NFLAMMATION

Lecture 3

Chemical Mediators in Inflammation and

Patterns of Acute Inflammation

Notes on Dr. Ammar C. Al-Rikabi's handout,
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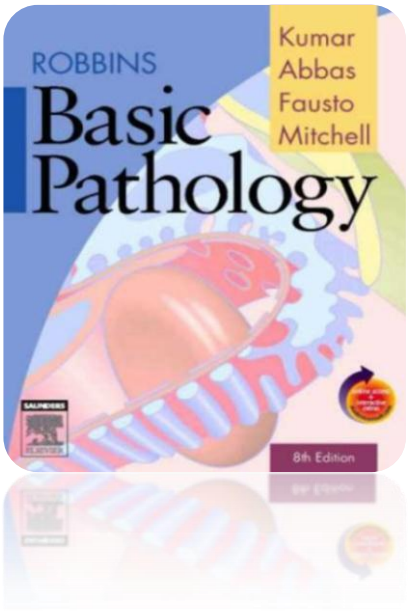

First year Medicine-Foundation Block

Pathology Team

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Please note: This paper does not replace the main sources, it's only a facilitator

Acknowledgement

Dear colleague, this paper was a result of hours and days of hard work
from both female & male pathology teams...
All what they want from you is "Dua'a"

Objectives:

Upon completion of this lecture, the student should:

-List and describe the outcome of acute inflammation.

-Recognize the different pattern of inflammation.

-Define the chemical mediators of inflammation.

-Know the general principles for chemical mediators.

-Know the cellular sources and major effects of the mediators.

-List the most likely mediators of each of the steps of inflammation.

Chemical mediators outcome of acute inflammation

Outcomes of Acute Inflammation:

Acute inflammation may have one of the four outcomes:

After inflammation, the tissue should go back to normal which as)*Complete resolution*
(known as complete resolution

in a limited amount is good Fibrosis)*Healing by connective tissue replacement (fibrosis)*
(for the tissue, if it exceeded that amount it is no longer good for the tissue

-*Progression of the tissue response to chronic inflammation*

-*Abcess formationn*

- **Some diseases start as chronic from the beginning, while others can start as acute and develop to chronic inflammation**
- **After macrophages clean the tissue they undergo apoptosis**
- **Apoptosis is not associated with inflammation, but inflammation is associated with apoptosis (in inflammation, some cells undergo apoptosis)**

Morphologic Patterns of Acute Inflammation

-Several types of inflammation vary in their morphology and clinical correlates. Why?

-The severity of the reaction

-specific cause

-the particular tissue

-site involved

Morphologic Patterns of Acute Inflammation

1 - SEROUS INFLAMMATION

2- FIBRINOUS INFLAMMATION

3- SUPPURATIVE OR PURULENT INFLAMMATION

4- ULCERS

1- SEROUS INFLAMMATION: marked by the outpouring of a thin fluid **(accumulation of large amounts of fluid due to separation between epidermis and dermis)**

If injury only affects the epithelium (epidermis) it will regenerate leaving no scar, if the injury reaches the connective tissue (dermis) it will leave a scar because the connective tissue cannot regenerate

2- FIBRINOUS INFLAMMATION:

(Fibrinogen turns to fiber(collagen) and accumulates in the cavity)

A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura (larger molecules such as fibrinogen pass the vascular barrier)

Fibrinous exudates may be removed by fibrinolysis, if not: it may stimulate the ingrowth of granulation tissue (*organization*)

3-**Morphologic Patterns of Acute Inflammation SUPPURATIVE OR PURULENT INFLAMMATION**:

characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid caused by as pyogenic (pus-producing) bacteria **(e.g. streptococci)**

Abscesses : localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space

4-**ULCERS**

An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue **(if the defect is only in the superficial layer(epithelium) it heals and it is called erosion not ulcer)**

Fistula : A tract between two surfaces.

Fistula is treated by surgery
We can find fecal material in the fistula
It is caused by an infection or chronic constipation
The difference between Fistula and sinus is that a fistula is opened from both sides while a sinus is opened from one side

What are mediators?

Chemical mediators of inflammation are substances produced during inflammation inducing a specific event in acute inflammation. **(Some chemical mediators are harmful if they are excessively produced e.g. excess histamine causes bronchospazm)**

General principles for chemical mediators

-The production of active mediators is triggered by:

microbial products

-host proteins, such as the proteins of the complement, kinin and coagulation systems

(these are themselves activated by microbes and damaged tissues)

General principles for chemical mediators

Most mediators have the potential to cause harmful effects.

Therefore, there should be a mechanism to checks and balances their action. -

Mediator function is tightly regulated by:

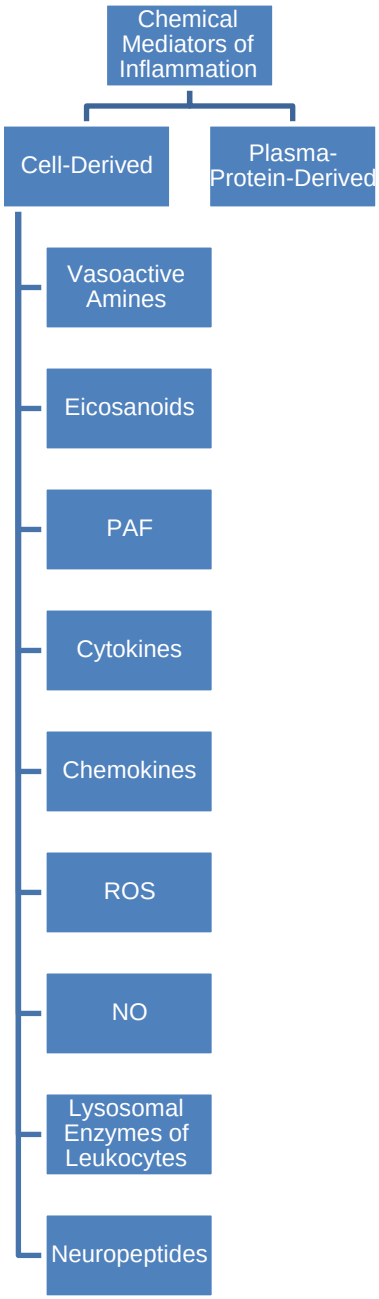
- decay (e.g. AA metabolites)

- inactivated by enzymes (kininase inactivates bradykinin)

- eliminated (antioxidants scavenge toxic oxygen metabolites)

Source of Chemical mediators

Plasma -derived:	Cell-derived:
1-Complement 2-kinins 3-coagulation factors Many in “pro-form” requiring activation (enzymatic cleavage)	1-Synthesized as needed (prostaglandin) 2-Preformed **(In cell),** sequestered **(in vacuoles)** and released (mast cell histamine)



Vasoactive Amines
Histamine & Serotonin

Among first mediators in acute inflammatory reactions

-Preformed mediators in secretory granules

Histamine

Source: many cell types, esp. mast cells, circulating basophils, and platelets

Stimuli of Release:

Physical injury

Immune reactions

C3a and C5a fragments

Leukocyte-derived histamine-releasing proteins

Neuropeptides

Cytokines (e.g. IL-1 and IL-8)

Actions:

1-ARTERIOLAR DILATION

2-INCREASED VASCULAR PERMEABILITY (venular gaps)

3-ENDOTHELIAL ACTIVATION

Inactivated by:

Histaminase

Serotonin
(5-HT) (5 Hydroxytryptamine)

Source: Platelets

Action: Similar to histamine

Stimulus: Platelet aggregation

-Eicosanoids :

Source:

Leukocytes

Mast cells

Endothelial cells

Platelets

-PAF :

(Cytokines are produced from macrophages and lymphocytes) -Cytokines:

Polypeptides

Actions:

Involved in early immune and inflammatory reactions

Some stimulate bone marrow precursors to produce more leukocytes

Cytokine of Acute inflammation:

Interleukin (IL-1) & TNF **(Very important in controlling inflammation)**

Chronic Inflammation:

Interferon-γ INF- γ & Interleukin (IL-12)

Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

- Chemokines (Chemo- attractants)

Small proteins

They are chemoattractants for leukocytes

Main functions:

Leukocyte recruitment & activation in inflammation

Normal anatomic organization of cells in lymphoid and other tissues

- Reactive Oxygen Species (ROS)

Synthesized via NADPH oxidase pathway

Source: Neutrophils and Macrophages

Stimuli of release: Microbes

Immune complexes Cytokines

Action: Microbicidial (cytotoxic) agent

- Nitric Oxide (NO)

Short-lived

Soluble free-radical gas

Functions:

Vasodilation

Antagonism of platelet activation (adhesion, aggregation, & degranulation)

Reduction of leukocyte recruitment

Microbicidial (cytotoxic) agent (with or without ROS) in activated macrophages

- Lysosomal Enzymes of Leukocytes

Neutrophils & Monocytes

Enzymes:

Acid proteases

Neutral proteases (e.g. elastase, collagenase, & cathepsin)

Their action is checked by:

Serum antiproteases (e.g. α1-antitrypsin)

Neuropeptides

Small proteins

Secreted by nerve fibers mainly in lung & GIT

Initiate inflammatory response

e.g. Substance P :

Transmits pain signals

Regulates vessel tone

Modulates vascular permeability

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Chemical Mediatoars of inflammation

PLASMA PROTEASES

A variety of phenomena in the inflammatory response are mediated by plasma proteins that belong to three interrelated systems

1. Kinin
2. the complement
3. clotting systems

Complement protein

C3a & C5a ➔ Increase vascular permeability (^ histamine) anaphylatoxins

C5a ➔ Chemotaxis

C3b ➔ Opsonization **(increases phagocytosis)**

C5-9 ➔ membrane attack complex **(Attract cell membrane of bacteria)**

Role of Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins Histamine Nitric oxide
Increased vascular permeability	Vasoactive amines Bradykinin Leukotrienes C4, D4, E4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	C5a Leukotriene B4 Chemokines IL-1, TNF Bacterial products
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites Nitric oxide