

MIRACLE Academy

قال تعالى (يَرْفَعُ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

تفريغ المناةة
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لجان الرفعات

Inflammation and Leukocyte Migration

Objectives

- Overview of the inflammatory process: initiation, inflammation, resolution, benefits and liabilities
- Major constituents
- Clinically relevant inflammatory processes
- Control of inflammation

Introduction

- “Inflame” – to set fire
- Inflammation is “A dynamic response of vascularised tissue to injury.”
- Inflammation: Local defense and protective response against cell injury or irritation or local vascular and cellular reaction, against an irritant.
- It is a protective response.
- It serves to bring defense & healing mechanisms to the site of injury.
- Inflammation is designated by adding the suffix (itis) to the end of the name of the inflamed organ or tissue. → like tonsillitis (the inflammation of tonsils)

Etiology

- Microbial infections: bacterial, viral, fungal, etc.
- Physical agents: burns, trauma--like cuts, radiation
- Chemicals: drugs, toxins, or caustic substances like battery acid.
- Immunologic reactions: rheumatoid arthritis.

بالنهاية كلهم رح يسببوا التهاب ورح نستخدم ال علاجهم
antiinflammatory drugs.

Types

- **Time course**
 - **Acute inflammation: Less than 48 hours**
 - **Chronic inflammation: Greater than 48 hours (weeks, months, years)**
- **Cell type** كل نوع من أنواع الinflammation له خلايا خاصة
 - **Acute inflammation: Neutrophils**
 - **Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).**

Cardinal Signs of Inflammation

- **Redness : Hyperemia.**
 - **Warm : Hyperemia.**
 - **Pain : Nerve, Chemical mediators.**
 - **Swelling : Exudation.**
 - **Loss of Function: Pain**
- because of increasing of blood flow to the site of inflammation.*
- because of nerve excitation and mediator release like prostaglandin.*
- because of vasodilation and histamine release.*
- Exudate is fluid that leaks out of blood vessels into nearby tissues*



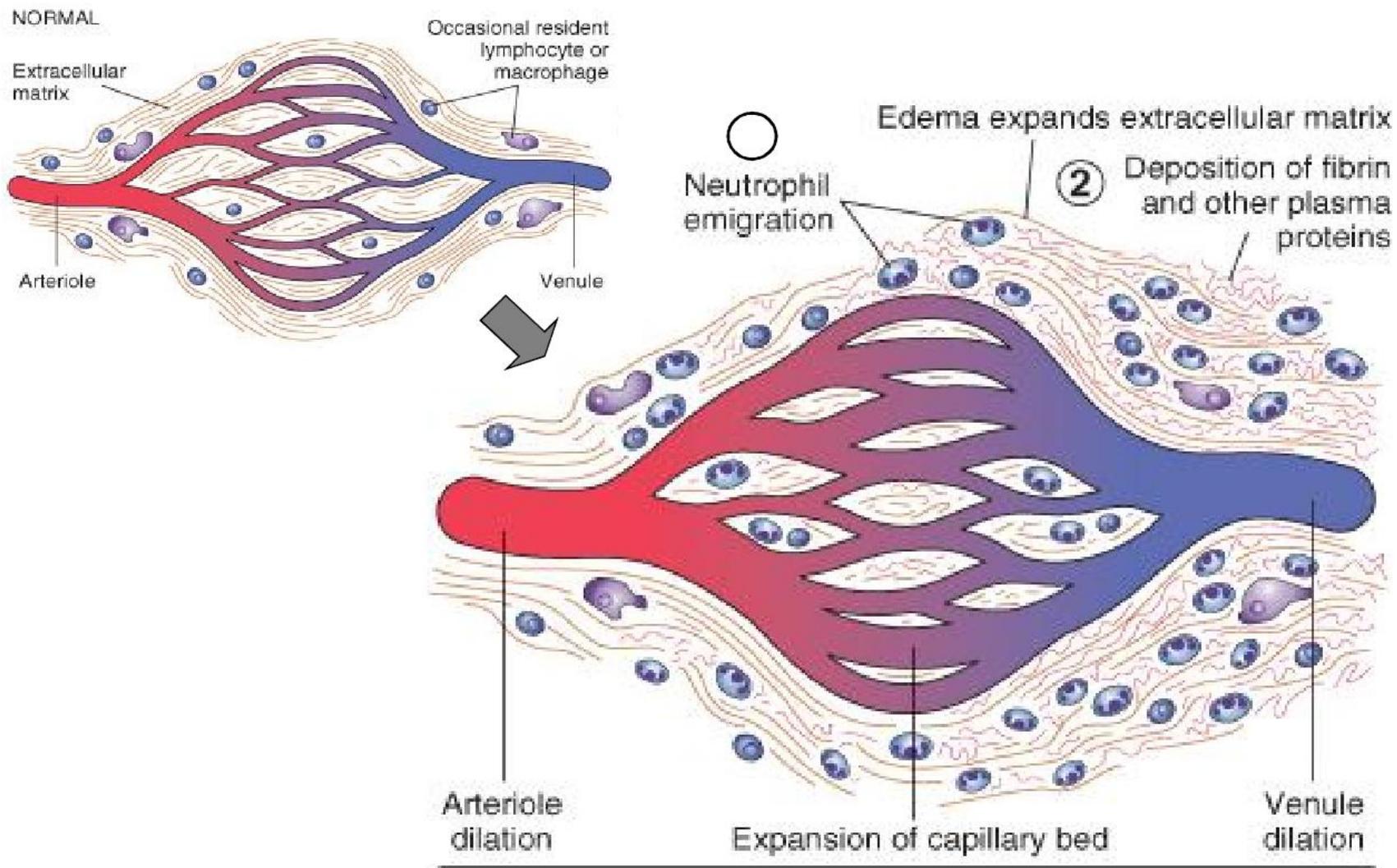
Pathogenesis

- The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.
- Three main processes occur at the site of inflammation, due to the release of chemical mediators :
 1. Increased blood flow (redness and warmth).
 2. Increased vascular permeability (swelling, pain & loss of function).
 3. Leukocytic Infiltration. → then this will cause pus formation.

1. Local Vascular Changes

- Initial temporary vasoconstriction for few seconds.
- Active vasodilatation of arterioles and capillaries by chemical mediators like histamine and passive dilatation of venules.
- Slowing of the circulation: outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood (stasis). *→ with time, this may cause clot formation.*
- Pavementation: the margination of leukocytes. Neutrophils become oriented at the periphery of vessels and start to stick.

margination is the lateral movement (drift) of leukocytes toward the endothelial walls



Increased blood flow

①

2. Leukocyte Exudation

Polymorphonuclear neutrophils

- Leukocytes (PMN's , Mphages, lymphocytes, mainly T) circulate in the blood, but often do their work in tissues.
- For T and B cells, circulation increases the chances that you'll meet your antigen.
- For both to do their jobs, however, you often have to leave the blood to enter either the lymph node or the site of damage.
- Once at the site of damage, you want to kill microbes, control the damage, and repair it.

وطبعا هاد كله مش لمسة سحرية بيكون بحاجة لأيام أو أسابيع أو شهور حسب نوع الinflammation

Leukocytes Extravasation

The leakage of lymph from a blood vessel into the tissue around it.

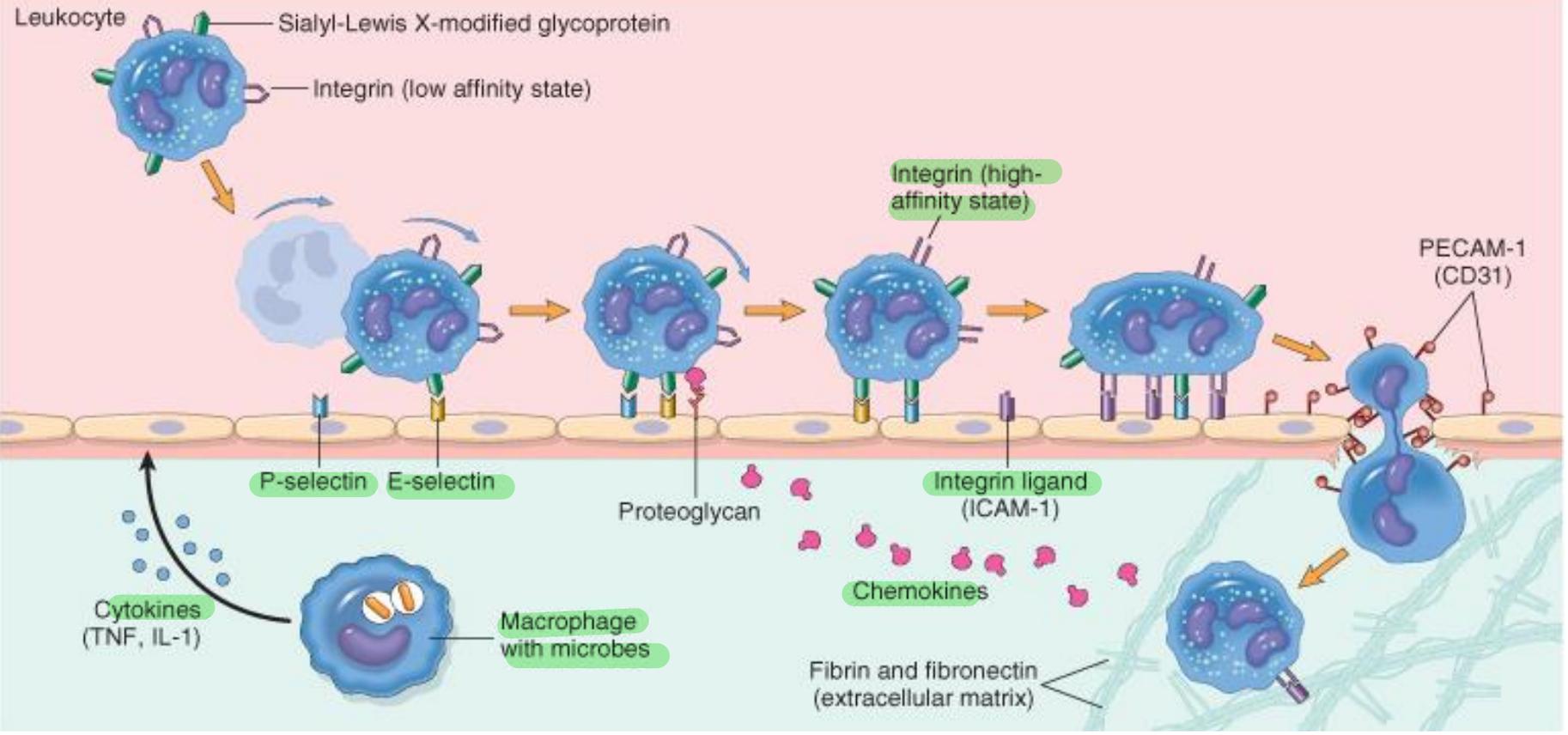
- Neutrophils are usually the first cells to move to site of infections or inflammations
- Neutrophils extravasation involves 4 main stages:
 1. Rolling: mediated by selectines
 2. Activation by chemoattractant stimulus
 3. Arrest and adhesion mediated by Integrins binding to Ig-family members
 4. Transendothelial migration

Rolling

**Integrin activation
by chemokines**

Stable adhesion

**Migration through
endothelium**



1. Rolling → تدرج

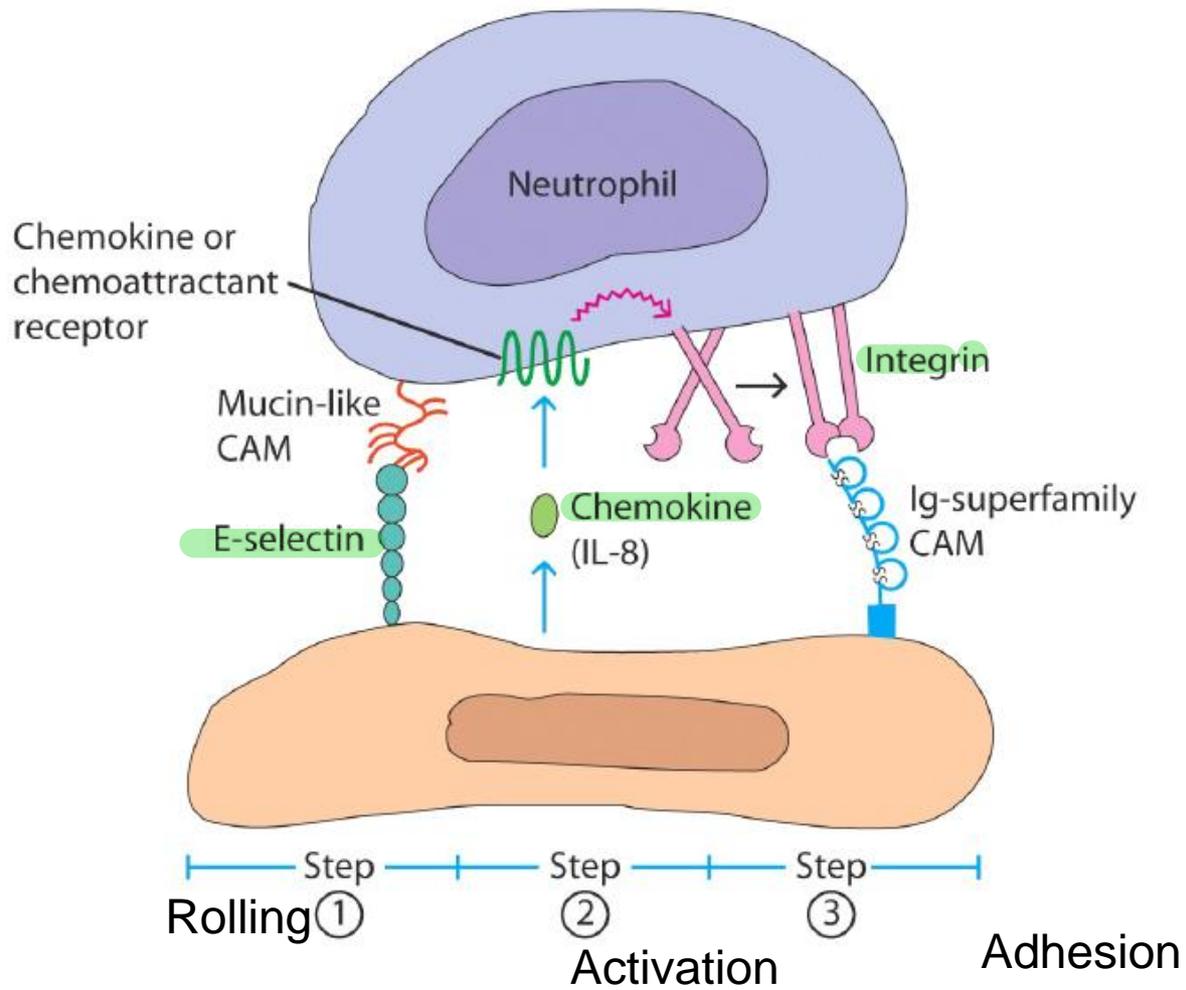
- In this step leukocytes attached loosely to the endothelium by low affinity selectines-carbohydrate interaction
- This interaction tether^{تربيط} the leukocyte briefly to endothelium but the shearing force of blood flow detached the cells soon
- Selectine molecules on another endothelial cells tether the leukocytes again, this process is repeated so the cells trumble over the endothelium “rolling”

2. Activation

- The process of rolling slows the cells enough to allow interactions between chemokines on the endothelium surface and receptors on leukocytes
- This binding leads to signal transduction events resulting in changes in confirmation and clustering of integrins on leukocytes

3. Firm Adhesion

- Binding of leukocytes to endothelium and slowing down of leukocytes allow binding of other adhesion molecules including integrins which leads to firm adhesion
- This allowed the leukocytes to binds more tightly to endothelium and it become less likely that blood force will detach them



4. Transendothelial Migration

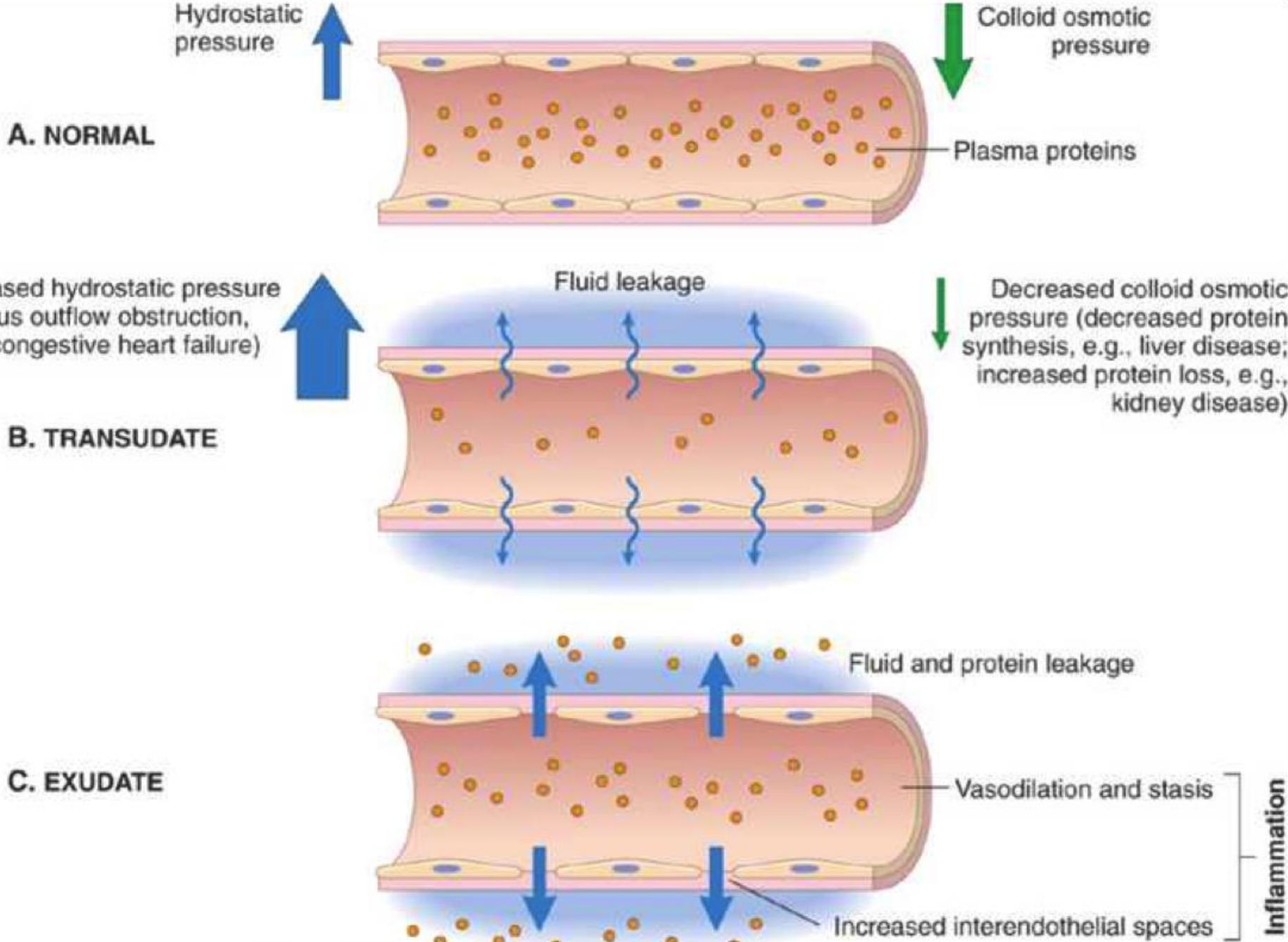
- Leukocyte then squeeze in between two neighboring endothelial cells without disrupting the integrity of these cells
- This is accomplished by binding of platelet endothelial cell adhesion molecule 1 (PECAM-1) on leukocyte with PECAM-1 on endothelial cells

من بعد هي الخطوة الـ Lymphocyte مار داخل الـ cell الـ inflamed

Lymphatics in Inflammation:

- Lymphatics are responsible for draining edema.
- Edema: An excess of fluid in the interstitial tissue or serous cavities; either a transudate or an exudate
- Transudate: An ultrafiltrate of blood plasma
 - permeability of endothelium is usually normal.
 - low protein content (mostly albumin)
- Exudate: A filtrate of blood plasma mixed with inflammatory cells and cellular debris.
 - permeability of endothelium is usually altered
 - high protein content.
- Pus: A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.

هاد الpus بيكون لونه أصفر أو أخضر حسب شدة الinflammation وطبعاً لما الواحد على الدكتور ويكون الالتهاب مجمع قيح ييفتحه الدكتور ويينظف كل السائل المتجمع وبعدين بيعقم الجرح والموضوع بيكون مؤلم خاصة اذا كان كبير مثل الالتهابات اللي بتصير بعد العملية



Function of Inflammatory Exudates

- Dilute the invading microorganism and its toxins. → to decrease its infectivity.
- Bring antibodies through the plasma to the inflamed area.
- Bring leukocytes that engulf the invading microorganisms.
- Bring fibrinogen through the plasma, which is converted, to fibrin mesh, helping in trapping the microorganism and localize the infection → to prevent the transmission of microbes to other sites

Inflammatory Mediators:

- Chemical substances synthesised or released and mediate the changes in inflammation.
 1. Histamine by mast cells - vasodilatation. → increase blood flow → cause redness and warming.
 2. Prostaglandins – Cause pain & fever.
 3. Bradykinin - Causes pain.
- Cytokines including ^{Tumor Necrosis Factor.} TNF, IL1, IL6, IL8
- Lipid mediators: prostaglandins, leukotrienes, and platelet activation factor

Cytokines and Inflammation

- Macrophages or DCs stimulated via innate immune receptors make pro-inflammatory cytokines, especially TNF (Tumor necrosis factor), IL-1, and IL-6
- TNF and IL-1 signal to endothelial cells to make them:
 - Leaky to fluid (influx of plasma; containing antibodies, complement components, etc.) → *this helps to bring the antibiotic and complement components to the site of infection*
 - Sticky for leukocytes, leading to influx of first neutrophils, later monocytes, lymphocytes
 - IL-6 promotes adaptive immune responses and has systemic effects (“acute phase response” of liver, including C-reactive protein or CRP; levels used clinically as an indication of systemic inflammation)

Your liver releases more CRP into your bloodstream if you have inflammation in your body

Negative Regulation of Inflammation

- Cells responding to innate stimuli stop making inflammatory mediators after short time period and convert to making anti-inflammatory lipids
- Killing the infectious agent and removal of the dead cells, debris, crystals, will stop stimulation of incoming inflammatory cells
- Systemic elevation of inflammatory cytokines (esp. IL-1) induce production of glucocorticoids, which are anti-inflammatory
- Regulatory T cells are also anti-inflammatory, both by blocking effector T cells and by inhibiting innate cells

Inflammation Outcomes

1. Abscess formation
2. Progression to chronic inflammation
3. Resolution--tissue goes back to normal
4. Repair--healing by scarring or fibrosis
5. Spread through lymphatics or blood or stream



Suppurative or Purulent Inflammation

- Pus: thick fluid containing viable and necrotic polymorph and necrotic tissue
- 1. Localized: ex. Abscess: Abscess is the localized collection of pus, commonly seen solid block of tissue - Example: dermis, liver, kidney, brain etc. Pus consists of partly or completely liquefied dead tissue mixed with dead or dying neutrophils and living or dead bacteria, formed of 3 zones
 - Small abscess is called boil or furuncle ^{دمل}
 - Large one carbuncle
 - Fistula pus الـ كمية كبيرة من discharge بتصير مكان الالتهاب وبيصير بتصير مثل فتحة كبيرة
- 2. Diffused: Spreading of pus to adjacent areas e.g. cellulites occurring in subcutaneous tissue . Usually caused by streptococci (gram positive bacteria)

Anti-Inflammatory Therapeutics

- NSAIDs: inhibitors of inflammation and fever (block prostaglandin synthesis)
- Glucocorticoids are also potent anti-inflammatory drugs
- Agents that block TNF are effective in treating rheumatoid arthritis, Crohn's disease, etc.
- Agents that block IL-1 are less effective for these diseases but are useful for some genetic inflammatory diseases (and are currently in clinical trials for more common conditions)