**Lec.no.1/ Tissue Repair**

**Dr. Rawaa G.Al-Tereihi**

**Tissue Repair and Healing by Fibrosis**

**Tissue Repair or (healing):**restoration of tissue architecture and function after an injury. It occurs in two distinct processes:

**1-Regeneration** **::** complete restitution of the lost or damaged tissue i.e. the tissue essentially returns to normal state.

**2- Repair ::** its most often consists of a combination of regeneration and scar formation by the deposition of collagen.

The relative involvement of regeneration and scarring in tissue repair depends on the ability of the tissue to regenerate and the extent of the injury, therefore scar formation is predominant in healing process that occurs when the extracellular matrix (ECM) framework is damaged by severe injury.

**Usually tissue repair involves both processes and it involves:**

a-- The proliferation of various cells ,and these cells produce growth factors, cytokines that are critical for regeneration and repair.

b--The interaction between cells extracellular matrix (ECM).

**The Control of Normal Cell Proliferation &Tissue Growth**

In adult tissue, the size of cell populations is determined by the rates of cell proliferation , differentiations ,and death by apoptosis as see in figure 1, therefore there are different types of cells that proliferate during tissue repair which are:

1-The remnants of injured tissue (which attempt to restore normal structure ) .

2-Vascular endothelial cells ( to create new vessels that provide the nutrients for the repair process).

3-Fibroblast(the source of fibrous tissue that fills the defect).

**Tissues Proliferative Activity**

the tissues are divided into three groups on the basis of the proliferative activity of their cells::

**1-Continuously dividing (labile tissues)**

Cells of these tissues are continuously proliferate throughout life, replacing those that are destroyed.These tissue include hematopoietic cells in the bone marrow and the majority of surface epithelia, such as stratified squamous surfaces of the skin, oral cavity, vagina, and cervix; the lining mucosa of all the excretory ducts of the glands of the body (e.g., salivary glands, pancreas, biliary tract); the columnar epithelium of the gastrointestinal tract and uterus.

**2- Quiescent (stable) tissues**

Cells of these tissues have low level of replication,these cells can under go rapid division in response to stimuli e.g. the parenchymal cells of liver, kidneys, and pancreas; mesenchymal cells, such as fibroblasts and smooth muscle; vascular endothelial cells.

**3- Non dividing (permanent) tissues** :

The cells of these tissues have left the cell cycle and can not undergo mitotic division in postnatal life e.g. neurons and cardiac muscle cells. These cells have long life span, therefore the injury in brain or heart is irreversible and result in scar.

**Stem cells**

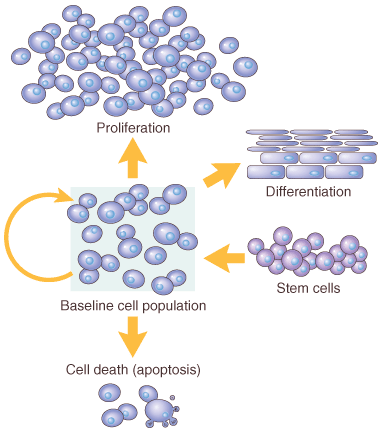
These cells have the ability to continuously divide and differentiate (develop) into different kinds of cells. ***Stem Cells characterized by two important features*** ::

1-Self-renewal capacity.

2-Asymmetric replication i.e. in every cell division, one of the cells retains its self-renewing capacity while the other enters a differentiation pathway and is converted to a mature, non-dividing cell.

In adults, stem cells with more restricted capacity to generate different cell types have been identified in many tissues as in skin ,the lining of the gut, the cornea and in the hematopoietic tissue **,In these tissues there is homeostatic equilibrium between the replication and differentiation of stem cells and the death of the mature, fully differentiated cells**..

Stem cells were first identified as pluripotent cells in embryos, and these were called embryonic stem cells and they had a role in the maintenance of tissue homeostatic equilibrium.



***Figure 1: Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, by cell death due to apoptosis, or by changes in the rates of proliferation or differentiation.***

**Kinds of Stem Cells**

|  |  |  |
| --- | --- | --- |
| Stem cell type | Description | Examples |
| Totipotent | Each cell can develop into a new individual | Cells from early (1-3 days) embryos |
| Pluripotent | Cells can form any (over 200) cell types | Some cells of blastocyst (5 to 14 days) |
| Multipotent | Cells differentiated, but can form a number of other tissues | Fetal tissue, cord blood, and adult stem cells |

**Cell Cycle and the Regulation of Cell Replication**

Cell Cycle is the sequence of events by which a cell duplicates its genome, synthesis the other constituents of the cell and eventually divides into two daughter cells, therefore cell division, DNA replication, and cell growth have to take place in a coordinated way to ensure correct division and formation of progeny cells containing intact genomes. **These events are themselves under genetic control,** as see in figure 2.

**The cell cycle is divided into two basic phases:**

**1-Interphase:** It represents the phase between two successive M phases, , though called the resting phase, is the time during which the cell is preparing for division by undergoing both cell growth and DNA replication in an orderly manner. **The interphase is divided into three further phases:**

**G1 presynthetic growth phase , S DNA synthesis phase**

**G2 premitotic phase**

**2- M Phase (Mitosis phase):**It represents the phase when the actual cell division or mitosis occurs and starts with the nuclear division, corresponding to the separation of daughter chromosomes (karyokinesis) and usually ends with division of cytoplasm (cytokinesis).

**The restriction point (R)** is defined as a point of no return in G1, following which the cell is committed to enter the cell cycle .

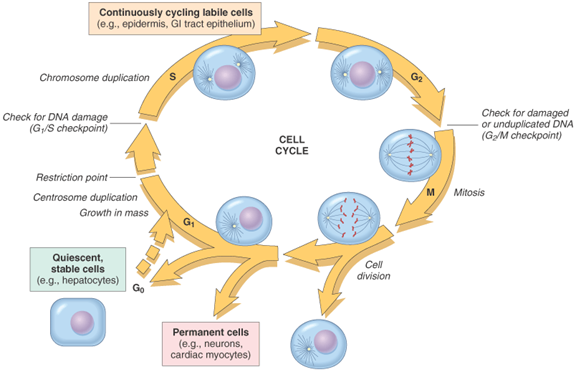
There are **two** main **checkpoints** in the cell cycle which act as own internal controls .

**G1 /S checkpoint** **prevents** the replication of cells that have defects in DNA. In the G1 /S checkpoint, cell-cycle arrest is mostly mediated through p53, which induces the cell-cycle inhibitor p21.

**G2 /M checkpoint monitors** the completion of DNA replication and checks whether the cell can safely initiate mitosis and separate sister chromatids. Arrest of the cell cycle by the G2 /M checkpoint involves both p53-dependent and independent mechanisms.

**Restriction point** is regulated by proteins called **cyclins,** and associated enzymes called **cyclin –dependent Kinases (CDKs). RB protein, the product of the RB gene , plays a key role in regulating the cell cycle. It is expressed in every cell type examined.**

When cells sense DNA damage, checkpoint activation delays the cell cycle and triggers DNA repair mechanisms. If the damage too sever, the cells are eliminated by apoptosis, or enter a nonreplicative state called senescence, through P53-dependent mechanisms. **Defect in cell-cycle checkpoint components is a major cause of genetic instability in cancer cells.**



**Figure 2:: shows the cell-cycle phases (G0 , G1 , G2 , S, and M), the location of the G1 restriction point, and the G1 /S and G2 /M cell-cyle checkpoints.**

**Cell proliferation can be triggered by:**

1--Growth Factors 2- Hormones

3-Cytokines 4-Signals from ECM

**Cytokines:**:These are protein substances produce by activated lymphocyte or macrophages and have an important functions as mediators of inflammation and immune response.

**Growth Factors:::**These polypeptide growth factors have a major role in regeneration and repair.These factors, may also promote cell survival, locomotion, contractility, differentiation and angiogenesis.All these growth factors function as **ligands** that bind to specific **receptors**, which deliver signals to the target cell. These signals stimulate the transcription of genes that may be silent in resting cells, including genes that control cell cycle entry and progression.

.e.g. Epidermal growth factor EGF, Vascular endothelial cell growth factor VEGF, Transforming growth factor alpha TGF-α.

**Signaling Mechanisms of Growth Factors Receptors**

The binding of a ligands such as growth factors and cytokines to specific receptors activated a process of receptor –mediated signal transduction, but according to the source of the ligand and the location of its receptor, there are **three** general modes of signaling named autocrine, paracrine, and endocrine, can be distinguished::

**1-Autocrine signaling**:: cells respond to the signaling molecules that they themselves secrete e.g. autocrine signaling plays a role in liver regeneration and lymphocyte proliferation induced by cytokines in some immune response.

**2-Paracrine signaling**:: one cell type produces the ligand, which then acts on adjacent target cells that express the appropriate receptor e.g. recruiting inflammatory cells to the site of infection an wound healing.

**3-Endocrine signaling**:: hormones synthesized by cells of the endocrine organs act on target cells distant from their site of synthesis usually carried by the blood.

