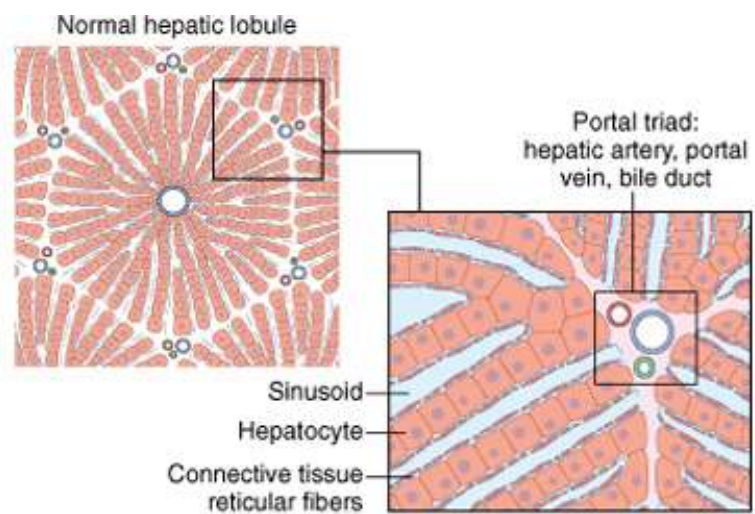


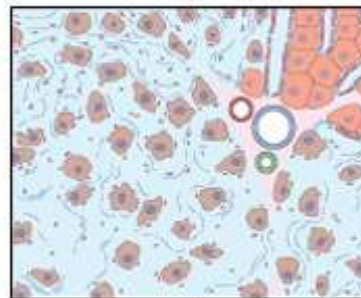
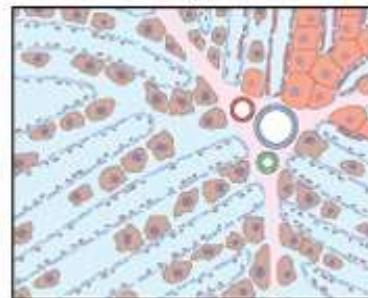
TISSUE REPAIR

- 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



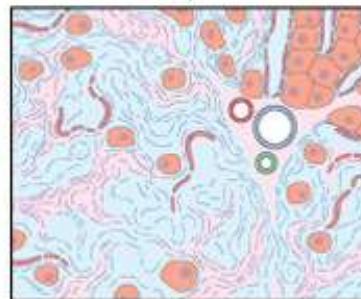
Injury to cells

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

- Important points :
 1. Cellular proliferation
 2. Growth factors
 3. The extracellular matrix

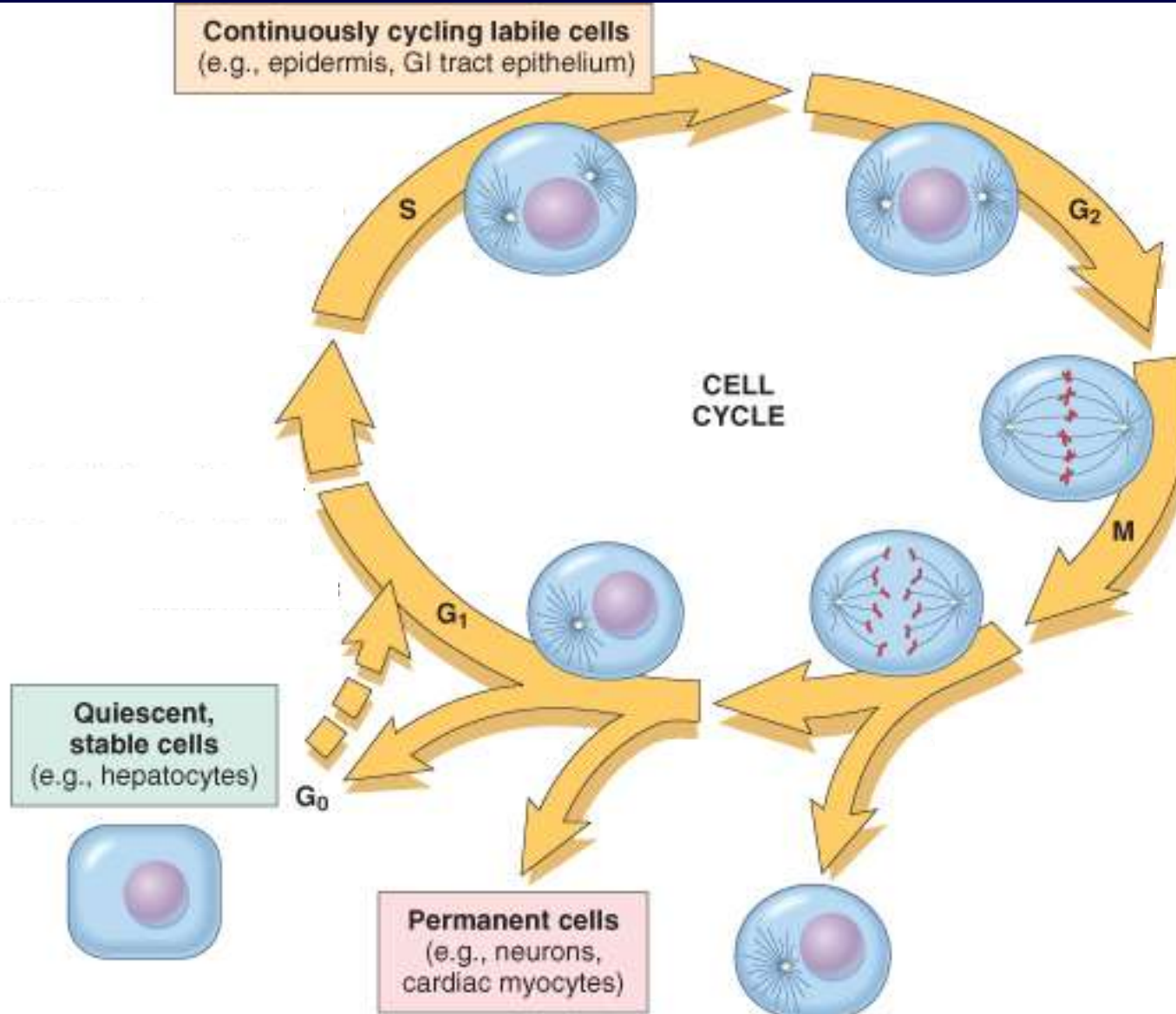
CELLULAR PROLIFERATION

- Cells that proliferate during tissue repair include
 1. Injured tissue remnants.
 2. Vascular endothelial cells.
 3. Fibroblasts.

The Cell Cycle

- Physiologic cell proliferation – repair
- Pathologic proliferation – cancer
- Key processes to the cell cycle are DNA replication and mitosis
- Steps:
 - Presynthetic growth phase 1 (G1)
 - DNA synthesis phase (S)
 - Premitotic growth phase 2 (G2)
 - Mitotic phase (M)
 - Non-dividing cells are either in the cell cycle arrest in G1 or they exit the cycle to enter a phase called G0

The Cell Cycle and Different Cell Populations



Proliferation Capacity

- Ability of tissues to repair themselves is influenced by their intrinsic proliferative capacity
- Three types of tissues
 - Continuously dividing tissues (labile tissues)
 - Stable tissues
 - Permanent tissues

- **Continuously dividing tissues (labile tissues)**
 - Lost and replaced by maturation from stem cells and by proliferation of mature cells.
 - These cells have a short life span
 - Bone marrow, skin, oral mucosa, GI tract, ducts draining exocrine glands

- **Stable tissues**

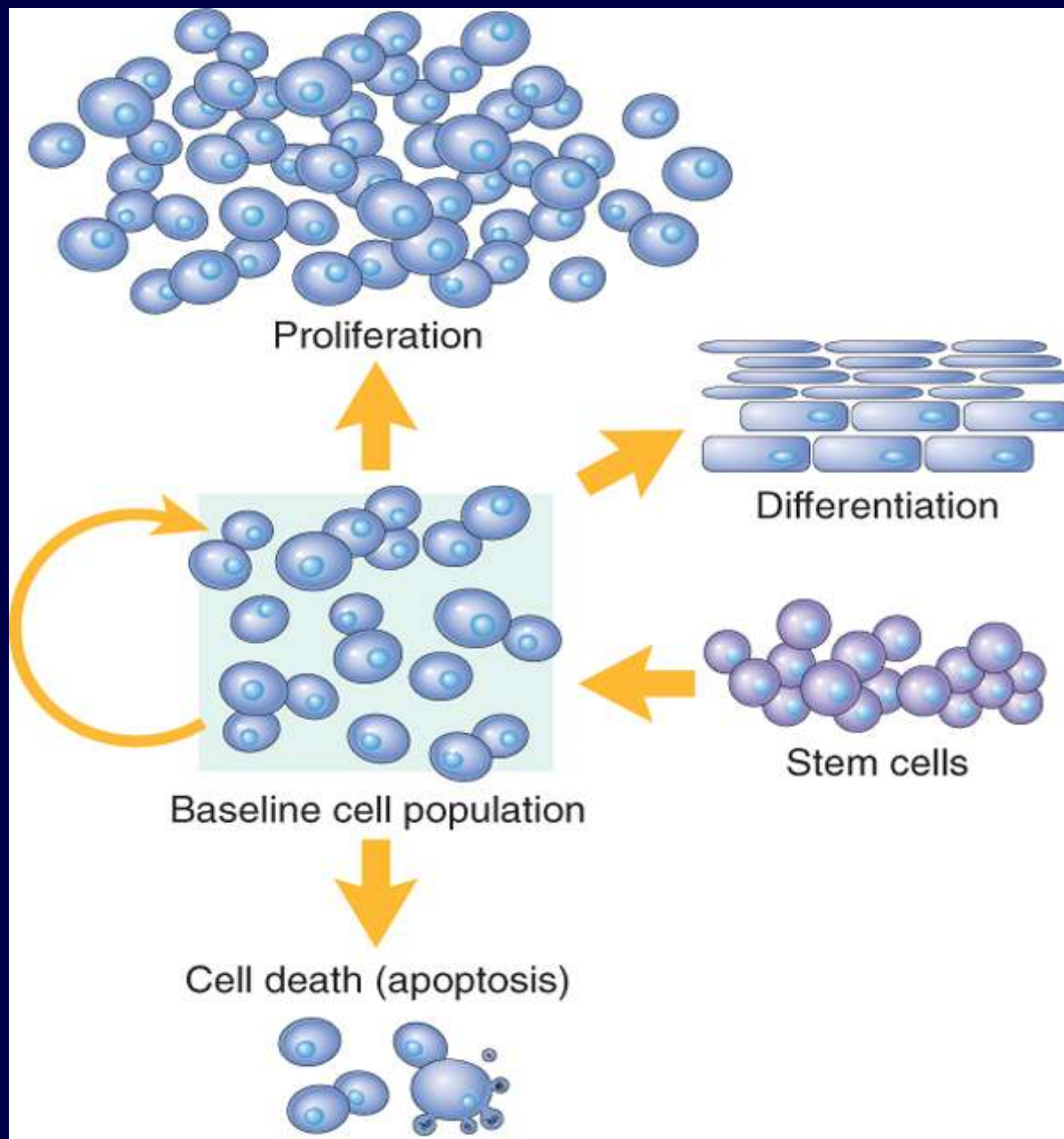
- Quiescent cells (G0 stage) – have minimal replicative activity - can proliferate in response to injury and loss of tissue mass.
- Constitute the parenchyma of solid tissues – long life span
 - kidney, liver, pancreas, endothelial cells, fibroblasts, smooth muscle cells

- **Permanent tissues**

- Terminally differentiated and nonproliferative in postnatal life.
- Long life span - neurons, cardiac and skeletal muscle.

Stem Cells

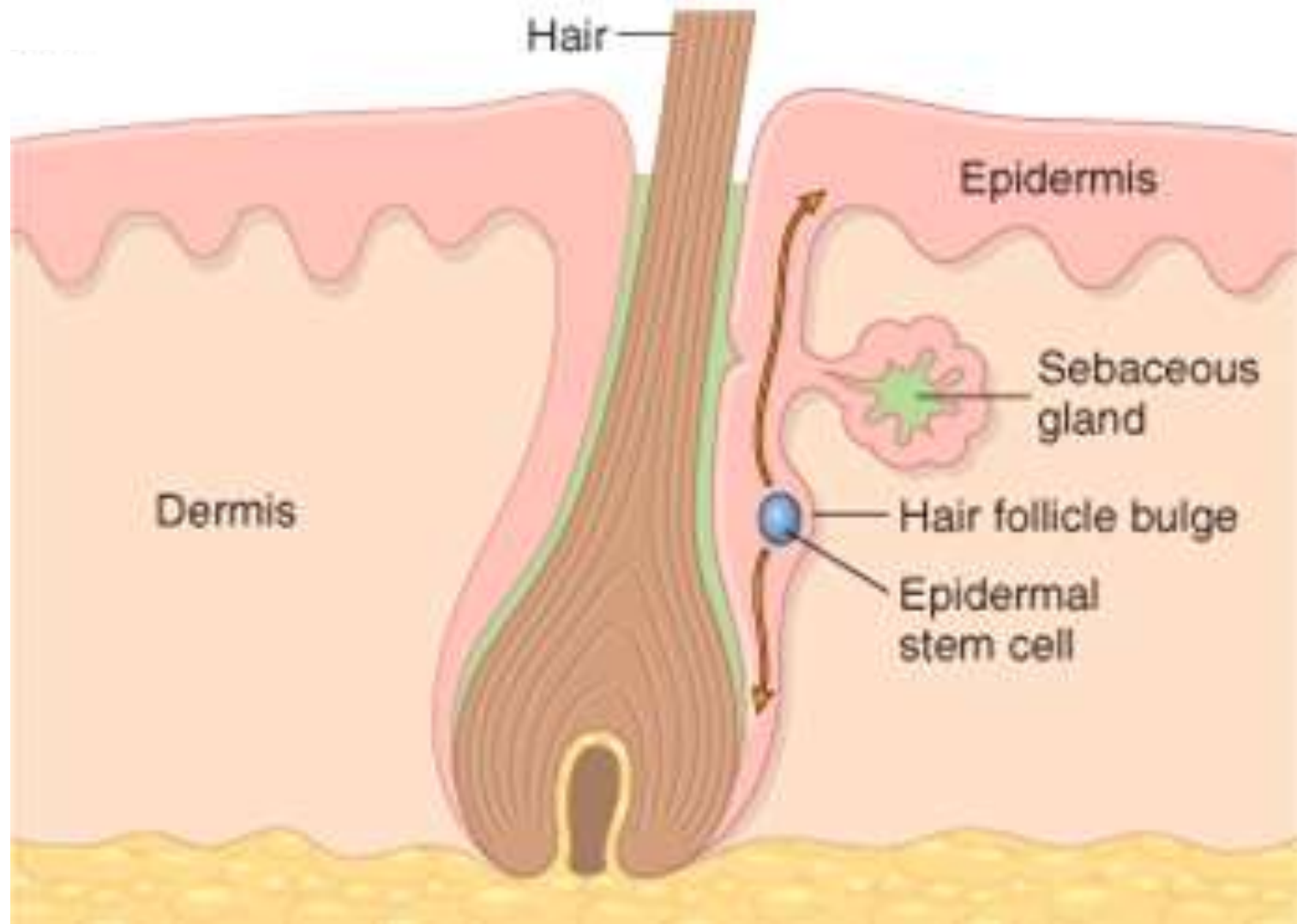
- Source of mature cells
- Homeostatic equilibrium between replication and differentiation of stem cells and the death of the mature , fully differentiated cells
 - Examples are skin and GI tract
- Two important characteristic properties of stem cells:
 1. Self-renewal capacity
 2. Asymmetric replication
 - Some differentiate to a specific cell type
 - Some remain undifferentiated
 - These maintain their self-renewal capacity



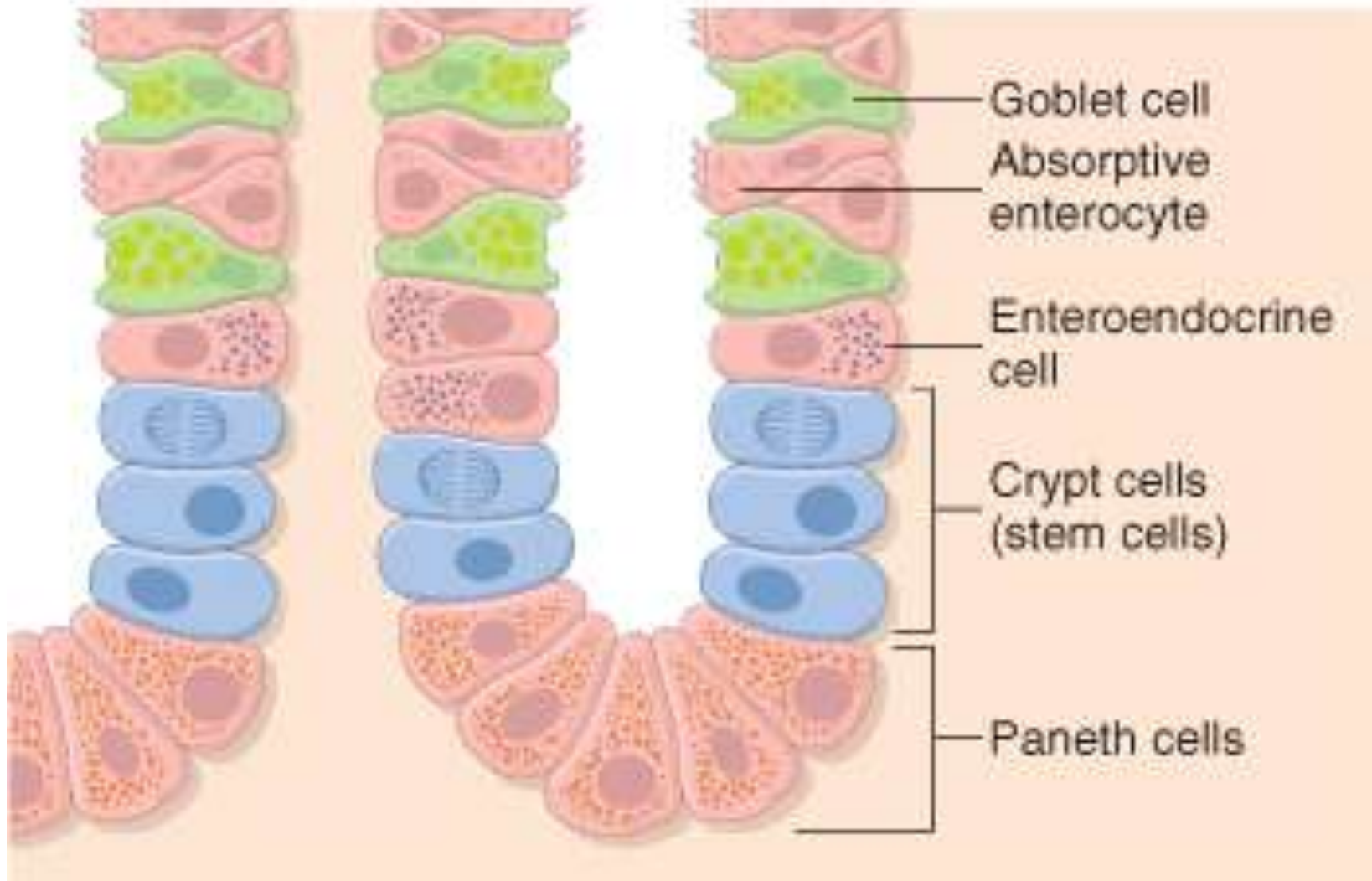
Stem Cells

- Pluripotent stem cells
 - Capacity to generate multiple cell lineages
 - When isolated from embryos – embryonic stem cells
- Tissue stem cells (adult stem cells)
 - Can generate multiple lineages
 - Bone marrow – fat, cartilage, bone, endothelium, muscle

Stem cells in skin



Stem cells in GI epithelium



GROWTH FACTORS

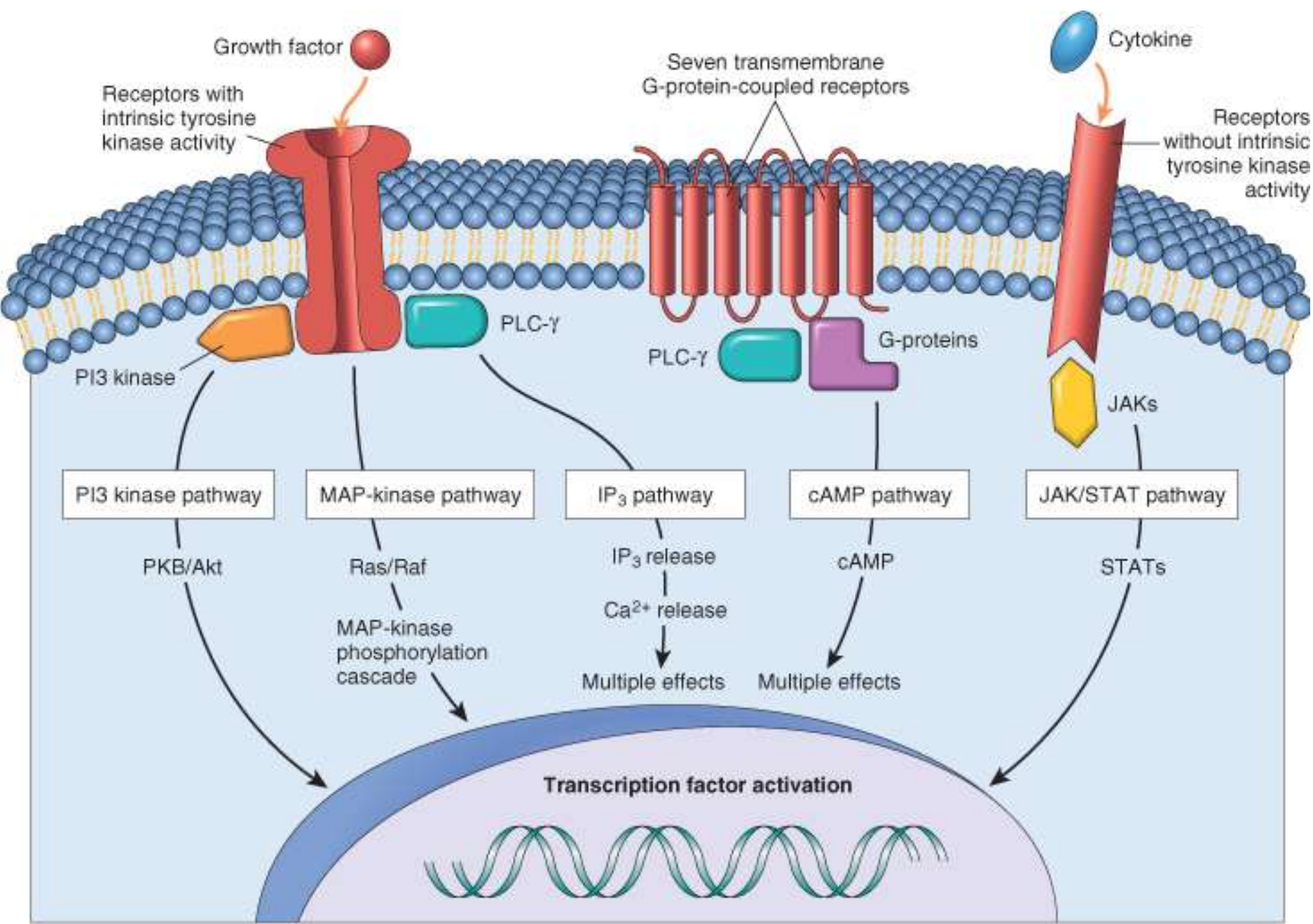
- Very important in tissue repair.
- Actions:
 - Stimulate cell division and proliferation
 - Promote cell survival
- Examples:
 - EGF
 - TGF
 - PDGF

Growth Factors

- Cell proliferation can be triggered by:
 - Growth factors, hormones, cytokines.
 - Growth factors produced by leukocytes, parenchymal cells, and connective tissue.

Growth factors effects:

- **Expanding cell population**
 - Stimulating cell division (mitosis)
 - Increase cell size (growth)
 - Protection from apoptotic death (survival)
- **Stimulate migration, differentiation, angiogenesis, contractility, and fibrogenesis**
- **Involved in growth control – can stimulate or inhibit**
- **May act on multiple cell types**



Growth factors

Growth Factor	Symbol	Source	Functions
Epidermal growth factor α	EGF	Platelets, macrophages, saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor α	TGF- α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and most epithelial cells
Heparin-binding EGF	HB-EGF	Macrophages, mesenchymal cells	Keratinocyte replication
Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of hepatocytes, epithelial cells, and endothelial cells; increases cell motility, keratinocyte replication
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Many types of cells	Increases vascular permeability; mitogenic for endothelial cells (see Table 3-3); angiogenesis
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction
Fibroblast growth factor 1 (acidic), 2 (basic), and family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Transforming growth factor β (isoforms 1, 2, 3); other members of the family are BMPs and activin	TGF- β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Tumor necrosis factor	TNF	Macrophages, mast cells, T lymphocytes	Activates macrophages; regulates other cytokines; multiple functions

Extracellular Matrix (ECM)

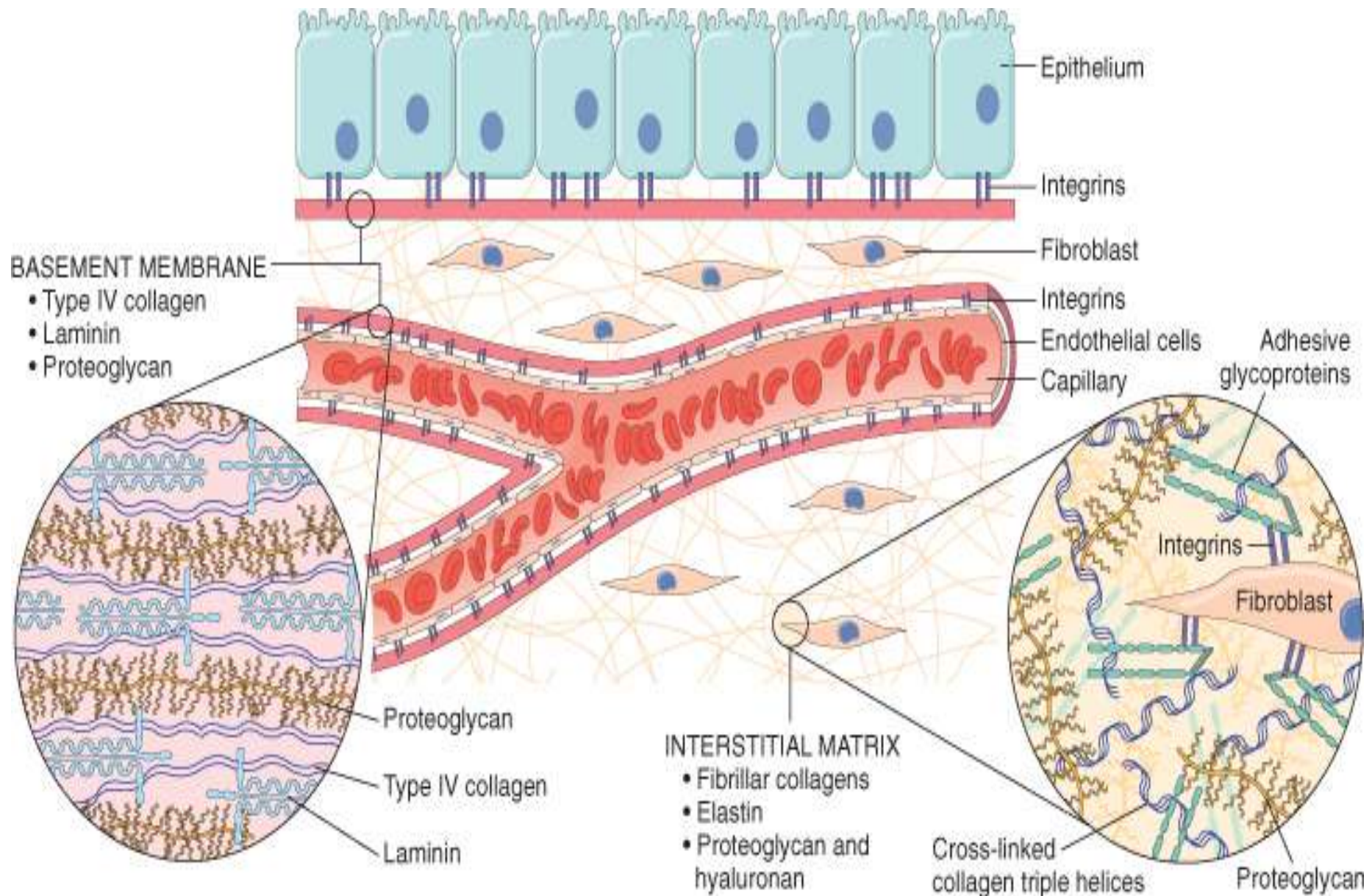
- Tissue repair depends on interactions between cells and ECM.
- Regulates proliferation, movement, and differentiation of cells within it.

- **Two forms of extracellular matrix:**
 - **Interstitial matrix**
 - Located in spaces between cells in connective tissue, and between epithelium and vascular/smooth muscle structures
 - **Basement membrane**
 - Interstitial matrix of connective tissue that is highly organized around epithelial, endothelial and smooth muscle cells
 - Found between epithelium and mesenchymal cells

THE EXTRACELLULAR MATRIX

- **Functions of ECM:**
 - Sequesters water and minerals
 - Gives cells a scaffold to adhere to
 - Stores growth factors

The Extracellular Matrix



THE EXTRACELLULAR MATRIX

- Bottom line: ECM regulates proliferation, movement, and differentiation of the cells living in it.
- If there is no ECM, there is no regeneration! There is a scar instead.

Role of Extracellular Matrix

- 1. Mechanical support : Anchorage, migration**
- 2. Control of growth**
Signals through cellular receptors - integrins
- 3. Maintenance of cell differentiation**
Proteins affect degree of differentiation
- 4. Scaffolding for tissue renewal**
Basement membrane needed for renewal of structure (stroma)
Labile and stable cells depend on ECM to reestablish normal structure
- 5. Storage of growth factors**
Allows for rapid response to injury and healing

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!

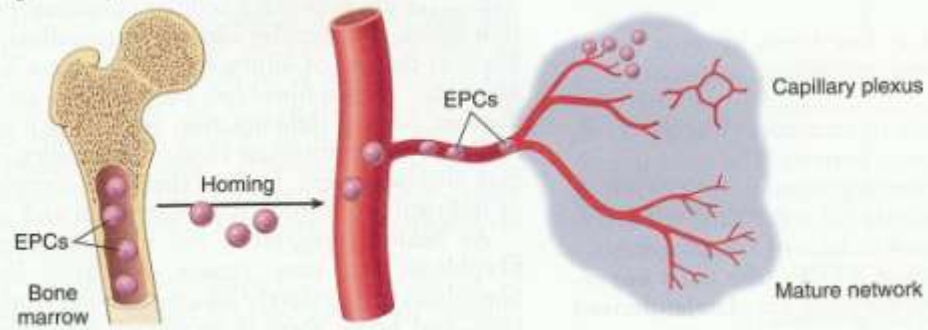
SCARRING

- If injury is severe, regeneration can't happen
- So, fibrosis (a scar) replaces the injured tissue
- Four components to this process:
 1. New vessel formation (angiogenesis)
 2. Fibroblast proliferation
 3. Synthesis of collagen (scar formation)
 4. Remodeling of scar

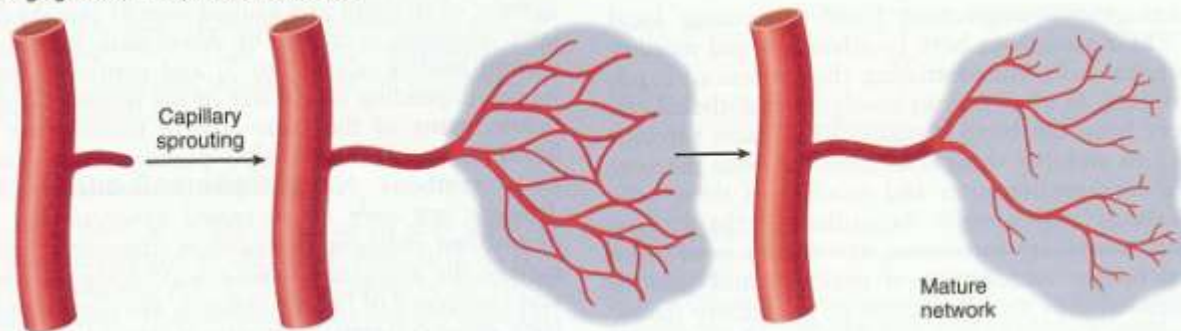
Angiogenesis

- **Two processes**
 - **Vasculogenesis** – new vascular network forms during embryonic development
 - **Angiogenesis (neovascularization)** – preexisting vessels send out capillary sprouts
 - Needed for healing at injury site
 - Increase to treat ischemia - cardiac
 - Tumor – allows for further growth - inhibit to control cancer

A. Angiogenesis by mobilization of EPCs from the bone marrow



B. Angiogenesis from preexisting vessels

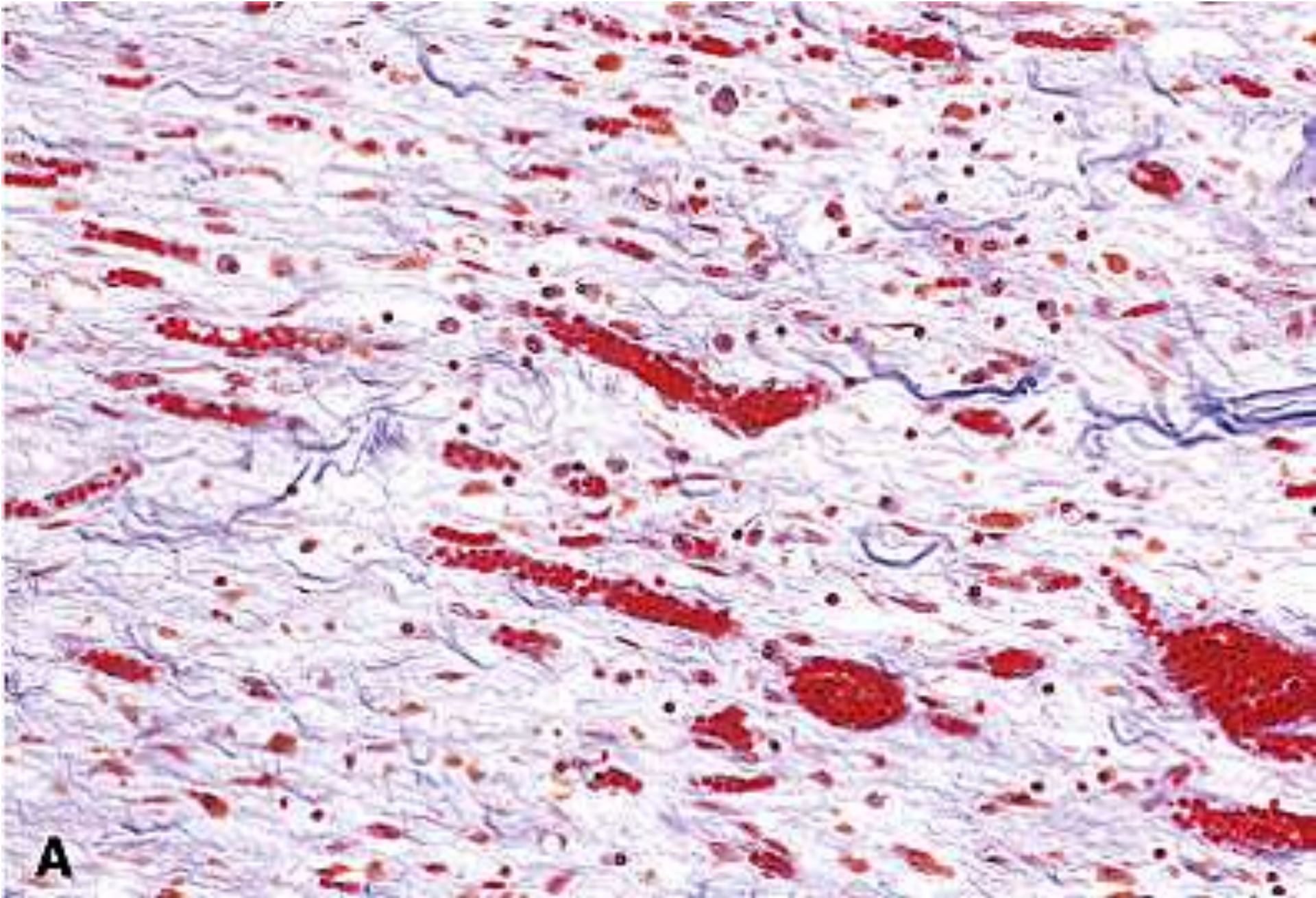


SCARRING

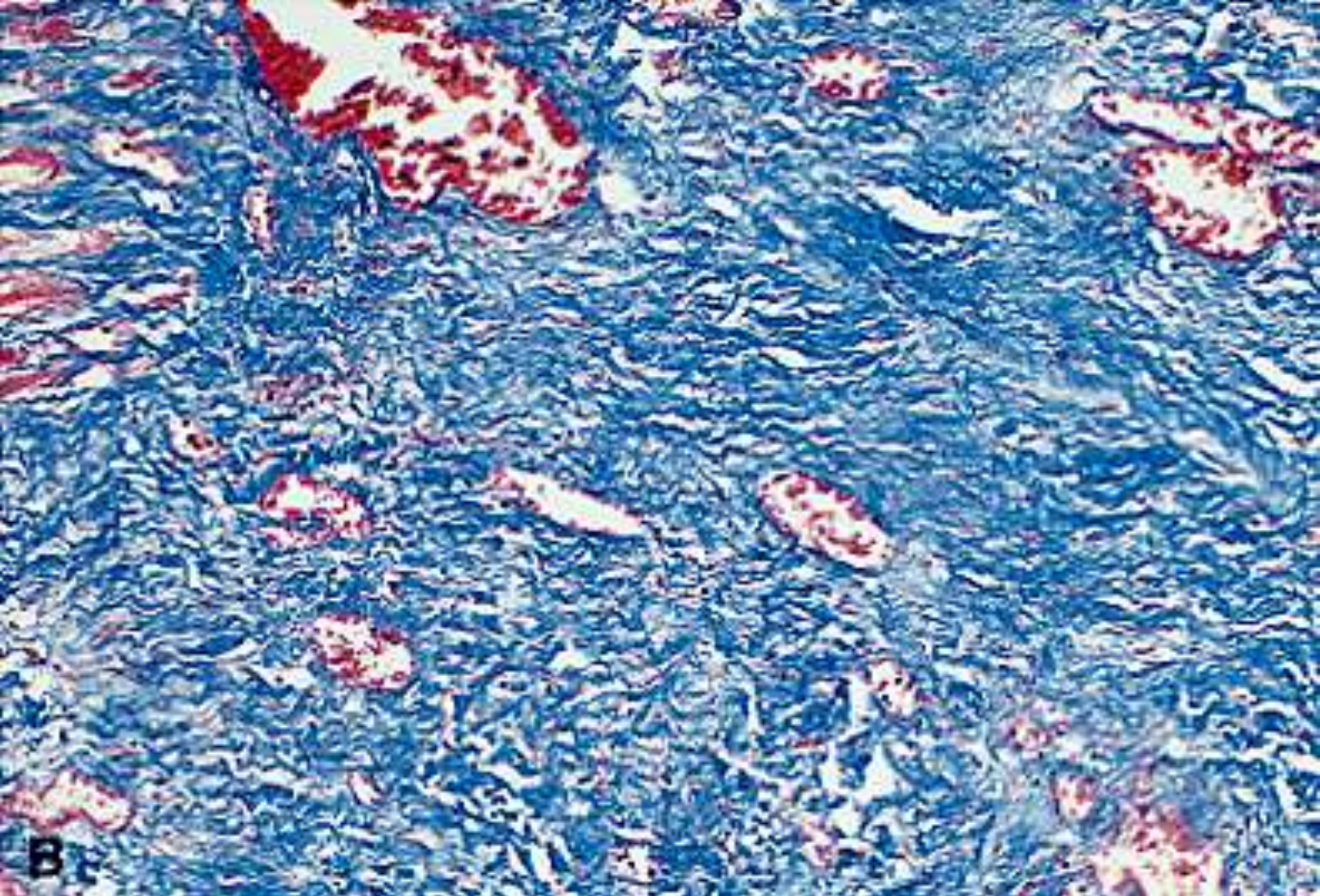
- By 24 hours:
 - Endothelial cells start proliferating
 - Fibroblasts emigrate
- By 3-5 days:
 - granulation tissue present
- Weeks later:
 - dense fibrosis (scar)
 - scar is remodeled over time

Scar Formation

- Builds on the granulation tissue framework
- There are 2 steps
 - Migration and proliferation of fibroblasts
 - Deposition of ECM by these cells
- Granulation tissue eventually becomes a pale, largely avascular scar
 - Composed of collagen, fibroblasts, elastic tissue
- Remodeling
 - Depends on the balance between ECM synthesis and degradation



Granulation tissue



Scar