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Cellular events in inflammatory process

A Graduation Project Submitted to the Department Council of the Internal and Preventive Medicine-College of Veterinary Medicine/ University of Al-Qadisiyah in a partial fulfillment of the requirements for the Degree of Bachelor of Science in Veterinary Medicine and Surgery.

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

فَتَعَٰلَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ ۗ وَلَا تَعْجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَىٰٓ إِلَيْكَ وَحْيُهُۥ ۖ وَقُل رَّبِّ زِدْنِى عِلْمًا ﴿١١٤﴾

صَدَقَ اللهُ العَظِيمُ

من سورة طه

Summary

Inflammation is a local response (reaction) of living vascularized tissues to endogenous and exogenous stimuli. The term is derived from the Latin "inflammare" meaning to burn. Inflammation is fundamentally destined to localize and eliminate the causative agent and to limit tissue injury. Thus, inflammation is a physiologic (protective) response to injury. Inflammation is itself not to be considered as a disease but as a salutary operation consequent either to some violence or to some diseases".

The inflammatory response involves a highly coordinated network of many cell types. Activated macrophages, monocytes, and other cells mediate local responses to tissue damage and infection. At sites of tissue injury, damaged epithelial and endothelial cells release factors that trigger the inflammatory cascade,

along with chemokines and growth factors, which attract neutrophils and monocytes. The first cells attracted to a site of injury are neutrophils, followed by monocytes,

lymphocytes (natural killer cells [NK cells], T cells, and B cells), and mast cells Monocytes can differentiate into macrophages and dendritic cells and are recruited via chemotaxis into damaged tissues. Inflammation-mediated.

Chapter one ((INTRODUCTION))

1- Introduction:

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation , and acts by removing injurious stimuli and initiating the healing process(1) . Inflammation is therefore a defense mechanism that is vital to health(2). Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation. However, uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases(3).

Cellular changes The most important feature of inflammation is the accumulation of white blood cells at the site of injury(4). Most of these cells are phagocytes, certain "celleating" leukocytes that ingest bacteria and other foreign particles and also clean up cellular debris caused by the injury(5). The main phagocytes involved in acute inflammation are the neutrophils, a type of white blood cell that contains granules of cell-destroying enzymes and proteins(6). When tissue damage is slight, an adequate supply of these cells can be obtained from those already circulating in the blood. But, when damage is extensive, stores of neutrophils—some in immature form—are released from the bone marrow, where they are generated. To perform their tasks, not only must neutrophils exit through the blood vessel wall but they must actively move from the blood vessel toward the area of tissue damage(7). This movement is made possible by chemical substances that diffuse from the area of tissue damage and create a concentration gradient followed by the neutrophils(8). The substances that create the gradient are called chemotactic factors, and the one-way migration of cells along the gradient is called chemotaxis. Large numbers of neutrophils reach the site of injury first, sometimes within an hour after injury or infection. After the neutrophils, often 24 to 28 hours after inflammation begins, there comes another group of white blood cells, the monocytes, which eventually mature into cell-eating macrophages. Macrophages usually become more prevalent at the site of injury only after days or weeks and are a cellular hallmark of chronic inflammation(9).

Chapter two literature review

2- literature review :

2-1-The cells in inflammation

2-**1-1-Neutrophils**:

which target microorganisms in the body, can also damage host cells and tissues (10)Neutrophils are key mediators of the inflammatory

response, and program antigen presenting cells to activate T cells and release localized factors to attract monocytes and dendritic cells (11).

2-1-2- Macrophages :

are important components of the mononuclear phagocyte system, and are critical in

inflammation initiation, maintenance, and resolution (12). During inflammation, macrophages present antigens, undergo phagocytosis, and modulate the immune response by producing cytokines and growth factors.

2-1-3- **Mast cells:**

which reside in connective tissue matrices and on epithelial surfaces, are effector cells that initiate inflammatory responses. Activated mast cell release a variety of inflammatory mediators, including cytokines, chemokines, histamine, proteases, prostaglandins, leukotrienes, and serglycin proteoglycans (13).

Inflammation resolution processes that rectify tissue homeostasis include reduction or cessation of tissue infiltration by neutrophils and apoptosis of spent neutrophils, counter-regulation of chemokines and cytokines, macrophage transformation from

classically to alternatively activated cells, and initiation of healing (14,15)

Chronic inflammation occurs when acute inflammatory mechanisms fail to eliminate tissue injury (16), and may lead to a host of diseases, such as cardiovascular diseases, atherosclerosis, type 2 diabetes, rheumatoid arthritis, and cancer (17).

2-1-4 Eosinophils:

Eosinophils are white blood cells that are responsible for combating Infection by parasitic helminthes and arthropods. The Eosinophils make up About 1.5% of the total White Blood cells(18).

The cytoplasmic granules are distinct. They are membrane bound Structure with a moderately dense matrix in which is embedded a dense Structure of crystalline appearance. The predominant protein in this crystalloid Is major basic protein (MBP) which is direct toxic to number of helminthes and protozoa. Moreover, eosinophils have a complement of enzymes similar to Those of neutrophils but lack detectable lysosome, phagocytin and neutrophilic Basic protein. They contain an eosinophilic oxidative proteins as major basic Protein, eosinophilic cationic protein, eosinophilic derived neurotoxin and Eosinophilic peroxidase. Moreover they contain anti-inflammatory enzymes as Histaminase, kinase and arylsulphatase. They are phagocytic and produce pus if Present sufficient numbers. The sources, generation time and life span of Eosinophils is similar to that of neutrophils(19).

2-1-**5-Lymphocytes:**

Lymphocytes originated from lymphoid stem cell in fetal life and Produced in lymph nodes, bone marrow, thymus and in the lymph follicles of Many mucous membranes Lymphocytes aren't phagocytic and primarily Associated with the host's immune response. They are less mobile than Macrophages and probably respond to chemotaxis. Each lymphocyte is preprogrammed during its maturation to recognize only one antigen but all Lymphocytes circulate in blood can recognize more than Antigen.(20)

Lymphocytes can classified into two main classes. The first is called B-Lymphocytes and the second is called T-lymphocytes.

T lymphocyte

T lymphocytes are a group of cells that have passed through the thymus (and been acted on by the hormone thymosin) during early biological life. T-cells are the center-piece of the immune system. T-cells of various sorts are Predominant throughout the lymph nodes except in and around germinal Centers (cortex of lymph nodes), periarterial lymphoid sheath in spleen white Pulp. Around 80% of circulating lymphocytes are T-cells.

Young T-cells differentiate into many subtypes, which act as regulators and Effector. T cells divided according to surface expression accessory molecules Into two subsets, T4 and T8. Following activation of T cell by specific antigen, The lymphocytes transform into effector cells T cell. The effector cell can Classify to those doing its function after contact with cells or that release of Soluble cytokine mediators(21).

B lymphocytes

Another class of lymphocytes, which when activated produce freely Circulating immunoglobulins (antibodies). B lymphocytes are responsible for humeral immunity. B-cells predominate in the follicles (germinal centers) of The lymph nodes and are more common than T-cells in the red pulp of the Spleen and in the bone marrow. Around 15% of circulating lymphocytes in the Peripheral blood are B-cells. Stimulation of B-lymphocytes by specific antigen Resulting in formation of plasma cell and synthesize antibodies specific for Stimulating antigen. In the germinal centers, antigen-antibody complexes are Presented to B-cells by the dendritic follicular cells. B-cells have surface Immunoglobulin, Fc receptors, C3b receptors, and CD40(22).

2-1-6-Epithelioid

Epithelioid cells are activated macrophages with abundant pale foamy Cytoplasm, vesicular nuclei. The epithelioid cells contain numerous Mitochondria, Golgi apparatus and abundant rough endoplasmic reticulum. They are less phagocytic than macrophages. The ultra-structure suggested that The function is mainly secretory rather than phagocytic.. Epithelioid surface Properties seem to be changed so that they lie closer to each other similar to Prickle cells in the squamous epithelium.

2-1-7-Giant cells

The giant cells are formed by fusion of the cytoplasm of macrophages. There May have two to three or up to two hundred nuclei. There have 3 types of giant Cells can seen in tissue. Langhan’s cells with nuclei around the periphery .

Foreign body giant cells with the nuclei arranged throughout the cell. A Touton Giant cell is similar to langhan’s cells because their nuclei are arranged in Circle, but the cytoplasm is foamy at the periphery and eosinophilic in the Center. The Touton giant

cells are present in inflammation involving large Quantities of lipid. Moreover multinucleated giant cells have a life span only of A few days.

2- 2- **Cellular response**

The cellular response has the following stages:

A. Migration, rolling, pavementing & adhesion of leukocytes

B. Transmigration of leukocytes

C. Chemotaxis

D. Phagocytosis

Normally blood cells particularly erythrocytes in venules are confined to the central (axial) zone and plasma assumes the peripheral zone. As a result of increased

vascular permeability , more and more neutrophils accumulate along the endothelial surfaces (peripheral zone).

A) **Migration, rolling, pavementing, and adhesion of leukocytes**

- ❖ Margination is a peripheral positioning of white cells along the endothelial cells.
- ❖ Subsequently, rows of leukocytes tumble slowly along the endothelium in a process known as rolling.
- ❖ In time, the endothelium can be virtually lined by white cells. This appearance is called pavementing
- ❖ Thereafter, the binding of leukocytes with endothelial cells is facilitated by cell

adhesion molecules such as selectins, immunoglobulins, integrins, etc which result in adhesion of leukocytes with the endothelium.

B). **Transmigration of leukocytes**

- Leukocytes escape from venules and small veins but only occasionally from

capillaries. The movement of leukocytes by extending pseudopodia through the

vascular wall occurs by a process called diapedesis[1]

The most important mechanism of leukocyte emigration is via widening of inter-endothelial junctions after endothelial cells contractions. The basement membrane is disrupted and resealed thereafter immediately(23).

- Chemotaxis is a unidirectional attraction of leukocytes from vascular channels towards the site of inflammation within the tissue space guided by chemical gradients (including bacteria and cellular debris) .

- The most important chemotactic factors for neutrophils are components of the complement system (C5a), bacterial and mitochondrial products of arachidonic acid metabolism such as leukotriene B4 and cytokines , Interleukin-L(IL-8). All granulocytes, monocytes and to lesser extent lymphocytes respond to chemotactic stimuli.

D) **Phagocytosis**

Phagocytosis is the process of engulfment and internalization by specialized cells

of particulate material, which includes invading microorganisms, damaged cells,

and tissue debris. These phagocytic cells include polymorphonuclear leukocytes (particularly neutrophiles), monocytes and tissue macrophages.

Phagocytosis involves three distinct steps.

1). **Recognition and attachment** of the particle to be ingested by the leukocytes:

Phagocytosis is enhanced if the material to be phagocytosed is coated with certain

plasma proteins called **opsonins**. These opsonins promote the adhesion between the

particulate material and the phagocyte's cell membrane.

2). **Engulfment:** During engulfment, extension of the cytoplasm (pseudopods) flow around the object to be engulfed, eventually resulting in complete enclosure of the

particle within the phagosome created by the cytoplasmic membrane of the phagocytic cell. As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes.(24)

3) **Killing or degradation**

The ultimate step in phagocytosis of bacteria is killing and degradation. There are two forms of bacterial killing

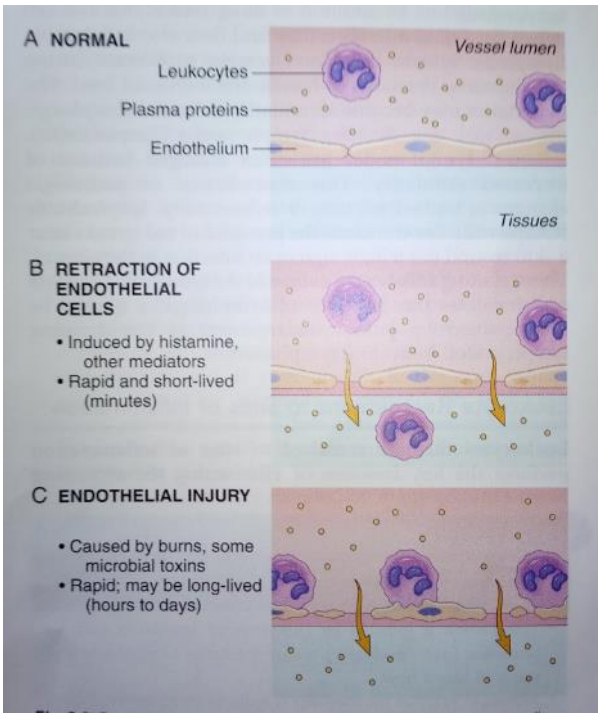

FIG 1: Mechanisms of increased vascular permeability in inflammation and their features and underlying causes(25).

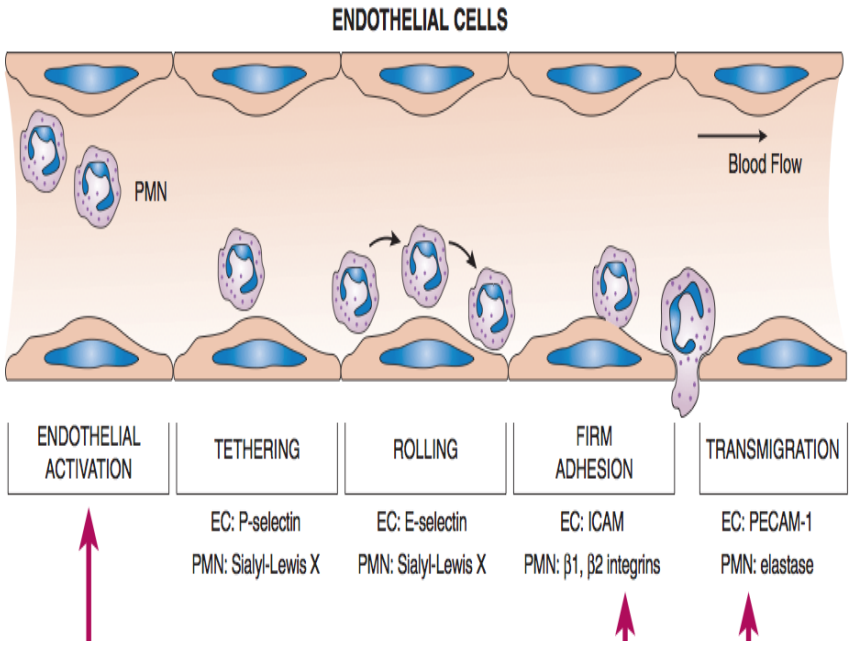

FIG 2: Mechanisms of increased vascular permeability in inflammation & Migration, rolling, pavementing, and adhesion of leukocytes(25).

Chapter three

CONCLUSIONS&Recommendation

CONCLUSIONS:

Acute inflammation is the initial rapid response of vascularised tissue to injury.

1.It occur for a short duration.

2.Itis characterized by fluid and plasma protein exudation and apredominantly neutrophilicleukocyte accumulation.

3.Inflammatory processes occur in 2 phase: vascular phase where vasodilation and increased vascular permeability occur, and a cellular phase, which is characterized by the infiltration of leukocytes to the site of injury.

4.Inflammation is induced by chemical mediators that are produced by host cells inresponse to injurious stimuli such as ; infection , trauma ,foreign bodies,immune reactions and tissue necrosis**.**

Recommendation

1. Conducting an experimental study on the most important factors and proteins that facilitate the inflammation process .

2.Conducting a molecular study on the most important genes that play an important role in inflammation

3.Highlight the most important factors and proteins that stimulate the cellular response**.**

4. A better understanding of inflammatory response pathways and molecular mechanisms will undoubtedly contribute to improved prevention and treatment of inflammatory diseases**.**

Chapter four

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