Tissue renewal. Regeneration and Repair

Injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process.

It can be broadly separated into **regeneration and repair**

Regeneration results in the complete restitution of lost or damaged tissue;

Repair may restore some original structures but can cause structural derangements.

In healthy tissues,healing, in the form of regeneration or repair, occurs after any insult that causes tissue destruction, and is essential for the survival of the organism.

Regeneration refers to the proliferation of cells and tissues to replace lost structures

Tissues with **high proliferative capacity**, such as the hematopoietic system and the epithelia of the skin and gastrointestinal (GI) tract, renew themselves continuously and can regenerate after injury, as long as the stem cells of these tissues are not destroyed

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a superficial skin wound heals through the regeneration of the surface epithelium.
Scar formation is the predominant healing process that occurs when the extracellular matrix (ECM) framework is damaged by severe injury

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Control of Normal Cell Proliferation and Tissue Growth

- Tissue Proliferative Activity
- Stem Cells
- Embryonic Stem Cells
- Reprogramming of Differentiated Cells:
- Induced Pluripotent Stem Cells
- Adult (Somatic) Stem Cells
- Stem Cells in Tissue Homeostasis

TISSUE PROLIFERATIVE ACTIVITY

The tissues of the body are divided into three groups on the basis of the proliferative activity of their cells:
continuously dividing (labile tissues),
quiescent (stable tissues),
and **nondividing** (permanent tissues)

STEM CELLS

Stem cells are characterized by their **self-renewal** properties and by their capacity to **generate differentiated** cell lineages

To give rise to these lineages, stem cells need to be maintained during the life of the organism.
Such maintenance is achieved by **two mechanisms**

obligatory asymmetric replication, in which with each stem cell division, one of the daughter cells retains its self-renewing capacity while the other enters a differentiation pathway,

stochastic differentiation, in which a stem cell population is maintained by the balance between stem cell divisions that generate either two self-renewing stem cells or two cells that will differentiate.

Adult (Somatic) Stem Cells

In the adult organism, stem cells are present in tissues that continuously divide

Regardless of their proliferative activity, somatic stem cells generate rapidly dividing cells known as **transit amplifying cells**.

These cells lose the capacity of self-perpetuation, and give rise to cells with restricted developmental potential known as **progenitor cells**

Cell Cycle and the Regulation of Cell Replication

- Growth Factors Signaling Mechanisms in Cell Growth Receptors
- and Signal Transduction Pathways Transcription Factors

GROWTH FACTORS

The proliferation of many cell types is driven by polypeptides known as growth factors.

These factors, which can have restricted or multiple cell targets, may also promote cell survival, locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth-promoting effects

Growth factors

Epidermal Growth Factor (EGF) and Transforming Growth Factor a (TGF-a).

Platelet-Derived Growth Factor (PDGF)

Vascular Endothelial Growth Factor (VEGF)

Fibroblast Growth Factor (FGF)

Transforming Growth Factor b (TGF-b) and Related Growth Factors

Signalling mechanisms in cell growth

- Autocrine
- Paracrine
- Endocrine

Mechanisms of Tissue and Organ Regeneration

The human liver has a remarkable capacity to **regenerate**, as demonstrated by its growth after partial hepatectomy

Restoration of liver mass is achieved **without the regrowth** of the lobes that were resected at the operation.

Instead, growth occurs by enlargement of the lobes that remain after the operation, a process known as **compensatory growth** or **compensatory hyperplasia**.

ECM

Mechanical support for cell anchorage and cell migration, and maintenance of cell polarity

Control of cell growth. ECM components can regulate cell proliferation

Maintenance of cell differentiation.

Scaffolding for tissue renewal. The maintenance of normal tissue structure requires a basement membrane or stromal scaffold.

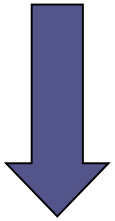
Establishment of tissue microenvironments. Basement membrane acts as a boundary between epithelium and underlying connective tissue.

Storage and presentation of regulatory molecules. For example, growth factors like FGF and HGF are secreted and stored in the ECM in some tissues.

Molecules of ECM

- Collagen
- Elastin, fibrillin and elastic fibers
- Cell adhesion proteins
- Glycosaminoglycans

NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)



INJURY

REGENERATION

Renewing tissues

Complete regeneration: Epidermis, GI tract epithelium, hematopoietic system

Stable tissues

Compensatory growth of liver and kidney

REPAIR

Wound

Wound healing,

Chronic inflammation

Fibrosis

scar formation

Healing by Repair, Scar Formation, and Fibrosis

- **Mechanisms of Angiogenesis**
- -Growth Factors and Receptors Involved in Angiogenesis
- -ECM Proteins as Regulators of Angiogenesis
- **Cutaneous Wound Healing**
- -Local and Systemic Factors That Influence
- **Wound Healing**
- -Pathologic Aspects of Repair Fibrosis

Mechanisms of Angiogenesis

Angiogenesis from Preexisting Vessels and precursor cells

Vasodilation

VEGF-induced increased permeability of vessel

Proteolytic degradation of the basement membrane of the parent vessel by matrix metalloproteinases (MMPs) and disruption of cell-to-cell contact between endothelial cells by plasminogen activator

Migration of endothelial cells toward the angiogenic stimulus Proliferation of endothelial cells, just behind the leading front of migrating cells

Maturation of endothelial cells, which includes inhibition of growth and remodeling into capillary tubes

Recruitment of periendothelial cells

Growth Factors and Receptors Involved in Angiogenesis

Proteins

Family members: VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D

Dimeric glycoprotein with multiple isoforms

Targeted mutations in VEGF result in defective vasculogenesis and angiogenesis.

Production

Expressed at low levels in a variety of adult tissues and at higher levels in a few sites, such as podocytes in the glomerulus and cardiac myocytes

Inducing agents

Hypoxia

TGF-β

PDGF

TGF-α

Receptors VEGFR-1

VEGFR-2

VEGFR-3 (lymphatic endothelial cells)

Targeted mutations in the receptors result in lack of vasculogenesis

Functions

Promotes angiogenesis

Increases vascular permeability

Stimulates endothelial cell migration

Stimulates endothelial cell proliferation

VEGF-C selectively induces hyperplasia of lymphatic vasculature

Up-regulates endothelial expression of plasminogen activator, plasminogen activator inhibitor1, and collagenase

Types of regeneration

- Physiological
- Reparative
- Pathological

Reparative regeneration

- Full (restitution) - recovery of tissue defect, which is identical to dead one.
- Incomplete (substitution) - filling defect of connective tissue (scar), function is compensated by hypertrophy cells surrounding scar .

Morphogenesis of regenerative process

- It consists of two phases:
- - Proliferation (young cambial cells)
- - Differentiation (fill in a tissue defect)

Pathological regeneration (disregeneration)

- - This perversion of regeneration process is accompanied by proliferation disorder and differentiation phases.
- Disregeneration involved in formation of tissue dysplasia and metaplasia.

Regeneration process depends on general and local conditions:

- **Systemic**:
- - age
- - food
- - condition of brain and endocrine glands
- **Local**:
- - Quality of damaging factor
- - Size of defect
- - Type of affected tissue
- - Remedial measures

Granulation tissue

- Unique part-time tissue, that body create under pathological conditions for implementation of protective and reparative functions of connective tissue. The highly vascularized tissue consisting of newly formed capillaries and cambium proliferating connective tissue cells – fibroblasts.

Wound healing

- **Types of wound healing:**
- - Direct closing of epithelium defect (by superimposing of epithelium on surface defect)
- - Healing under a scab (under crust formed by coagulated blood and lymph, there is a restoration of small defects)
- - Healing by first intention (when skin is damaged and underlying tissue in absence and presence of festering wounds smooth edges)
- - Healing by secondary intention (with extensive wounds to disrupted tissue infection and suppuration)

Regeneration of bone tissue

- Primary bone fusion (osteoblastic granulation tissue - soft callus; deposition of calcium salts - hard callus)
- Secondary bone fusion (cartilage - mature bone)

Regeneration of brain tissue

- Defects are replaced by glial scar tissue or cysts formed, filled with detritus or tissue fluid.