Inflammation

Done by: Nadeen Zuadat

Redness, Swelling, pain, Hotness, Loss of function.

Signs

Inflamation

- protective response, not a disease
- Self - controlled
- protects us from bacteria and injurious agents
- innate immune System (non-specific immune System).

involves three things:

- host cells
- Chemical mediators
- Blood vessels

What is collateral damage? The damage for our own cells caused by the cells and chemical mediators produced by inflammation. ← Thats why we take anti-inflammatory drugs.

(unintending outcomes)

* Note: There is a good balance between inflammatory and anti-inflammatory mechanisms.

cells will undergo death by apoptosis — chemical mediators will decay

Main inflammatory cells:
1. Neutrophils ← First Line of defense. — Acute inflam. within 1 hour.
2. Monocyte — 24-48 hours
3. Lymphocytes (B & T) & plasma cells. — several days

chronic

* Monocyte is the predominant cell in chronic inflam.

* Note: All inflammatory cells have a receptor.

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Steps:

1. Recognition → receptors
   pattern-recognition → Non-specific receptors

2. Vasodialation → The cell signals for more cells to move to the inflammatory site
   - Redness
   - Hotness
   - Swelling
   - Pain

   ← As a result vasodialation

3. Transmigration:
   - cells migrate blood → tissues
   - Directional movement (chemotaxis) (chemical, movement)
   - Movement toward the infectious agent.

* difference between hotness and fever

Localized	generalized
- Sign of inflammation	- Not necessarily a sign of inflammation
- related to vasodialation	- related to mediators (PGIs)

infection & inflammation

- Disease
- protective mechanism.

* infection causes inflammation, but its not only the only cause.

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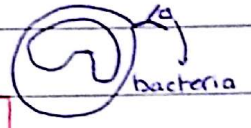
So, back to receptors:

Receptors

Specific receptors
- Detect one specific antigen.
- used in immunologic reactions.

Non-specific receptors (Pattern recognition receptors)
- They recognize a pattern of molecules.
- In inflammation, we need non-specific receptors
- Recognizes many antigens
- For example: They can recognize DNA, Despite the sequence of DNA (They see a pattern)
- Other example: They can recognize all the family of polysaccharide in bacteria

Two families



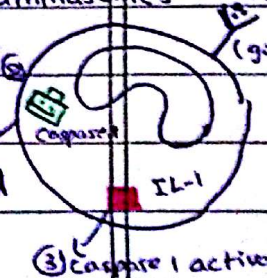
Toll-like receptors

- Only recognize infectious agents such as LPS, DNA, RNA, endotoxins ---
- Found either on the plasma membrane / inside the cytoplasm.
- So, they can recognise extracellular & ingested microbes.
- ... bacteria → infection → nucleus → DNA → mRNA → transcription → translation → Synthesis of inflammatory mediators

Inflammosomes

- multi-protein cytoplasmic complexes.
- Recognizes products of cell injury,
- For example: DNA in the cytoplasm, mitochondrial components leaking out, crystals)
- =P ... لما الواحد ياكل وناس ... → ↑ purine → uric acid crystals → inflammasomes
- like Toll-like receptors are either found on the cell membrane or inside the cytoplasm.

inflammatory reaction.



Q* How can we stop the inflammatory response

By blocking IL-1

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Back to the second step:

Vascular changes in acute inflammation

The first thing that happens → transient vasoconstriction for 1 or 2 second (Due to neural reflex)

increase in permeability

most common mechanisms of vasodialation:

[1] contraction of endothelial cells → Gap junctions widens → lymphocyte move out.

* immidiate but short lived.

cause / common signal (mediator) ⟹ Histamine because it is the first to act not the most potent

[2] Endothelial cell damage:

Any destruction to endothelial cells → increased permeability.

* can start immediately but lasts for several hours / days.

[3] Transcytosis:

Transcellular transport of certain extracellular components.

[4] Angiogenesis (Neovascularization) new blood vessels are formed.

- Because they are not well-formed → high permeability.

* inflammation → vasodialation → ↑ permeability → cells & Fluids move out → Edema

Exudate

- cells, cellular debris, proteins go out
- high specific gravity.

Transudate.

- change in pressure → water only goes out. (E.g.)
- Low specific gravity.

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Leukocyte recruitment

Driving WBCs toward the infection site.

Steps [1] Margination [2] Rolling [3] firm adhesion [4] Transmigration [5] chemotaxis.

[1] Margination: Moving of WBCs toward the margins of blood vessels, in order to reach the tissue (site of infection).

Vasodialation → water moves out → blood becomes more viscous → So WBCs will move slower. → Developement of stasis

Imp — The only PHYSICAL step.

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[2] Rolling: Loose attachment and detachement of WBCs to the endothelial cells → most of the Kinatic energy will be lost → stop completely

SELECTINS: Loose adhesion between Endothelial cells & WBCs

- E-selectins → Endothelium
- P-selectins → platlets and endothelium.
- L-selectins → Leukocytes

— Note: Selectins will be expressed only when the inflammation starts (They need to be synthesized).

Cytokines → increase the expression of selectins → Synthesis or Secretion of selectins

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[3] Firm adhesion:-

BY INTEGRINS

نفس الادكي اللي حكينا عن selectin موجود هون

- IL-1 & TNF activate endothelial cells to express integrin Ligands

Inactive integrin $\xrightarrow{\text{Chemical mediator}}$ Active integrin

[1] conformational changes.

[2] Polymerization.

[4] Transmigration:

(WBCs / blood ⟶ tissue)

- stimulated by chemokines.

- WBCs have to penetrate two barrier which are the endothelial cells & the cell membrane.

[1] Endothelial cells:-

[1] contraction of endothelial cells ⟶ permeability increases ⟶ WBCs will squeeze through Gap junctions.

↑ The 1st mechanism alone is not enough.

[2] PECAM1 ⟶ Binds to WBCs and helps them leave vessels through junctions.

[2] Cell membrane:

No junctions / its just supportive

So, how can they go out? They'll break the basement membrane through enzymes (collagenases for example).

* How do WBCs move? Through Diapedesis forming pseudopods

Ameba. اميبا

5 Chemotaxis:-

WBCs → injurious agent.

This needs certain mediators → bacterial products
- → Cytokines, especially chemokines (IL-8
- → complement component (C5a).
- → Products of arachidonic acid (Leukotriens B4).

Leukocyte activation → To get rid of the injurious agent.

Through → 1- phagocytosis: → Macrophages & neutrophils

لـ ← الموجودة

→ Three steps
- * Recognition: can recognize host proteins which are the opsinons.
- * Engulfment
- * Killing by → Lysosomal enzymes such as acid hydrolases (elastase).
  - (intracellularily)
  - → ROS (reactive oxygen species)
  - → oxygen free radicals → unstable → highly reactive.

زي لما الواحد ياكل كيكه P=

Killing of the كيكه happens inside our body=P

Imp

Steps of forming these radicals:

Oxygen —NADPH oxidase→ Oxygen superoxide.
- NADPH oxidase: U. regulated ← needs 6-7 subunits to be activated.

Oxygen Superoxide —Dismutase→ Hydrogen peroxide (H_2O_2)

Hydrogen peroxide —Myeloperoxidase→ OCl^- → extremly toxic.
- Myeloperoxidase: U imp enzyme in neutrophils.

Notes: viral infections → Lymphocytes first reacts.

Eosinophils → Allergic reactions.

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2- Intracellular destruction of phagocytosed microbes and dead cells.

3- Production of mediators.

4- Liberation of substances that kill extracellular microbes and dead tissues → Ex: NET → Trap.

Neutrophil ← N, E → Extracellular

- Extracellular fibrillar networks produced by* neutrophils, in response to an* extracellular infection.

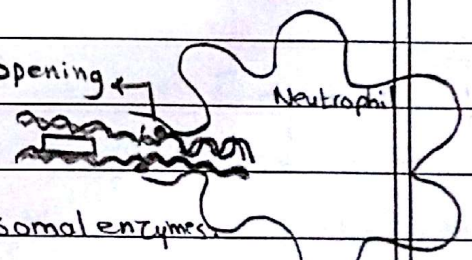
- contain nuclear chromatin and enzymes.

هون زي الكبكه الحزبانه (1) بصيرلها Killing inside =P

The Killing happens outside the cell! ← - Trap & Kill infectious agents

The trap contains:

* Anti-microbial substances like Lysosomal enzymes and toxic materials, DNA ⇒ irreversible injury.



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Kinin System

Complement System

Locally produced

Pre formed & stored (Act quickly) → Histamine & Serotonin

cell derived mediators

Need to be synthesized Longer time

plasma Protein derived mediators

- Inactive → Active at the site of inflammation
- In the blood
- Synthesized in the Liver.

either

Chemical mediators

→ most of them are proteins

One mediator → several actions

One mediator → several cells (receptors)

regulated by:

Quick decay → Arachidonic acid metabolites

Enzymatic inactivation.

Histamine By → histaminase.

BradyKinin By → Kininase.

Elimination

- Oxygen free radicals by antioxidants.

Inhibition → complement inhibitory Proteins.

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Families of chemical mediators

cell derived

- pre synthesized → Vasoactive amines
  - Histamine
    - vasodialation
    - ↑ permeability
    - Edema
    - Preformed in mast cells, basophils & platelets.
    - Inactivated by histaminase.
  - Serotonin.
    - 5c histamine
    - imp ↓ Vasoconstrictor
    - Neurotransmitter
    - imp for clot formation.
- need to be synthesized → Arachidonic acid metabolites
  - present in cell membrane
  - During inflammation, phospholipase A_2 releases it from membrane cytoplasm
  - AA → 20 carbons / 4 double bonds.
  - Also called Eicosanoids.
  - source: sea food & eggs.
  - pathway:

Phospholipid
↓ phospholipase A_2
Arachidonic acid
↓ Two families of enzymes

- Cyclooxygenase → Prostaglandins
  - $PGF_{2\alpha}$ / PGI_2 / PGD_2 / PGE_2 ←
  - TXA_2 ←
- Lipooxygenase → Lipoxins + Leukotriens
  - LTA_4, LTB_4 ←

Cyclooxygenase pathway:-

produces:

PGE_2
PGD_2] Same effect

- Vasodialation.
- Edema.
- Pain & Fever

PGI_2 (Prostacyclin) — Opposing effect
Thromboxane A_2

PGI_2

- Produced from endothelial cells by prostacyclin Synthase.
- Vasodialation
- inhibits platelet aggregation.

Thromboxane A_2

- produced from platelets by Thromboxane Synthase A_2
- vasoconstriction
- platlet aggregation & clot formation.

Lipooxygenase pathway:

Leukotriens

imp: 1- LTB_4 → chemotactic agent that is produced mainly in neutrophils.

LTC_4
LTD_4
LTE_4] causes 1- bronchospasm.
2- ↑vascular permeability
- produced mainly in mast cells.

Lipoxins.

LXA_4
LXB_4

imp. * Anti-inflammatory effect.
- inhibit neutrophil adhesion & chemotaxis.

Non-steroidal anti-inflammatory drugs

COX1
↓
TXA_2
↓
Vasoconstrictor & platlet agonist
- antitrombotic activity

COX2
↓
PGI_2
↓
vasoconstrictor & inhibitor of platelet aggregation
→ prothrombic activity

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Chemical mediators — continued.

1* Cytokines: - TNF
- IL-1
- IL-6

TNF, IL-1:
- Endothelial activation.
- Stimulate expression of Adhesion molecules on endothelial cells.
- Systemic effects: fever, Lethargy, Decreased blood pressure.

- chemokines: For chemotaxis
  most imp chemotactic agent: IL8

2* Neuropeptides: - Substance P
- Transmit pain signals
- prostaglandins (ذي مينج)

3* Nitric Oxide: (NO) - Source of nitrogen free radicals
imp in phagocytosis

- Synthesized by Nitric oxide Synthase (NOS) has several types
  - Type 1: Neuronal — No role in inflammation
  - Type 2: Inducible — imp. role in inflammation.
    in macrophages & endothelial cells.
  - Type 3: secreted in endothelial cells
    imp in vasodilation.

→ Effects of NO: - Microbicidal
- Vasodilator
- Anti-inflammatory effect → Reduced Leukocyte recruitment

(Lipophilic)

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Histamine
Nitric Oxide
Platlet activating factor
PGs E_2 & D_2
Prostacyclin

} Vasodilation.

Nitric oxide
Lipoxins
↓
Anti-inflammatory effects.

خلصنا الـcell-derived mediators بيناتنا

plasma derived mediators بال

1. Complement System 2. Coagulation System 3- Kinin System.

* They are Synthesized in the Liver under the influence of IL-6.

II Complement System:

($C_1 \rightarrow C_9$)

- One complement activates the others, So all the complement chemotactic agents System becomes activated.
- other mediators stimulate the complement System Such as cytokines & Kinin System mediators.

Three pathways by which the complement System is activated

Classical pathway
- During immunological reactions (Antigen - Antibody).

Alternative Pathway
Bacteria (polysaccarides) + complement component (direct contact)

Lectin - mannose pathway
Sugar from our body + mannose from the microbe

T3

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C_{5a} → imp. for chemotaxis.

C_{3a} → imp for inflammation (anaflatoxin).

Classical pathway → by C_3 convertase

Lectin pathway → C_3 → Lysis

Alternative pathway → by C_3 convertase.

C_{3b} → opsonin.

The complement System Kills by

① Opsonization

② inflammation

③ Mac complex (membrane attack complex) → Attacks the membrane → Lysis

[2] Kinin System

Kininogen (inactive form) —Kallikrein→ Kinin (Active form.) effects:

- → Activates pain receptors (Prostaglandins & neuropeptides يزيد)
- → Vasodialation.
- → chemotactic agent
- → stimulates complement System.

[3] Coagulation System:

HAGEMAN FACTOR (coagulation factor 12)

Activates:

- → clotting cascade → Fibrin
- → Anti-clotting (Fibrinolytic) System → plasmin
- → Kinin System mediators.

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- Systemic effects of inflammation - Acute phase proteins.

1. Fever
2. increased heart rate & blood pressure.
3. Leukocytosis (increase no. of WBCs in the blood). but they are inactive
4. ↑ acute phase proteins

لما تكتر بزيدوا

upto (40-100.000)

which means Leukemia like ← Leukemoid

Caused by cytokines (TNF, IL-1, IL-6)

Fever → starts with pyrogens

- → External → The bacteria itself (bacteria LPS)
- → internal < IL-1, TNF > cytokines

↓

prostaglandins

↓

hypothalamus effect.

Fever need cytokines & prostaglandins.

- Acute phase proteins:-
- Some types of inflammation increase the acute phase proteins:-

* CRP → C reactive protein → الهم، الهم.
* SAA → serum Amyloid protein

} - They act as opsinons.

* Fibrinogen → ↑ fibrinogen ⇒ ↑ aggregation.

(Pw) * under the influence of fibrinogen → ESR increases

Erythrocyte sedimentation rate

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Outcomes of acute inflammation

- Resolution, regeneration & repair
- chronic inflammation
- Scarring → Extensive damage.

Morphologic patterns of inflammation:-

From mildest → most severe.

1. serous inflammation: vasodialation
   - Transudate & changes in pressure. (mild inflammation)
   - زي الحروق الخفيفة
   - blister (epidermis انفصل عن dermis منفصل عن Fluid.

   doesn't mean zero cells but they are minimal, occasional

   what is the outcome? Resolution ← imp

2. Fibrinous inflammation:
   - water + fibrin (mesh work of fibrin)
   - What we can see under the microscope
   - complete resolution or scarring may happen depending on the severity.
   - Damage will happen to the pericardium (not) the heart itself.

   Fibrin (Polymerization)

3. Suppurative:

   Pus ⟺ neutrophils.

   usually → Severe enough to cause scar.

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4 Ulcer: I'm losing the tissue.

usually doesn't happen in a solid organ (~~Liver~~, ~~Lung~~)

examples: Stomach ulcer (peptic ulcer), esophageal ulcer.

Chronic inflammation

- The cells have changed neutrophils (polynuclear) → mononuclear cells → Kidney shaped & Macrophages.

- So the most dominant cells in chronic inflammation → Monocytes (Macrophages).

- tissue destruction, repair (Angiogenesis & Fibrosis) → also present in acute inflammation but to a lesser extent

Causes:
- Toxic substances (prolonged) → like the uric acid crystals.
- Acute inflammation —becomes→ chronic.
- The infection stays persistent (TB, fungi, virus).

Notes: Normally, we have macrophages in our body for protection purposes.

Naming of macrophages (According to the place)

- Liver → Kupffer cells.
- CNS → microglial cells
- lung → Alvelar macrophages
- Spleen & Lymph nodes → Sinus histiocytes.

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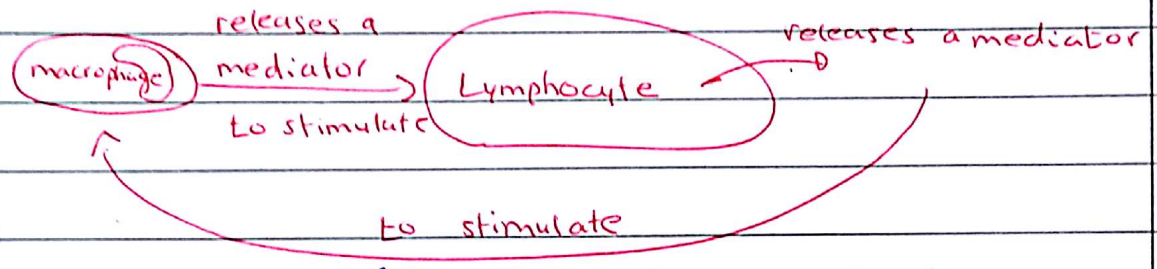
② According to the pathway they are stimulated by :-

Macrophage : stimulated by 2 pathways

- Classical (M_1) → inflammatory cells & phagocyte
- Alternative (M_2) → Anti-inflammatory

→ Other cells of chronic inflammation:

* Lymphocytes: Macrophages & Lymphocytes love each other.



(Bidirectional stimulation)

* plasma cells: - Develop from Activated B-Lymphocytes.
  - produce antibodies against persistant antigens or against altered tissue component.

* Eosinophils: - imp in
  - → parasitic infection.
  - → Immunologic reaction & Allergy. (mediated by IgE)

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Granulomatous inflammation.

- A specific type of chronic inflammation, seen mainly in TB.
- Occurs ① when there is persistent T cell response to certain Microbes
  ② when there is a forein body (Like glass), that cant be eaten by macrophages.
- Diseases that cause granuloma: TB - Leprosy - Sarcoidosis.
- caseous necrosis ⟺ $\boxed{\text{Only}}$ in TB.
- Sometimes necrosis might happen in the center → cells completely die & converted to Pink material
  * under the microscope (cheese-like appearance)
  * No cell boundaries remain.

Good Luck everyone!

Nadeen Ziadat

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