A 56-year-old man has experienced severe chest pain for the past 4 hours. On physical examination he is tachycardic. Laboratory studies show a serum troponin I of 9 ng/mL. A coronary angiogram is performed emergently and reveals acute thrombosis of the left anterior descending coronary artery. In this setting, an irreversible injury to myocardial fibers will have occurred when which of the following cellular changes occurs?

A. Blebs form on cell membranes
B. Cytoplasmic sodium increases
C. Glycogen stores are depleted
D. Intracellular pH diminishes
E. Nuclei undergo karyorrhexis
Healing and Repair Concepts
- Regeneration vs Repair
- Models of Healing – Skin Wounds

What happens when cells are injured?
- Possible outcomes:
  - Adaptation
  - Repair (Heal)
  - Death

Repair
- With injury, body seeks to maintain normal structure and function
- Repair of injured cells initiated when inflammation begins
- "Healing" occurs via
  - Regeneration
  or
  - Scar Formation
Regeneration

- Replacement of damaged cells by replicating cells of the same type

Scar formation

- Replacement by connective tissue

Both may occur simultaneously

Robbins, Figure 3-23

Regeneration

- Connective tissue framework (extracellular matrix) of tissue remains intact
  - serves as scaffolding for orderly replacement of *residual uninjured* cells
- Cells must have capacity to divide
  - cell types have differing capabilities
    » Labile, Stable, Permanent

“Term Check”

*Extracellular Matrix (ECM)*

- Network of interstitial proteins
  - Comprises significant portion of most tissues
- Functions
  » Mechanical support
  » Control of cell proliferation
  » Growth factors
  » Scaffold for tissue regeneration
- Provides boundary between epithelium and underlying connective tissue
  » Tissue microenvironments
“Term Check”

**Extracellular Matrix (ECM)**

- Network of interstitial proteins
  - Two forms
    - Interstitial matrix
    - Basement membrane
  - Protein composition
    - Fibrous structural proteins
      - Collagens, Elastins
    - Water hydrated gel
      - Proteoglycans, hyaluronan
    - Adhesive glycoproteins

---

**Labile Tissues**

- Cells are constantly being lost and must be continually replaced by new cells
- New cells derived from
  - stem cells
  - rapidly proliferating immature progenitors
- Examples
  - Hematopoietic cells of bone marrow
  - Squamous epithelium of skin, oral cavity, cervix, vagina
  - Columnar epithelium of GI tract
**Stable Tissues**

- Low, no level of replication  
  - G0 cell cycle
- Rapidly divide when stimulated  
  - G1 cell cycle and beyond
- Example
  - Liver
  - Kidney, pancreas
  - Smooth muscle cells, fibroblasts, endothelial cells

---

**Permanent Tissues**

- Terminally differentiated, nonproliferative in postnatal life
- Examples:
  - 
  - 

---

Driven by signals of growth factors and from SCF
Regeneration Summary

• Regeneration of injured cells & tissues
  – Involves cell proliferation
  • Which is driven by growth factors
  • Dependent on integrity of ECM

Growth Factors Involved in Regeneration/Repair

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Source</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal Growth Factor (EGF)</td>
<td>Activates macrophages, keratinocytes, other cells</td>
<td>Mitogenic for keratinocytes, stimulates keratinocyte migration</td>
</tr>
<tr>
<td>Transforming Growth Factor – α (TGF–α)</td>
<td>Activates macrophages, keratinocytes, other cells</td>
<td>Stimulates proliferation of hepatocytes, other epithelial cells</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Macrophage 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 and stimulates proliferation of fibroblasts; stimulates ECM proteins synthesis</td>
</tr>
<tr>
<td>Fibroblast growth factor (FGFs)</td>
<td>Macrophages, mast cells, endothelial cells</td>
<td>Chemotactic, mitogenic for fibroblasts, stimulates angiogenesis, ECM protein synthesis</td>
</tr>
<tr>
<td>Transforming growth factor – β (TGF–β)</td>
<td>Platelets, macrophages, endothelial cells, fibroblasts</td>
<td>Chemotactic, stimulates angiogenesis, inhibits acute inflammation</td>
</tr>
</tbody>
</table>

Any Greek Mystery Buffs?
Example: Liver Regeneration

• Partial hepatectomy (for living donor transplant, tumor resection)
  – Up to 90% of liver regenerates by proliferation of residual hepatocytes
  • Driven by cytokines, growth factors
  – Chronic liver injury (hepatitis)
  • Proliferative capacity of hepatocytes is impaired
  • Progenitor cells of liver contribute to repopulation
  – What happens with extensive liver abscess?

Scar Formation

• Replacement of damaged tissue with connective tissue
• Why this?
  – Injured tissues incapable of regeneration
    • i.e. Myocardial infarction
  – Supporting structures (ECM) severely damaged, stem cells lost

“Definition check”
Connective Tissue/Scar

• Dense bands of collagen
• Fibroblasts
**Scar Formation**

• **Con**
  – Connective tissue cannot perform function of lost parenchymal cells

• **Pro**
  – Scar usually provides enough structural stability for injured tissue to continue function

---

**Steps in repair by scar formation**

- Macrophages are key players!
  - Cell proliferation:
    - epithelial cells
    - endothelial cells → angiogenesis
    - fibroblasts
  - Remodeling

Source: Robbins Basic Pathology
Angiogenesis

- New blood vessel development from existing vessels
  - Roles in
    - healing
    - development of collaterals at sites of ischemia
    - tumor growth

Definitions:
- Endothelial cells – inner lining of vessel wall
- Pericytes – cells with contractile properties

Important mediators:
- VEGF,
- FGFs,
- PDGF,
- TGF-β

...a little more on VEGF

- Vascular Endothelial Growth Factor
- Family of growth factors
  - Promote angiogenesis (new blood vessel formation)
  - Increase vascular permeability
  - Stimulate endothelial cell migration, proliferation
- Expressed at low levels in most adult tissues
- Hypoxia = important inducer
- Mutations = defective angiogenesis and vasculogenesis

Migration & Proliferation of Fibroblasts

- Fibroblasts synthesize connective tissue proteins
- Recruitment, activation driven by many growth factors (PDGF, FGF, TGF-β)
Granulation tissue

- Definition: Specialized tissue that fills in defects in organs when non-regenerative cells and/or connective tissue framework is destroyed
- Consists of:
  - Proliferating fibroblasts laying down immature connective tissue (type III collagen)
  - Proliferating new blood vessels
- Present only during healing or attempt to heal destroyed tissue

Remodeling

- Definition: Process of transforming granulation tissue into a scar; reorganizing deposited connective tissue into stable scar
  - With time blood vessels become less prominent, collagen matures (type III collagen replaced by type I collagen)
  - The outcome of the repair process is influenced by a balance between synthesis and degradation of ECM proteins

Definition Time

- The degradation of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs)
  - Dependent on metal ions (e.g., zinc) for their activity.
  - MMPs include
    - Collagenases, which cleave fibrillar collagen
    - Gelatinases, which degrade amorphous collagen and fibronectin
    - Stromelysins degrade a variety of ECM constituents, including proteoglycans, laminin, fibronectin, and amorphous collagen.
Trichrome stain
(stains mature collagen blue)

Granulation tissue
Mature Scar

Clinical Model:
Healing of Skin Wounds

- Laceration – defect in skin
- Inflammatory reaction
- Blood clot (fibrin, fibronectin) forms
- Epithelium regenerates to cover defect
- Cells proliferate and migrate into defect
  - Macrophages: remove debris, secrete cytokines
  - Fibroblasts: produce extracellular connective tissue matrix
  - Myofibroblasts: contract the wound
  - Modified fibroblasts with functional features of contractile
    smooth muscle cells
- Simultaneously capillaries (endothelium) at edge of defect proliferation and extend into the
  defect under the influence of chemical mediators
- Over weeks to months defect filled with granulation tissue, becomes remodeled into mature
  collaged (scar)
- Wound acquires strength through the process

Healing by First vs Second Intention

Healing by First Intention
- Clean, uninfected surgical incision approximated by surgical sutures
- Epithelial regeneration principle mechanism of repair
- Small scar
- Minimal contraction of wound

Healing By Second Intention
- Large skin wound
  - Extensive destruction, contaminated, infected
  - Edges are not approximated
- Larger clot, more intense inflammation
- Wound granulates in without closing gap with sutures
- Process of healing same but takes longer because of size of defect
- Wound contraction by myofibroblasts
Skin ulcer

Large gap between edges of lesion

Thin layer of epidermal re-epithelialization
Granulation Tissue
Re-epithelisation
Wound contraction

Wound Strength

- 1 week --> 10% normal
  - Collagen synthesis
  - Collagen modification
    - Cross linking, increased fiber size
- 3 months --> 70-80% normal

Factors which Impair Repair

- Infection
- Nutritional deficiencies
- Glucocorticoids
  - Anti-inflammatory, inhibit TGF-β production
- Poor perfusion
- Diabetes mellitus
- Foreign bodies
- Type of tissue (Stable or labile cells vs permanent cells)
- Extent of injury
- Location of injury
Ask WHY?

- Why does infection impair wound healing
- Why does nutrition impact wound healing?
- Why do glucocorticoids impair wound healing?

NEJM Video

Basic Laceration Repair

Videos in Clinical Medicine
Basic Laceration Repair
October 26, 2006
Thomsen TW, Barsky D A; Setnik G S.
Excessive Scarring

- **Keloid**
  - Accumulation of exuberant amount collagen
  - Raised scars, grow beyond wound boundaries
  - More common in African Americans

Excessive Scarring

- **Hypertrophic scar**
  - Excess production of scar tissue localized to the wound
  - May regress

Robbins Figure 3.28
Fibrosis in Organs

- Deposition of collagen is part of normal wound healing

- **Fibrosis** refers to excessive deposition of collagen and other ECM components in a tissue/organ
  - Fibrosis can lead to disease, may be chronic and disabling
    - Scleroderma
    - Cirrhosis
    - Pulmonary fibrosis (idiopathic, secondary to exposures)

Q#1

A 55-year-old woman underwent laparotomy for a perforated sigmoid colon diverticulum. A wound infection complicated the postoperative course, and surgical wound dehiscence occurred. Primary closure was no longer possible, and the wound “granulated in.” Six weeks later, the wound is only 10% of its original size. Which of the following processes best accounts for the observed decrease in wound size over the past 6 weeks?

A. Elaboration of adhesive glycoproteins
B. Increase in synthesis of collagen
C. Inhibition of metalloproteinases
D. Myofibroblast contraction
E. Resolution of subcutaneous edema

Wound Dehiscence

- **Dehiscence** (Latin, “split apart”)
- Opening of healing or partially healed wound with separation of its edge
- Can be result of
  - mechanical factors
  - infection
  - ischemic necrosis of sutured edges
A 55-year-old woman underwent laparotomy for a perforated sigmoid colon diverticulum. A wound infection complicated the postoperative course, and surgical wound dehiscence occurred. Primary closure was no longer possible, and the wound "granulated in." Six weeks later, the wound is only 10% of its original size. Which of the following processes best accounts for the observed decrease in wound size over the past 6 weeks?

A. Elaboration of adhesive glycoproteins  
B. Increase in synthesis of collagen  
C. Inhibition of metalloproteinases  
D. Myofibroblast contraction  
E. Resolution of subcutaneous edema

Q#2

A 31-year old firefighter suffers extensive third-degree burns over his arms and hands. This patient is a high risk for the development of which of the following complications of wound healing?

A. Contracture  
B. Dehiscence  
C. Keloid  
D. Squamous cell carcinoma

Image Source: Surgical-tutor.org.uk
Summary

- Regeneration can occur in organs and tissues composed of mitotically labile and stable cells
- Organs composed of postmitotic (permanent) cells cannot regenerate
- Wound healing is the best example of repair in which the granulation tissue plays a key role
- Crucial components of wound healing are the cells, such as fibroblasts, macrophages, and their products, including ECM proteins.

Q#3

A 26-year-old riding a motor cycle hits a tree. He incurs blunt force abdominal trauma. In response to this injury, cells in tissues of the abdomen are stimulated to enter the G1 phase of the cell cycle from the G0 phase. Which of the following cell types is most likely to remain in G0 following this injury?

A. Smooth muscle
B. Endothelium
C. Skeletal muscle
D. Fibroblast
E. Hepatocyte

Answers to multiple choice questions

#1 - D
#2 - A
#3 - C