Healing I
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Regeneration & Repair

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Healing

Regeneration and Repair

Healing: It is the process of restoration of the integrity to an injured tissue, in which there is an attempt at replacement of the injured cells by healthy living tissue.

Healing consists of two processes:

- ***Regeneration*** of specialized cells by proliferation of the survival cells (i.e. regeneration of the injured tissue by the surrounding survival parenchymal cells of the same type.
- A ***connective tissue response*** characterized by the formation of granulation tissue and its subsequent maturation. Some authors refer to this connective tissue response as the ***repair*** reaction.

In general speech; Regeneration involves restitution of tissue components; repair involves "patching" rather than restoring.

The relative roles of these two processes varies between tissues depending on:

1. The nature and severity of the injury.
2. The duration of the injury.
3. The ability of the surrounding survival cells to divide (cell proliferation and growth potential).

CELL CYCLE

The cell cycle, or cell-division cycle, is the series of events that take place in a cell that causes it to divide into two daughter cells. These events include the duplication of its DNA (DNA replication) and some of its organelles, and subsequently the partitioning of its cytoplasm, chromosomes and other components into two daughter cells in a process called cell division. It consists of a series of steps at which the cell checks for the accuracy of the process and instructs itself to proceed to the next step. The cycle consists of the

1-presynthetic growth phase 1 (G1)

2-the DNA synthesis phase (S)

3-the premitotic growth phase 2 (G2)

4-and the mitotic phase (M)

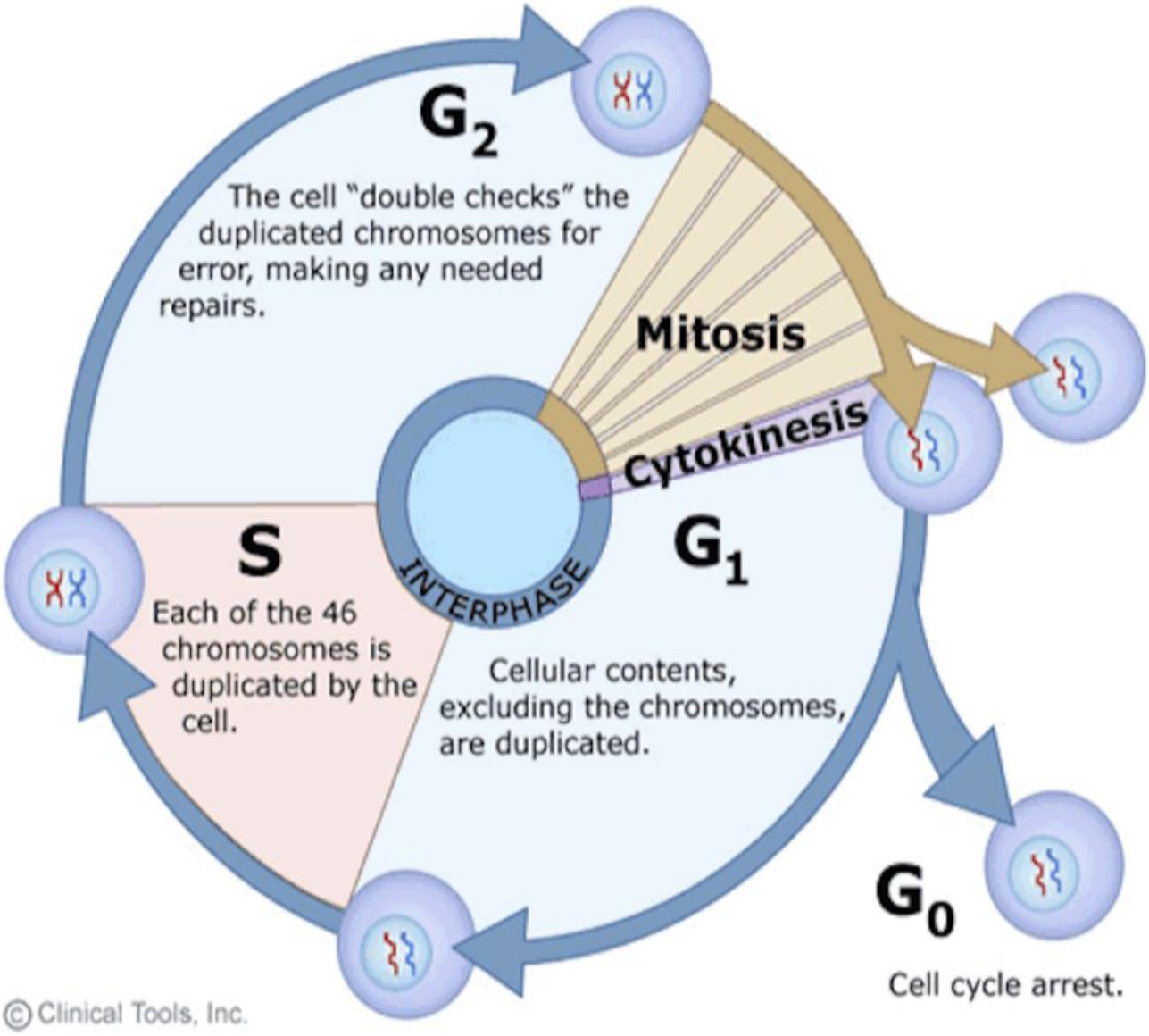
Non-dividing cells are either in cell cycle arrest in G1 or they exit the cycle to enter a phase called G0.

Any stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the G0/G1 transition and the entry of cells into the G1.

Further progression is determined by the ability of the cell to pass through an intrinsic quality control mechanism for cell integrity, known as checkpoint control.

Cell cycle checkpoint controls: Cell cycle checkpoints are control mechanisms in the eukaryotic cell cycle which ensure its proper progression. Each checkpoint serves as a potential termination point along the cell cycle, during which the conditions of the cell are assessed, with progression through the various phases of the cell cycle occurring only when favorable conditions are met. There are many checkpoints in the cell cycle, but the three major ones are: the G1 checkpoint, also known as the Start or

restriction checkpoint or Major Checkpoint; the G2/M checkpoint; and the metaphase-to-anaphase transition, also known as the spindle checkpoint.



Regeneration

Regeneration: (generate, to bring to life) is the renewal of a lost tissue in which the lost cells are replaced by identical ones.

The capacity for such regeneration varies between tissues depending on the cells proliferative potential.

Classification of cells by their proliferative potential:

The cells in the body divide at different rates. Some mature cells do not divide at all, whereas others complete a cell cycle every 16 to 24 hours.

A. Labile cells (continuous replicators): These cells undergo frequent division throughout life replacing those lost, so they have excellent regeneration ability. The cells of lymph node, bone marrow (lymphoid and heamatopoietic systems) and most of covering and protective epithelia (skin, endometrium, alimentary, respiratory, urinary mucosa) are best examples of labile cells.

- **Stem cells** are continuous labile cells that are programmed to divide continuously and one daughter cell of each division becomes another stem cell. Stem cell is either

1. **Unipotent stem cells:** give rise to daughter cell that differentiate into only one type of cell, e.g. the basal cells of the epidermis mature only into keratinized cells, which eventually desquamate.
2. **Pluripotent stem cells:** generate more than one cell type e.g. bone morrow stem cells (Hemocytoblats) yield erythrocytes, neutrophils, basophils, eosinophils, monocytes, lymphocyte, and megakaryocytes.

Tissues composed of labile cell regenerate after injury, provided that enough stem cells remain.

B. Stable cells (Quiescent cells): Quiescence is a cellular state in which a cell remains out of the cell cycle but retains the capacity to divide. They can undergo rapid division in response to a variety of stimuli. This group includes:

- The parenchyma of most solid tissues and most of secretory epithelial structures (liver, pancreas, kidney and endocrine glands).
- Mesenchymal cells, such as fibroblasts and endothelial cells, are stable cells that can be stimulated to proliferate during healing.

C. Permanent cells (non-replicators): These cells lose their ability to divide either at birth or shortly thereafter, e.g. neurons, cardiac myocytes, and cells of the lens and striated muscles. So tissues that consist of this type of cells have no effective regeneration.

Control of cell proliferation

Cell proliferation can be triggered by:

1-Chemical mediators; such as growth factors, hormones, and cytokines. These are involved in the stimulation or inhibition of cell growth. **2-Signals from the extracellular matrix (ECM)**

Growth factors: Growth factor is a protein that expands cell populations by stimulating cell division usually accompanied by increased cell size and by promoting cell survival. Most growth factors, in addition to stimulating cellular proliferation, they stimulate migration, differentiation, and enhance the synthesis of specialized proteins (such as collagen in fibroblasts).

Growth factors that are involved in repair are produced by:

1-Leukocytes that are recruited to the site of injury or are activated at

this site, as part of the inflammatory process.

2- Parenchymal cells or connective tissue cells in response to cell injury or loss.

Repair

Repair: Is the replacement of damaged tissue by granulation tissue, which matures to form scar. It is also defined as the orderly process by which a wound is eventually replaced by a scar.

Many of the constituents of the extracellular matrix of connective tissue plays a major role in healing

Extracellular matrix:

The extracellular matrix is a complex of macromolecules that provides:

- Structural support for tissue.
- Modulate various functions of the constituent cells such as proliferation, differentiation, cell movement and attachment.

The principal compounds, which make up the extracellular matrix, are:

- Collagens.
- Structural glycoproteins.
- Glycosaminoglycans.
- Proteoglycans.
- Elastin.

***Collagen:** The most abundant of the extrcellular matrix proteins are the collagens, which constitute a family of closely related proteins. The principal cells involved in the synthesis of the collagens (and other extracellular matrix proteins) are fibroblasts and related cells such as osteoblasts. The resultant collagen molecules align to form collagen fibrils. Then several collagen fibrils aggregate to form collagen fibers.

Collagen is of many types:

1. **Type I**: This type is formed of large fibrils. It is found in dermis, tendon, bone and dentine.
2. **Type II**: Thicker than type I. It is found in hyaline cartilage and intravertebral disc.
3. **Type III**: This type of collagen forms the reticular network of many parenchymatous organs where support of the tissue is needed. It is found in blood vessels, heart valves and also the dermis.
4. **Type IV**: It does not form fibrils. It is found in basement membrane.
5. **Type V**: Only detected by electron microscopy. It is widely distributed but comprises only a small fraction of the total collagen content of any tissue. It forms membranous sheaths surrounding connective tissues such as muscle and schwann cells. It is also found in basement membrane.

The most Important type of collagen, in healing, are type III and I.

In all normal tissues there is continual collagen turnover, synthesis being balanced by degradation due to fibroblast and macrophage collagenases.

❖ **Structural glycoproteins**: These are molecular weight glycoproteins. They are named as structural glycoproteins because they serve as matrix adhesion molecules. Among these proteins:

A. *Fibronectin*: It is the most abundant structural glycoproteins, which exists in two major forms:

1. Plasma fibronectin
2. Tissue fibronectin.

Functions of fibronectin:

- It acts as a link between cells and matrix.

- It controls the structure of the extracellular matrix.
- It has binding sites for fibrin, which is of great importance in the initial stages of the healing process.

B. ***Laminin***: it is found in basement membrane, where it is closely associated with other proteins such as collagen type IV. It is involved in cell-matrix adhesion.

❖ **Glycosaminglycans and proteoglycans**: They have the following characteristics:

- These are hydrophilic compounds, attracting water and acting as hydrated gel.
- They have the capacity to bind to collagens and fibroectin.
- They may participate in the structural organization of the extracellular matrix.

An example of these compounds is the hyaluronic acid.

❖ **Elastin**: This protein forms the central core of elastic fibers. It is found in large amounts in arteries such as aorta and in the dermis.

With most forms of injury there is:

- Loss of specialized cells.
- Loss or damage to the surrounding matrix and connective tissue.

In these cases, healing occurs by fibrosis following acute inflammation i.e. organization of fibrin with the formation of granulation tissue, which subsequently matures into fibrous tissue.

Granulation tissue

Granulation tissue: It is a richly vascular connective tissue (fibrovascular tissue).

It is consider as the initial response in wound healing.

It has two major components:

- Proliferating capillaries.
- The cellular compartment: cells are mostly fibroblasts, myofibroblasts, macrophages, lymphocytes and plasma cells.

Regarding proliferating capillaries:

The process of capillary proliferation is called ***angiogenesis*** or ***neovasculization***, in which capillary endothelial cells proliferate and grow into the area to be repaired. Initially they are solid buds but soon they open into vascular channels. The vessels are arranged as a serious of loops arching into the damaged area. The process of angiogenesis is stimulated in part by fibronectin. In the beginning the vessels formed are fragile thin-walled capillaries, by time they mature to form arterioles and venules.

Regarding cellular component:

At the same time of angiogenesis, fibroblasts are stimulated to divide and to secrete collagen and other matrix components, fibroblasts (in granulation tissue-wound healing) also acquire bundles of muscle filaments and attached to adjacent cells. These modified fibroblasts are called ***myofibroblasts*** and display features and functions of both fibroblasts and smooth muscle cells as well as these cells play an important role in wound contraction.

This combination of capillary loops and myofibroblasts is known as ***granulation tissue.***

Within time, the amount of interstitial collagen increases, the fibroblast cells will become elongated and thinner. At the same time, there is a process of devasculization, some vessels undergoing atrophy. For some considerable time there is a continued process of remodeling of the matrix, one of the effects of which is a gradual shrinkage of the scar.