic cells. Circulating proteins recognize microbes that have entered the blood.
- The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation.

**Summary of last slides ,quoted from Robbins book



Some definitions that you have to be familiar with :-

-Depending on the amount of the FLUID inside the vessel we have a hydrostatic pressure that is responsible for the movement of the fluid from inside to outside

- Depending on the amount of plasma proteins we have colloid pressure which related to the absorption of the fluid from outside to inside"according to the concentration of the plasma proteins "

**They are in equilibrium state in the normal conditions **

Physiology 🤩 “Do you remember what happened at 11 September?”

But we have another story when it comes to acute inflammation “ لازم تطلع من سنة تانية فاهمهم منيح كثير رح يهروكم أسئلة فيهم بالجراحة .." د.موسى

1-Exudate

2-Transudate

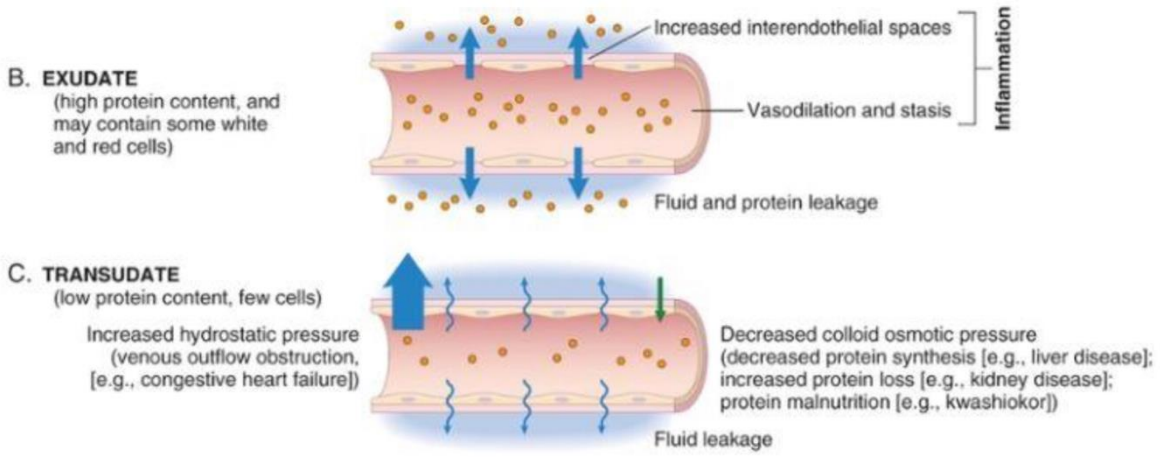
Both of them are initial phases of the initial phase acute inflammation

EXUDATE:- always have high protein &cellular content that sneak outside the B. V.

TRANSUDATE:- related to the fluid mainly so it is completely opposite ,the protein content & the cellularity are low.

*Exudate indicates severe acute inflammation or cancer

*it's important to know if it was exudate or transudate because they differ in their causes.



IMAGINE

You received a pleural or peritoneal fluid for examination, first you have to at its structure and Color

- Clear & yellow => most likely a transudate
- Thick , creamy sometimes bloody => perhaps it is an exudate

** the exudate indicates severe acute inflammation or maybe cancer and other sever condition ,however transudate related to liver diseases , kidney diseases or malnutrition so there is a problem in the colloid pressure or could be hypoproteinemia *

Veryyyyy imp.->

Transudate	Exudate
Low protein	High protein
Low cell content	Many cells & debris
Low specific gravity	Higher specific gravity
Caused by osmotic/hydrostatic pressure imbalance	Caused by increased vascular permeability and denotes inflammatory reaction

EDEMA & PUS

Edema:-is basically excess fluids in the interstitium or serous cavities . Patients with heart failure or liver failure ,they have severe lower limb edema (due to the movement of the fluid from the intravascular comp to interstitium causing severe swelling in the leg)

A lot of cases we are going to examine that have unilateral or bilateral pleural effusion or ascites those can be either transudate or exudate ,removing part of it to examine the protein &. Cellularity content and the malignancy in these fluids (especially older patients)

** Edema is just fluid and most of the time it's due to osmotic hydrostatic, oncotic pressure imbalance.**

** transudate is a filtrate of blood. It is due to increased pressure in the veins and capillaries that forces fluid through the vessel walls or to a low level of protein in blood serum. Transudate accumulates in tissues outside the blood vessels and causes edema (swelling)** for more justification

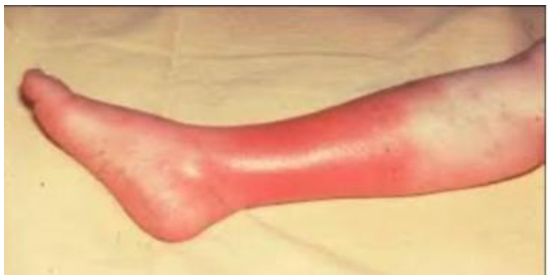
Pus :-indicates an exudative process which is purulent (mean increased numbers of inflammatory cells which is in red and white blood cells,microbes ,debris and proteins)

" 🙂 لازم تطلع من سنة تانية تميز بينهم منيح"

Pus= the content of an abscess, when you squeeze the injury & inflammation into your fingertip when it becomes yellow and collects purely debris (this is actually the treatment of small abscess &it is a purulent exudate=pus)

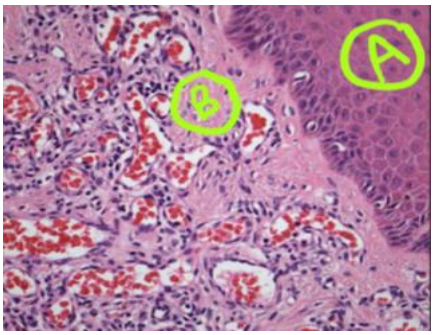
Vascular changes (early events)

As you see in this picture, this is not a normal leg, this patient has a disease called cellulitis (acute cellulitis), where the infection is involving the skin and subcutaneous tissue so you should take a section from this and look at it in the microscope.



A- this is the squamous epithelium

B-is the submucosal epithelium with numerous engorged and congested



*blood vessels with a lot of red blood cells will give the red color (redness) when you examine the patient by your eye.

So ,how the previous case happen ?

1) the initial phase of inflammation or vasodilation is mediated by multiple chemical mediators of inflammation.

The major mediator which is responsible for the vasodilatation effect is the histamine which will increase blood flow causing the submucosa of validation and heat

so initially there is immediate vasodilation due to the release of histamine, sometimes and certain books they will tell you that there is indication of an exudative process which is purulent (mean increased numbers of inflammatory cells which is rich in red and white blood cells,microbes, debris and protein).

* the major effect of histamine is redness

actually a phase before that which is called the reflex transient vasoconstriction from the initial stimulus whether it's trauma or bacteria or heat or whatever, but for all practical purposes the first vascular phase of inflammation is actually the vasodilation due to histamine release.

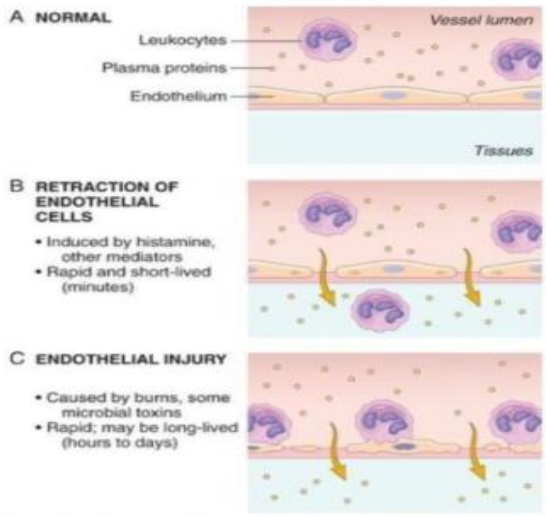
The initial phases is a little bit passive. This followed by more active process which will lead to leakage of more material from inside the blood vessel to the interstitium due to increased vascular permeability, both processes the initial vasodilatation followed by more and active process of increased vascular permeability will cause stasis which means the blood would stay over there does not move and this is what we call in pathology congestion and this will lead to the cutaneous changes termed erythema

Neutrophils or the Polymorphonuclear cells accumulate and adhere to the endothelium of the cells then try to migrate outside into the interstitium in the initial phases of acute inflammation in a process which we called Diapedesis

Diapedesis: the movement of the neutrophils and other white blood cells from the intravascular compartment to the extravascular compartment in the initial phases of inflammation.

The main driver of the initial phase of vascular events is histamine.

In normal equilibrium state, everything is moving smoothly, there is no movement in the blood vessels diameters, or movement of the cells or proteins from inside to the outside. look at the figure



3.3 Principal mechanisms of increased vascular permeability in inflammation and

Vasodilation has 2 phases:

1) initial phases inflammation (quick, transient).

The initial change which happens due to histamine and also other chemical mediators of inflammation but the major one is histamine is there is retraction of the endothelial cells, there will be retracted movement, there will be more gaps in between those endothelial cells and this is basically the immediate rapid and short-lived process where fluids can move cells and proteins and fluid can move from the intravascular compartment to the extravascular compartment.

This will be followed by phase 2 (severe) as I mentioned a more active energy requiring step where will be really damage to the endothelial cells and there will be more gaps between the endothelial cells, sometimes the basement membrane where more cells and more proteins move out.

Basement membrane is a very important structure to epithelial cells. Laminin and collagen4 are the main components of the basement membrane.

this process either it is a short a short lived, for example in burns or microbial toxin induced changes or it is a little bit more long lived.

*Lymphatic vessels and lymph nodes

What are the roles of lymphatic vessels and lymph nodes?

Remember we talked in anatomy that there are many groups of lymph nodes: cervical lymph nodes, axillary lymph nodes, inguinal lymph nodes, and para aortic lymph nodes.

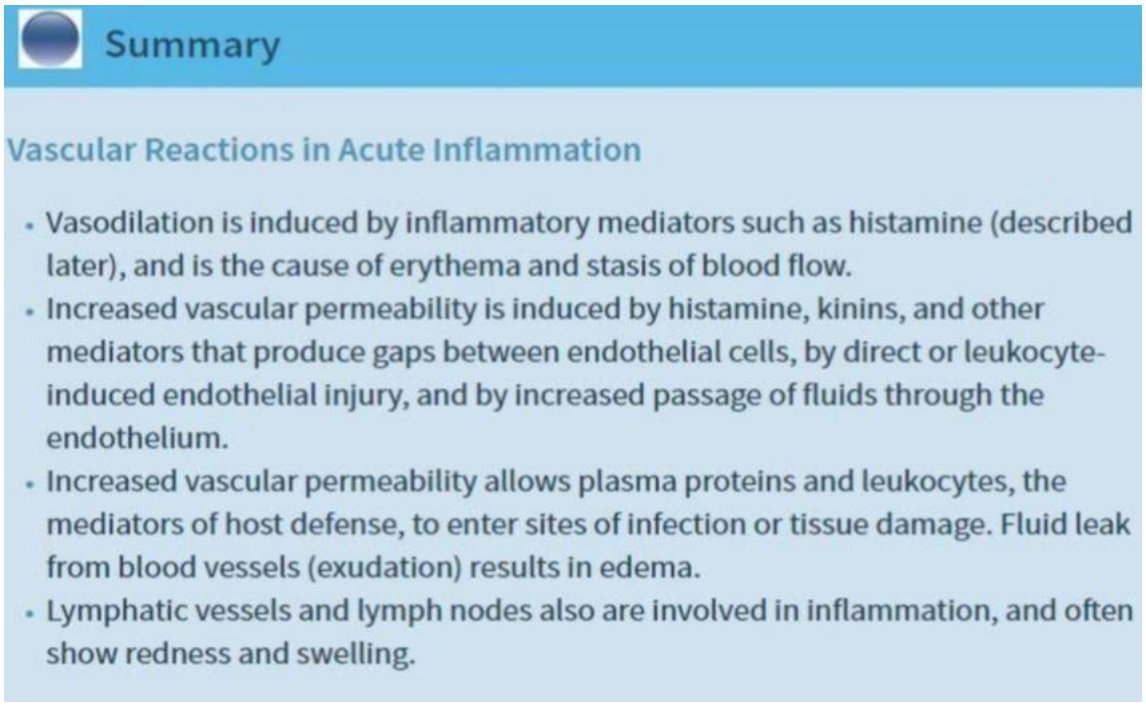
Those are lymphatic tissues where they drain many of the active processes in your body where they drain a lot of metabolic changes, in addition to draining and infiltration of cancer cells, this is why whenever we see somebody within enlarged lymph node what we call lymphadenopathy..e.g cervical ,auxiliary , and inguinal.

especially if it's not responding to a initial treatments, such as antibiotics this is the serous and these patients come back to the hospital for further investigation, where we try to figure out the major cause of lymph node enlargement whether it still inflammatory infectious, or we are dealing with stage 3 cancer (cancer from somewhere draining into those lymph nodes).

Sometimes there will be an inflammation of those lymphatic vessels which drain to the lymph nodes, we call it lymphangitis and this will lead to a lymphatic vessel proliferation and drainage of fluids into these lymph nodes causing enlargement.

The presence of enlarged lymph nodes not responding to initial antibiotics or whatever treatment we give them, we call it the persistent lymphadenopathy, always requires further investigation to make sure are we dealing with reactive inflammatory lymphadenitis or more serious process.

summary of what we have explained



What is the leukocyte role in inflammation special in acute inflammatory process?

Almost all the leukocytes play role in inflammation

1) The main component of acute inflammatory cell response is the macrophages and neutrophils, they are responsible for eliminating the microbes and the enemies by the process of Phagocytosis.

2)They are also secrete mediators which will recruit more inflammatory cells at the site of injury.

3) Remember that the migration of leukocytes from the intravascular compartment to the outside, is not a simple process, it's a multi-process which will require movement of those inflammatory cells toward the wall from inside and then adhesion then transmigration then movement toward the site of injury so we will talk about these processes also in details.

**This table is extremely important

TABLE 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular traps.
This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

*it gives you an overview of the differences between neutrophils and macrophages, their origin from where the life span of each one

remember that the lifespan of neutrophils is very short and this is why you see the more in the acute inflammatory process and if you see them in tissues and the microscopic examination this indicates an acute process rather than chronic process meaning couple days, response for activating stimuli which is more rapid in the neutrophils more prolonged in macrophages and the production of the reactive oxygen species, nitric oxide and degranulation all of them and there are difference between neutrophils and macrophages just try to read the table in more details and memorize the differences between macrophages**

-Now let's talk a little bit about the adhesions of white blood cells to the endothelium-.

We mentioned before, that after the initial vascular phase of inflammation with retraction and damage to the endothelial cells, where proteins and cells can migrate from the intravascular compartment to the extravascular compartment, the white blood cells mainly, when they move from inside to outside there are multiple steps and this is an active process, where we have margination, followed by rolling and adhering of those cells to the vascular wall, and this process also requires some receptors (selectins: initial weak adherence) and then followed by (integrins: firm strong adherence), and then letting the cells to going out from the intravascular compartment to extravascular compartment.

This carton explains the steps of how neutrophils or a macrophage moves from inside the lumen into the extravascular compartment, so that they can perform their function.

Margination is the first step, which means the movement of WBCs (neutrophils and macrophage) from the center of lumen toward the wall of it.

Then Rolling on the wall, they will be initially fast because of the initial E-selectin process where the adhesion is weak, then it will slow down, followed by the stronger attachment by integrin ligand (ICAM-1) and it's really slow down the rolling process, to prepare the neutrophils to move from inside to outside of the blood vessel.

Then the cell will move out from inside the blood vessel into the outside by a more active process which is utilizing the CD31, (CD called cluster designation), those are proteins mainly present on the surface of the cell and in each cell which is differentiated to the right side have specific types proteins.

So in the transmigration the PECAM-1 (which is another name for CD31) will damage the endothelial cells and basement membrane, so there will be a big hole in the wall, allowing the neutrophils to squeeze itself outside, (in some books they will say movement of neutrophils from inside to outside is diapedesis, other say the transmigration is called diapedesis), so those are the steps which you have to understand..

Quick summary:

Migration à Rolling à Selectins (weak attachment) à Integrins (strong attachment) à Transmigration or Diapedesis (movement of the cell itself outside through an active destruction of the endothelial cells and the basement membrane through CD31.

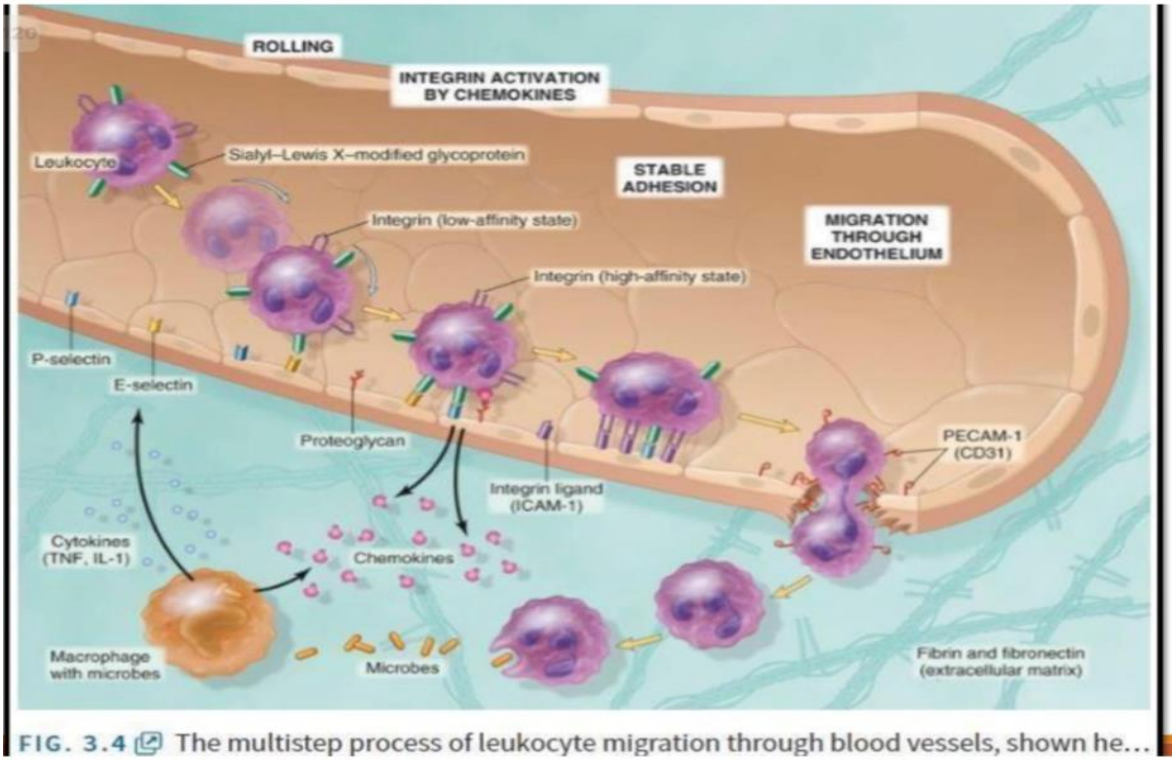


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

Then we will go to interstitium, and they will start releasing chemical mediators of inflammation, and continue their phagocytosis and intracellular killing which are steps will be explained more in details

This table isn’t required->.

TABLE 3.4 Endothelial and Leukocyte Adhesion Molecules

Family	Molecule	Distribution	Ligand
Selectin	L-selectin (CD62L)	Neutrophils, monocytes T cells (naïve and central memory) B cells (naïve)	Sialyl-Lewis X/PNAd on GlyCAM-1, CD34, MAdCAM-1, others; expressed on endothelium (HEV)
	E-selectin (CD62E)	Endothelium activated by cytokines (TNF, IL-1)	Sialyl-Lewis X (e.g., CLA) on glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
	P-selectin (CD62P)	Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin; platelets	Sialyl-Lewis X on PSGL-1 and other glycoproteins; expressed on neutrophils, monocytes, T cells (effector, memory)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naïve, effector, memory)	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	MAC-1 (CD11bCD18)	Monocytes, DCs	ICAM-1 (CD54), ICAM-2 (CD102); expressed on endothelium (upregulated on activated endothelium)
	VLA-4 (CD49aCD29)	Monocytes T cells (naïve, effector, memory)	VCAM-1 (CD106); expressed on endothelium (upregulated on activated endothelium)
	α4β7 (CD49DCD29)	Monocytes T cells (gut homing naïve effector, memory)	VCAM-1 (CD106), MAdCAM-1; expressed on endothelium in gut and gut-associated lymphoid tissues
Ig	CD31	Endothelial cells, leukocytes	CD31 (homotypic interaction)

CLA, Cutaneous lymphocyte antigen-1; *GlyCAM-1*, glycan-bearing cell adhesion molecule-1; *HEV*, high endothelial venule; *ICAM*, intercellular adhesion molecule; *Ig*, immunoglobulin; *IL-1*, interleukin-1; *MAdCAM-1*, mucosal adhesion cell adhesion molecule-1; *PSGL-1*, P-selectin glycoprotein ligand-1; *TNF*, tumor necrosis factor; *VCAM*,

This is what you need to know:

The selectins are group of proteins which are present in the endothelial cells and they are responsible for the initial weak attachment with these white blood cells, for preparing them for the next group of proteins

Integrins where stronger attachments are present and they will hold a neutrophil or WBC’s close to the endothelial cells for preparing them for PECAM-1 or CD31

PECAM-1 or CD31 where the destruction of the basement membrane will happen and the cell will squeeze itself and sneak into the outside of the blood vessels.

This is summary of the previous slides.

CD31 (PECAM-1), platelet endothelial cell adhesion molecule which is expressed on leukocytes and endothelial cells.

WBCs (through transmigration process) will pierce through the wall by collagenases (enzyme) to destroy plasma membrane, because the major components of the basement membrane is collagen type 4 and laminin.

Collagenase will increase or reduced by the function of CD31, for making a hole and helping WBCs to move outside

"Do your best. One day, you will be someone's hero". ♥