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**Tissue repair processes**

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The entire array of biological processes in the organism occurs thanks to strictly controlled processes, namely cell proliferation and differentiation, which are regulated by various groups of factors, with the most significant being: polypeptide growth factors, components of the cellular matrix, hormones, cytokines, etc.

The main processes in cell proliferation are DNA replication and mitosis, and the series of steps that control these processes constitute the cell cycle. The cell cycle can be defined as the interval in the life of a cell between two consecutive divisions.

**Phases of the cell cycle:**

* **G1** – **presynthetic growth phase** is the phase in which the synthesis of specific substances and the occurrence of biological activities specific to each cell take place. The length of G1 is variable and influences the duration of the cell cycle.
* **S** – **DNA synthesis phase** is the phase during which DNA molecule replication takes place in the nucleus. Each chromosome ends up with two DNA molecules.
* **G2** – **premitotic phase** is the period during which the cell prepares to enter division, and chromosomes begin to condense. Cell growth continues, and proteins related to division are synthesized.
* **M** – **mitotic phase** is the phase of cell division.

According to the proliferative capacity of tissue-forming cells, tissues are divided into:

**Labile tissues**: cells that are constantly in the process of proliferation, stem cells continuously mature and proliferate into mature forms.

**Stable tissues**: cells in the G0 phase of the cell cycle, showing minimal replicative activity but can respond to damage with proliferation if adequately stimulated (e.g., liver, pancreas, kidneys, smooth muscle tissue, endothelial cells, and fibroblasts).

**Permanent tissues**: terminally differentiated cells without proliferation in postmitotic life. Examples include neurons, cardiomyocytes, and skeletal muscle cells (except for endomysial satellite cells that enable repair). In the end stage of repair process of damaged permanent tissue, a **scar** is formed.

**Growth Factors**

Growth factors are polypeptide molecules synthesized by leukocytes, thrombocytes, parenchymal cells, and stromal cells. They act by:

* Stimulating cell proliferation by binding to specialized receptors, expressing genes whose products release CDK from inhibitors, preventing apoptosis, and controlling growth (stimulating proto-oncogenes).
* Inducing migration.
* Promoting differentiation.
* Supporting angiogenesis.
* Facilitating fibrogenesis.
* Modulating contractility.

Growth factors act through different mechanisms:

*Autocrine signaling*: Signal induction on the cell secreting it.

*Paracrine signaling*: Transmission of signals to neighboring cells.

*Endocrine signaling*: Transmission through the bloodstream to distant target cells.

**Extracellular Matrix (ECM)**

The extracellular matrix is a dynamic macromolecular matrix synthesized locally. It forms a network around cells, continually remodeling and regulating proliferation, differentiation, and cell movement.

ECM appears in two main forms:

**Interstitial matrix**: A three-dimensional amorphous gel synthesized by mesenchymal cells (fibroblasts, etc.) in spaces between epithelial, supportive, vascular, smooth muscle structures, and connective tissue cells. It consists of fibrillar and non-fibrillar collagen, fibronectin, elastin, hyaluronic acid, and proteoglycans.

**Basement membrane**: Comprising laminin and non-fibrillar collagen type IV, it forms a highly organized interstitial matrix around epithelial, endothelial, and smooth muscle cells.

Three fundamental components of ECM:

1. Fibrous structural proteins: Collagen and elastin.
2. Aqueous gels: Proteoglycans (glycosaminoglycans and heparin sulfate), hyaluronic acid.
3. Adhesive receptors and adhesive glycoproteins

Functions of ECM:

* Mechanical support – resistance to stretching (collagen, elastin), elasticity, and lubrication (proteoglycans and hyaluronic acid).
* Control of cell proliferation and differentiation through cell receptors – integrins.
* Structural framework for tissue renewal, establishing the tissue microenvironment. **Complete tissue regeneration requires an intact extracellular matrix.**
* Storage and release of regulatory molecules (EGF, FGF, HGF) for rapid mobilization during regeneration and repair.

**Angiogenesis** is the process of blood vessel formation.

Blood vessels can arise:

- Through vasculogenesis during embryonic development from angioblast precursor endothelial cells. In adulthood, vasculogenesis occurs through processes such as the replacement of damaged endothelial cells, reendothelialization of vascular implants, neovascularization, and tumorigenesis.

- Neoangiogenesis involves angiogenesis from existing capillary sprouts of blood vessels.

Steps of angiogenesis:

* Vasodilation in response to nitric oxide and increased permeability induced by VEGF.
* Proliferation and migration of endothelial cells.
* Inhibition of proliferation and remodeling of capillary tubes.
* Recruitment of perivascular cells – pericytes (for capillaries) and smooth muscle cells (for blood vessels), stabilizing the newly formed blood vessels.

**Repair processes**

Tissue regeneration is a crucial biological process that leads to the renewal of dead or damaged tissues in both physiological and pathological conditions.

The replacement of damaged or lost tissue can occur in two ways:

1. **Regeneration**: A process leading to complete tissue renewal with newly synthesized tissue composed of cells that are structurally and functionally similar or identical to the damaged cells.
2. **Repair in a general sense, fibroplasia, cicatrization**: Involves incomplete tissue renewal through the proliferation of newly formed connective tissue that structurally and functionally differs from the damaged tissue.

**Regeneration**

**Regeneration** is the process of tissue replacement with the same type of tissue. It occurs in two ways:

1. From surrounding undamaged differentiated cells that migrate, proliferate, and undergo dedifferentiation before redifferentiating in the area of damaged tissue.
2. From the stem cells of the tissue that proliferate and undergo differentiation.

It is a general rule that differentiated tissues have a lower capacity for regeneration than simple tissues, but there are many exceptions. For example, highly differentiated liver cells regenerate faster than muscle cells and cells of the renal tubules.

**Regeneration of Labile Cells**

In physiological conditions, the regeneration of *epithelial cells* involves proliferation (division) and differentiation of so-called reserve (stem) cells present near the basal membrane of almost all epithelia.

The regeneration of *blood elements* occurs throughout life from stem cells in the bone marrow, proliferating and differentiating through a series of transitional forms characteristic of each type of blood element.

Regeneration goes through three stages:

1. Formation of a blood clot and the development of acute inflammatory reactions within the first 24 to 36 hours.
2. Cell migration over the denuded surface begins after 1 hour, and increased mitotic activity of basal cells of the surrounding epithelium occurs at the end of the first day. This proliferative activity ensures the replacement of cells that have migrated along the extracellular matrix and continues the ongoing migration. The regeneration process takes longer if the basal membrane is damaged.
3. Differentiation: Epithelial differentiation begins 4 days after injury through the rearrangement of proliferating cells. Complete tissue renewal takes more than 6 weeks.

**Regeneration of Stable Cells**

Complete regeneration of tissues composed of stable cells occurs only if the connective tissue framework, acting as a guide for the migration of proliferating cells, is undamaged. Otherwise, tissue replacement involves fibroplasia, where damaged tissue is partially or completely replaced by connective tissue, resulting in a **scar formation**.

The principle of regeneration in stable cells is best exemplified by the **liver**, which has the highest regenerative capacity. Even if 90% of the tissue is removed, chemical and metabolic liver damage with preserved extracellular matrix in the form of reticulin patern can be fully regenerated structurally and functionally within two weeks. Besides proliferating differentiated hepatocytes, there is a population of stem cells at the border between hepatocytes and the smallest bile duct segments, capable of differentiating into hepatocytes and bile duct epithelium. However, if the connective tissue framework is disrupted, fibroplasia and cicatrization occur, creating scar tissue in the liver.

Regarding other stable cells, **glomeruli in the kidney** lack regenerative ability, while the **epithelium of renal tubules** can regenerate if the basal membrane is preserved, through proliferation, migration, increased mitotic activity, and functional differentiation within three weeks. **Smooth muscle cells** (uterus, gastric and colonic walls, blood vessels) have regenerative capacity, but larger lesions are replaced by scar tissue. **Endothelial cells** have mitotic division ability, but the speed depends on the type and size of blood vessels, resulting in weaker regeneration in the aorta compared to capillary blood vessels.

**Regeneration of Permanent Cells**

**Cardiomyocytes** lose the ability to divide after birth and can only increase in size (hypertrophy). After myocardial infarction, damage in the myocardium is replaced by scar tissue (fibroblasts and collagen type I). **Neurons** in the central nervous system do not regenerate after injury, leading to permanent loss of structure and function with the formation of a glial scar or cavity, known as a pseudocyst.

**Peripheral nerve regeneration** is possible only if the body of the nerve cell is preserved. The regeneration process passes through several phases occurring in the nerve cell body, in the proximal and distal segments of the severed nerve, and in the surrounding tissue. In the nerve cell body, there is axonal reaction, involving decentralization of the nucleus. Axonal and myelin (Wallerian) degeneration in the proximal and distal segments is enzymatically degraded by inflammatory cells and macrophages. After this, Schwann cells proliferate at the proximal end, creating a cell bridge as a guide for the growth of axonal sprouts that are later myelinized.

After regeneration, the nucleus of the neuron again occupies a central position.

**Repairation by Connective Tissue**

Repairation by connective tissue involves the replacement of damaged tissue with connective tissue, often triggered by inflammation. The initial phase of repair coincides with the inflammatory process.

During fibroplasia, damaged and necrotic tissue is replaced by granulation tissue, which is highly vascularized connective tissue with inflammatory cells – **vascular granulation tissue**. It has a granular surface, a pink color, is edematous, soft in consistency, vulnerable, insensitive to pain, and resistant to infection. As it matures, fibroblasts and myofibroblasts multiply alongside a complex capillary network and residual macrophages, forming **fibrovascular granulation tissue**. Further maturation involves fibroblasts filling the space between blood vessels, synthesizing collagen – **fibrous granulation tissue**. Eventually, with maturation, there is a reduction in blood vessels and cellular elements, depositing dense collagen fibers – scar formation.

*A scar is a permanent, irreversible change that leads to a reduction in tissue and organ function*.

Four components are present in the process of fibroplasia:

**1**. angiogenesis

**2.** migration and proliferation of fibroblasts

**3.** ECM deposit

**4**. maturation and reorganization

***I Angiogenesis***

Angiogenesis is a dynamic process of creating new blood vessels by budding of endothelial cells from an existing blood vessel..

Phases of angiogenesis:

**1**. Activated endothelial cells proliferate and, with their proteolytic enzymes (plasminogen activator, collagenases), degrade the basement membrane and extracellular matrix components. This phase allows capillary bud formation.

**2**. Endothelial cells, in the form of solid strips, migrate through the extravascular space of angiogenic stimuli (necrotic tissue fibrin) and anastomose with each other.

**3**. Leading-edge endothelial cells show significant proliferative activity and secrete laminin, while endothelial cells closer to the parent blood vessel create components of the basement membrane, primarily collagen type IV.

**4**. Under the influence of growth factors (VEGF, bFGF) and interaction with ECM components (collagen IV and laminin), endothelial cells mature and differentiate, forming a capillary tubule and a capillary loop or vascular cascade.

Newly formed blood vessels mature into capillaries, arterioles, and venules, while mesenchymal cells transform into pericytes and smooth muscle cells. Periendothelial cells influence vessel maturation, providing structural support, controlling endothelial cell proliferation, vascular permeability, and tone.

**II Migration and Proliferation of Fibroblasts**

Fibroblasts originate from pre-existing local fibroblasts and mesenchymal stem cells, proliferate, follow capillary loops, and create various ECM components. The newly formed capillary blood vessels are highly permeable, providing an excellent medium for fibroblast growth stimulated by growth factors (PDGF, bFGF, and TGF-β), as well as cytokines (IL-1 and TNF-α).

**III Deposition of Extracellular Matrix (ECM)**

Initial ECM of granulation tissue mainly contains fibronectin, proteoglycans, and tenascin. Collagen synthesis by fibroblasts starts on the third day of the lesion and becomes more extensive, followed by remodeling. Collagen synthesis is stimulated by growth factors (TGF-β, PDGF, bFGF) and cytokines (IL-1, 4, TNF) produced by fibroblasts, macrophages, and granulocytes. The most significant fibrogenic growth factor is TGF-β, which stimulates fibroblast migration and proliferation, collagen and fibronectin synthesis.

**IV Tissue Remodeling**

Represents the final phase of the repair process, where granulation tissue is replaced by scar tissue, and ECM composition changes under the control of matrix metalloproteinases and their tissue inhibitors. Along new lines of stress, deposited collagen fibers undergo degradation, and new ones are deposited, with synthesis surpassing degradation. Collagen bundles become cross-linked and resilient.

In conclusion, repair by connective tissue involves angiogenesis, migration and proliferation of fibroblasts, deposition of ECM, and tissue remodeling. This intricate process aims to restore tissue integrity but results in scar formation, which may compromise overall tissue and organ function.

**Wound Healing**

Wound healing implies structural damage with tissue loss. The process of wound healing is a complex and dynamic phenomenon involving a series of coordinated processes:

* Inflammation
* Migration and Proliferation of Epithelial and Connective Tissue Cells
* Angiogenesis
* Synthesis of Epithelial and Endothelial Basement Membrane and Other ECM Components
* Remodeling of Connective Tissue and Parenchyma

During wound healing, three fundamental phases are distinguished:

***1. Phase of Initial Bleeding and Reactive Inflammation***:

-Initial bleeding provides fibrinogen, plasma fibronectin, platelets, and EGF. Fibrin and plasma fibronectin polymers bind to fragments of disrupted collagen and other ECM components, creating a wound matrix.

-Activated platelets release (PDGF, TGF-α, β, GM-CSF, IL-1,6), inducing chemotaxis of polymorphonuclear leukocytes (PMN), monocyte-macrophage system cells, and proliferation of stromal cells, fibroblasts, endothelial, and smooth muscle cells.

-PMNs migrate along a specific chemokine gradient, producing various growth factors and cytokines (TGF-α, β, GM-CSF, IL-1, 6).

-Monocytes-macrophages remove dead tissue and fibrin through collagenases, elastases, plasminogen activators, phagocytosis, and lysosomal enzyme degradation, producing growth factors (TGF-α, β, GM-CSF, bFGF) that stimulate fibroblast and endothelial cell ingrowth or granulation tissue formation.

***2. Proliferative Phase***:

Dominated by the process of epithelialization and granulation tissue formation.

-Epithelial cells migrate until they come into contact (contact inhibition phenomenon). Fibrin and plasma fibronectin serve as the initial substrate for epithelial cell migration, and later, permanent components of the basement membrane are synthesized: fibronectin, laminin, and collagen type IV.

-Blood vessels grow into the wound area through angiogenesis.

-Fibroblast activation results in proliferation and migration, synthesizing collagens, fibronectin, glycosaminoglycans, and collagenases.

**3.Maturation and Remodeling Phase of Connective Tissue**:

Collagen bundles composed of collagen type I are deposited, filling the wound defect, and fibroblasts transform into fibrocytes.

\*Types of Wound Healing:

**Primary Intention Healing (per primam)**: Refers to the healing of primarily surgical incisions, non-infected wounds with the apposition of cut edges using surgical sutures, resulting in a discrete, linear, and sedentary scar.

**Secondary Intention Healing (per secundam):** Involves wound healing where there is a substantial tissue defect, preventing the approximation of wound edges. The tissue defect is gradually filled with granulation tissue, which matures into connective tissue scars of various sizes over time.