TISSUE REPAIR

REGENERATION & HEALING BY FIBROSIS

Critical to survival is the ability to repair the damage caused by injurious agents & inflammation.

Repair *refers to the restoration of tissue architecture and function after an injury.* This occurs by regeneration and/or healing.

Regeneration is the complete restoration of the damaged components of the affected tissue i.e. the tissue essentially returns to a normal state.

Healing is a reparative process characterized by laying down of connective (fibrous) tissue that results in *scar formation*. This mode occurs when

1. The injured tissues are incapable of complete regeneration, or

2. The supporting structures of the tissue are severely damaged

Although the resulting fibrous scar is not normal, it provides enough structural stability that allows the injured tissue to function. Both regeneration and healing by fibrosis contribute in varying degrees to the ultimate repair.

Repair involves

A. The proliferation of various cells, and

B. Close interactions between cells and the extracellular matrix (ECM).

THE CONTROL OF CELL PROLIFERATION

Several cell types proliferate during tissue repair. These include

1. The remnants of the 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. Fibroblasts (the source of the fibrous tissue that fills defects).

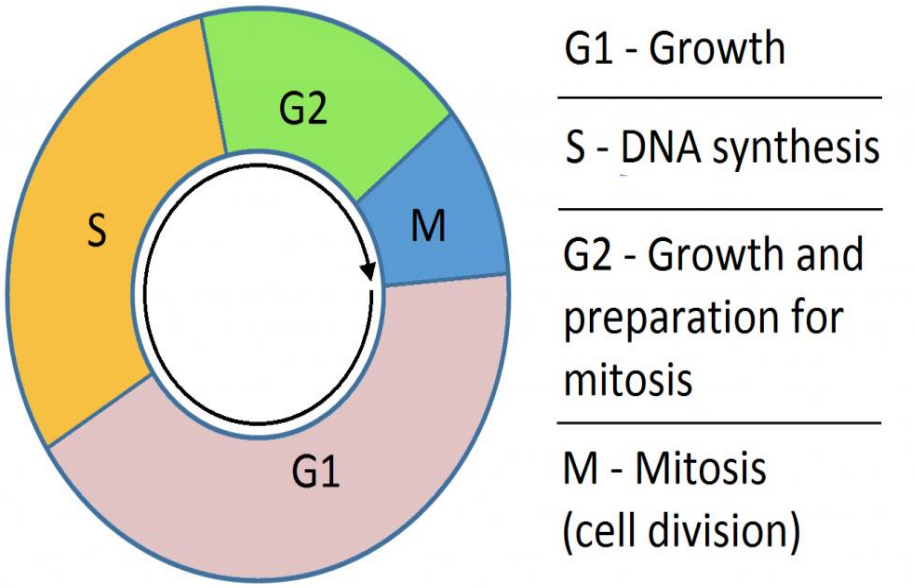
*The proliferation of the above cell types is driven by **growth factors**.*

The normal size of cell populations in any given tissue is determined by a balance of cell proliferation, cell death by apoptosis, and emergence of new differentiated cells from stem cells.

THE CELL CYCLE

The *cell cycle represents the sequence of events that control DNA replication & mitosis in the proliferation of cells*. 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 **presynthetic growth phase 1 *(G_1)*, the DNA synthesis phase *(S)*, the premitotic growth phase 2 *(G_2)*, and the mitotic phase *(M)*.**



Non-dividing cells are either in cell cycle arrest in G_1 or they exit the cycle to enter a phase called G_0.

Any stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the *G_0/G_1 transition* and the entry of cells into the G_1. 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*.

Checkpoint controls prevent DNA replication or mitosis of damaged cells and either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis. Progression through the cell cycle from G_1 is regulated by proteins called *cyclins*, which form complexes with enzymes called *cyclin-dependent kinases (CDKs)*. These complexes regulate the phosphorylation of proteins involved in cell cycle progression leading to DNA replication and mitosis, and thus are required for cell cycle progression.

A major action of growth factors is to overcome the checkpoint controls by liberating the suppression of CDK activity. Once cells enter the S phase, the DNA is replicated and the cell progresses through G_2 and mitosis.

Proliferative Capacities of Tissues

Tissue repair is critically influenced by the intrinsic proliferative capacity of the constituent cells. Based on this criterion, the tissues of the body are divided into three groups:

1. Continuously Dividing Tissues (***labile tissues***)**:** cells of these tissues are continuously being lost and replaced by maturation from stem cells and by proliferation of mature cells. Labile cells include hematopoietic cells in the bone marrow and the majority of surface epithelia. *These tissues can readily regenerate after injury provided the pool of stem cells is preserved.*

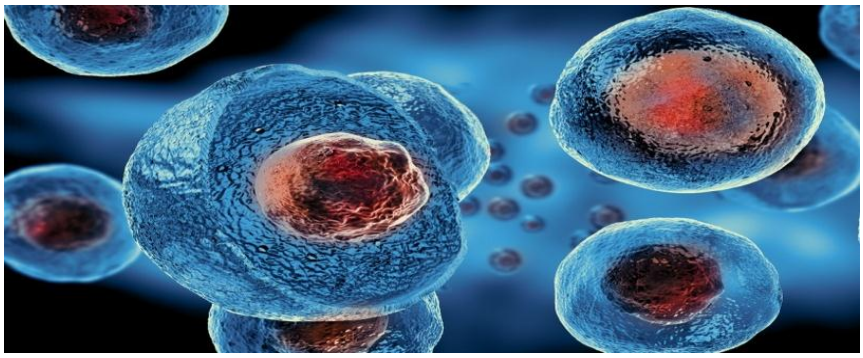
2. Stable Tissues: cells of these tissues are quiescent (in the G_0 stage of the cell cycle) and have only minimal replication activity in their normal state. However, these cells are capable of proliferating in response to injury or loss of tissue mass. *Stable cells constitute the parenchyma of most solid tissues, such as liver & kidney*. They also include endothelial cells, fibroblasts, and smooth muscle cells; the proliferation of these cells is particularly important in wound healing. *With the exception of liver, stable tissues have a limited capacity to regenerate after injury.*

3. Permanent Tissues: cells of these tissues are terminally differentiated and non-proliferative in postnatal life. The majority of neurons and cardiac muscle cells belong to this category. Accordingly, injury to brain or heart is irreversible and results in a scar. Skeletal muscle is usually classified as a permanent tissue, but satellite cells

attached to the endomysial sheath provide some regenerative capacity for this tissue.

Stem Cells

In most continuously dividing tissues the mature cells are terminally differentiated and short-lived. As mature cells die they are compensated for by identical differentiated cells generated from stem cells. Thus, in these tissues there is a homeostatic equilibrium between the replication and differentiation of stem cells and the death of the mature, fully differentiated cells. Such relationships are particularly evident in the multilayered epithelium of the skin and the gastrointestinal tract, in which stem cell positions have been identified near the basal layer of the epithelium. Cells differentiate progressively as they migrate to the upper layers of the epithelium; they ultimately die and are shed from the surface of the tissue.



Stem cells are characterized by two important properties:

1. Self-renewal capacity

2. Asymmetric replication.

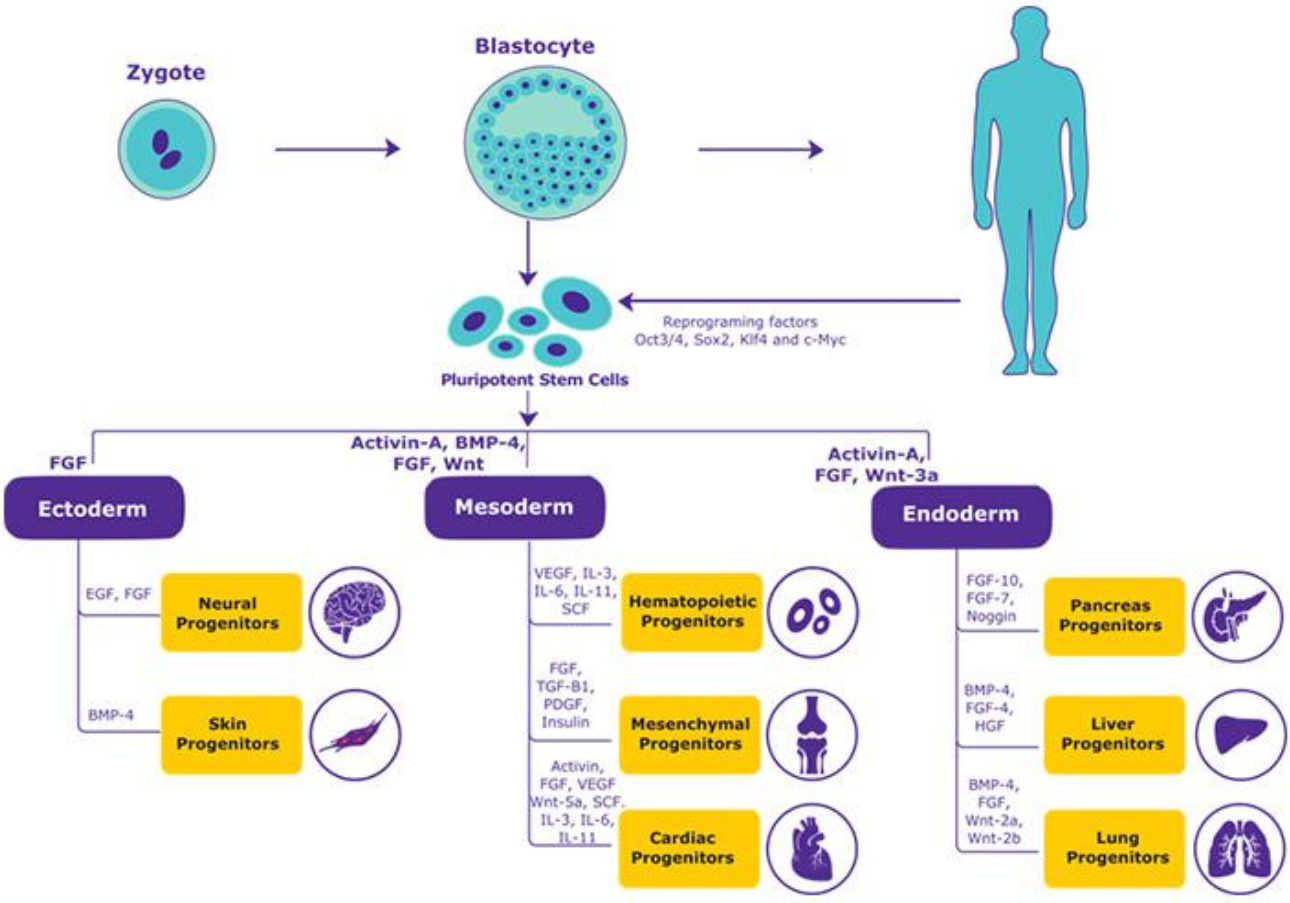
Asymmetric replication of stem cells means that after each cell division, some progeny enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity. Stem cells with the capacity to generate multiple cell lineages (*pluripotent stem cells*) can be isolated from embryos and are called ***embryonic stem cells*** and several other tissues of adult individuals like the bone marrow and are called ***adult stem cells***. The new field of ***regenerative medicine*** has a main objective of regeneration and repopulation of damaged organs using embryonic or adult stem cells.

GROWTH FACTORS

Cell proliferation can be triggered by

1. Growth factors, 2. Hormones, 3. Cytokines and 4. Signals from the ECM

The polypeptide growth factors have a major role of promoting cell survival and proliferation, which are important in regeneration and healing. Thus, these proteins expand cell populations by stimulating cell division as well as by promoting cell survival through protection from apoptotic death. Most growth factors also stimulate migration, differentiation of cells as well as the synthesis of specialized proteins (such as collagen in fibroblasts).



They induce cell proliferation by binding to specific receptors and by doing so affect the expression of genes through

1. Relieving blocks on cell cycle progression (thus promoting replication),

2. Preventing apoptosis

3. Enhancing the synthesis of cellular proteins in preparation for mitosis

A major activity of growth factors is to stimulate the function of growth control genes, many of which are ***proto-oncogenes*** (so named because mutations in them lead to unrestrained cell proliferation characteristic of neoplasia (oncogenesis).

The binding of a ligand (growth factor) to its receptor triggers a series of events by which extracellular signals are transduced into the cell, leading to the stimulation or repression of gene expression.

Many of the growth factors that are involved in repair are produced by leukocytes that are recruited & activated at the site of injury, as part of the inflammatory process. Other growth factors are produced by the specialized tissue (parenchymal) cells or the stromal (connective tissue) cells in response to cell injury or loss.