Healing and Repair

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NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)

INJURY

REGENERATION

Renewing tissues
Complete regeneration:
Epidermis, GI tract epithelium, hematopoietic system
Compensatory growth of liver and kidney

Stable tissues

REPAIR

Wound
Wound healing, scar formation

Chronic inflammation
Fibrosis
Critical to survival of an organism is the ability to **repair** the damage.

**Repair or healing** refer to the restoration of tissue architecture and function after an injury.

2 types of reactions:

1. **Regeneration**
   - Proliferation of cells and tissues to replace lost or damaged cells and tissue.
   - Normal structure is restored

2. **Scar formation or fibrosis**
   - Normal structure is permanently altered
AUTOCRINE SIGNALING

Target sites on same cell

PARACRINE SIGNALING

Secretory cell

Adjacent target cell

ENDOCRINE SIGNALING

Hormone secretion into blood by endocrine gland

Distant target cells
INJURY

Cellular and vascular response

Stimulus removed (acute injury)

- Parenchymal cell death (intact tissue framework)
  - Superficial wounds
  - Some inflammatory processes
  - REGENERATION
    - Restitution of normal structure
    - Examples:
      - Liver regeneration after partial hepatectomy
      - Superficial skin wounds
      - Resorption of exudate in lobar pneumonia

- Parenchymal cell death (damaged tissue framework)
  - Deep wounds
  - REPAIR
    - Scar formation; Organization of exudate
    - Examples:
      - Deep excisional wounds
      - Myocardium infarction

Persistent tissue damage

- FIBROSIS
  - Tissue scar
  - Examples:
    - Chronic inflammatory diseases (cirrhosis, chronic pancreatitis, pulmonary fibrosis)
Response after injury

- Regeneration or renewal
- Scar formation

Both processes involve the **proliferation** of various cells and close interactions between cells and the ECM.

Ref: Robbins Basic Pathology (9th Edition)
Some tissues are able to replace the damaged cells and essentially return to a normal state. This occurs by proliferation of residual (uninjured) cells that retain the capacity to divide, and by replacement from tissue stem cells.
Scar formation

- If the injured tissues are incapable of degeneration, or if the supporting structures of the tissue are severely damaged.

Ref: Robbins Basic Pathology (9th Edition)
Cell and tissue regeneration

1. The control of cell proliferation
2. Proliferation capacity of tissue
3. Associated cells and signals
   1. Stem cells
   2. Growth factors
   3. ECM
4. Role of generation in tissue repair
The control of cell proliferation

Living cells go through a series of stages known as the **cell cycle**. The cells grow, copy their chromosomes, and then divide to form new cells.

**G1 phase.** The cell grows.

**S phase.** The cell makes copies of its chromosomes. Each chromosome now consists of two sister **chromatids**.

**G2 phase.** The cell checks the duplicated chromosomes and gets ready to divide.
Continuously cycling labile cells
(e.g., epidermis, GI tract epithelium)

Chromosome duplication
S

Check for DNA damage
(G₁/S checkpoint)

Restriction point
Centrosome duplication
G₁
Growth in mass

Quiescent, stable cells
(e.g., hepatocytes)

Permanent cells
(e.g., neurons, cardiac myocytes)

Check for damaged or unduplicated DNA
(G₂/M checkpoint)

M
Mitosis

Cell division

© Elsevier 2005
Key facts about cell cycle

• The role of growth regulation, the cell cycle has multiple controls

• The cycle consists of
  - **G1** phase (presynthetic growth phase I)
    - non dividing cells are either in cell cycle arrest in G1 Or they exit the cycle to enter G0
  - **S** phase (DNA synthesis phase)
  - **G2** Premitotic growth phase 2
  - **M** (mitotic phase)

• Any stimulus that initiates cell proliferation, such as growth factors need to promoted the G0/G1 transitions and the entry of cells into the first, i.e. G1, phase of the cycle.
Key facts about cell cycle (cont.)

- Checkpoint control = an intrinsic quality control mechanism for cell integrity
- Checkpoint controls prevents DNA replication or mitosis of damaged cells and either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis.
- Cyclins = proteins that
Proliferation capacity of tissue

Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, cell death by apoptosis, or changes in the rates of proliferation or differentiation.

Ref: Robbins Basic Pathology (9th Edition)
Proliferation capacity of tissue

- According to regenerative capacity of the cell, the tissue of the body can divide into 3 groups.

**Labile tissues**

Cells of these tissues are continuously being lost and replaced by maturation from stem cells and by proliferation of mature cells.

**Stable tissues**

Cells of these tissues are quiescent and have only minimal replicative activity in their normal state. However, these cells are capable of proliferating in response to injury or loss of tissue mass.

**Permanent tissues**

The cells of these tissues are considered to be terminally differentiated and nonproliferative in postnatal life.
**Example**

<table>
<thead>
<tr>
<th>Labile cells</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous epithelium of skin, mouth, vagina and cervix</td>
<td></td>
</tr>
<tr>
<td>Columnar epithelium of intestinal tract</td>
<td></td>
</tr>
<tr>
<td>Transitional epithelium of urinary tract</td>
<td></td>
</tr>
<tr>
<td>Bone marrow cells</td>
<td></td>
</tr>
</tbody>
</table>

![Diagram](image-url)
Transitional Epithelia of Urinary Bladder

(Note Binucleated cells)

Locations:
- Urinary Bladder
- Ureter
- Proximal Urethra

Functions:
- Distension (only)
<table>
<thead>
<tr>
<th>Stable cells</th>
<th>Liver hepatocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alveolar cells of lung</td>
</tr>
<tr>
<td></td>
<td>Epithelium of kidney tubules</td>
</tr>
</tbody>
</table>

![Diagram of liver and kidney structures](image_url)

**Kidney H&E**
- **distal tubules**
- **collecting tubule**
- **thin tubules**
Cardiac muscle
- has striated, branched, uninucleated fibers.
- occurs in walls of heart.
- is involuntary.

Skeletal muscle
- has striated, tubular, multinucleated fibers.
- is usually attached to skeleton.
- is voluntary.
Several cell types proliferate during tissue repair.

- **The remnants of the injured tissue** restore normal structure.
- **Vascular endothelial cells** create new vessels that provide the nutrients needed for the repair process.
**Fibroblasts** the source of the fibrous tissue that forms the scar to fill defects that cannot be corrected by regeneration.
Associated cells and signals

I. Stem cells
II. Growth factors
III. ECM
Stem cells are characterized by two important properties: 
Selfrenewal capacity and asymmetric replication.

What is a Stem Cell?

- A single cell that can...
  - Replicate itself, or...
  - Differentiate into many cell types.

Ref: https://www.caricord.com/images/image.jpg
**Adult stem cells**

- also called tissue stem cells, are less undifferentiated than ES cells and are found among differentiated cells within an organ or tissue.

Although, like ES cells, they also have self-renewal capacity, this property is much more limited.

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**Stem cell niches**

= specialized microenvironments within the organ

- Have been identified in many organs - brain, skin, cornea
- Signals from other cells in such niches keep the stem cells quiescent and undifferentiated.

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Ref: https://theingredientsobsession.files.wordpress.com/2015/01/scrt81-1-l.jpg
Mesenchymal stem cells

Hematopoietic stem cells, the **bone marrow** also contains a somewhat distinctive population of tissue stem cells, often called *mesenchymal stem cells*.

These cells can give rise to a variety of mesenchymal cells, such as chondroblasts, osteoblasts, and myoblasts. Hence, there is great interest in their therapeutic potential.

Ref: https://goo.gl/images/z63LEi
Growth factors

(MITCHELL, et al. 2016)
<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Sources</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal growth factor (EGF)</td>
<td>Activated macrophages, salivary glands, keratinocytes, and many other cells</td>
<td>Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue</td>
</tr>
<tr>
<td>Transforming growth factor-α (TGF-α)</td>
<td>Activated macrophages, keratinocytes, many other cell types</td>
<td>Stimulates proliferation of hepatocytes and many other epithelial cells</td>
</tr>
<tr>
<td>Hepatocyte growth factor (HGF) (scatter factor)</td>
<td>Fibroblasts, stromal cells in the liver, endothelial cells</td>
<td>Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Mesenchymal cells</td>
<td>Stimulates proliferation of endothelial cells; increases vascular permeability</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes</td>
<td>Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis</td>
</tr>
<tr>
<td>Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)</td>
<td>Macrophages, mast cells, endothelial cells, many other cell types</td>
<td>Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis</td>
</tr>
<tr>
<td>Transforming growth factor-β (TGF-β)</td>
<td>Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts</td>
<td>Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation</td>
</tr>
<tr>
<td>Keratinocyte growth factor (KGF) (i.e., FGF-7)</td>
<td>Fibroblasts</td>
<td>Stimulates keratinocyte migration, proliferation, and differentiation</td>
</tr>
</tbody>
</table>

ECM, extracellular membrane.
Role of the Extracellular Matrix (ECM) in Tissue Repair

ECM occurs in two basic forms:
1. interstitial matrix
2. basement membrane

Ref: http://apbiocellorganelles.weebly.com
Matrix metalloproteinase regulation. The 4 mechanisms shown include (1) regulation of synthesis by a variety of growth factors or cytokines, (2) inhibition of synthesis by corticosteriods or transforming growth factors β (TGF-β), (3) regulation of the activation of secreted but inactive precursors, and (4) blockade of the enzymes by specific tissue inhibitors of metalloproteinases (TIMPs).

**ECM** - extracellular matrix  
**EGF** - epidermal growth factor  
**IL-1** – interleukin 1  
**PDGF** - platelet-derived growth factor  
**TNF** - tumor necrosis factor.
ECMs

1. Collagen
2. Elastin
3. Proteoglycan and Hyaluronic acid
4. Adhesive glycoproteins and adhesion receptors
   I. Fibronectin
   II. Laminin
   III. Integrin

Image adapted from Ricard-Blum 2011 and Chung and Uitto 2010
The collagens are composed of three separate polypeptide chains braided into a ropelike triple helix.

Some collagen types (e.g., types I, II, III, and V) form fibrils by virtue of lateral cross-linking of the triple helices.
The fibrillar collagens form a major proportion of the connective tissue in healing wounds and particularly in scars.

Other collagens are nonfibrillar and may form basement membrane (type IV) or be components of other structures such as intervertebral disks (type IX) or dermal–epidermal junctions (type VII).
<table>
<thead>
<tr>
<th>Type</th>
<th>Class identification</th>
<th>Function</th>
<th>Area specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrils (diameter ~40-100 nm)</td>
<td>Tensile Strength</td>
<td>Dermis (main feature in reticular dermis)</td>
</tr>
<tr>
<td>III</td>
<td>Fibrils (diameter ~20-40 nm)</td>
<td>Tensile Strength</td>
<td>Boundary zones of the dermis and basal and periderm cells of the epidermis</td>
</tr>
<tr>
<td>IV</td>
<td>Network forming</td>
<td>A component of basement membrane (BM) and induce cytoskeletal rearrangements</td>
<td>Lamina densa of BM</td>
</tr>
<tr>
<td>V</td>
<td>Fibrils (inconsequential component to COL type I and III)</td>
<td>Determination of fibril structure</td>
<td>Basal and periderm cells of the epidermis and dermal cell surfaces</td>
</tr>
</tbody>
</table>
| VI   | Beading filament foaming | • Cell-cell and cell-matrix communication  
• Regulates ECM assembly and fibroblast motility | Bapillary dermis immediately below DEJ |
| VII  | Anchoring fibrils    | Attach cells to DEJ                                                        | DEJ |
| XVII | Transmembrane        | Formation of hemidesmosomes                                                | BM |
| XIX  | fibril-associated collagens with interrupted triple helices | Formation of specialized BM                                                | BM |
Genetic defects in these collagens cause diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome.

**Osteogenesis imperfecta (OI)**, also known as brittle bone disease, is a group of genetic disorders that mainly affect the bones. It results in bones that break easily.

**Ehlers-Danlos syndrome** is a group of disorders that affect connective tissues supporting the skin, bones, blood vessels, and many other organs and tissues. Defects in connective tissues cause the signs and symptoms of these conditions, which range from mildly loose joints to life-threatening complications.
The major components of the extracellular matrix (ECM), including collagens, proteoglycans, and adhesive glycoproteins. Note that although there is some overlap in their constituents, basement membrane and interstitial ECM differ in general composition and architecture. Both epithelial and mesenchymal cells (e.g., fibroblasts) interact with ECM through integrins. For simplification, many ECM components have been left out (e.g., elastin, fibrillin, hyaluronan, syndecan).
Elastin

This is especially important in the walls of large vessels (which must accommodate recurrent pulsatile flow), as well as in the uterus, skin, and ligaments.

Defects in fibrillin synthesis lead to skeletal abnormalities and weakened aortic walls
Elastin

The ability of tissues to recoil and return to a baseline structure after physical stress is conferred by elastic tissue. Morphologically, elastic fibers consist of a central core of elastin surrounded by a meshlike network of fibrillin glycoprotein.
Proteoglycans form highly hydrated compressible gels conferring resilience and lubrication (such as in the cartilage in joints).

Ref: http://www.buzzle.com/images/buzzle/structure-of-proteoglycans.jpg
They consist of long polysaccharides, called glycosaminoglycans or mucopolysaccharides (examples are dermatan sulfate and heparan sulfate), linked to a protein backbone.

**Hyaluronan** (also called hyaluronic acid), a huge mucopolysaccharide without a protein core, is also an important constituent of the ECM that binds water, and forms a viscous, gelatin-like matrix.

HA provides compressibility to tissues, proteoglycans also serve as reservoirs for growth factors secreted into the ECM (e.g., fibroblast growth factor [FGF], HGF).
Some proteoglycans are integral cell membrane proteins that have roles in cell proliferation, migration, and adhesion—for example, by binding growth factors and chemokines and providing high local concentrations of these mediators.
Adhesive glycoproteins and adhesion receptors

Ref: https://goo.gl/images/PBpwZq
Tissue fibronectin forms fibrillar aggregates at wound healing sites; plasma fibronectin binds to fibrin within the blood clot that forms in a wound, providing the substratum for ECM deposition and re-epithelialization.
**Integrins** (leukocyte adhesion to endothelium)

**main cellular receptors** for ECM components, such as fibronectins and laminins

some of the integrins as leukocyte surface molecules that mediate firm adhesion and transmigration across endothelium at sites of inflammation, and we shall meet them again when we discuss platelet aggregation

Ref: [https://www.molvis.org/molvis/v12/a22/v12a22f6.gif](https://www.molvis.org/molvis/v12/a22/v12a22f6.gif)

Ref: [https://goo.gl/images/oJVzsj](https://goo.gl/images/oJVzsj)
Laminin

(820-kDa, is the most abundant glycoprotein in basement membrane)

connects cells to underlying ECM components such as type IV collagen and heparan sulfate. Besides mediating attachment to basement membrane, laminin can also modulate cell proliferation, differentiation, and motility.

Ref: https://goo.gl/images/VAkWeo
Functions of ECMs

1. Mechanical support
2. Control of cell proliferation
3. Scaffolding for tissue renewal.
4. Establishment of tissue microenvironments.
Processes of scar formation

I. Formation of new blood vessels (angiogenesis)

II. Migration and proliferation of fibroblasts and deposition of connective tissue

III. Maturation and reorganization of the fibrous tissue (remodeling)
Steps in repair by scar formation

Injury to a tissue that has limited regenerative capacity first induces inflammation.

Ref: Robbins Basic Pathology (9th Edition)
Clears dead cells and microbes, if any. This is followed by formation of vascularized granulation tissue and then deposition of ECM to form the scar. ECM, extracellular matrix.

*Ref: Robbins Basic Pathology (9th Edition)*
Angiogenesis is the process of new blood vessel development from existing vessels, primarily venules.

Angiogenesis involves sprouting of new vessels from existing ones and consists of the following steps:

1. Vasodilation occurring in response to NO and increased permeability induced by VEGF
2. Separation of pericytes from the abluminal surface
3. Migration of endothelial cells toward the area of tissue injury

Mechanism of angiogenesis. In tissue repair, angiogenesis occurs mainly by growth factor–driven outgrowth of residual endothelium, sprouting of new vessels, and recruitment of pericytes to form new vessels.

Ref: Robbins Basic Pathology (9th Edition)
A. Angiogenesis by mobilization of EFCs from the bone marrow

B. Angiogenesis from preexisting vessels
Growth factors Involved in Angiogenesis

- The **VEGF family of growth factors** includes VEGF-A, -B, -C, -D, and -E and placental growth factor (PlGF).
- The **FGF family of growth factors** has more than 20 members; the best characterized are FGF-1 (acidic FGF) and FGF-2 (basic FGF).
- **Angiopoietins Ang1 and Ang2** are growth factors that play a role in angiogenesis and the structural maturation of new vessels.

Growth factors Involved in ECM deposition

*Transforming growth factor-β (TGF-β)*
Functions.-
1. stimulates the production of collagen, fibronectin, and proteoglycans, and it inhibits collagen degradation
2. an anti-inflammatory cytokine that serves to limit and terminate inflammatory responses
Growth factors Involved in ECM deposition (cont.)

- **Platelet-derived growth factor (PDGF)**
  causes migration and proliferation of fibroblasts and smooth muscle cells and may contribute to the migration of macrophages

- **Cytokines**
  may also function as growth factors and participate in ECM deposition and scar formation.
An overview of the major types of cells surface receptors and their principal signal transduction pathways leading to transcription factor activation. Shown are receptors with intrinsic tyrosinase activity, seven transmembrane G-protein-coupled receptors, and receptors without intrinsic tyrosinase kinase activity.

cAMP, Cyclic adenosine monophosphate; IP3, inositol triphosphate; JAK, Janus kinase; MAP kinase, mitogen-activated protein kinase; P13 kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B (also known as Akt); PLC-Y, phospholipase CY, STAT, signal transducers and activators of transcription.
The glycosaminoglycan chains can also bind free FGF-2 from the ECM and mediate interactions with cell surface FGF receptors.

The cytoplasmic tail of syndecan attaches to the intracellular actin cytoskeleton and helps maintain the architecture of epithelial sheet.

Proteoglycans in the ECM and on cells act as reservoirs for growth factors. Heparan sulfate binds basic fibroblast growth factor (FGF-2) secreted into the ECM. Any subsequent injury to the ECM can release FGF-2, which stimulates the recruitment of inflammatory cells, fibroblast activation, and new blood vessel formation.

Syndecan is a cell surface proteoglycan with a transmembrane core protein and attached extracellular glycoaminoglycan side chains.
Cutaneous wound healing

Specialize cells types first clear the inciting injury and then progressively build the scaffolding to fill in any defect.

1 Epithelial Regeneration

2 Formation of connective tissue scar

Three main phases of wound healing

The event of wound healing overlap to a great extend and cannot be completely separated from each other.

Wound contraction occurs only in healing by second intention.
Based on the nature of wound, the healing of cutaneous wounds can occur by

- **Healing by First Intention**
- **Healing by Second Intention**

**Healing by First Intention**

- Clean/ uninfected surgical incision approximated by surgical sutures.

- Focal disruption of epithelial basement membrane continuity and death of a relatively few epithelial regeneration predominates over fibrosis
• Small scar is formed but minimal wound contraction.

• The incisional space first fills with fibrin-clotted blood, which rapidly invaded by granulation tissue and covered by new epithelium.

• **24 hr**
  
  Neutrophils are seen at the incision margin, migrating toward the *fibrin clot*. Basal cells at the cut edge of epidermis begin to show increased mitotic activity.
Epithelial cells from both edge have begun to migrate and proliferate along the dermis, depositing basement components as they progress.

By day 3, Neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins, but these are vertically oriented and do not bridge the incision.

Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.
• **By day 5**
Neovascularization reaches its peak as granulation tissue fills the incisional space.

Collagen fibrils become more abundant and begin to bridge the incision.

The epidermis covers the normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface **keratinization**.

• **During the second week**
There is continued collagen accumulation and fibroblast proliferation.

The leukocyte infiltrate, enema, and increased vascularity are substantially diminished.

The long process of ‘blanching’ begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.
• **By the end of first month**
The scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis.

However, the dermal appendages destroyed in the line of the incision are permanently lost. The tensile strength of the wound increases with time, as described later.
More complex, more intense of inflammatory reaction
Abundant development of granulation tissue

- Large wounds
- Abscess formation
- Ulceration
- after infarction in parenchymal organ

**Key processes**
1. Wound contract by - myofibroblast
2. Accumulation of ECMs
3. Formation of a large scar
Steps in wound healing by first intention (*left*) and second intention (*right*). In the latter case, note the large amount of granulation tissue and wound contraction.

Ref: Robbins Basic Pathology (9th Edition)
Much larger amount of granulation tissue are formed. Larger defects require a greater volume of granulation tissue to fill in the gaps and provide the underlying framework for the regrowth of tissue epithelium.

Greater volume of scar tissue

Wound contracting:
Within 6 weeks, large skin defects may be reduced to 5%- 10% of the original size, largely by contraction.
• Related cell = myofibroblast
which are modified fibroblasts exhibiting many of the ultrastructural and Functional features of contractile smooth muscle cells.
Conclusions

General model of tissue repair in brief

Clotting occurs, caused by clotting proteins and plasma proteins, and a scab is formed.

Epithelial cells multiply and fill in over the granulation tissue.

Restored epithelium thickens; the area matures and contracts.

Inflammatory chemicals are released from injury.

White blood cells seep into the injured area.

Granulation tissue restores the vascular supply.

Underlying area of scar tissue.
Granulation tissue showing numerous blood vessels, edema, and a loose ECM containing occasional inflammatory cells. Collagen is stained blue by the trichrome stain; minimal mature collagen can be seen at this point.
Trichrome stain of mature scar, showing dense collagen with only scattered vascular channels. ECM, extracellular matrix.
Healing of skin ulcers. **A**, Pressure ulcer of the skin, commonly found in diabetic patients. **B**, A skin ulcer with a large gap between the edges of the lesion. **C**, A thin layer of epidermal re-epithelialization, and extensive granulation tissue formation in the dermis. **D**, Continuing re-epithelialization of the epidermis and wound contraction.
Keloid. **A,** Excess collagen deposition in the skin forming a raised scar known as a keloid. **B,** Thick connective tissue deposition in the dermis.
Hepatic regeneration and Scarring events

Diagram showing the process of hepatic regeneration and scarring events.

1. Normal hepatic lobule
   - Portal triad: hepatic artery, portal vein, bile duct
   - Sinusoid
   - Hepatocyte
   - Connective tissue reticular fibers

2. Injury to cells
   - Proliferation of residual cells within intact matrix

3. Injury to cells and matrix
   - Deposition of connective tissue; proliferation of residual cells within disrupted matrix

4. Regeneration
   - REGENERATION

5. Repair by scarring
   - REPAIR BY SCARRING
References


4) Robbins Basic Pathology 8th and 9th edition
The overview: Tissue Repair (0.52 min)
https://www.youtube.com/watch?v=4Wb0RaoMg5E

Scar Tissue Formation (2.44 min)
https://youtu.be/gRXTcFKHBwY

Wound Healing (3.27 min)
https://youtu.be/RiKu9sgFizY