Healing and Repair

- **Repair** : the **restoration** of **tissue architecture** and **function** after an injury.

Tissue Repair

• **Repair involves 2 types of reactions:**

1. **Regeneration** of injured tissue by **Parenchymal Cells** of the same type (return to normal).
2. **Healing by fibrosis** Replacement by connective tissue → scar (when damaged tissue **can not** regenerate or **ECM has been destroyed**).

- **Fibrosis** refers to **extensive deposition of collagen** as a consequence of **chronic inflammation** in **Lungs, liver, kidneys, heart.**
- **Organization**: **fibrosis develops in tissue space** occupied by inflammatory exudate. Like : **Organizing pneumonia.**

• **Regeneration** & **Scarring** involve **SIMILAR** mechanisms including:

- Cell migration
- Proliferation
- Differentiation
- Matrix synthesis

Cell repair involves proliferation of :

1.Remnants of injuried cells
2.endothelial cells
3.fibroblasts

Control of cell growth & differentiation

• **Number of cells in a tissue is determined by:**

1. Rate at which **new cells enter** the tissue.
2. Rate at which **cells exit** the tissue.

• **Rate of entry of new cells is determined by:**

1. **Proliferation** rate
2. Cell **death**
3. Cell **differentiation**

• **Increase cell number in a tissue is a result of:**

1. **Increase** cell **proliferation**
2. **Decrease** cell **death**

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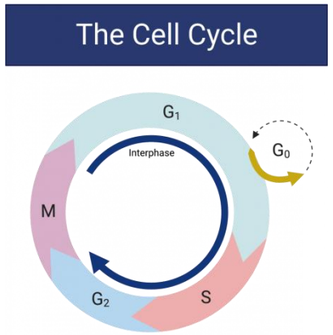
• **Stimuli of cell proliferation**

1. Injury 2. Cell death 3. Mechanical deformation of tissue 4. Excess of stimulators 5. Deficiency of inhibitors

• **Cell growth can be accomplished by:**

1. **Shortening the length** of cell cycle.
2. Decrease **rate of cell death**.
3. Induction of **resting cells in G0 to enter the cell cycle**.

Cell cycle



• **Phases:**

1. G1: Pre-synthetic growth phase.
2. S: DNA-synthetic phase.
3. G2: pre-mitotic growth phase
4. M: Mitotic phase

G0 = Quiescent cell (outside cell cycle).

- Progression of cells through cell cycle phases is controlled by: the **levels** & **activities** of a **family of proteins called CYCLINS** which are activated by complexing with proteins called **cyclin-dependent kinases (CDK).**

A- The Proliferative Potential Of Cells

- The ability of a cell to proliferate is **inversely correlated** with the degree of differentiation.
- Depending on the **regenerative capacity** of the cells and the **relationship to the cell cycle**, the cells of the body are divided **into 3 groups**:

• **First: Labile cells**

- **Continuously** dividing & dying cells
- Regeneration occurs from stem cells that have **unlimited capacity** to proliferate
- Stem cell -------- Cell with **ability to divide** (cell renewal)
- Stem cell ------ **non-mitotic cell** (carry on the normal function of the tissue).
- **Labile cells include:**

1. **Hematopoietic** cells in B.M
2. **Stratified Sq.** epitheluim, **skin, oral cavity, vagina, cervix**
3. **Cuboidal** epithelium of **exocrine organs draining ducts**, salivary glands, pancreas, biliary ducts
4. **Columar** epithelium of **GIT, uterus, fallopian tubes**.
5. **Transitional epithelium of urinary tract**.

• Second: Stable cells

- Quiescent (or **have only low level replicative capacity**) in their normal state but they can undergo **rapid division in response to injury.**

- Stable cells include:

1. Parenchyma of solid glandular tissues **as liver, kidney, pancreas**
2. **Endothelial cells**
3. **Fibroblasts**
4. **Smooth muscle**

• Third: Permanent cells

- Terminally differentiated & **nonproliferative** **in post natal life.**
- **Permanent cell include:**

1. Neurons
2. Cardiac muscle cells
3. Skeletal muscle cells (satellite cells attached to endomysial sheath have some regenerative capacity)

- Injury of permanent cell is **irreversible & result In Only Scar.**

Stem cells

- Are **undifferentiated cells** responsible for **generation of cells in tissues**.
- **Characteristic features** :

1-self-renewal capacity

2-asymmetric replication

- **Asymmetric Replication** of stem cells : means that after each division **some cells enter the differentiation** pathway while **others remain undifferentiated** retaining self renewal capacity.

• Types of stem cells :

1- **Embryonic** stem cells in blastocyst.

2- **Adult** (tissue) stem cells

Soluble Mediators

- Cell growth & differentiation are dependent **on extra-cellular signals** derived **from soluble mediators of ECM.**
- The most important signals **are polypeptide growth factors** present in **serum** or produced **locally by cells.**
- Growth factors can act on **one cell type** or **on multiple cell types.**

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Functions :

1-induction of **cell proliferation**

2-**relieve blocks on cell cycle** progression

3-**prevent apoptosis**

4-**enhancement** of cellular protein **synthesis**

Types of signaling

1-Autocrine Signaling

-GFs act on **the same cells** that secret them.

-examples

1.Immune response

2.Compensatory epithelial hyperplasia

2-Paracrine signaling

- act on **cells in the immediate vicinity** of the cell that secrete them.

- examples

1.**Recruiting inflammatory** cells to the site of infection

2.Wound **healing**

3-endocrine signaling

-a regulatory substance as a hormone is **released into blood** and **acts on target cells at distance**.

B- Extracellular Matrix & Cell Matrix interaction

• Function of ECM:

1. It gives **support & rigidity** to the skeleton
2. It **regulates cell** proliferation ,movement & differentiation of the cells within it.

ECM is of 2 forms:

1. Intersitital matrix

- Presents in **spaces between cells** in **connective tissue** & **between epithelium** & **supportive vascular & smooth muscle structures**.
- It is synthetized by **mesenchymal cells as fibroblasts.**

• Interstitial matrix is composed of:

1-fibrillar & non-fibrillar collagen. 2-fibronectin. 3-elastin.

4-proteoglycans. 5-hyaluronan.

2. Basement Membrane

- Around **epithelial** cells, **endothelial** cells & **smooth muscle** cells.
- Composed of :

1- **collagen type IV.**

2- laminin.

3- proteoglycan.

a.Collagen

-it gives the tissue its **tensile strength** that results from its **cross linking** which is **Vit C-dependent.**

-associated diseases of its deficiency:

a.Oseogenesis imperfecta

b.Ehlers-Danlos syndrome

b.Elastic fibers

- It gives **tissue elasticity & recoil**.
- Large **blood vessels wall ,uterus, skin & ligaments**.
- Composed of **Core of elastin** surrounded by **a network of fibrillin glycoprotein**.
- Defect in **fibrillin synthesis** → Marfan syndrome (skeletal abnormalities & weakened aortic wall).

C- Repair By Connective Tissue / Fibrous

• Repair occurs by **replacement of Non-Regenerated** parenchymal cells **with connective tissue.**

• Repair begins **within 24 hours of injury** by the **emigration of fibroblasts** and the induction of **fibroblast** and **endothelial cell** proliferation.

• By **3 to 5 days**, a specialized type of tissue that is characteristic of healing, called **granulation tissue is formed**.

- **Gross Appearance:** The term granulation tissue derives from the **pink, soft, granular gross appearance**, such as that seen beneath the scab of a skin wound.
- **Histologic Appearance** : is characterized by **proliferation of fibroblasts** and new thin-walled, delicate capillaries (**angiogenesis**), in a loose ECM.
- Granulation tissue then progressively **accumulates connective tissue matrix,** eventually → **the formation of a scar**.

✓ **Repair by connective tissue deposition consists of 4 sequential processes:**

1. **Angiogenesis**.
2. Migration & proliferation of **fibroblasts**.
3. **Deposition** of **ECM**(scar formation).
4. **Maturation** and **reorganization** of the fibrous tissue (Remodeling).

1-Angiogenesis

• Neoangiogenesis:

It is the **formation of new capillary buds** from pre-existing vessels to produce **new vessels.**

Function:

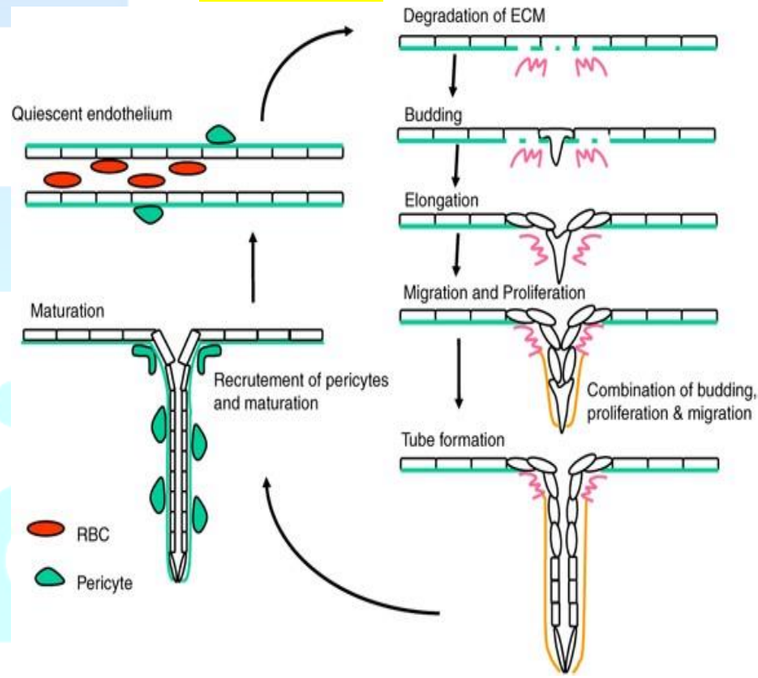
1.**Healing** process

2.**Collateral circulation** at the site of ischemia

3.**Tumor growth**

Steps Of Neoangiogenesis

1. **Vasodilatation** in response to **NO** & **increased permeability** induced by **VEGF**.
2. Proteolytic **degradation of the parent vessel BM** to form **capillary bud**.
3. **Migration of endothelial cells** from the original capillary toward an angiogenic stimulus.
4. **Proliferation of the endothelial cells** behind the leading edge of migrating cells.
5. **Inhibition of endothelial cell proliferation** & remodeling into capillary Tube.
6. Recruitment of **periendothelial cells (pericytes & smooth muscles) to form the mature vessel.**



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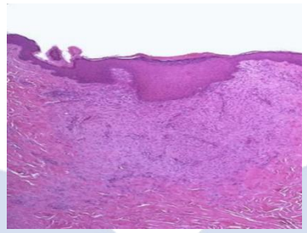
2/3- Scar Formation



• It builds on **granulation tissue formation** 3-5 days.

• It **involves 2 steps:**

1. **Migration & proliferation of fibroblasts** into site of injury.
2. Deposition of **ECM** by proliferating fibroblasts.

4- ECM & Tissue Remodeling

• **Maturation** & **reorganization** of the fibrous tissue.

• The outcome of repair process is the **BALANCE between ECM synthesis & degradation.**

• The degradation of collagen & ECM components by **metalloproteinases** which depend on **zinc ions for activation**.

Metalloproteinases.

• **These include:**

- **Collagenases** → **fibrillar** collagen.
- **Gelatinases** → **amorphous collagen & Fibronectin**.
- **Stromelysins** → **Proteoglycans, laminin,** fibronectin & amorphous collagen.

• **Source of these enzymes:**

1-Fibroblasts 2-Macrophages 3-Neutrophils 4-Synovial cell 5-Some epithelial cells.

-Synthesis of these enzymes in stimulated by:

GFs: **PDGF, EGF, IL-1,TNF**

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