Inflammation and Repair

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I. INFLAMMATION

- Egyptian papyrus – 3000 B.C.
- Celsus (Roman in 1st century A.D.)
  Rubor – *Tumor* – *Calor* – *Dolor*
  redness - swelling - heat - pain
- Virchow added *functio laesa*

A. Definitions

- A complex reaction in vascularized tissue.
- Blood vessels are key:
  1. They react.
  2. Fluid and leukocytes accumulate in the extravascular tissue.
- **Acute Inflammation** - "the immediate and early response to an injurious agent" *
- **Chronic Inflammation** - "inflammation of prolonged duration (weeks or months) in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously" *
- **Exudate** - ↑ vascular permeability, high protein, cell debris, s.g. > 1.020
- **Transudate** - normal vascular permeability, low protein (mostly albumin), plasma ultrafiltrate, driven by hydrostatic pressure, s.g. < 1.012
- **Edema** - interstitium or cavity; exudate or transudate.
- **Purulent exudate** - neutrophil rich & parenchymal cell debris

B. Acute Inflammation

- **Three major components:**
  1. "alterations in vascular caliber that lead to an increase in blood flow,
  2. structural changes in the microvasculature that permit the plasma proteins and leukocytes to leave the circulation, and
  3. emigration of the leukocytes from the microcirculation and their accumulation in the focus of injury" *

- **Process Summary:**

1. transient vasoconstriction of arterioles (lasts seconds).
2. vasodilatation; arterioles then capillaries (increased flow = redness).
3. slowing and stasis:
   - ↑ permeability = fluid to interstitium
   - ↑rbc concentration
   - PMN margination
4. PMN rolling
5. PMN adhesion
6. PMN extravasation
7. Phagocytosis

- **Vascular Permeability – Causes :**

1. protein exits vessels with resulting ↓ in intravascular osmotic pressure and ↑ in intravascular hydrostatic pressure.
2. endothelial gaps at intercellular junctions:
   - immediate transient response
   - histamine, bradykinin, leukotrienes, substance P.
   - in small venules
3. endothelial retraction
   - cytoskeletal changes
   - delayed (4-6 hours)
   - long lived ($\geq$ 24 hours)
   - in vitro - yes; in vivo - ?
   - IL-1, TNF, Inf-γ, hypoxia, injury.
4. direct endothelial injury
   - burns, lytic bacteria
   - immediate sustained
   - arterioles, capillaries, and venules
5. leukocyte mediated endothelial injury
   - venules
   - pulmonary and glom. Capillaries
6. delayed prolonged leakage
   - delay 2-12 hours
   - lasts hours to days
   - sunburn !
   - thermal, x-ray, UV, bacterial toxin
7. transcytosis
8. angiogenesis

- **Leukocyte Extravasation Sequence**

1. Endothelium – surface adhesion molecules, *selectins &* CAM's, appear:

- Rapidly – histamine, thrombin, PAF redistribute P-selectin
- Hours (new protein syn.) – IL-1, TNF up regulate E-selectin , ICAM-1 & VCAM-1
- *Selectins* bind– mucin-like glycoproteins (Sialyl-Lewis X PSL-1 & ESL-1)
- *CAM*'s bind integrins

2. **Selectins** produce weak and transient binding resulting in **rolling**.
3. **Integrins** up regulate and are activated with resultant ↑ affinity and **firm adhesion** results.
4. Transmigration (diapedesis):
   - assisted by ICAM-1 and PECAM-1
   - primarily in venules
   - collagenases degrade basement memb.

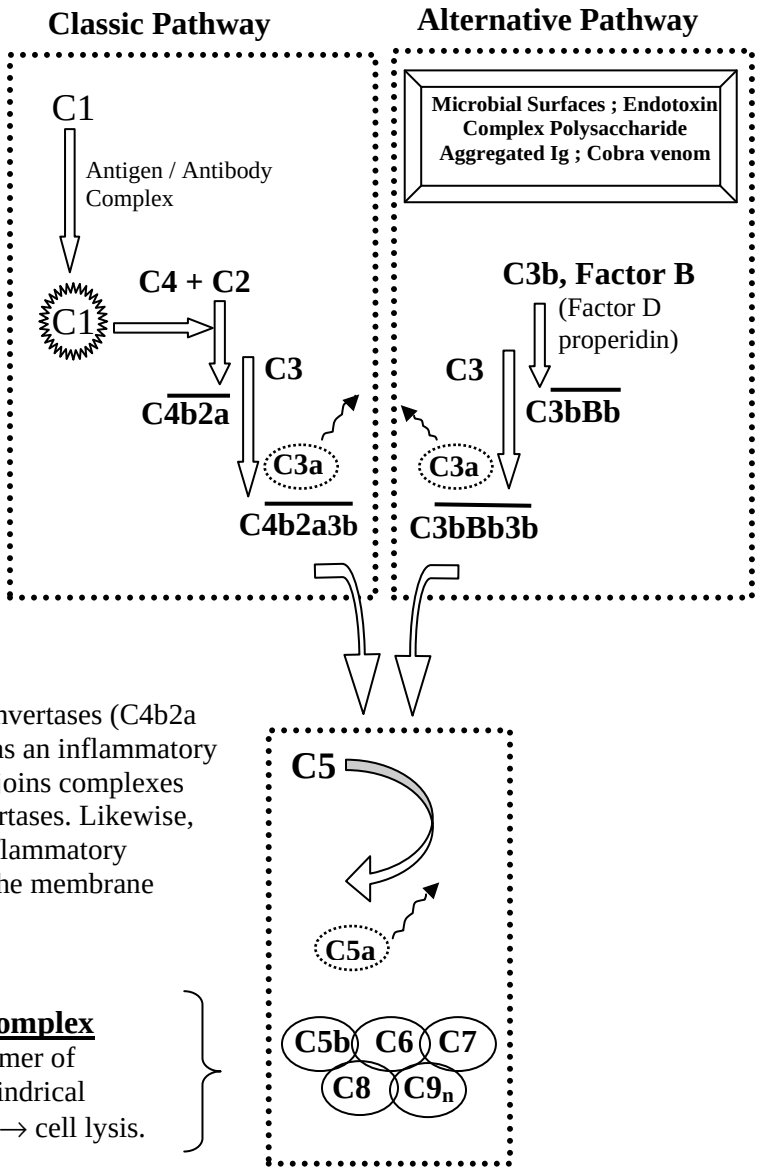
- **Chemotaxis – Factors Include:**
  1. Exogenous agents as bacterial products, peptides with N-formyl methionine
  2. Endogenous mediators:
     - Complement – C5a
     - Lipoxygenase – leukotriene B_4
     - Cytokines, chemokines – IL-8
     - Phospholipase C on $PIP_2 \rightarrow IP3 + DAG \rightarrow Ca^{++}$ release and influx → contractile proteins (pseudopod power)

- **Phagocytosis**
  1. Recognition and attachment
     - Opsonins coat target and bind to leukocytes.
     - Examples:

Opsonin	Leukocyte Receptor
IgG , F_c fragment	$F_c\gamma R$
C3b	CR1, 2, 3
Collectins –carbohydrate binding proteins.	C1q

  2. Engulfment
  3. Killing / degredation
     - reactive oxygen species in lysosomes and extracellular.
     - Oxygen independent: bacteriacidal permeability increasing protein, lysozyme, lactoferrin, major basic protein, defensins.

C. Complement System



Convertases
Cleavage of C3 by C3 convertases (C4b2a or C3bBb) liberates C3a as an inflammatory mediator and C3b which joins complexes that function as C5 convertases. Likewise, C5 liberates C5a as an inflammatory mediator and C5b joins the membrane attack complex.

Membrane Attack Complex
C5b, C6, 7, 8 and a polymer of multiple C9's form a cylindrical transmembrane channel → cell lysis.

- **Inflammatory Mediators from Complement**

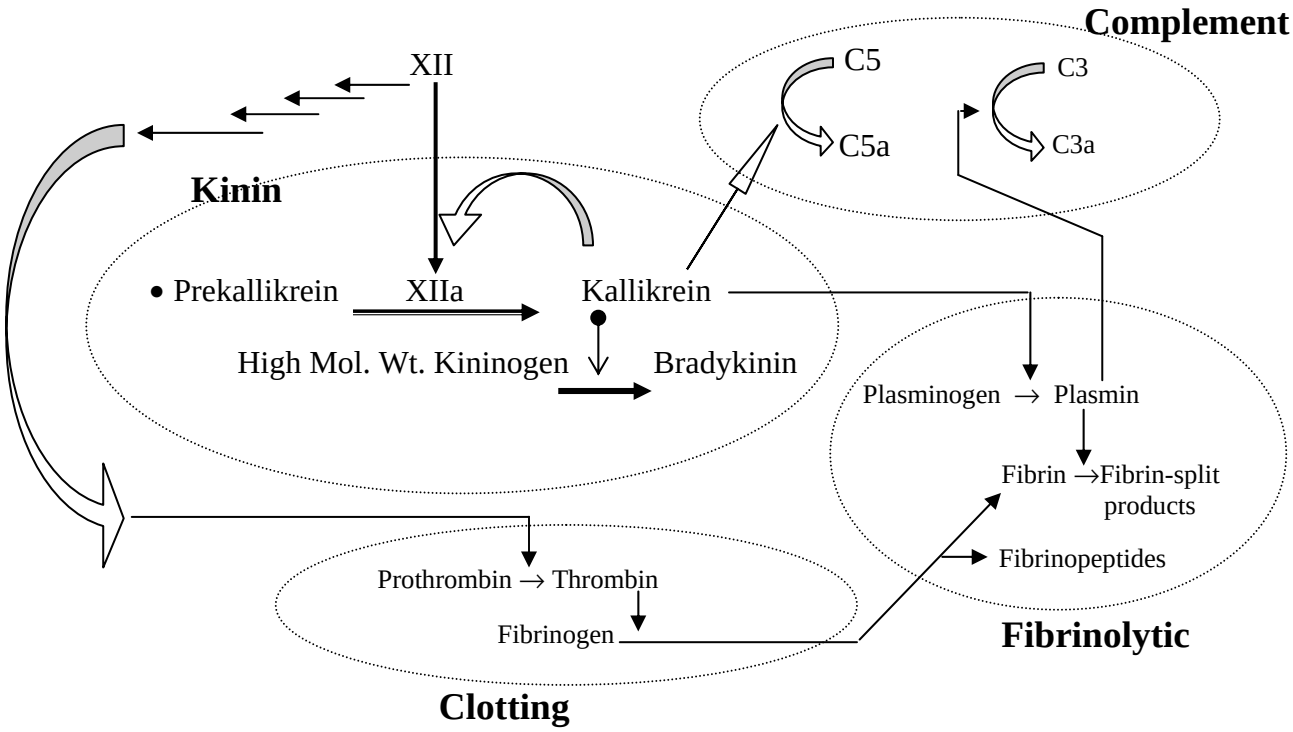
1. **Anaphylatoxins:** C3a, C5a, & C4a trigger mast cells to release histamine and cause

vasodilatation. C5a also activates the lipoxygenase system in pmn's and monocytes → release of inflammatory mediators.

2. **Leukocyte activation, adhesion, & chemotaxis**: C5a activates leukocytes, promotes leukocyte binding to endothelium via integrins, and is chemotactic for pmn, mono, eos, & bas.
3. **Phagocytosis**: C3b and C3bi are opsonins.
4. **Control**: Convertases are destabilized by "decay accelerating factor" -DAF. Inability to express DAF causes *paroxysmal nocturnal hemoglobinuria*. C1 inhibitor (C1INH) deficiency causes *hereditary angioneurotic edema.*

D. Plasma Mediator Systems - Interact

1. **Kinin**
2. **Clotting**
3. **Complement**
4. **Fibrinolytic**



- Bradykinin - potent biomolecule !

1. Vasodilatation
2. Increased vascular permeability
3. Contraction of smooth muscle
4. Pain on injection
5. Short life, kininase degrades

- Kallikrein

1. autocatalytic
2. converts C5 to C5a
3. chemotactic

- Fibrinopeptides

1. ↑ vascular permeability
2. chemotactic

- Fibrin Split Products

1. ↑ vascular permeability

- Thrombin

1. ↑ leukocyte adhesion
2. fibroblast production

- Factor Xa

1. Binds effector cell protease receptor - 1
2. ↑ vascular permeability
3. leukocyte exudation

- Factor XII activated by:

1. Plasmin
2. Kallikrein
3. Collagen & basement membrane
4. Activated platelets
5. Co-actor = HMWK

E. Arachadonic Acid Metabolism

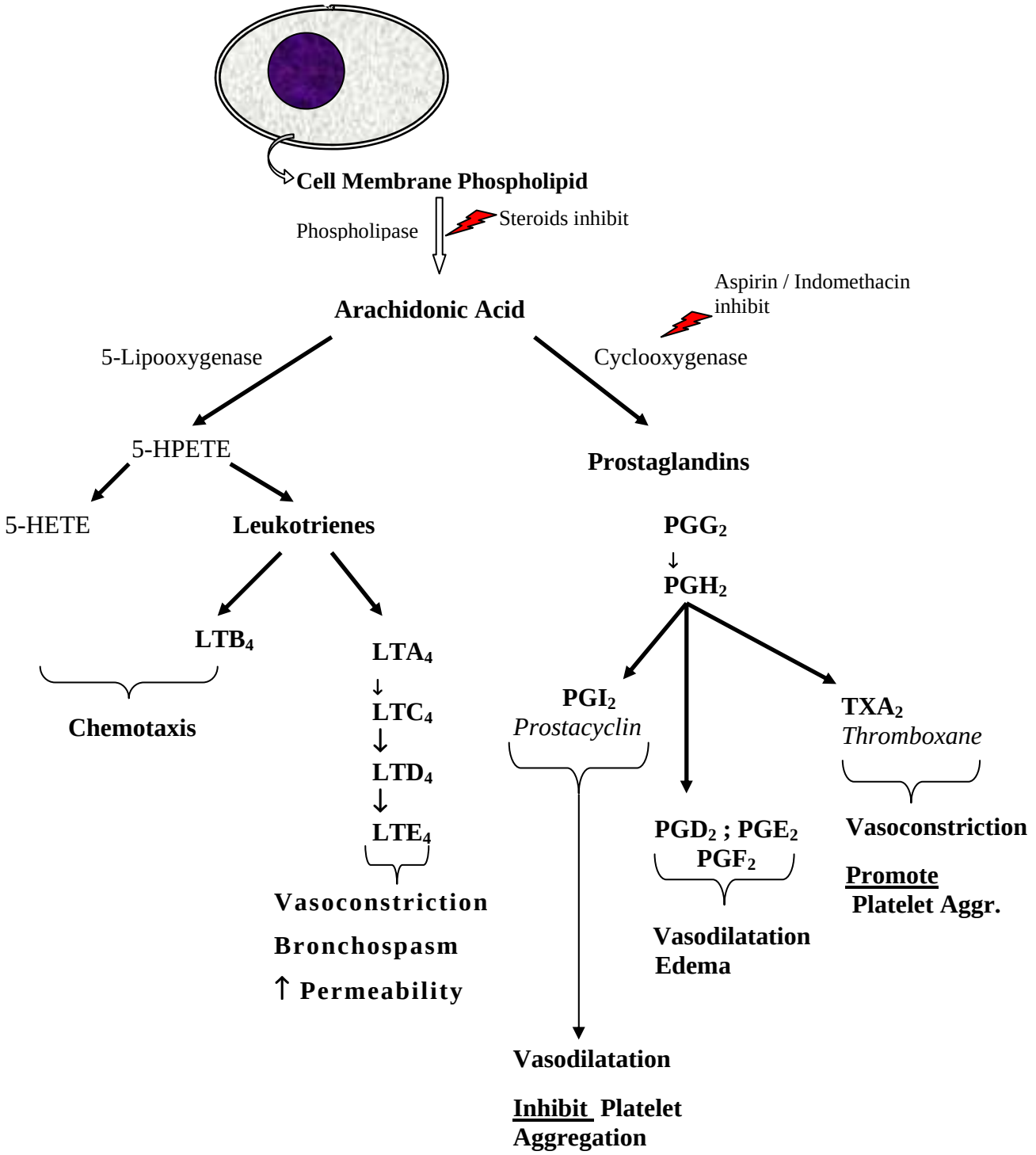
- AA is a 20 carbon polyunsaturated fatty acid
- From diet or linoleic acid (essential fatty acid)
- Esterified in membrane phospholipids
- Released by phospholipases, mechanical, chemical and physical means

- AA metabolites = eicosanoids
- **Cyclooxygenases** synthesize

1. Prostaglandins
2. Thromboxanes

- **Lipoxygenases** synthesize

1. Leukotrienes
2. Lipoxins



F. Platelet-Activating Factor

- Made by plt, bas, mast, pmn, mono/macφ, endothelium.
- *Very Potent* – 100 to 10,000 x stronger than

- histamine in ↑ permeability and vasodilatation.
- Vasoconstriction & brochoconstriction.
- Leuk. adhesion, chemotaxis, degranulation & oxidative burst.

G. Cytokines

- Five classes

1. Lymphocyte function
2. Natural immunity
3. Activate inflammatory cells
4. Chemokines
5. Stimulate hematopoiesis

- **Lymphocyte function**

1. Macrophages make IL-1 & TNF-α
2. T-cells make TNF-β (lymphotoxin)
3. Can be autocrine, paracrine, endocrine
4. IL-1, TNF, IL-6 = acute φ responses as fever, ↓appetite, slow wave sleep, ↑circ. pmn, ↑ACTH, ↑cort. steroid.
5. TNF notable for role in septic shock and maintenance of body mass (cachexia in cancer from ↑↑ TNF-α).

- **Natural immunity**

1. TNF-α and IL-1β
2. Type I interferons : Inf-α & Inf-β
3. IL-6

- **Activate inflammatory cells**

1. Activators of macrophages during cell mediated immunity:
   Inf-γ, TNF-α &β, IL-5, 10, & 12

- **Chemokines**
  1. Small 8-10 kD proteins , paired Cys repeats and two internal disulfide bonds (4 classes).
  2. Activators and chemoattractants for leukocytes.
  3. Leukocyte specific (see table below)

Leukocyte Affected	**By Chemokines**
Neutrophils	IL-8; Gro-α, β, γ
Monocytes	MIP-1α, β; MCP-1, 2, 3

Eosinophils	Eotaxin
Lymphocytes	Lymphotaxin
Basophils	IL-8, MIP-1α, MCP-1,3, RANTES

MIP = macrophage inflammatory protein
MCP = macrophage chemoattractant protein

- **Stimulate hematopoiesis**

1. IL-3, 7; c-kit ligand, CSF's (GM-CSF, M-CSF, G-CSF), stem cell factor.

H. Nitric Oxide

- Made by nitric oxide synthetase (NOS) in endothelium (eNOS), macrophages (iNOS), and specific neurons in the brain (nNOS).
- Vasodilatation by relaxing smooth muscle.
- ↓ platelet aggregation
- inhibits mast cells
- ↓ regulates leukocyte recruitment

I. Chronic Inflammation

- "inflammation of prolonged duration (weeks or months) in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously" *

- Occurs in:

1. Persistent infections – AFB, fungi, Treponemes
   - Low toxicity
   - Delayed hypersensitivity
   - Granulomatous inflammation

2. Prolonged exposure potentially toxic agents
   - Silica
   - Toxic plasma lipids → atherosclerosis

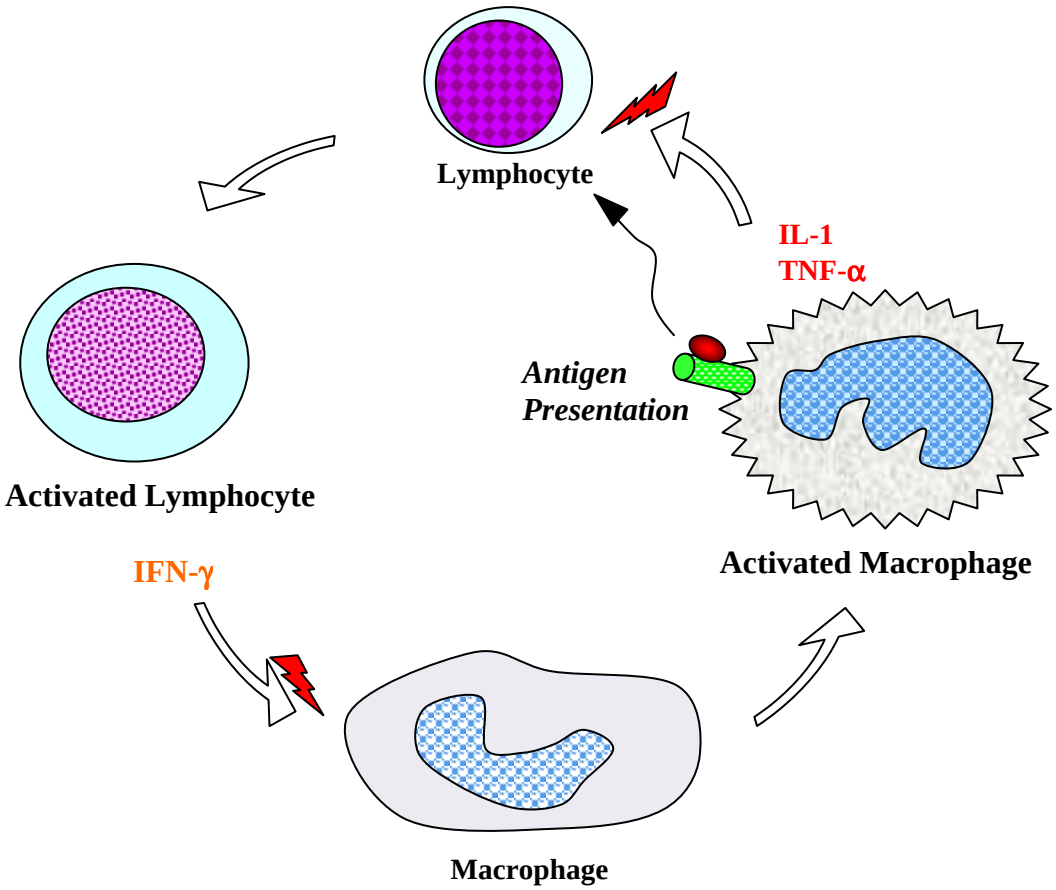
3. Autoimmunity
   - Rheumatoid arthritis
   - Lupus

- Macrophage has prominent role due the large repertoire of products it can produce when activated.

- Key macrophage events:
    1. Recruitment from circulation
    2. Local Proliferation
    3. Immobilization
    4. Differentiation (microglia, kupffer, alveolar macrophage, osteoclasts).

- Granulomas may be foreign body or immune with **T-cell involvement.**

- Lymphocytes & Macrophages work in concert.



II. TISSUE REPAIR

A. Connective Tissue Repair

- Starts as early as 24 hours
- Granulation tissue at 3 – 5 days.
- Four Components:

1. **Angiogenesis** – formation of new blood vessels
   - Vascular endothelial growth factor (VEGF)
     1. receptors only on endothelium
     2. produced in a variety of cells
     3. production stimulated by hypoxia, TGF-α, TGF-β, & PDGF
   - Process order:
     1. Degredation of basement membrane on parent vessel for capillary sprout
     2. Migration of endothelial cells to angiogenic stimulus
     3. Proliferation of endothelium
     4. Maturation and remodeling
     5. Recruitment of peri-endothelial cells

2. **Migration and proliferation of fibroblasts**
   - Many growth factors and inflammatory mediators involved.
   - TGF-β one of the most important via:
     1. causes fibroblast migration & proliferation
     2. ↑ collagen and fibronectin
     3. ↓ degredation of ECM by metalloprot.

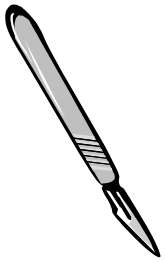
3. **Deposition of Extracellular Matrix**

4. **Maturation and Organization – Remodeling**
   - Balance – deposition vs. degredation
   - Zn dependent matrix metalloproteinases:

   1. Interstitial collagenases – type I, II, III collag.
   2. Gelatinase – type IV collagen & fibronectin
   3. Stromeolysins – variety of ECM
   4. Membrane Bound Matrix Metalloproteinases

   - Tissue Inhibitors of Metalloproteinase (TIMP)

B. Wound Healing



Healing by First Intention

- Or primary union
- Clean, uninfected, surgical incision with sutures
- Order of events:

1. blood clot forms.
2. < 24 hours – PMN's appear.
3. 24-48 hrs cut edges of epidermis thicken from basal cell hyperplasia, and epithelium migrates for union.
4. by day 3 – PMN's replaced by macrophages. Granulation tissue invades. Collagen at margins.
5. Incision filled with gran. tissue. Maximal neovascularization. Collagen bridges gap. Epidermis covers & is mature.
6. Second week – collagen deposition and fibroblast proliferation.
7. First month- scar with cellular connective tissue and no inflammatory cells.
8. Third month – 70-80% of maximum strength,

Healing by Second Intention

- Large tissue defect to fill
- Differs from primary union:

1. More fibrin, more debris → more intense inflammation.
2. More granulation tissue formed.
3. Wound contraction aided by myofibroblasts.

- **Factors that influence healing**

1. Nutrition – vitamin C
2. Metabolic status – diabetes hinders
3. Circulatory status
4. Hormones – glucocorticoids inhibit
5. Infection
6. Mechanical stress
7. Foreign bodies
8. Size, locations and type of the wound.

References

* Robbins Pathologic Basis of Disease, 6th edition, edited by Ramzi Cotran, published by Saunders, © 1999.