جامعة تكريت

كلية طب الاسنان

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المرحلة الثالثة

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Definition

Inflammation is a defensive process that a living body initiates against local tissue damage.It takes the form of a

Complex reaction of blood vessels,certain plasma components and blood cells and cellular and structural components of connective tissue.

Acute inflammation has two major components:

1)Vscular changes

2)Cellular events.

Vascular

Changes in the vascular caliber and flow.
Increased vascular permeability.

A)Changes in vascular caliber and flow

1)Vasodilation is one of the earliest manifestations of acute inflammation;sometimes it follows a transient constriction of arterioles,lasting few seconds.

The result is increased blood flow, which is the cause of heat and redness (erythema) at the site of inflammation. Vasodilation is induced by the action of several mediators, notably histamine and nitric oxide (NO), on vascular smooth muscle.

2)Vasodilation is quickly followed by increased permeability of the microvasculature, with the outpouring of protein-rich fluid into the extravascular tissues.

3)-The loss of fluid and increased vessel diameter lead to slower blood flow, concentration of red cells in small vessels, and increased viscosity

a condition termed stasis.,As stasis develops, blood leukocytes, principally_neutrophils, accumulate along the vascular endothelium, migrate through the vascular wall into the interstitial tissue

B)Increased vascular permeability(vacular leakage)

A hallmark of acute inflammation is increased vascular permeability leading to the escape of a protein-rich exudate into the extravascular tissue, causing edema.Several mechanisms are responsible for the increased vascular permeability:

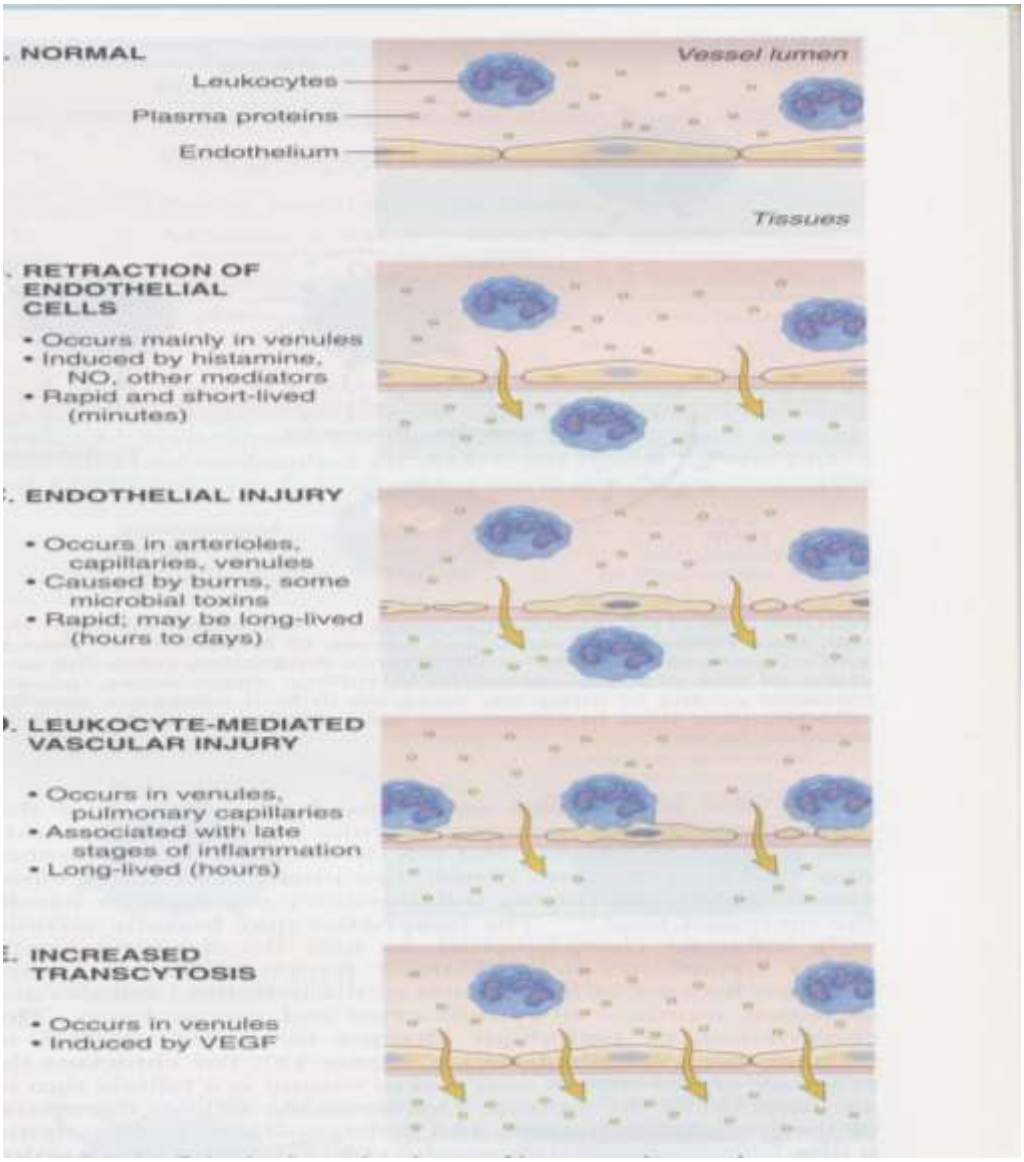
a)Contraction of the endothelial cells resulting in increased interendothelial spaces.(most common),and is elicited by histamine,bradykinin,and nitric oxide.

b)Endothelial injury resulting in endothelial cell necrosis and detachment.

For example in burns. In such a case the leakage starts immediately after the injury and is sustained for several hours until the damaged vessel is thrombosed or repaired.

c)Leukocyte mediated vascular injury

d)Increased transcytosis which means increased transport of fluids and proteins through the endothelial cells .a process that is promoted by certain factors like VEGF.


NORMAL
Leukocytes
Plasma proteins
Endothelium
Vessel lumen
Tissues
RETRACTION OF ENDOTHELIAL CELLS
• Occurs mainly in venules
• Induced by histamine, NO, other mediators
• Rapid and short-lived (minutes)
ENDOTHELIAL INJURY
• Occurs in arterioles, capillaries, venules
• Caused by burns, some microbial toxins
• Rapid; may be long-lived (hours to days)
LEUKOCYTE-MEDIATED VASCULAR INJURY
• Occurs in venules, pulmonary capillaries
• Associated with late stages of inflammation
• Long-lived (hours)
INCREASED TRANSCYTOSIS
• Occurs in venules
• Induced by VEGF

Principle mechanisms of increased vascular permeability.

Cellular events

Reaction of leukocytes in inflammation

The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis namely neutrophils and macrophages.

The process involving leukocytes in inflammation consists of 1)recruitment of leukocytes from the blood into the extravascular tissues,2) recognition of microbes and necrotic tissue,3)and removal of the offending agent.

1)Recruitment of leukocytes from the blood to the extravascular tissues.

Sequence consists of the following:

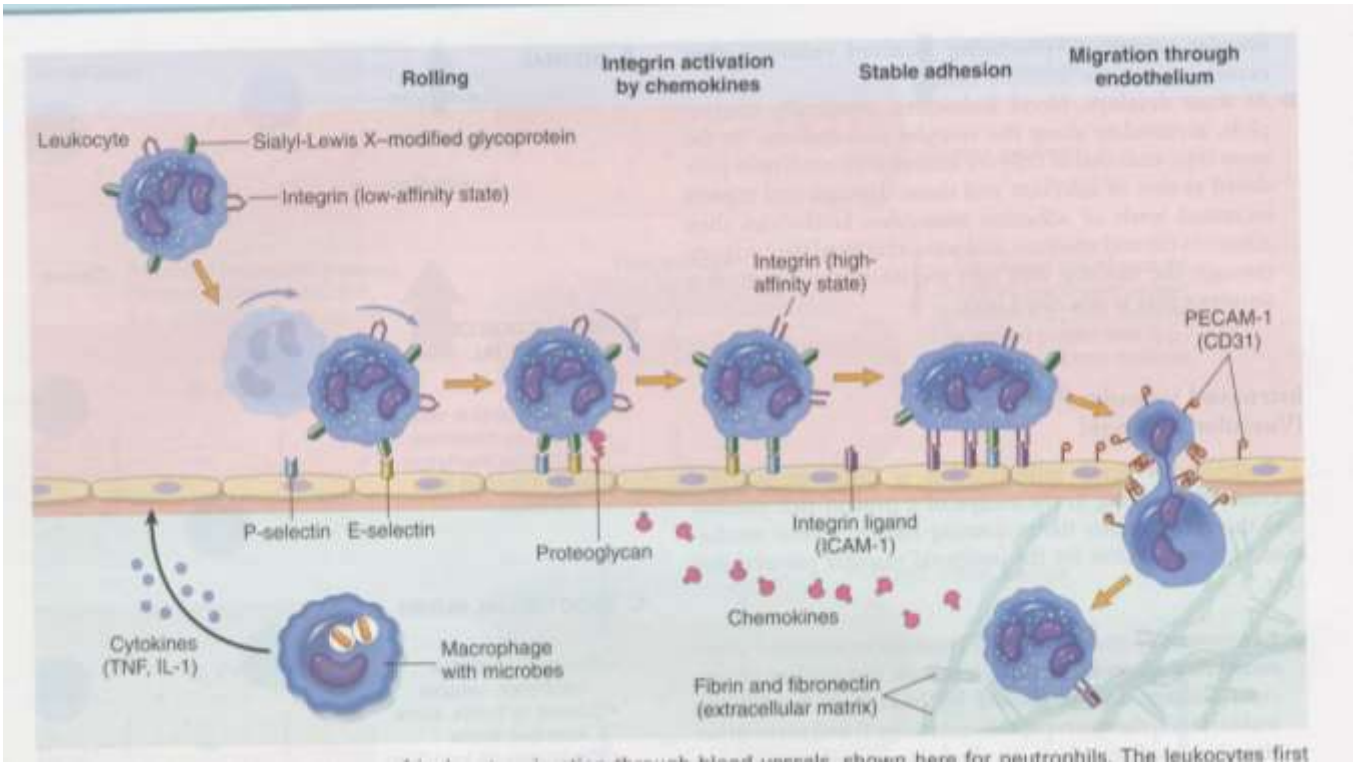
1)Margination,rolling and firm adhesion to the endothelium.

In normally flowing blood ,red blood cells are cofined into a central axial lumen ,displacing leukocytes toward the wall of the vessel.Because blood flow slows early in inflammation(stasis),hemodynamic condition change,and more white cells assume a peripheral position a long the endothelial cells.This process of leukocyte redistribution is called *margination.*Subsequently The leukocytes adhere to the endothelium,detach and bind again,thus *rolling* on the vessel wall.Finally the cells come to rest at some point where they *adhere firmly.*

The adhesion of leukocytes is to the endothelial cells is mediated by complementary adhesion molecules on the two cell types whose expression is enhanced by secreted proteins called cytokins.
The initial rolling is mediated by a family of proteins called selectins.
There are three three types of selectins; one expressed on the leukocytes(L-selectin),one on the endothelium(E- selectin),and one in the platelets and on the endothelium.(p-selectin).

Macrophages,mast cells and endothelial cells secrete several cytokins

Including(tumor necrosis factor



2) Leukocyte migration through endothelium:

The next step step in the process of leukocyte recruitment is migration of leukocytes through the endothelium ,called transmigration or diapedesis

Chemokins act on the adherent leukocytes and stimulate the cells to migrate through the interendothelial spaces toward the the chemical concentration gradient,that is,toward the site of injury or infection where the chemokins are being produced.

3)Chemotaxis of leukocytes.

After exiting the circulation ,leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis ,which is defined as locomotion oriented along a chemical gradiant.Both exogenous and endogenous substances can act as a chemoattractants.The most common exogenous agents are bacterial products. Endogenous chemoattractants include several chemical mediators:

a)cytokins(e.g,IL-8),b) componants of the complement system particularly C5a,c)arachidonic acid(AA) metabolities,mainly leukotrieneB4(LTB4).

2) Recognition of microbes and dead tissues

Once leukocytes (neutrophils,macrophages) have been recruited to the site of infection or cell death,they must be activated to perform their functions.The responses of leukocytes consist of two sets of events:

1)recognition of the offending agents,which deliver signals that 2) activate the leukocytes to ingest and destroy the offending agents and amplify the inflammatory reaction.

Leukocytes express several receptors that can recognize the external stimuli and deliver activating signals

***Receptors for microbial products:Toll-like receptors(TLRs).**

***Gprotein –coupled receptors**

***Receptors for opsonins**

***Receptors for cytokins one of the most important of these cytokins is inerferone Gamma (IFN-gamma).**

3) Removal of the offending agents

Recognition of the microbes or dead cells by the receptors expressed in the leukocytes induced several responses that are reffered to *leukocytes activation.* **Now what is the next step after leukocytes activation?**

The next step is destruction or removal of the offending agents.

The functional responses that are most important for destruction of microbes are phagocytosis and intracellular killing.

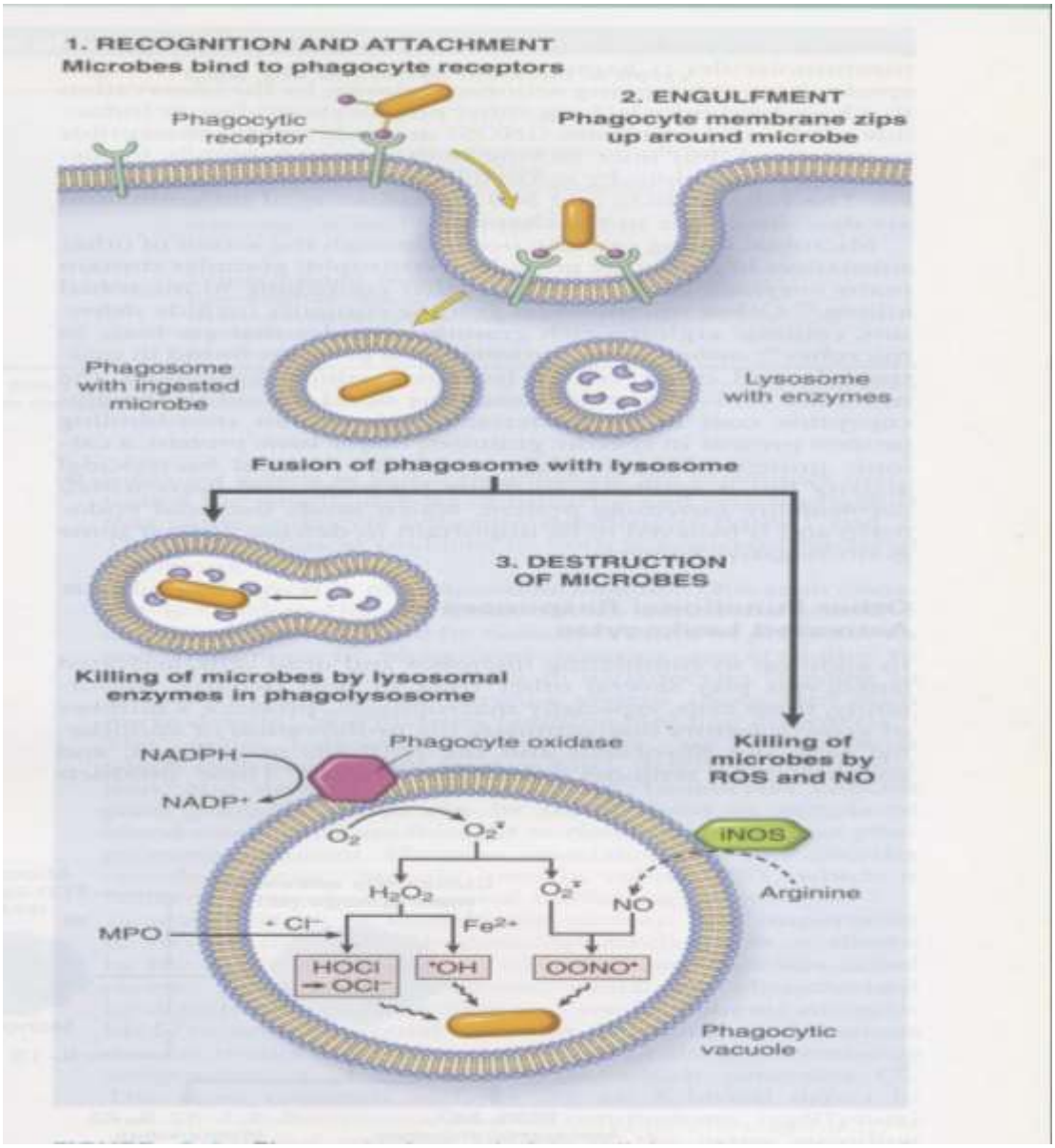
Phagocytosis

It involves three steps:

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

2)Its engulfment ,with subsequent formation of a phagocytic vacuole,and,

3)Killing or degradation of the ingested material.



The figure above describe phagocytosis and intracellular destruction of the microbes.Phagocytosis of a particle(e,g,bacterium) involves binding to receptors on the leukocyte membrane,engulfment which means

extensions of the cytoplasm(pseudopods) flow around the particle and the plasma membrane pinches off to form a vesicle (phagosome) that encloses the particle.This is followed by destruction of the ingested particles within the phagolysosome by lysosomal enzymes and by reactive oxygen and nitrogen species.

Mediators of Inflammation

Mediators are generated either from cells or from plasma proteins.

Cell derived mediators are normally sequestered in intra cellular granules,as vasoactive amines like histamine ,serotonin.

1)Histamine the richest sources are the mast cells that are present in the connective tissue adjacent to blood vessels.It is also found in blood basophils,and platelets.It is produced in response to

a) physical injury as truma ,cold or heat b)binding of antibodies to mast cells which underlies allergic reactions as in asthma.

c)fragments of the complement system called anaphylatoxins(C3a,C5a)

d)histamine-releasing proteins derived from leukocytes,

e) neuropeptides(e.g,substance P).F)cytokins(IL-1,IL-8).

Histamine causes dilation of arterioles and increases the permeability of venules.

2) Serotonin produced mainly within platelets dense body granules.,

Produced during platelet aggregation .the action is the same as histamine.

3)Arachidonic acid (AA)Metabolites.prostaglandins,Leukotrins,and Lipoxins

-AA is a 20-carbon poly unsaturated fattyacids that is derived from dietary sources. It does not occur free in the cell but is normally esterified in the

membrane phospholipids.Mechanical,chemical,and physical stimuli can releaseAA from membrane phospholipids through the action of cellular

Phospholipases,mainly phospholipasesA2.AA-derived mediators also called eicosanoids ,are synthesized bytwo major classes of enzymes :

Cyclooxygenases(cycloxygenase pathway),the metabolities via this pathway includePGD2,PGE2which causes vasodilation and increase vascular permeability

Thromboxane A2(TXA2) causes vasoconstriction, promote platelet aggregation.prostacycln(PGI2) which causes vasodilation and inhibit platelet aggregation.

Lipoxygenase pathway

Metabolities via this pathway include leukotrinsC4,D4,E4 which causes vasoconstriction,bronchospasm and increased vascular permeability.

4) platelet activating factor released from IgE sensitized basophils or mast cells causes increase vascular permability

5)Reactive oxygen species may be released extracellularly from leukocytes after exposure to microbes.

6)Nitric oxide is a factor derived from the endothelial cells and it ha dual functions it relaxes vascular smooth muscle and promote vasodilation and it inhibit leukocyte recuitement.

7)Tumor necrosis factor and interleukin 1 as a cytokins

Morphologic Patterns of Acute Inflammation

1-SEROUS INFLAMMATION

Serous inflammation is marked by the outpouring of a thin fluid that may be derived from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities accumulation of fluid in these cavities is called an effusion. The skin blister resulting

from a burn or viral infection represents a large accumulation of serous fluid, either within or immediately beneath the epidermis of the skin.

2-FIBRINOUS INFLAMMATION

With greater increase in vascular permeability, large molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited in the extracellular space. A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulantstimuluS (e.g., cancer cells). A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura. Histologically, fibrin appears as an eosinophilic meshwork of threads or sometimes as an amorphous coagulum. Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. If the fibrin is not removed, over time it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue (organization) within the pericardial sac leads to opaque fibrous thickening of the pericardium and epicardium .

3-SUPPURATIVE OR PURULENT INFLAMMATION; ABSCESS

This type of inflammation is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, liquefactive necrosis, and edema fluid. Certain bacteria (e.g., staphylococci) produce this localized suppuration and are therefore referred to as pyogenic (pus-producing) bacteria. A common example of an acute suppurativeinflam-mation is acute appendicitis. Abscesses are localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space. They are produced by deep seeding of pyogenic bacteria into a tissue , Abscesses have a central region that appears as a mass of necrotic leukocytes and tissue cells.

4- ULCERS

An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue Ulceration can occur only when tissue necrosis and resultant

inflammation exist on or near a surface. It is most commonly encountered in (1) the mucosa of the mouth, stomach, intestines, or genitourinary tract; and (2) the skin and subcutaneous tissue of the lower extremities in older persons who have circulatory disturbances that predispose to extensive ischemic necrosis.

Out come of acute inflammation:

***Complete resolution** **in a perfect state all inflammatory reactions,once they have succeeded in neutralizing and eliminating the injurious stimuli,should end with restoration of**

The site of acute inflammation to normal. ,and it is the usuall out come when the injury is limited or short lived or when there has been little tissue destruction and the damaged cells can regenerate.resolution involves reoval of cellular debries and microbes by macrophages and resorption of edema fluid by lymphatics.

***Healing by connective tissue replacement (fibrosis).**This occurs after substantial tissue destruction,or when inflammation involves tissues that are incapable of regeneration or when there is abundant fibrin exudation in tissues or serous cavities(pleura,peritoneum) that cannot be adequately cleared.in such a condition the connective tissue grows into the area of damage converting it into a mass of fibrous tissue a process called organization.**

***Progression of the response to chronic inflammation** This may follow acute inflammation or the response may be chronic from the onset.Acute to chronic transition occurs when the acute inflammatory response cannot be resolved,as a result of either the persistence of the injurious agent or some interference with the normal process of healing. For example ,bacterial infection of the lung may begin as a focus of acute inflammation (pneumonia),but its failure to resolve may lead to extensive destruction and formation of a cavity in which the inflammation continues leading to chronic lung abscess.**

CHRONIC INFLAMMATION

Chronic inflammation is inflammation of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations. It may follow acute inflammation or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestations of an acute reaction. this latter type of chronic inflammation is the cause of tissue damage in some of the most common and disabling human diseases, such as rheumatoid arthritis atherosclerosis tuberculosis, and pulmonary fibrosis.

CAUSES OF CHRONIC INFLAMMATION

Chronic inflammation arises in the following settings:-

A -Persistent infections by microorganisms that are difficult to eradicate, such as mycobacteria, and certain viruses, fungi, and parasites. These organisms often evoke an immune reaction called delayed-type hypersensitivity.

B - Prolonged exposure to potentially toxic agents, either exogenous o

Endogenous. An example of an exogenous agent is particulate silica,,a nondegradable material when inhaled for prolonged periods, result in an inflammatory lung disease called silicosis.Atherosclerosis,is thought to e a chronic inflammatory process of the arterial wallinduced ,at least in part, by endogenous toxic plasma lipid components.

C)Immune mediated inflammatory disease

Chronic inflammation plays an important role in agroup of diseases that are caused by excessive and inappropriate activation of the immune system. Under certain conditions immunereactions develop against the individual's own tissues, leading to autoimmune diseases.

MORPHOLOGIC FEAUTERS

In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, chronic inflammation is characterized by:-

1-Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.

2- Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.

3 –Attempts at healing by connective tissue replacement of damaged tissue, accomplished by proliferation of small blood vessels (angiogenesis) and, in particular, fibrosis.

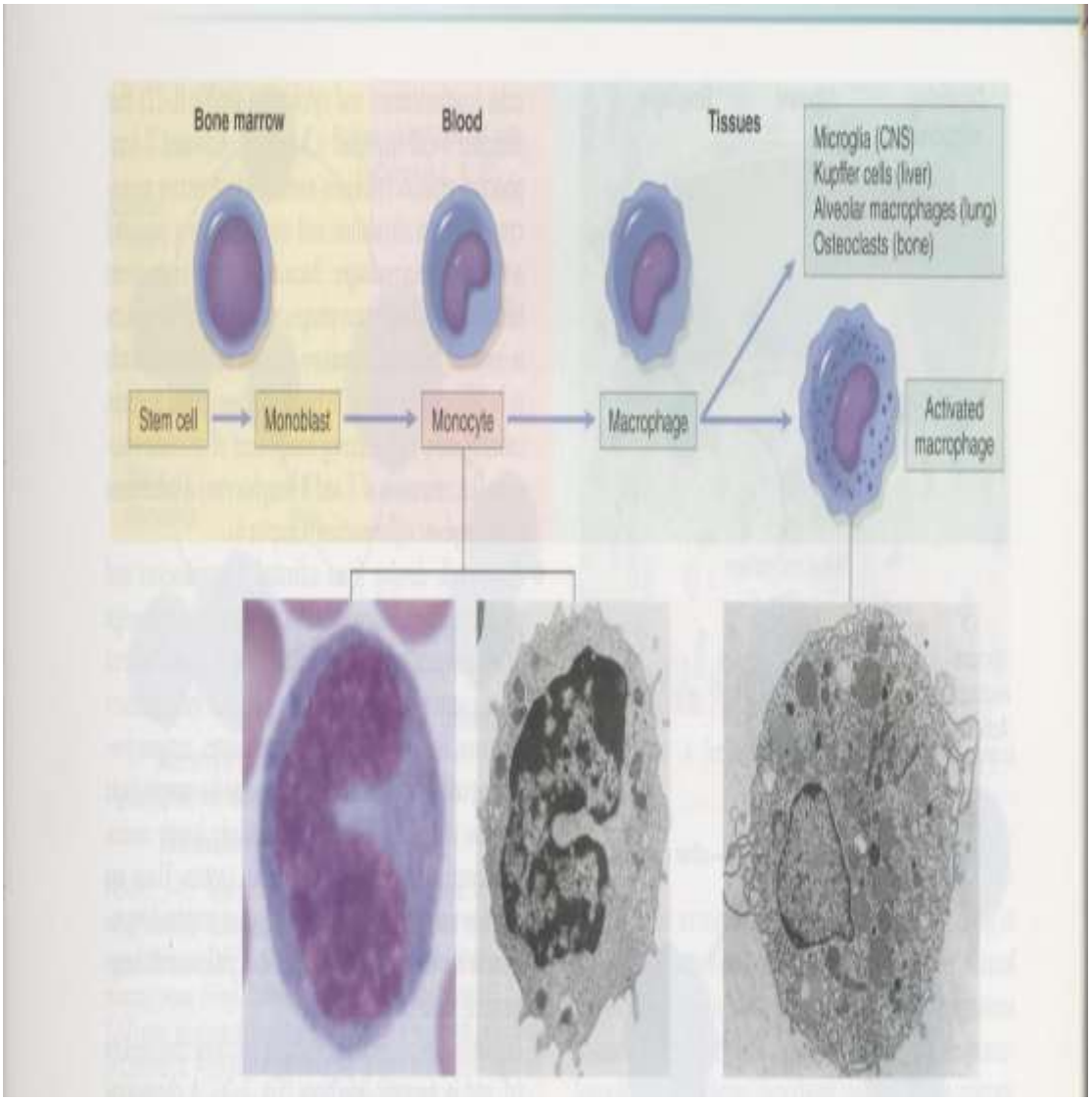
Role of macrophages in chronic inflammation

The macrophages is the dominant cellular player in chronic inflammation .

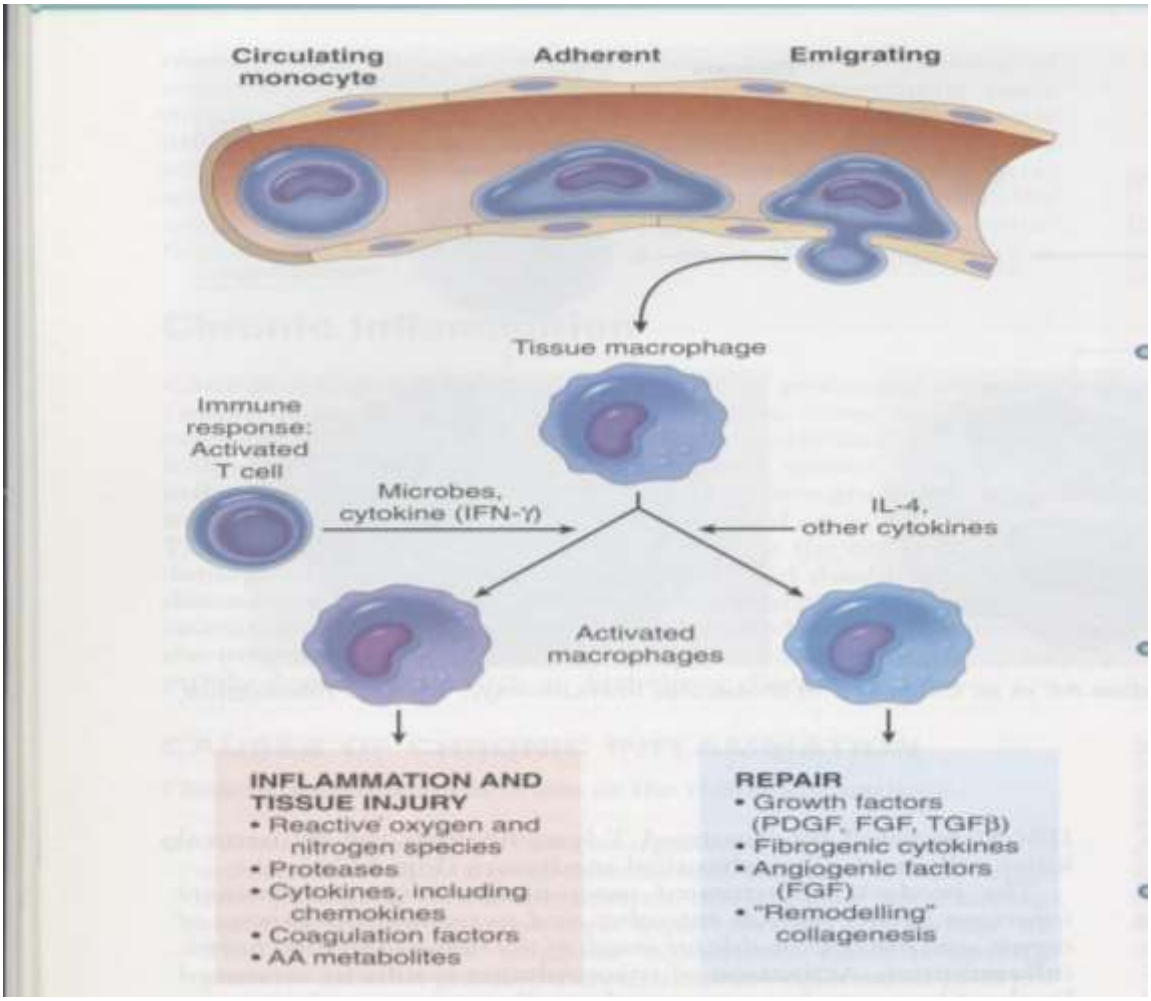
Macrophages are one components of the mononuclear phagocytic system

The mononuclear phagocytic system (sometimes called reticuloendothelial cells) consists of closely related cells of bone marrow origin,including blood monocytes and tissue macrophages.Macrophages are diffusely scattered in in the connective tissue or located in organs as in the liver.(kupffer cells),spleen,and lymph nodes.,lungs.Mononuclear monocytes arise from a common precursor in the bone marrow, which gives rise to blood monocytes.From the blood ,monocytes migrate to various tissues and differentiate in to macrophages.The haif life of blood monocytes is about 1 day,whereas the half life of tissue macrophages is

several months or years.extravasation of monocytes is governed by the same chemical mediators and adhesion molecules that activate neutrophils.When a monocyte reaches the extravascular tissue it undergo transformation into alarger phagocytic cell ,the macrophages.MACROPHAGES can be activated by a variety of simuli including microbial products,cytokins,the products of activated macropgages serve to eliminate the injurious stimuli.



Maturation of mononuclear phagocytes.



The role of activated macrophages in chronic inflammation.**Macrophages are activated by non immunologic stimuli such as endotoxins or by cytokines from immune activated T-cells. The products made by activated macrophages that cause tissue injury and fibrosis are indicated.AAarachidonic acid;PDGF(platelet derived growth factor);FGF(fibroglast growth factor);TGF(transforming**

Growth factor).

Other cells involved in chronic inflammation are:

Lymphocytes: are mobilized in both antibody mediated and cell mediated immune reaction.

Plasma cells: develop from activated B Lymphocytes and produce antibodies against persistent foreign or self antigens in the inflammatory site.

Eosinophils: are abundant in immune reaction mediated by IgE and in parasitic infection.

Mast cells: are distributed in connective tissues and participate in both acute and chronic inflammatory reactions.