Cellular Events in Inflammation

Editing File

Objectives:

- ★ Describe the steps involved in extravasation of leukocytes from the blood to the tissues.
- ★ Know the steps at which selectins and integrins act.
- ★ Describe the meaning and utility of chemotaxis. Understand the role that chemokines play in inflammation.
- ★ Describe the steps involved in phagocytosis and the role of IgG and C3b as opsonins and receptors.
- ★ List the mechanisms of microbial killing.
- ★ Know various defects in leukocyte function.

Color Code:

Female's Notes
Male's Notes
Important
Extra

Pathology Team 441

MED441
KING SAUD UNIVERSITY

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Overview

Click here

A critical function of inflammation is to deliver leukocytes to the site of injury "LEUKOCYTE EXTRAVASATION" and to activate the leukocytes to perform their normal functions in host defense.

Leukocytes Function:

Ingest offending agents → **Kill bacteria and other microbes** → **Get rid of necrotic tissue and foreign substances.**

They may induce tissue damage and prolong inflammation, since the leukocyte products that destroy microbes and necrotic tissues can also injure normal host tissues.

Phases of inflammation:

1 Recruitment of leukocytes

2 Removal of offending agents

Definition: A multistep process involving attachment of circulating leukocytes(الموجودة في الدورة الدموية) to endothelial cells and their migration through the endothelium (**extravasation**)

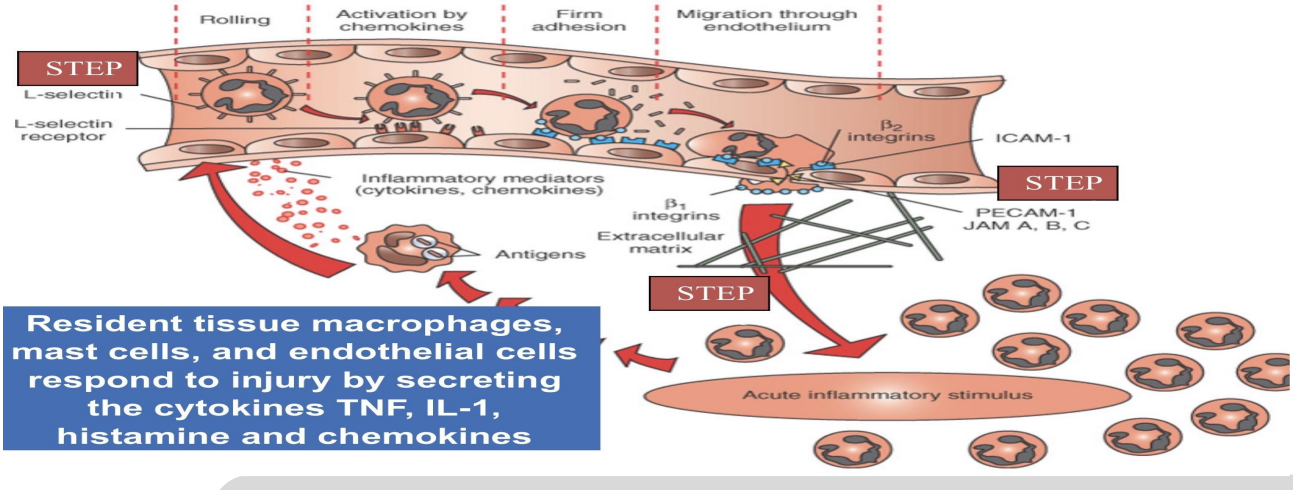
In the lumen:
i. Margination
ii. rolling
iii. adhesion to endothelium
(NORMALLY DOESN'T)

3 Steps

Transmigration across the endothelium (**diapedesis**)

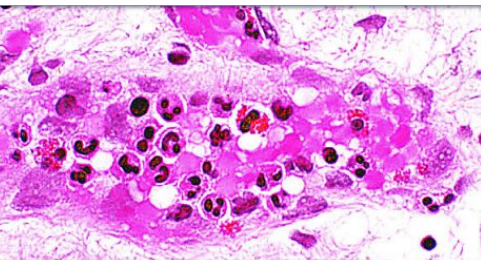
Migration in interstitial tissues toward a chemotactic stimulus **(Chemotaxis)**

Histamine have major role in higher sensitivity type 1 and role in inflammation.Histamine causes vasodilation and increase vascular permeability.

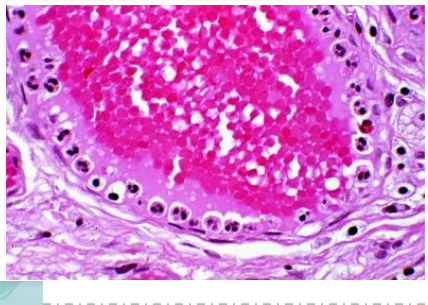


*Before anything happened Resident tissue macrophages,mast cells, and endothelial cells respond to injury by secreting the **cytokines TNF**, **IL-1, histamine and chemokines which stimulate selectin** and stimulate the cells to migrate toward the site of injury or infection

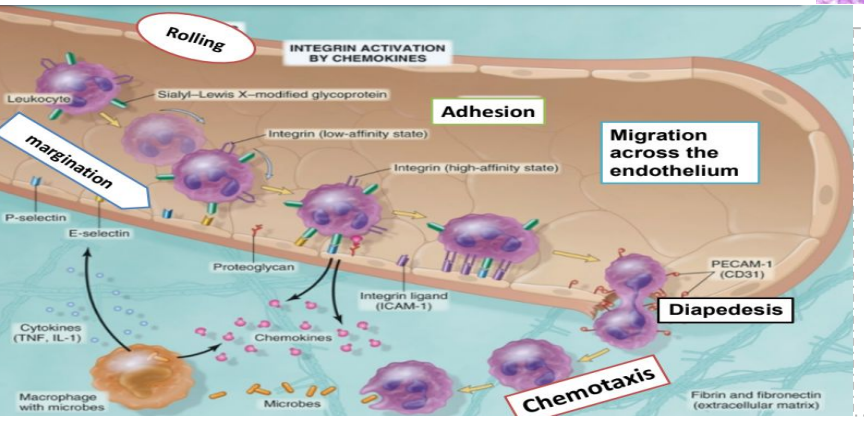
1.1 Margination and 1.2 rolling (In the lumen)



neutrophils in the center of venule in normal situation



Neutrophils in inflammation



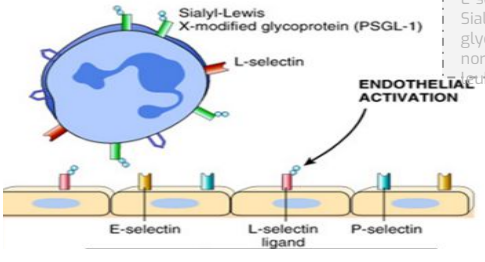
Margination is the first step of leukocytes action during acute inflammation cells.
Because blood flow slows early in inflammation (stasis), the endothelium can be lined by neutrophils (**pavementation**)

1.3 Adhesion molecules and receptors (overview)

	The site	Activated by	Bind to
E-selectin	endothelium	TNF&IL-1	Sialyl-Lewis X Glycoprotein PSGL-1 (In leukocytes)
P-selectin	Endothelium & platelets	Weibel-Palade bodies	Sialyl-Lewis X Glycoprotein PSGL-1
L-selectin	**Endothelium** & leukocytes	------	Integrins
Integrins	leukocytes	C5a & LTB4	L-selectin (ligands)
ICAM-1 & VCAM-1	Endothelium	TNF&IL-1	Integrins
PECAM-1	**extracellular matrix and on cell surfaces.**	Histamin	Doesn't bind “contraction”

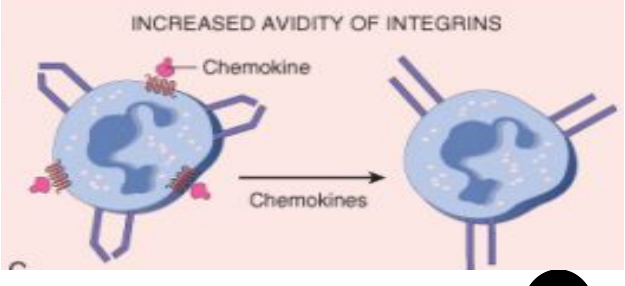
1.3 Adhesion molecules and receptors (In the lumen)

Selectins (carbohydrate-binding adhesion molecules)ألتصاق ضعيف"In endothelium and consist of: lueckucyts
1. E-selectin: confined to endothelium induced by TNF&IL-1
bind to Sialyl-Lewis X glycoprotein and slow the leukocytes
2. P-selectin: present in endothelium and platelets from Weibel-Palade bodies
bind to Sialyl-Lewis X glycoprotein and slow the leukocytes
3. L-selectin: expressed on most leukocyte and endothelium



E-selectins + Sialyl-Lewis X glycoprotein are normally on leukocytes' surface

Integrins ألتصاق قوي/تكون مغلقة عادةً لكن وقت inflammation تتحفز وتفتح
An adhesion molecule which is seen mainly located on **leukocytes** and activated during acute inflammation (in normal situation they are inactive)
made up of α and β glycoproteins chains,expressed on leukocytes and bind to ligands on endothelial cells (L-selectin)
Activated by C5a & LTB4 (small proteins that stimulate movement of neutrophils and induce changes in the blood vessels walls) resulting in firm adhesion with vessel wall



The immunoglobulin family molecules
ICAM-1 (intercellular adhesion molecule 1)
VCAM-1 (vascular cell adhesion molecule 1)

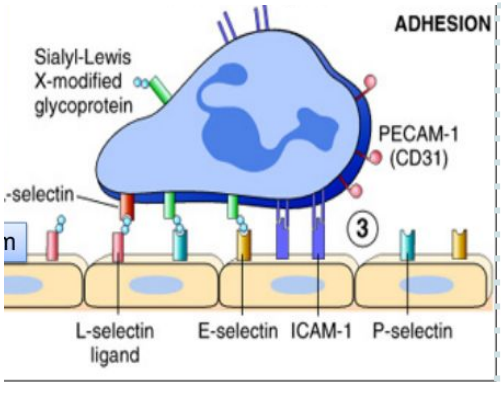
Activated by IL-1 and TNF
On venular endothelial cells.

Mucin-like glycoproteins: PECAM-1
Platelet endothelial cell adhesion molecule
these glycoproteins are found in the extracellular matrix and on cell surfaces.

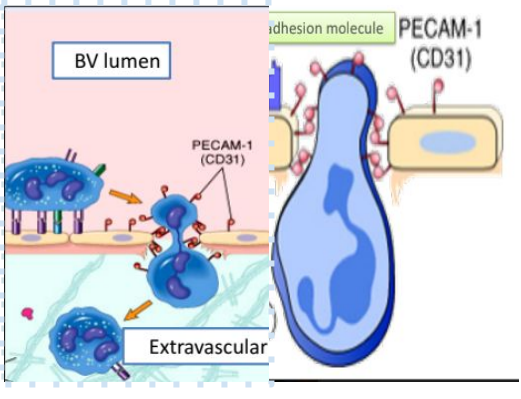
Neutrophils moving along the venular endothelium dissolve the venular basement membrane (release type IV collagenase) exposed by previous histamine-mediated endothelial cell contraction and enter the interstitial tissue.

*all leukocytes use the same pathway to migrate from the blood

2. Transmigration or Diapedesis

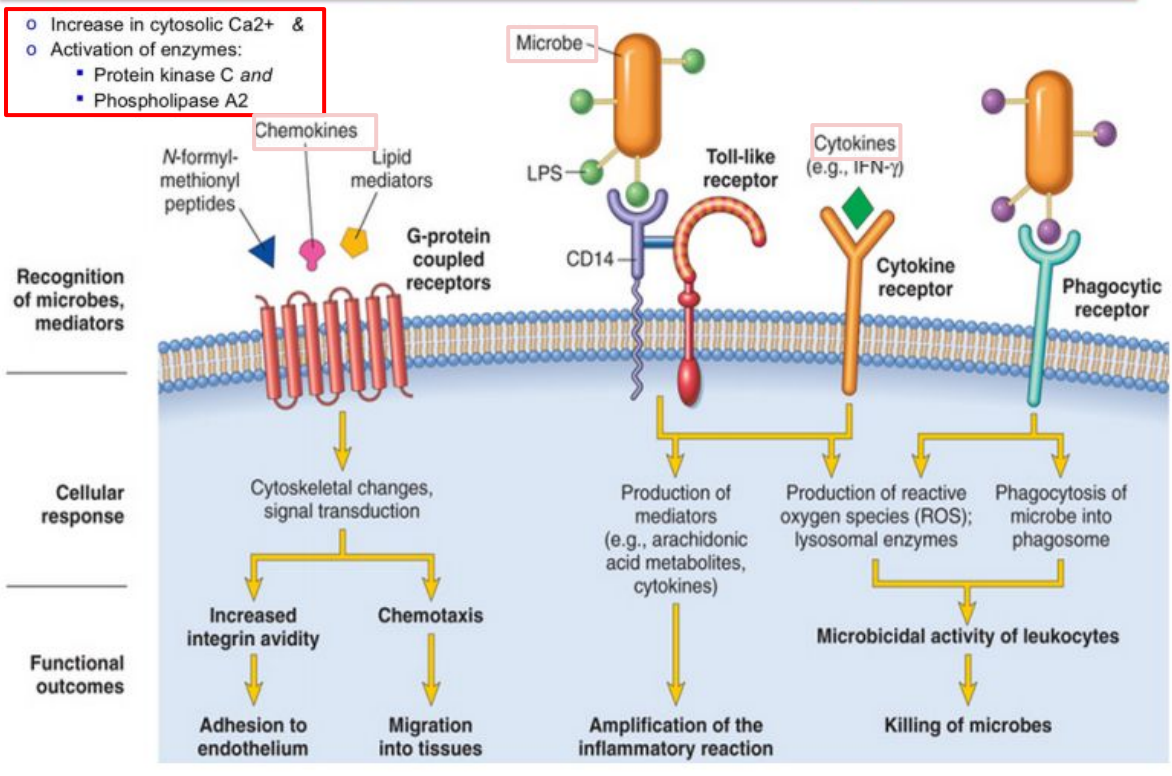


2-Migration of the leukocytes through the endothelium is called: Transmigration or **Diapedesis** occurs in the postcapillary **venules**



3. Chemotaxis

Definition : locomotion oriented along a chemical gradient(Chemoattractants)
Neutrophils are attracted by bacterial products, IL-8, C5a & LTB4
All these chemotactic agents bind to specific seven-transmembrane
G-protein-coupled receptors on the surface of leukocytes



Dr.note: The chemotactic agents may be cytokines or microbial toxin or chemokines

Steps of Leukocytes activation

- Phagocytosis (Further explanation on the next two slides)
- Intracellular destruction
- Liberation of substances that destroy
- extracellular microbes and dead tissues
- Production of mediators

Phagocytosis

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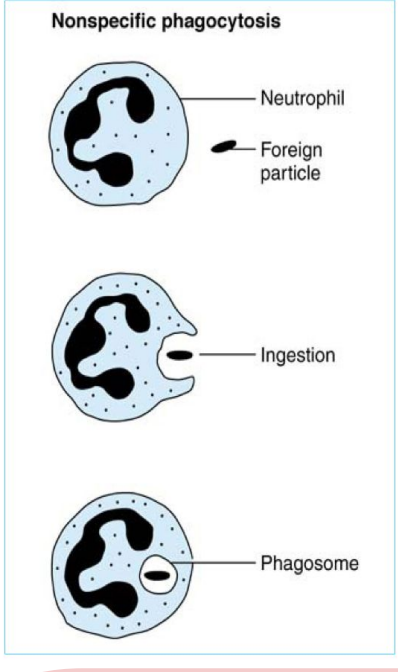
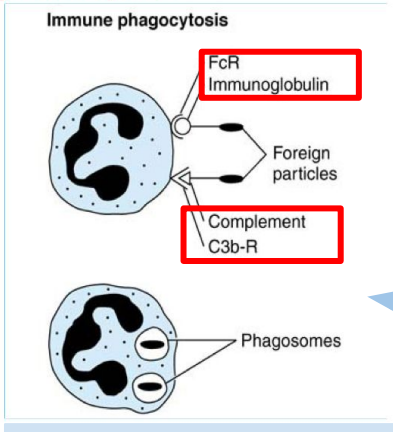
Phagocytosis involves three distinct but interrelated steps

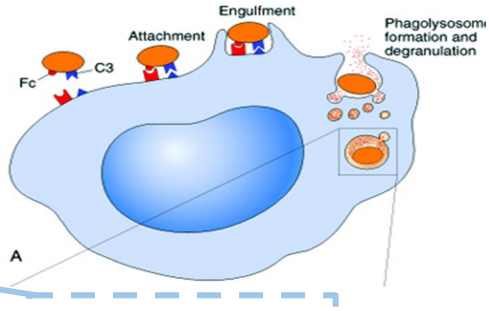
1st	**Recognition and Attachment** of the particle to be ingested by the leukocyte
2nd	**Engulfment**, with subsequent formation of a phagocytic vacuole
3rd	**Killing or Degradation** of the ingested material.

Phagocytosis by neutrophils





Immune phagocytosis is much more efficient than non specific phagocytosis



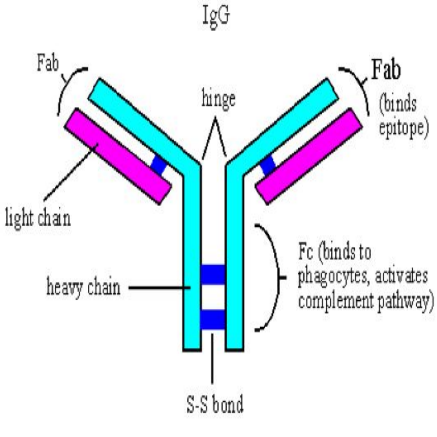
Stimulation of receptors on the cell membrane of leukocytes

1. Recognition & Attachment (opsonization)

The process of coating a particle, such as a microbe, to target it for phagocytosis
The substances that do this are opsonins.
These substances include:

- antibodies (IgG) Immunoglobulin G e.g. FC
- complement proteins (C3b)
- And others: **lectins** (mannose-binding lectin (MBL), **collectins,fibronectin, fibrinogen, and C-reactive protein**
- These can coat microbes and are recognized by receptors on phagocytes (Fc and C3b receptors).

هم الأهم : IgG, C3b

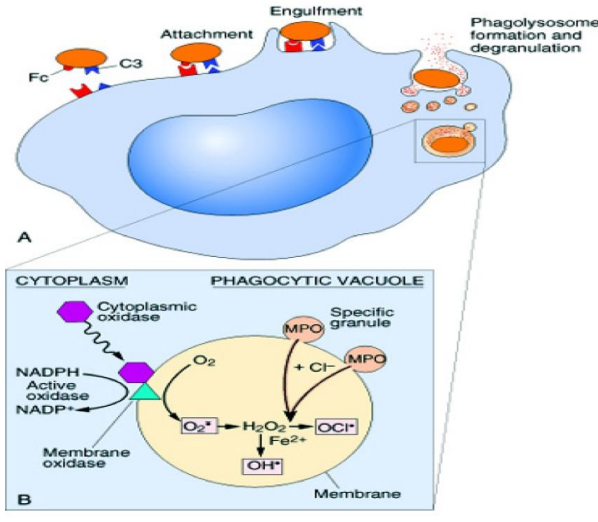


2. Engulfment

During engulfment, extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed, eventually resulting in complete enclosure of the particle within a phagosome

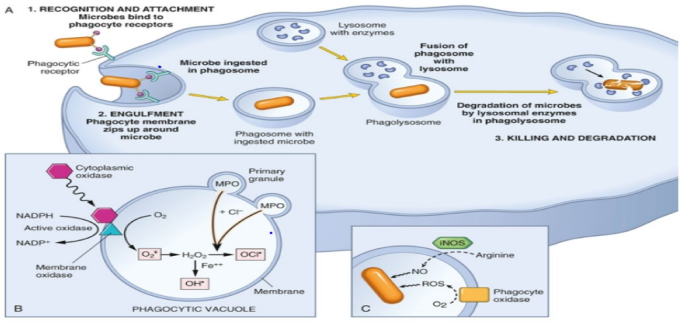
The phagocytic vacuole then fuses with a lysosomal granule, resulting in phagolysosome

The hydrolytic enzymes of the lysosomes will hydrolyze the cell membrane of the microbe



3. Killing & Degradation

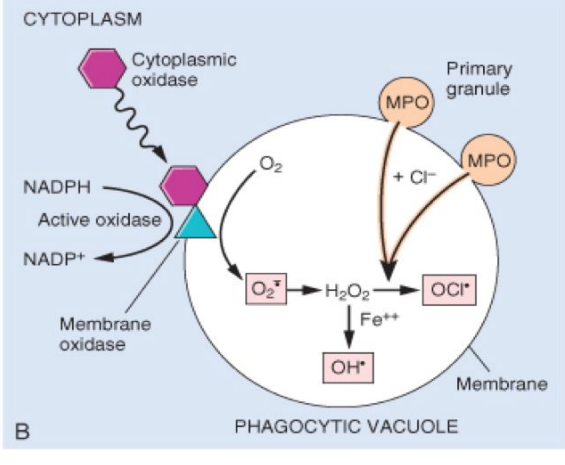
Mechanism was explained in the video from the previous slide



Oxygen-dependent

The H2O2-MPO-halide system is the most efficient bactericidal system in neutrophils

$$O_2 \xrightarrow{\text{Oxidase}} O_2^- \xrightarrow{\text{SOD}} H_2O_2 \xrightarrow{\text{MPO}} HOCl$$



Oxygen-independent

through the action of substances in leukocyte granules. These include :

- Bactericidal permeability increasing protein (BPI)
- Lysozyme
- Lactoferrin
- Major basic protein
- Defensins

Neutrophil granules contain other enzymes, such as elastase, that also contribute to microbial killing the lysosomes will release its hydrolytic enzymes and destroy the cell membrane of the microbe

· Can potentiate further inflammation by damaging tissues
·These harmful proteases are controlled by a system of anti-proteases in the serum

It's a good mechanism but not efficient as the oxygen dependent

Leukocyte Adhesion Deficiency

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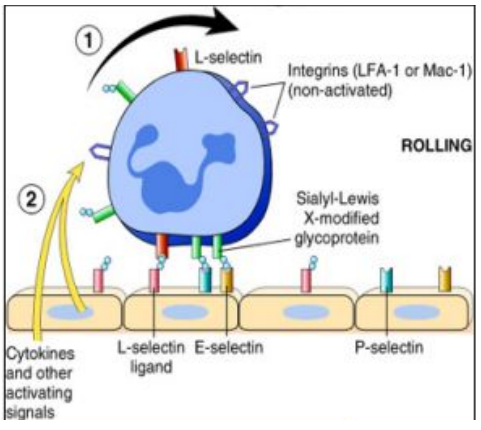
1. LAD type 1 is a deficiency of β2-integrin

These normally binds selectins.

2. LAD type 2 is mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (PSGL-1)



Clinical findings:

- Delayed separation of umbilical cord الحبل السري
- Increased circulating neutrophils (leukocytosis due to loss of the marginating pool)
- **Poor wound healing**
- **Recurrent bacterial infection that lack pus formation** عدوى بكتيرية متكررة

The type of emigrating leukocyte varies with the age of the inflammatory response
In **most** forms of acute inflammation: neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, then are replaced by monocytes in 24 to 48 hours
neutrophils are more **numerous** in the blood, they respond more **rapidly** to chemokines,but are **short-lived**; they undergo apoptosis and disappear after **24 to 48 hours**,whereas monocytes survive longer.
In viral infections → lymphocytes
hypersensitivity reactions and parasitic → eosinophil
Chronic inflammation→ lymphocytes, plasma cells and macrophages

Properties of Neutrophils & Macrophages

	neutrophils	macrophage
origin (اعرفوا أنهم من bone marrow)	Hematopoietic stem cells(HSC) bone marrow	1-(HSC) bone marrow (inflammatory reaction) 2- residents cell from yolk sac or liver in fatel (stem cell)
Lifespan	24/28h	1- days to week (inflammatory) 2- years (residents)
Their response	Rapid -short lived-degranulation and enzymatic activity	Slow -prolonged - new gene transcription

Defects in leukocytes function

Chèdiak-Higashi syndrome

Protein involved in organelle membrane fusion(no-phagolysosomes)

- Protein trafficking defect (microtubule defect)deficiency of formation of phagolysosomes
- Autosomal recessive

Clinical features

- Increased risk of pyogenic infection
- Neutropenia (defect in generation from BM) low neutrophils count
- Giant granule formation (granules formed cannot move in cytoplasm)
- Defective primary hemostasis (platelet granule are not secreted)
- Albinism No production of melanin pigments
- Peripheral neuropathy

Chronic granulomatous disease

Decreased oxidative burst
it's a genetic disease which appears from birth

Click here

1 X-linked: NADPH oxidase (membrane component)

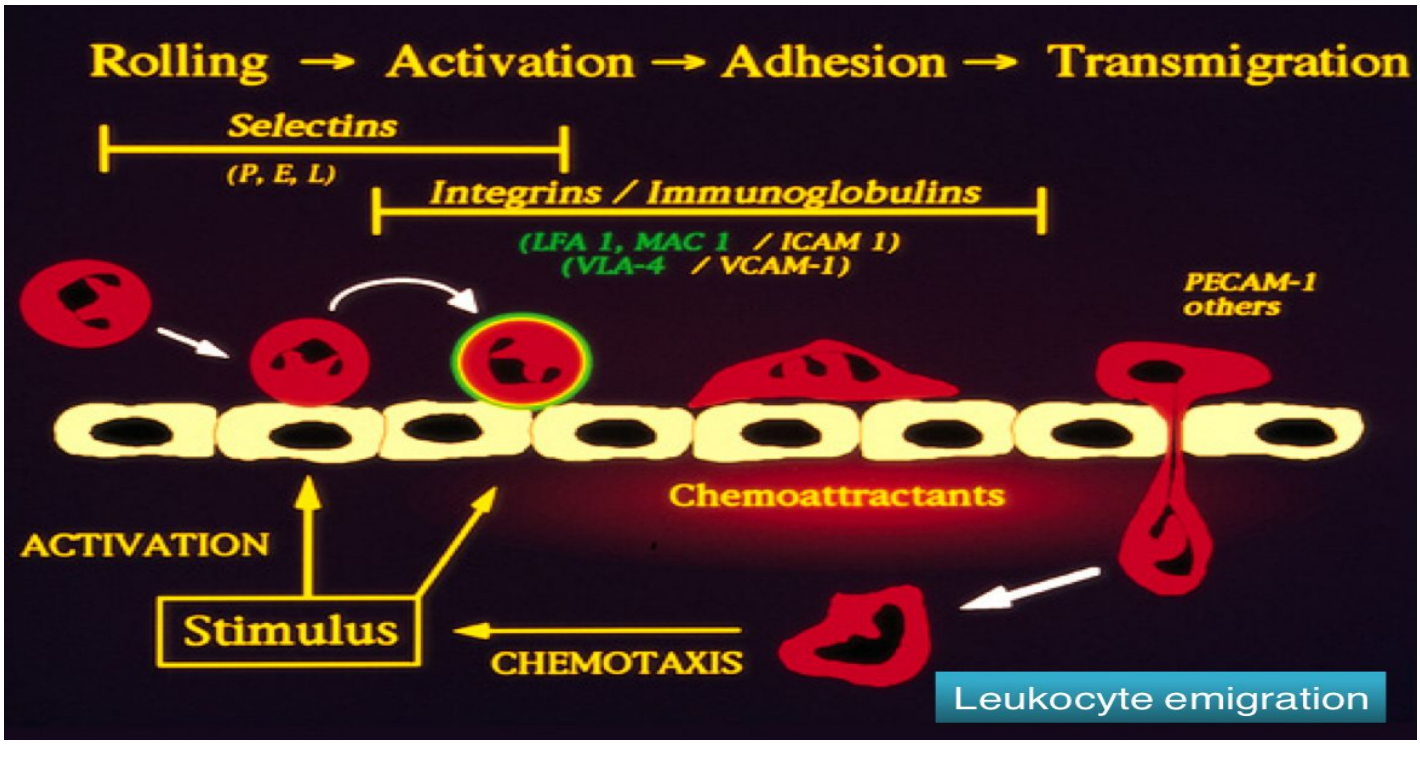
2 Autosomal recessive:

- NADPH oxidase (cytoplasmic components)
- Myeloperoxidase deficiency: (absent MPO-H2O2 system) pt. have increased risk of candida infection

Infection and granuloma formation with catalase positive organisms e.g. S aureus, Norcardia and Aspergillus

Defects in leukocytes function

Genetic	Acquired (The activities will decrease)
Leukocyte adhesion deficiency 1&2	**Cause:** Thermal injury, diabetes, malignancy, sepsis, immunodeficiencies –Chemotaxis
Chèdiak -Higashi syndrome	**Cause:** Hemodialysis, diabetes mellitus –Adhesion
Chronic granulomatous disease: 1. X-linked: NADPH oxidase (membrane component) 2. Autosomal recessive: • NADPH oxidase (cytoplasmic components) • Myeloperoxidase deficiency	**Cause:** Leukemia, anemia, sepsis, diabetes, neonates, malnutrition –Phagocytosis and microbicidal activity



★ MCQs

Q1: What is the first step of leukocytes action?			
A. Transmigration	B. Opsonization	C. Engulfment	D. none
Q2: From the following receptors , which one is founded on the surface of leukocyte ?			
A. ICAM-1	B. VCAM-1	C. P-selectin	D. L-selectin
Q3:Phagocytosis is accomplished by which leukocyte?			
A. Neutrophils	B. plasma cell	C. T cells	D. none
Q4: Which of the following substance is opsonin			
A. IL-1	B. FC	C. C3b	D. B&C
Q5: The acquired defect that will lead to chemotaxis reduction			
A. Leukemia	B. Malnutrition	C. Thermal injury	D. Hemodialysis
Q6: The mechanism that uses free radials to kill the microbe is			
A. Migration	B. Oxygen dependent	C. Opsonization	D. Oxygen independent

★ SAQ

Q1:What are the neutrophils attracted by in chemotaxis?
Slide 5
Q2:what are the difference between neutrophils and macrophages?
Slide 8
Q3:what is opsonization?
Slide 6
Q4: how does the oxygen independent degradation works ?
Slide 7

Answers: Q1:D Q2:D Q3:A Q4:D. Q5:C. Q6:B

★ Case Question

By 441 pathology team

A male come to hospital due to recurrent fever infections due to weakness in his immune system response, the tests shows a decrease in white blood cells count, which of the following could be the cause of this low immunity ?

Diabetes

Kidney failure

Liver Failure

Malnutrition

Answer :

Diabetes : because it's one of the acquired factors that cause defects in leukocytes function

“Champions keep playing until they get it right.”

Leaders:
Lama Al-Jamili
Salem Abokhanjar

Sub-Leader:
Manar Al-Abdullah

Members:

Lama Bin Salamh
Rahmah Alzahrani
Noyer Awad
Rahaf alamri
Layan Alhelal
Taif alshehri
Renad Aldawayan
laila almeshariy
Alanoud Albawardi
Reema Alrashedi

Shouq Alhathal
Tarfa albaz
Jumana AL-qahtani
Lama Alrumaih
Ayah Sayed
Shahad Helmi
Norah Alsewailem
Leen Alhadlaq
Arwa Alenzi
Reem Al Kulaibi

Mohammed Alwahibi
Sultan Alosaimi
Rakan alobaid
Abdullah Abdulrazaq
Ibrahim Al Hazza

Organizer:
Aya Alhossain

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