# Session Objectives

- 1. Discuss and explain the basic principles of **healing, repair, and regeneration in regards to different types of tissues (labile, stable, permanent), and differentiate some important growth factors (e.g., PDGF, VEGF, TGF-beta, FGF-2) which mediate the healing/repair process.**
- 2. Describe **granulation tissue** and discuss the role of **angiogenesis** and the **importance of connective tissue elements, which include collagen**, in healing and repair.
- 3. Discuss and compare **healing by first and second intention.**
- 4. Discuss/describe **wound contraction and connective tissue remodeling.**
- 5. Give examples of tissue and organs in the process of healing/repair and **describe factors which deter that process**.

# REGENERATION

- Replacement of damaged or dead cells/tissue by cells of the same type
- May occur by proliferation of differentiated cells that survive injury and retain capacity to proliferate (e.g., hepatocytes)
- May occur when tissue stem cells and their progenitors contribute to restoration of damaged tissue (e.g. skin, GI mucosa)
- Tissues with high proliferative capacity
- **Intact basement membrane…and intact immature cells**
- **Must have intact connective tissue scaffold**



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# Cell types based on proliferation potential

- **Labile cells:** renewing cellular populations…(continuously dividing):
  - Examples: epithelial cells, lymphoid, hematopoietic, GI mucosa
- **Stable Cells:** low rate of proliferation or no proliferation… have the ability to re-enter the cell cycle under specific stimuli (quiescent):
  - Examples: parenchymal cells, liver, kidney, smooth muscle cells, osteoblasts, chondroblasts, endothelial cells, smooth muscle, fibroblasts
- **Permanent Cells:** terminally differentiated, (nondividing):
  - Examples: neurons, cardiac muscle, skeletal muscle



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# GROWTH FACTORS

- Proteins which regulate cell proliferation
- Macrophages important sources - may also come from epithelial and stromal cells
- Function as ligands that bind to specific receptors which deliver signals to target cells
- Signals stimulate transcription of genes that may be silent in resting cells, including genes that control cell cycle entry and progression



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# IMPORTANT GROWTH FACTORS

- PDGF causes migration and proliferation of fibroblasts, smooth muscle cells, monocytes to inflammatory areas and healing skin wounds
- VEGF important in **new blood vessel formation (angiogenesis),** promotes angiogenesis in chronic inflammation, wound healing, and tumors
- FGF-2 contributes to re-epithelization of skin wounds, induces new blood vessel formation, etc.
- **TGF-beta is potent fibrogenic agent** - stimulates fibroblast chemotaxis, enhances production of collagen, fibronectin, and proteoglycans; inhibits collagen degradation, anti-inflammatory

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

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# REPAIR BY CONNECTIVE TISSUE DEPOSITION (SCAR)

- Inflammation
- Angiogenesis
- Migration and proliferation of fibroblasts
- Scar formation
- Connective tissue remodeling
- Prototype – skin
- **Most healing is combination of regeneration and repair; depends on ability of tissue cells to proliferate, integrity of ECM, resolution or chronicity of injury or inflammation**

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# GRANULATION TISSUE

- Migration, **proliferation of fibroblasts and deposition of loose connective tissue along with new vessels and leukocytes (mostly macrophages)**
- New vessel formation - angiogenesis
- Type III collagen (immature) synthesis
- Cellular-cellular interactions via (growth) factors
- Sit in ECM: glycoproteins and proteoglycans
- Glycoproteins- for cross linking of collagen fibers to make stronger
- Proteoglycans – for hydrated gel formation (increased tissue turgor)



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# ANGIOGENESIS

- **VEGF** – most important growth factor, especially in chronic inflammation, wound healing, and tumors; promotes vasodilation by stimulating production of NO; also increases vessel permeability

- **VEGF-A -** most important in angiogenesis; stimulates survival, proliferation and motility of endothelial cells, initiating sprouting of new capillaries, promotes vasodilation and contributes to vessel lumen formation

- **FGF-2** stimulates proliferation of endothelial cells and promotes migration of macrophages and fibroblasts to damaged area

- **Newly formed vessels fragile,** stabilization requires recruitment of pericytes and smooth muscle cells and deposition of ECM proteins; angiopoeitins 1 and 2, PDGF, and TGF-beta participate in stabilization and these processes

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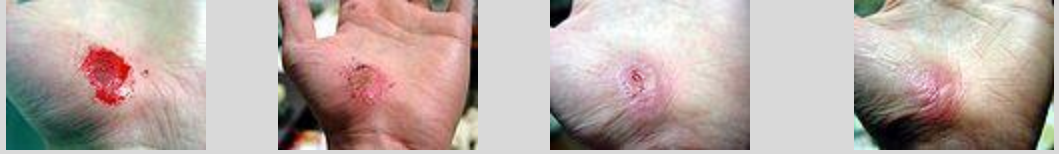
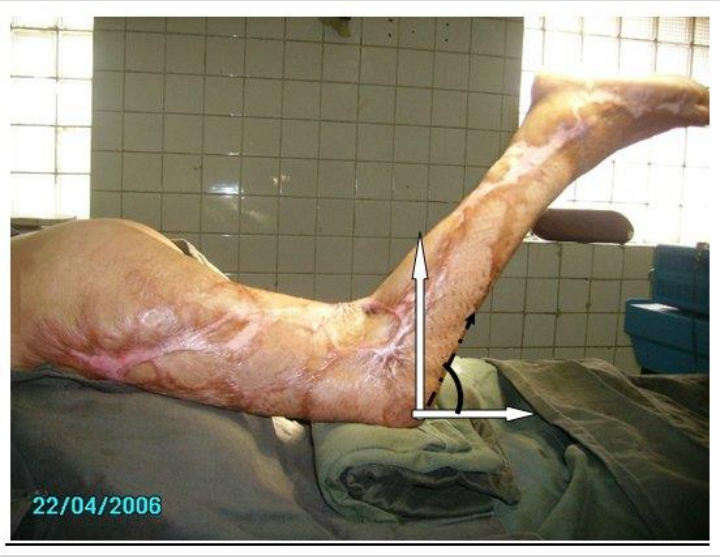



# Phase III: Maturation

- **Type III collagen is replace by type I**
  - Acquires final tensile strength
- **Remodeling: scar tissue becomes avascular and acellular**




- Wound contraction- wound edges pull together to close the defect
  - **Myofibroblasts-** fibroblasts with muscle filaments
    - Display feature of fibroblasts and smooth muscle cells



http://www.slideshare.net/csbrprasad/inflammation-1

# Healing by combinations of regeneration and repair

- Best example - skin wound
- Healing by **first intention or primary union** (epithelial regeneration):
  - When injury **only involves epithelial layer**
  - Clean skin wounds **(e.g., surgical excision)** – death of limited number of epithelial and connective tissue cells
- Healing by **second intention**
  - Edges of skin cannot be brought together
  - **tissue loss greater**
  - epidermal cells need longer time to cover surface
  - **more intense inflammatory reaction**
  - **abundant granulation tissue, extensive collagen deposition forming substantial scar**



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# REGENERATION OF THE LIVER

Partial hepatectomy of 60% of the liver → doubling of the size of the liver remnant within 1 month

- Mechanism= proliferation of remaining hepatocytes and repopulation from progenitor cells
- Situation where proliferative capacity of hepatocytes is impaired (e.g chronic liver injury)
- NOT regrowth of the lobes that were resected
- **Primary phase** – hepatocytes primed by cytokines made by Kupffer cells (macrophages) to receive and respond to GF signals
- **Growth factor phase** – hepatocytes are stimulated into metabolism
- **Termination phase** – hepatocytes return to quiescence

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# HEALING – REVIEW (continued)

- 24 to 48 hours - epithelial cells move from wound edge along cut margins of dermis, deposit basement membrane components; produce thin, continuous epithelial layer
- Increase in collagen fibrils to bridge incision
- Fibroblasts, vascular endothelial cells proliferate to form **granulation tissue** by **5 to 7 days**, fills wound, neovascularization maximal
- Wbc infiltrate, edema, increased vascularity disappear by second week
- **TGF-beta is most important fibrogenic agent: causes fibroblast migration and proliferation, increased synthesis of collagen and fibronectin, and decreased ECM degradation by MMPs**

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# HEALING REVIEW (continued)

- Increased collagen accumulation and regression of vascular channels – original granulation tissue scaffold converted to **pale, avascular scar made up of fibroblasts, dense collagen, elastic tissue, other ECM components**

- By end of first/second month – scar is composed of **acellular connective tissue without inflammation, covered by intact epithelium**



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# Summary Slide

- Definitions of healing, repair, regeneration
- Labile, stable, permanent cells – see slide 6
- Three phases of wound healing
- Repair by scar – granulation tissue, angiogenesis, connective tissue deposition (collagen and ECM)
- Example of skin injury – healing by primary and secondary intention
- Wound contraction, connective tissue remodeling, tensile strength
- Liver regeneration, examples of repair and healing
- Deterrents to wound healing – see slide 38
- Complications of wound healing – slides 39 - 42