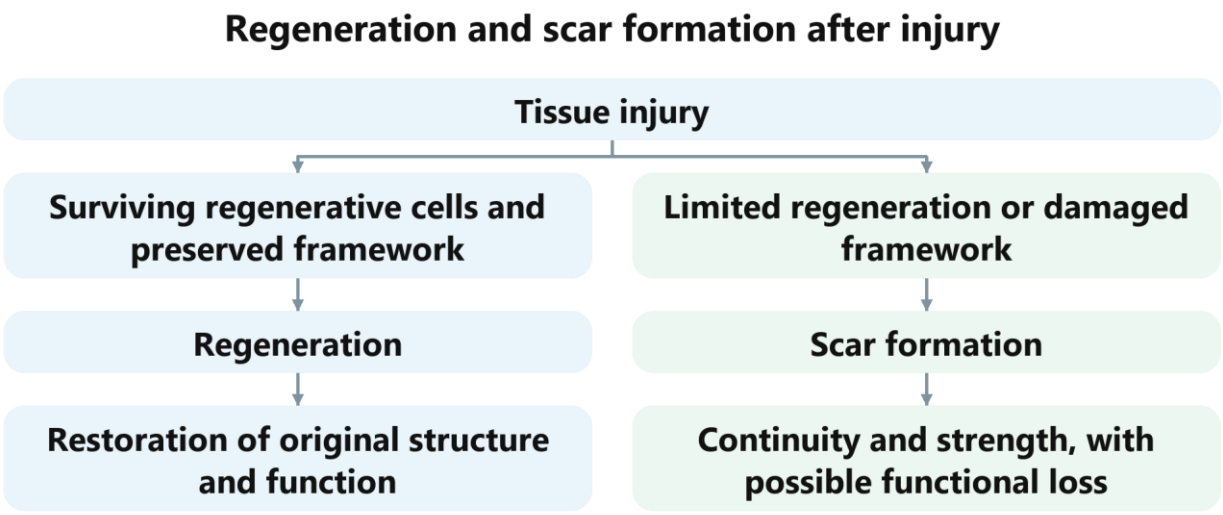
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Pathology - Topic 4 - Healing and repair

Repair and Regeneration

- **Repair** is the restoration of tissue continuity after injury through regeneration, scar formation or a combination of both.



Regeneration and scar formation after injury

Repair and Its Determinants

- The balance depends on the survival of functional cells, regenerative capacity and preservation of the extracellular framework.

Regeneration

- **Regeneration** replaces lost cells with cells of the same type and can restore normal structure and function.
    - It is most effective when the injury is limited and the supporting framework remains intact.

Scar Formation

- **Scar formation** replaces lost tissue with connective tissue when complete regeneration is not possible.
    - A scar restores strength and continuity but may not reproduce the specialised function of the original tissue.

The Role of Cells and Matrix

Cell Proliferation

- Surviving mature cells and tissue stem cells can proliferate in response to appropriate growth signals.

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A. Labile Cells

- **Labile cells** divide continuously throughout life, with tissue stem cells supplying replacements for cells lost from renewing populations.
- Surface epithelia, gastrointestinal crypt cells and bone-marrow haematopoietic cells are important examples.

B. Stable Cells

- **Stable cells** are normally quiescent but can re-enter the cell cycle after injury or loss of tissue.
- Examples include hepatocytes, renal tubular cells, fibroblasts and endothelial cells.
- Hepatocytes can proliferate after partial loss of liver tissue when surviving cells and the supporting environment remain suitable.

C. Permanent Cells

- **Permanent cells**, including most mature neurons and cardiac muscle cells, have very limited proliferative capacity, so substantial injury usually heals by scarring.
- Skeletal muscle has limited regenerative capacity through satellite cells rather than division of mature muscle fibres.

Importance of the Supporting Framework

- Chronic destruction of the framework favours fibrosis and distorted regeneration rather than restoration of normal architecture.

Extracellular Matrix

- The **extracellular matrix** provides mechanical support and signals that regulate cell movement, survival and differentiation.
  - It contains structural proteins such as collagen, adhesive proteins and hydrated ground substance.
- A preserved basement membrane guides orderly epithelial regeneration.
  - Extensive matrix destruction makes it difficult to rebuild the original tissue arrangement.
- Fibronectin and related adhesive proteins support attachment and migration of cells into the wound.

Signals That Coordinate Repair

Growth Factors

- Vascular endothelial growth factor promotes new-vessel formation and increases vascular permeability.
- Fibroblast growth factors support endothelial growth, fibroblast activity and migration of epithelial cells.
- Platelet-derived growth factor attracts and stimulates fibroblasts and other repair cells.

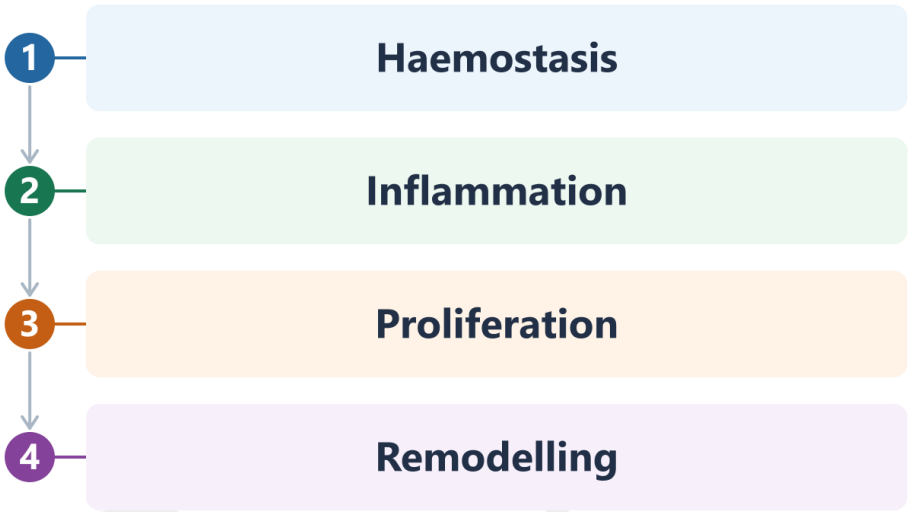
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- Transforming growth factor beta stimulates collagen synthesis and inhibits its degradation, making it an important mediator of fibrosis.

Phases of Wound Healing

- Wound healing proceeds through haemostasis, inflammation, proliferation and remodelling.

An Overlapping Sequence



- These phases overlap rather than starting and stopping at precise times in every wound.

1. Haemostasis and Early Inflammation

- Platelets and fibrin form a clot that limits bleeding and provides a temporary framework for migrating cells.
  - Platelet-derived signals recruit inflammatory and repair cells.
- Neutrophils remove bacteria and debris early in the response.
  - Macrophages then clear dead cells and coordinate repair through cytokines and growth factors.

2. Formation of Granulation Tissue

Composition and Appearance

- **Granulation tissue** consists of new capillaries, fibroblasts, loose extracellular matrix and inflammatory cells.
- Its delicate capillaries give it a pink-red, granular and easily bleeding appearance.

Angiogenesis and Matrix Formation

- Angiogenesis begins when endothelial cells respond to signals such as vascular endothelial growth factor.
- They migrate and proliferate to form vascular channels, which later mature and acquire supporting cells.
- Fibroblasts enter the wound and produce extracellular matrix.

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- TGF-beta promotes matrix synthesis and fibrosis, while platelet-derived growth factor and other signals support fibroblast recruitment and proliferation.

Maturation of New Vessels

- Basement-membrane breakdown allows endothelial migration, after which vascular tubes are stabilised by pericytes and smooth-muscle support.
- Immature vascular junctions allow fluid leakage, contributing to the moist oedematous appearance of early granulation tissue.

3. Epithelialisation and Contraction

A. Epithelialisation

- Epithelial cells migrate across the wound surface and proliferate to restore the epithelial barrier.
- A moist, viable surface and a suitable supporting matrix help this process.

B. Wound Contraction

- Myofibroblasts contract the wound and draw its edges towards one another.
- Contraction is particularly important in large open wounds that heal by secondary intention.

4. Collagen Remodelling

Changes in Collagen and Scar Structure

- Early collagen is reorganised, cross-linked and partly replaced by stronger, more organised collagen bundles.
- Matrix metalloproteinases and their inhibitors regulate matrix breakdown and remodelling.
- The number of vessels and cells decreases, and the scar becomes paler and firmer.

Tensile Strength and Mechanical Support

- Tensile strength rises gradually but usually does not return to the full strength of uninjured skin.
- Early type III collagen is remodelled into a stronger framework rich in type I collagen.
- Sutures and the clot initially provide more mechanical support than the small amount of newly synthesised matrix.

Microscopic Sequence in a Clean Incised Skin Wound

1. The First Day

- A fibrin-rich clot closes the narrow wound gap, and neutrophils collect near the margins.
- Basal epithelial cells at the edges increase mitotic activity and begin migrating beneath the surface clot.

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2. Approximately Two to Five Days

- Epithelial continuity is re-established across a small clean wound, although the underlying tissue remains mechanically weak.
- Macrophages replace many neutrophils and remove debris while releasing mediators that recruit repair cells.
- Capillary buds, fibroblasts and loose extracellular matrix form granulation tissue, which progressively occupies the wound space.

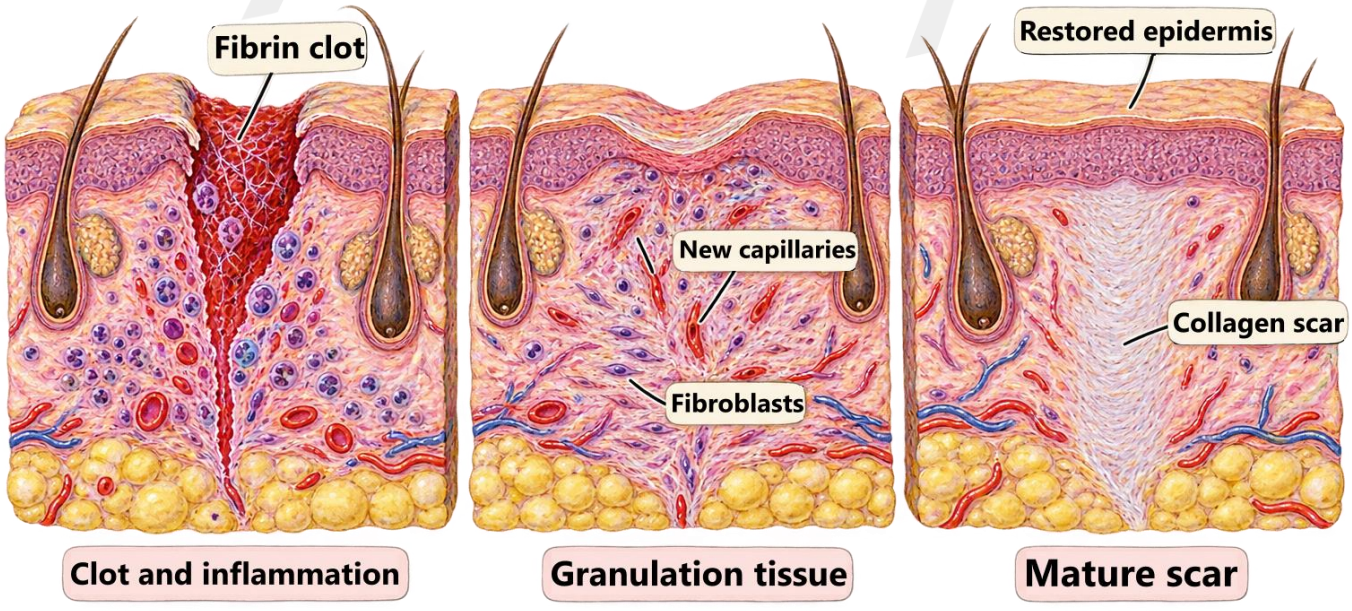
3. The Following Weeks and Months

- Collagen accumulates and bridges the incision, while inflammatory cells and small vessels diminish.
- The scar becomes paler, less cellular and stronger as collagen is reorganised and cross-linked.
- These times describe an uncomplicated wound and vary with site, wound size, infection and patient factors.

Types of Wound Healing

- A wound may heal by primary or secondary intention according to tissue loss, wound-edge approximation and the extent of repair required.

Healing According to Wound Configuration



Primary-intention wound healing progresses from a small clot to granulation tissue and a collagen-rich scar

1. Primary Intention

Wound Type and Typical Example

- Healing by **primary intention** occurs when a clean wound has closely approximated edges and limited tissue loss.

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