Tissue Repair
Tissue Repair

• Tissue repair = restoration of tissue architecture and function after an injury

• Occurs in two ways:
  – Regeneration of injured tissue
  – Replacement by connective tissue (scarring)

• Usually, tissue repair involves both processes.

• Involves cell proliferation, and interaction between cells and extracellular matrix.
Normal hepatic lobule

Portal triad: hepatic artery, portal vein, bile duct

Sinusoid

Hepatocyte

Connective tissue reticular fibers

Injury to cells

Injury to cells and matrix

Proliferation of residual cells within intact matrix

Deposition of connective tissue; proliferation of residual cells within disrupted matrix

REGENERATION

REPAIR BY SCARRING
Cellular Proliferation

- Lots of cells proliferate during tissue repair:
  - injured tissue remnants
  - vascular endothelial cells
  - fibroblasts

- We need to know about:
  - the cell cycle
  - the proliferative capacities of different tissues
  - stem cells
  - growth factors
  - the extracellular matrix
Mechanisms regulating cell populations

• Cell numbers can be altered by increased or decreased rates of stem cell input, by cell death due to apoptosis.

• or by changes in the rates of proliferation or differentiation.
Continuous dividing (labile) tissues

Stable tissues

Permanent tissues
1- Continuously dividing (labile) tissues

- Cells are continuously proliferating
- Can easily regenerate after injury
- Contain a pool of stem cells
- Examples: bone marrow, skin, GI epithelium
2- Stable tissues

- Cells have limited ability to proliferate
- Limited ability to regenerate (except liver!)
- Normally in $G_0$, but can proliferate if injured
- Examples: liver, kidney, pancreas
3- Permanent tissues

• Cells can’t proliferate

• Can’t regenerate (so injury always leads to scar)

• Examples: neurons, cardiac muscle
Blastocyst

- Endoderm
  - Mesodermal progenitor cell
    - Epithelial cells of liver, lungs, GI tract
  - Hematopoietic progenitor cell
    - Myocytes, osteoblasts, chondrocytes, adipocytes, endothelial cells
    - Bone marrows cells, red blood cells
    - Keratinocyte precursors, neurons, oligodendrocytes, ependymal cells

- Ectoderm
Epidermal stem cells located in the bulge area of the hair follicle serve as a stem cells for the hair follicle and the epidermis.

Intestinal stem cells are located at the base of a colon crypt, above Paneth cells.
Liver stem cells (known as oval cells) are located in the canals of Hering (thick arrow), structures that connect bile ductules (thin arrow) with parenchymal hepatocytes.

Corneal stem cells are located in the limbus region, between the conjunctiva and the cornea.
Differentiation pathways for pluripotent bone marrow stromal cells. Activation of key regulatory proteins by growth factors, cytokines, or matrix components leads to commitment of stem cells to differentiate into specific cellular lineages.
Therapeutic cloning
The Cell Cycle and Different Cell Populations

- Continuously cycling labile cells (e.g., epidermis, GI tract epithelium)
  - Chromosome duplication
  - Check for DNA damage (G₁/S checkpoint)
  - Restriction point
  - Centrosome duplication
    - Growth in mass

- Quiescent, stable cells (e.g., hepatocytes)
  - G₀

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

- CELL CYCLE
  - S: Chromosome duplication
  - G₂: Check for damaged or unduplicated DNA (G₂/M checkpoint)
  - M: Mitosis
  - G₁: Cell division
  - G₀: Quiescent, stable cells (e.g., hepatocytes)
  - Permanent cells (e.g., neurons, cardiac myocytes)
Growth Factors

• Very important in tissue repair.

• Actions:
  • stimulate cell division and proliferation
  • promote cell survival

• Huge list! Usually have “GF” in name:
  • EGF
  • TGF
  • PDGF
The Extracellular Matrix

- ECM is the network that surrounds cells
- Two forms: interstitial matrix and basement membrane
- Does lots of things!
  - Sequesters water and minerals
  - Gives cells a scaffold to adhere to
  - Stores growth factors
The Extracellular Matrix

- Basement Membrane:
  - Type IV collagen
  - Laminin
  - Proteoglycan

- Interstitial Matrix:
  - Fibrillar collagens
  - Elastin
  - Proteoglycan and hyaluronan

- Fibroblast
  - Integrins
  - Epithelium
  - Adhesive glycoproteins

- Cross-linked collagen triple helices

- Endothelial cells
  - Capillary
The Extracellular Matrix

- Bottom line: ECM regulates proliferation, movement, and differentiation of the cells living in it.

- If you screw up your ECM, you can’t regenerate! You’ll form a scar instead.
Regeneration

- **Occurs all the time in labile tissues**
  - Cells are constantly being lost and replaced
  - If demand increases, supply increases easily

- **Occurs in limited form in stable tissues**
  - Remove one kidney: the other one undergoes hypertrophy and hyperplasia
  - Remove half of the liver: it will grow back

- **Only occurs if residual tissue is intact!**
Scarring

- If injury is severe, regeneration can’t happen
- So, fibrosis (a scar) replaces the injured tissue
- Four components to this process:
  - new vessel formation (angiogenesis)
  - fibroblast proliferation
  - synthesis of collagen (scar formation)
  - remodeling of scar
Scarring

- By 24 hours:
  - Endothelial cells start proliferating
  - Fibroblasts emigrate

- By 3-5 days:
  - Granulation tissue present

- Weeks later:
  - Dense fibrosis (scar)
  - Scar is remodeled over time
Summary:

1. make granulation tissue
2. turn it into a chunk of collagen
Granulation tissue
Scar
SKIN WOUND HEALING

• First intention

• Second intention
Granulation tissue
first intention healing

second intention healing
Skin Wound Healing

Healing by First Intention

• Occurs in small wounds that close easily
• Epithelial regeneration predominates over fibrosis
• Healing is fast, with minimal scarring/infection

• Examples:
  • Paper cuts
  • Well-approximated surgical incisions
Skin Wound Healing

Healing by First Intention: Timeline

– By 24 hours

– By 3-7 days

– Weeks later
Skin Wound Healing

Healing by First Intention: Timeline

- By 24 hours

  - clot forms
  - neutrophils come in
  - epithelium begins to regenerate
Skin Wound Healing

Healing by First Intention: Timeline

– By 3-7 days

• macrophages come in
• granulation tissue is formed
  ➢ new blood vessels
  ➢ fibroblasts
• collagen begins to bridge incision
• epithelium increases in thickness
Skin Wound Healing

Healing by First Intention: Timeline

– Weeks later

• granulation tissue gone
• collagen is remodeled
• epidermis full, mature
  (but without dermal appendages!)
• eventually, scar forms
Skin Wound Healing

Healing by Second Intention

- Occurs in larger wounds that have gaps between wound margins
- Fibrosis predominates over epithelial regeneration
- Healing is slower, with more inflammation and granulation tissue formation, and more scarring
- Examples:
  - Infarction
  - Large burns and ulcers
  - Extraction sockets
Skin Wound Healing

Differences from healing by first intention:

- More inflammation
- More granulation tissue
- Wound contraction
Why Do Good Wounds Go Bad?

- Extrinsic factors
  - Infection
  - Diabetes
  - Steroids

- Type of tissue injured (labile vs. permanent)

- Aberrant cell growth or ECM production
  - Keloid scars
  - Proud flesh
Keloid
Keloid
Keloids
• Not all injuries result in permanent damage; some are resolved almost completely

• More often, there is some degree of scarring

• Scar is usually good (provides a resilient patch) but occasionally bad (can cause permanent dysfunction)
PARTIAL HEPATECTOMY

Cytokines
- TNF
- IL-6
- Others

Growth factors
- HGF
- TGF-α
- Others

Growth inhibitors
- TGF-β
- Activin
- Others

Adjuvants
- Norepinephrine
- Insulin
- Thyroid hormone
- Growth hormone

↓ Cell cycle inhibitors
↓ Growth factors
↓ Metabolic demands