Inflammation & Repair

Inflammation :- It is the local response of living tissues to injury due to any agent

Inflammo - I ignite, I set alight

It is a complex reaction to injury that attempt to self protection to remove harmful stimuli, including damaged cell, irritant, pathogens and being the healing process.

It comprises "Vascular response" & migration and activation of Leukocytes. It basically start body defense reaction, but may turn potentially harmful (Anaphylaxis, Allergy, R. arthritis)

Ethology or Causes of Inflammation :-

1. Infective Agents - Viruses, Bacteria, Fungi, parasites & toxines
2. Physical Agents - Heat, Cold, radiation, mechanical trauma
3. Chemical Agent - Org & Inorganic poisons
4. Immunological Agent - Cell mediated & Antigen-Antibody reaction
5. Inert Materials - Foreign bodies

Signs of Inflammation :→

↳ Cardinal Sign -

1. Rubor - Redness
2. Tumour Swelling
3. Calor - Heat
4. Dolour - Pain

] = proposed by Cornelius Celsus in 1st century of AD (53 BC - 7 AD)

5. Functio Laesa - loss of function - added later by Virchow

Types of Inflammation

A. Acute - Short duration
B. Chronic - Long duration

Signs -

(A) Rubor (Redness) - due to ↑ blood supply at inflammed area (Vasodilatn & Vascular permiability)

(B) Tumour (Swelling) - due to accumulatin of fluids

(C) Calor (Heat) - ~~but~~ due to ↑ Hot blood supply & metabolic activity at inflammed area

(d) Dolour (Pain) - due to pain producing molecules - 5HT, bradykinin, Prostaglandins & lactic acid

(e) Functio laesa (loss of functn) - Due to pain, toxic metabolite & reduced nutrients/O_2 supply

Types of Inflammation

(1) Acute Inflammatin :- It is a transient process, which occurs with in minute, hr or day of cell injury, it is of short duration, representing the early body reaction & followed by repair

features :-

(a) Accumulatn of Fluids, plasma at affected area
(b) Intravascular activatin of Platelets
(c) Poly morphonuclear neutrophils as inflammatory cells

Etiology of Acute Inflammation ⇒

(a) Infections - Virus, pyogenic bac, fungi etc
(b) Trauma - burn, frostbite, irradiation, mechanical
(c) Hypersensitivity reactn - parasites, tubercular bacilli
(d) chemical → corrosive, Acid, base, bac toxins
(e) Tissue Necrosis - ischemic infarction

Signs :— All 5 Sign - Rubour, Calor, Tumour, Dolour, Functio laesa

Events in Acute Inflamation

(A) Vascular Events → Alteratn in vasculature size & permiability
(B) Cellular Events - Immigratn of leukocyte (Neutrophils) from microcirculatn & their accumulatn in the focus of injury

VASCULAR EVENTS -

Immidiate transient Vasoconstrictn of arterioles
↓ Histamine, prostacyclins PGI_2, PAF, Bradykinins, & NO
Persistant progressive Vasodilation of Arteriole
↓
opening of new capillary beds (Local heat & redness)
↓
↑ blood volume in microvasculature
↓
Elevatin of local hydrostatic pressure
↓
Transudation of Fluid into extracellular space
↓ Further injury, Histamine, Leukotriens, PAF, IL-1, kinins
Increased Vascular permiability & escape of ~~exdte~~ exudate into interstinum
[Hallmark of Acute Inflammatn]
↓
STASIS

Leukocyte Migration to tissue

Events

1. Haemodynamic changes :-

(i) Transient Vasoconstriction - Immediate vascular response irrespective of type of injury, mainly arterioles

mild injury - 3-5 second

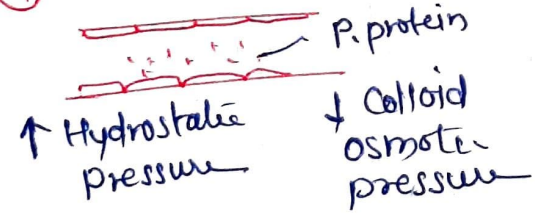
Sever injury - 5 min

(ii) Persistant Progressive Vasodilation :- mainly in arterioles due to release of mediators - Histamine, PGI_2, NO

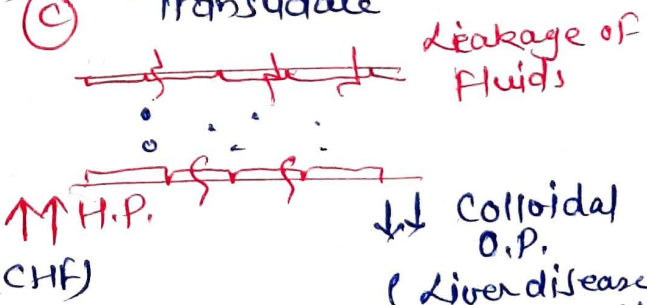
→ 30 min after injury
→ ↑ blood Volume
→ Redness & Heat

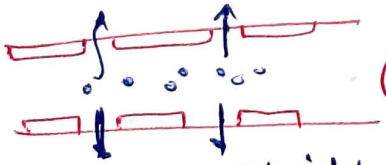
(iii) ↑ Hydrostatic Pressure

(A) Normal



(C) Transudate





(B) Exudate

Fluid & Protein leakage
vasodilam & stasis

→ Transudate of fluid
→ Swelling

(IV) Slowing or Stasis –

→ ↑ Conc of Red cell & ↑ viscosity

(V) Leukocyte Marginatian – Peripheral orientation of leukocyte (Neutrophil) along with vascular endothelium

→ Stick to the vascular endothelium briefly

→ move & migrate through the gaps btw the endothelial cells – extravascular space

→ That is known as Emigration

2. Altered Vascular Permiability

- Accumulation of fluids in interstitial compartment which comes from blood plasma

→ Escape of fluids due to vasodilation & ↑ Hydrostatic pressure

→ Subsequently Exudate

Mechanism of ↑ vascular Permiability –

↳ Endothelial cell contraction – ↑ intracellular gap (20 -60 µ)

↳ Various mediators (Histamine, leukotriens, IL-1, TNF etc)

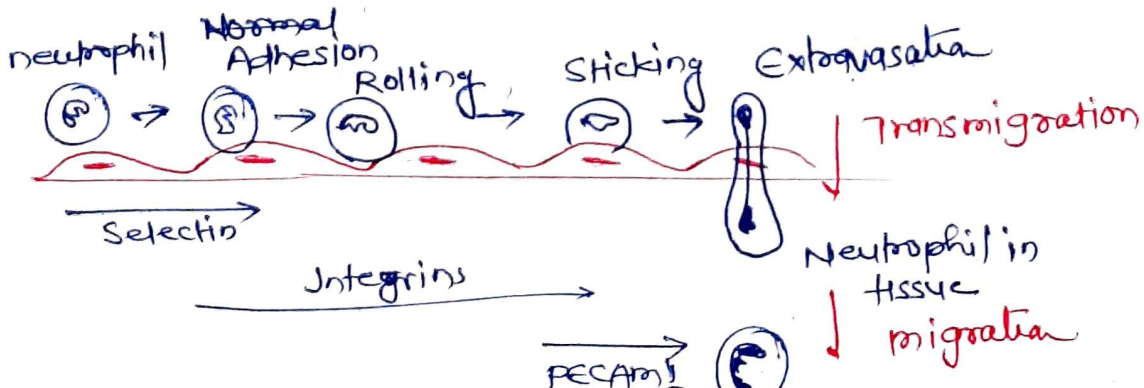
↳ Direct or leukocyte induced endothelial injury

↳ Increased transcytosis of fluid

↳ Leakage from new blood vessels

CELLULAR EVENTS

1. Extravasation of leukocyte – movement of from vessel lumen to interstitial space



2. Phagocytosis :- Leukocytic engulfment of microbes, foreign particles & cellular debris.

Effects of Acute Inflammation

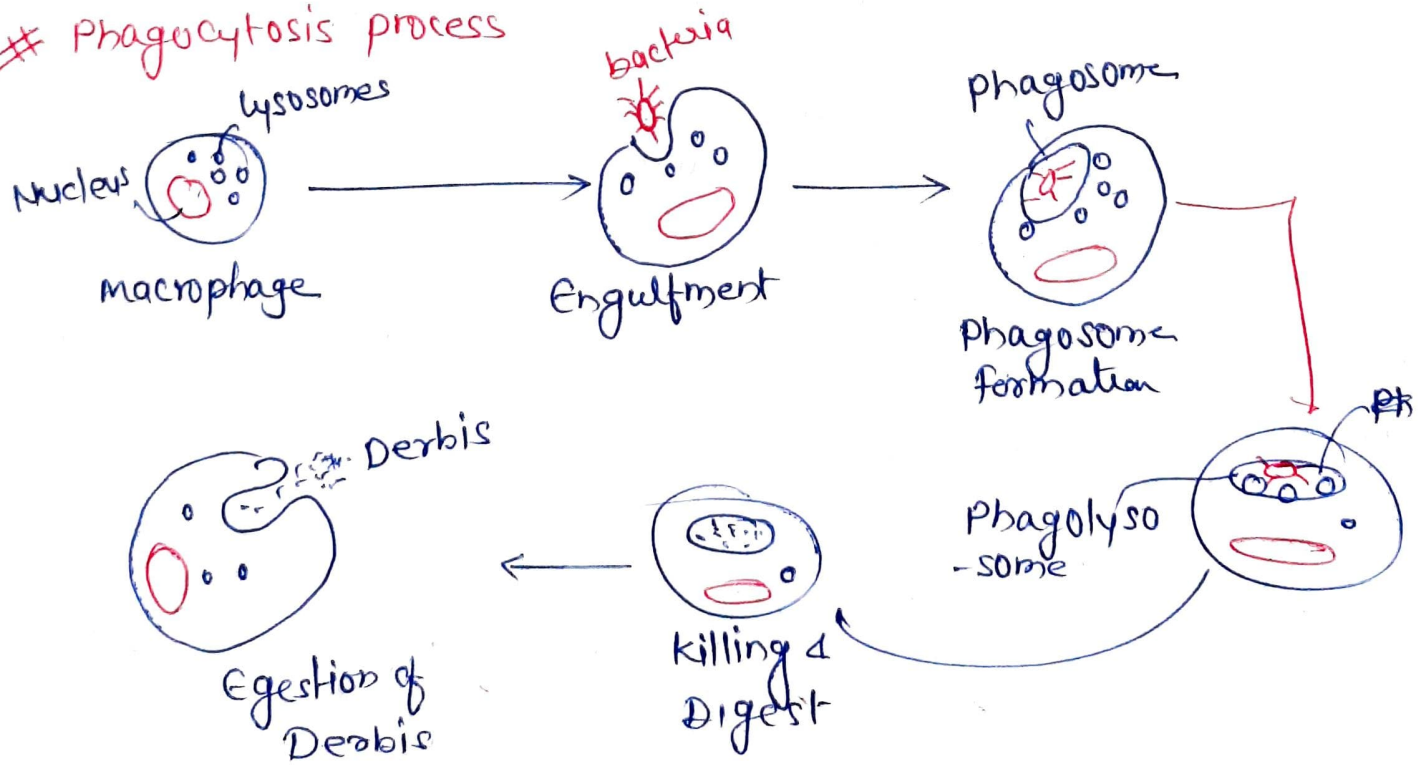
① Beneficial Effects :-

- Dilution of toxins
- Host defence system
- entry of Antibodies, due to ↑ permiability
- Transportation of drug to inflammatory or affected site
- Transportation of Nutrients & O_2 to ⊛ injury area
- Formation of from exuded fibrinogen

② Harmful Effects :-

- Digestion of normal cells & tissues (Enz- Protease, collagenase)
- Swelling (Epiglottis in ~~Epiglottit~~ Epiglottitis due to H. influenzae & may obstruct the airway)
- In appropriate inflammatory response - (Allergy, fever, Type I hypersensitivity reach)

Phagocytosis process



Result or Fate of Acute Inflammation
Manifestation / Outcome -

① **Resolution** :- complete restoration of the inflammed tissue back to normal status.

② **Fibrosis** - formation of fibrous scaring occurs in the affected area of damage, due to large amount of damaged tissue unable to regenerated.

③ **Abscess formation / Suppuration / Pus formation** -

Result of extensive tissue necrosis by pyogenic bacteria

↓

Intense neutrophil infiltration with fragments of necrotic tissue, cell debris, & fibrin

↓

Pus / Abscess

④ **Chronic inflammation** :- Persistant / recurrent acute inflam. may lead to chronic inflammation. Inflammation & healing proceed side by side

Types of Acute inflammation

1. **Serous Inflammation** → infiltration of serous (watery exudate) This is occurs due to irritation, Ag-Ab reaction, in lose tissues like lungs, skin, serous cavities etc.
   e.g. early stage of pneumonia

2. **Fibrinous inflammation** - It is mostly occurs in Fibrinous pneumonia. This is provoked by bacterial pest-eurella, Salmonella, Staphylococci etc.

3. **Diphtheritic inflammation** - Fibrinous exudate is deposited in the mucous mem. along with the coagulative necrosis of mucosal epithelium
   e.g. Diphtheria infection

4. Catarrhal Inflammation :- characterized by excessive mucous formation. e.g. - occurs in trachoeitis

5. Suppurative inflammation - inflammation accompanied by formation of pus.

e.g. pus producing infects - staphylococci, streptococci, pseudomonas etc

Systemic Effects on Acute inflammation -

- ↳ Fever - (release of PGs, IL1, TNF, etc)
- ↳ Leukocytosis - ↑ Leukocyte count
- ↳ Lymphagitis
- ↳ Shock - in sever cases due to release of cytokines (TNF-α)

- Examples of Acute inflammatory disease

- ↳ Acute meningitis
- ↳ Pneumonia
- ↳ Acute Appendicitis
- ↳ Acute pyelonephritis
- ↳ Asthma

CHEMICAL MEDIATORS OF INFLAMMATION

1. Cell Derived :- These are released either from the cells storage of granules or synthesised in the cells

These substance (endogenous) mediate the process of inflammation. e.g., - Vasoactive amines, Lipid products, Cytokines, product of complement activation, Autocoids

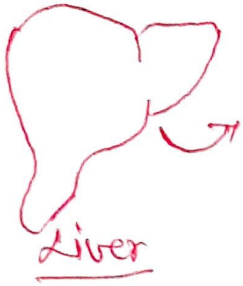
Cell Derived Mediators

- Secretory granules → Histamine, Serotonin → Source: Mast cell, Basophil, Platelets
- Newly Synthesized
  - Prostaglandins – leukocytes, Mast cells
  - leukotriens – " "
  - PAF – leukocyte, EC (endothelial cells)
  - ROS – leukocyte
  - Nitric Oxide – Macrophage, EC
  - Cytokines – Macrophages, Lymphocyte, EC, Mast cell
  - Neuropeptides – leukocyte, Nerve fibers

Mediators	Actions
Histamine ↑ Vasoactive Amines ↓ **Serotonin**	- Vasodilation, Increased vascular permiability, endothelial activatn pain & itching, - Response to stimuli - Physical Injury, Antibodies mediated, complement product (Anaphylotoxin), Neuropeptides (Substance-P,) & Cytokines (IL-1, IL-8) ↳ Vasoconstriction, Other action like Histamine but less potents ↳ present in platelet, neuroendocrine cells & GIT
Ecosanoids → Prostaglandins (PGs)	→ Pain, Fever
PGD_2 & PGE_2	→ Vasodilation, Bronchodilation, ↑ vascular permiability
$PGF2\alpha$	→ Vasoconstriction, Bronchoconstriction
TXA_2 (Thromoxane)	→ Vasoconstrictn, Bronchoconstriction, Platelet-Aggregation
PGI_2 (Prostacyclin)	- Vasodilatn, Bronchodilatn, ↓ Platelet Aggregation

Mediators	Actions
Leukotriens	– slow Reacting Substance of Anaphylaxis → Produced by mast cell & leukocyte by actn of Lipooxigenase (5-LOx) on Arachidonic acid.
LTC_4, LTD_4 & ~~LTD~~ LTE_4	→ ↓ Vasoconstriction, Bronchospasm, ↑ permiability of venules, → Asthmatic Agents
LTB_4	→ Chemotactic & Neutrophil activator → Cell adherence → ROS formatn → release of lysosomal Enz
Lipoxins	→ Generate from Arachidonic a by Lipoxigenase → Supress the inflammatn by inhibiting ~~recru~~ recruitment of leukocyte → ↓ chemotaxis & cell adhesion to endothelium
Cytokines	→ Mediate & regulate Immune & inflammatory reaction → Ck are the proteins produced by activated lymphocytes, macrophages; & dendritic cells. → ↑ leukocyte Adherence, thrombosis, Fibroblastic proliferatn, & acute phase reaction
· Interleukin IL-1	– stimulate expressin of endothelial adhesion molecules & secretn of other cytokines, Fever
IL-8	– chemotactic for neutrophil
TNF (Tissue Necrotic factor)	– Similar as IL-1
Platelet Activating Factor (PAF)	– ↑ platelet Aggregation & vascular permiability
Nitric Oxide (NO)	– Vasodilatation, antiplatelet effect & microbicidal
ROS	– endothelial damage & increased vascular permiability

2. **Plasma derived** :- They are synthesized by from liver. After the release form liver, the mediators required to activation. These are also known as Plasma Protease



Release in Plasma

- Complement Activatn
  - C3a, C5a]- Anaphylaxis
  - C3b
  - C5b-9 (mem. attack complex)]- ↑ permiabi-lity
- Clotting factor XII (Hagemen) Activatn
  - Kinin System → Bradykinin (↑ permiability)
  - Coagulatn/Fibrinolysis System → Fibrin split product → ↑ vascular permiability

Common Properties of Mediators –

1. These are release either form the cell derived or plasma derived.
2. All mediators are release in response to certain stimuli like, injurious agents, damage tissue, mediators
3. Mediators act on different targets
4. They have short life span after ~~tee~~ release

BASIC PRINCIPLE OF WOUND HEALING - SKIN

summary & basic steps :—

1. Stage of inflammation
2. Stage of granulation tissue formation & organisation
3. Stage of epithelialisation
4. Stage of scar formation & restoration
5. Stage of maturation

Repair :→ Restoration of tissue architecture & function after injury is termed repair.

It is occur in two way —

1. Regeneration — The injured tissue reverts to normal after replacement of damaged components by the active proliferation of residual cells as well as maturation of stem cell.
2. Healing with scar formation :— If the individual tissue is incapable of complete restoration to original state or if their is sever damage to supporting structure, repair occurs by a laying down of connective tissue. This is called "Healing with scar formation"

HEALING :—

It is the natural process by which the body repairs itself. It is the bodies response to injury in an attempt to restore normal structure & function. That is a Repairing system of body, that can be happened in two way —

(I) Regeneration
(II) Scarformation

Mechanism of Wound Healing :—

(A) Regeneration
(B) Repair

Most organ will heal using a mixture of both process.

(A) ~~RENER~~ REGENERATION

Regeneratn is the renewal or ~~resfor~~ restoratn process of body in which healing takes place by proliferatn (cell division) of parenchymal cells & usually results in complete restoratn of the original tissue.

Depending upon the capacity of cell to divide the cells of body ~~can bod~~ can be divided into following three groups -

(I) **Labile Cells** - These cells continously multiply throughout life under normal physiological condition.
e.g., ↳ surface epithelial cells of epidermis,
↳ Alimentary tract,
↳ Respiratory tract
↳ urinary tract
↳ Vegina
↳ uterine, endometrium
↳ Haematopoietic cells of bone merrow
↳ cells of lymph node & spleen

(II) **Stable Cells** - These cells, ~~a~~ decrease or loss their ability to proliferate after ~~ado~~ adolescen, but retain the capecity to multiply in response to certain stimuli throughout the adult life.
e.g. → Liver, pancrease, kidneys, adrenal & thyroid → parenchymal cells, &
- mesenchymal cells of - Smooth muscles, Fibroblasts, Vascular endothelium, Bone & Cartilage cells.

(III) **Permanent Cells** - These are the cells which loss their ability to proliferate around the time of birth.
e.g. - Neurons
myocardiocyte (Cardiac Muscles)

Regeneratn depends on many variables - GFLR, inhibitor, Signal transductn pathways, transcriptn factors
e.g. TNF & IL - promots the cell proliferation

B. REPAIR :-

Repair is the replacement of injured damage tissue by fibrous tissue. It takes place by participatn of mesenchymal cells (connective tissue of stem cells, fibrocytes, & histocytes), endothelial cells, macrophages, platelets, & the parenchymal cells of injured tissue/organ.

Two process are involved in Repairing →

I. FORMATION OF GRANULATION TISSUE
II. CONTRACTION OF WOUNDS

I. Formatn of Granulation Tissue: — (Tissue apears granular & pink)

Three phases are involved :—

1. Phase of inflammation –

injury / Trauma → clotting of blood at site of injury → Acute Inflammatory Response/Reactn

Exudatn of plasma, neutrophils & monocytes with in 24 h → Digestion of foreign body

2. Phase of clearance –

Neutrophils, macrophages, Necrotic tissue → Release of Autolytic & hydrolytic enzyme → clear off the necrotic tissue, Debris & RBCs

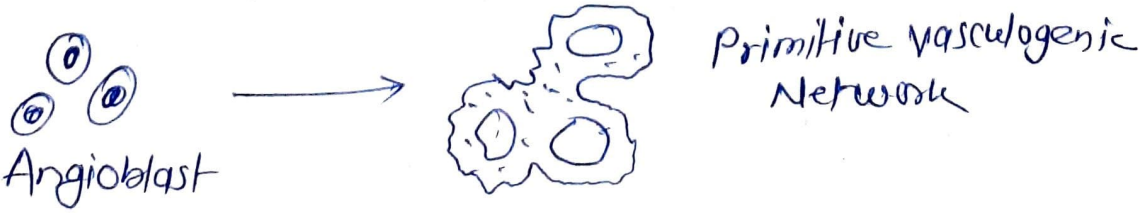
3. Phase of ingrowth of Granulation tissue –

↳ This phase contains two main process

(a) Angiogenesis (neovascularization)

↳ It is the physiological process to formation of new blood vessels from preexisting vessels

Vasculogenesis : ↳ Involves formatn of primitive vascular structures from angioblast



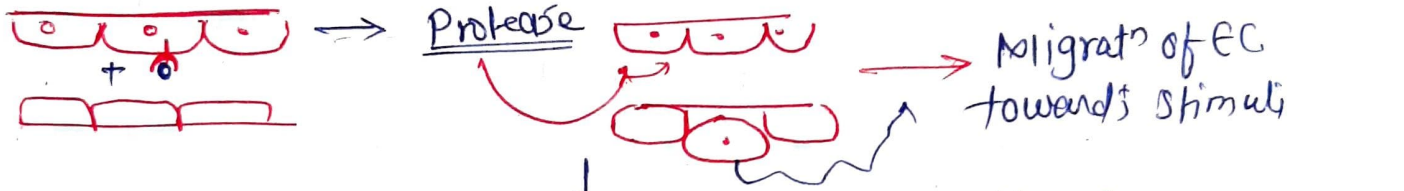
Angiogenesis –

Activation of Receptors on endothelial cells in Preexisting vessels by Angiogenic growth factors (~~VEGF~~ VEGF, FGF)

Hypoxia, TGF-β, TGF-α (+) VEGF → GFR (+) EC → Activate Tyrosine Kinase Receptor → (+) Proliferation, motility of EC

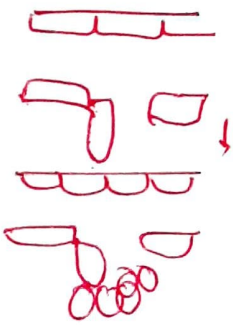
↓

Release of endothelial Protease → that degradate the basement mem, to allow Endothelial cell (EC.) to escape from original (parent vessels) ~~to~~ vessels walls to surrounding matrix



↓

Migration of EC towards area of Angiogenic stimulus



↓

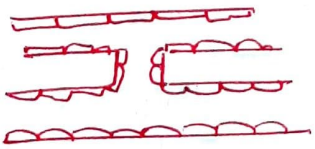
Proliferation of EC behind the migrating cells

↓

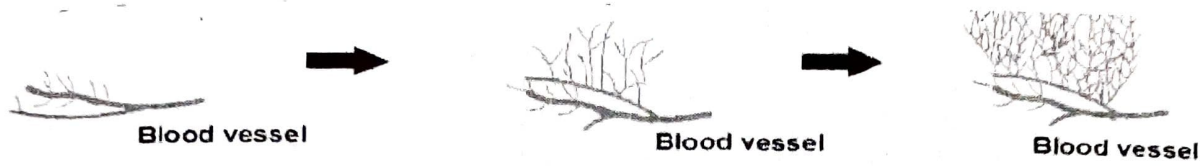
Remodelling of EC in to capillary tubes

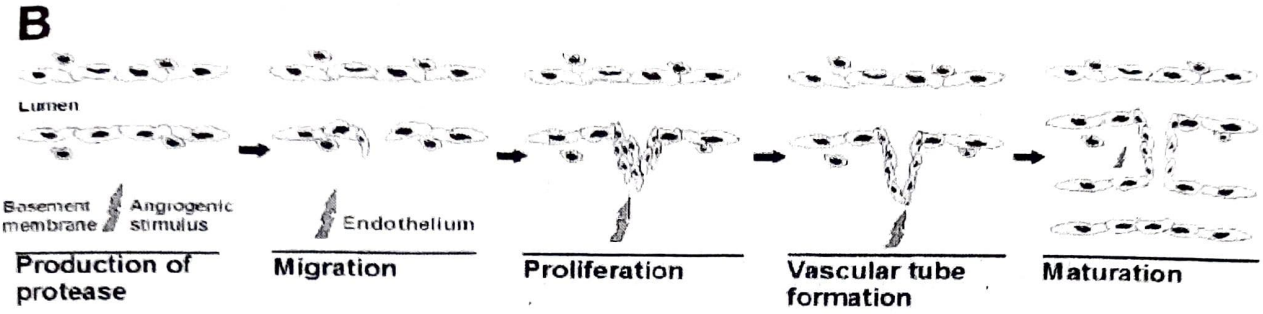
↓

Maturation



- VEGF – vascular endothelial GF (VEGF-A,B,C,D)
- FGF – Fibroblast Growth factor
- TGF – Transforming Growth factor
- EC – endothelial cell
- GFR – Growth factor Receptor

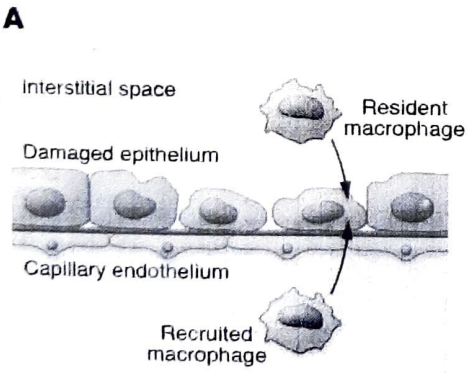




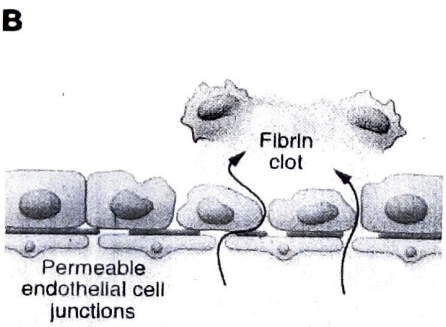
(b) Fibrogenesis – It is the development or proliferation of fibrous tissue or fibres at damaged area.

FGF (Fibroblast Growth Factors) are involved, FGF bind with familial receptor which has tyrosine kinase activity & stimulate proliferation of EC & promote migration of macrofages & fibroblast to damaged area

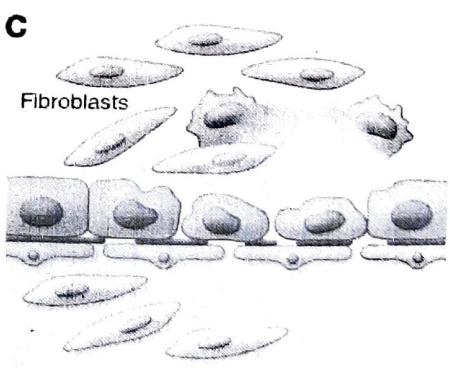
fibrogenesis, results in formation of inactive looking scare known as "Cicatrisation"



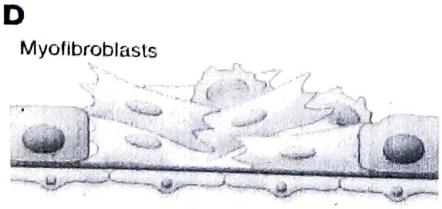
Immune activation and polarization
^{64}Cu-BMV101, ^{68}Ga-BMV101, MPO-Gd, ^{99m}Tc-RIP



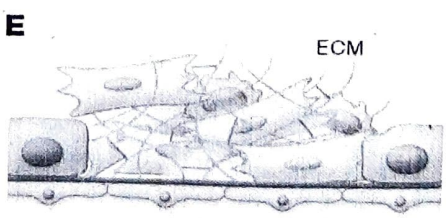
Vascular leak and extravascular coagulation
Gadofosveset, EP-2104R, Gd-P, ^{111}C-BMT-126088



Fibroblast recruitment, invasion, proliferation, and persistence
^{111}C-BMT-126088



Fibroblast activation and myofibroblast differentiation
^{68}Ga-DOTANOC, ^{111}In-Octreotide, ^{99m}Tc-3PRGD2, RGD-USPION, ^{99m}Tc-CRIP, ^{111}In-A20FMDV2, [^{18}F]FP-R01-MG-F2



Matrix accumulation and cross-linking
Gd-Hyd, Gd-OA, EP-3533, CM-101, ^{99m}Tc-CBP1495, ^{99m}Tc-collagelin, ^{68}Ga-CBP8, Gd-FSMA

II. Contraction of Wounds –

The wound starts contracting after 2-3 days & process is completed by the 14th days. During the periods, the wound is reduced by approx 80% of its original size.

Mechanism – Proposed mech.

1. Wounds get contracted due to dehydrations, a result of removal of fluid by drying of wounds

2. Contractn of collegen was thought to be responsible for wound contraction, but the contraction proceed at a steg when the collegen content of granulation tissue is very small.

3. The role of myofibroblast (appearing in active granulatn tissue) in wound contractn was apparently found conclusive