**Lecture 5 General pathology Dr. Ali H. Murad**

***Tissue Repair***

***Healing by Regeneration and Fibrosis***

***Tissue repair***

It is restoration of tissue architecture and function after an injury, involving the proliferation of various cells, and close interactions between cells and the extra-cellular matrix (ECM).

***Types of tissue repair:*** The type of repair is determined by the tissue capacity for proliferation, and the severity of damage to the supporting structures of the tissue. Accordingly, we have two types of repairs:

**1- Regeneration**: Repair by replacement of the damaged components by the same original tissue so returning to a normal state.

**2- Fibrosis**: Repair by extensive deposition of collagen fibres, ending with scar formation.

***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

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**.

***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 G1 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.

***Proliferative Capacities of Tissues:***

The ability of tissues to repair themselves is influenced by their intrinsic proliferative capacity. According to this capacity, tissues are divided into three groups:

***1-Labile tissues (Continuously Dividing Tissue***

Cells of these tissues are continuously being lost and replaced by proliferation and maturation of stem cells. These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.

**Stem cells**: are the original embryonic cells that have the inherent property of proliferation. Stem cells are characterized by:

1- Prolonged self-renewal capacity.

2- Asymmetric replication i.e. after each cell division, one cell will be differentiated while other cell remains undifferentiated, retaining their self-renewal capacity.

3- They have very broad differentiation capabilities, being able to generate any cell like fat, cartilage, bone, endothelium, and muscle. Examples: in the multi-layered 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 die and are shed from the surface of the tissue.

***Tissues contain labile cells:***

1- Hematopoietic cells in the bone marrow.

2- The majority of surface epithelia (the stratified squamous surfaces of the skin, oral cavity, vagina, and cervix).

3- The cuboidal epithelia of the ducts draining exocrine organs

(e.g., salivary glands, pancreas, biliary tract);

4- The columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes and the transitional epithelium of the urinary tract.

***Homeostasis:***

Homeostasis means keeping a constant number of cells and tissue size to get normal shape and function. The normal size of cell populations is determined by a balance between cell proliferation, cell death by apoptosis, and emergence of new differentiated cells from stem cells. In these tissues the mature cells are terminally differentiated and short lived. As mature cells die the tissue is replaced by the differentiation of 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.

The normal size of cell populations in any given tissue is determined by a balance of

1-cell proliferation

2-cell death by apoptosis

3**-**The emergence of new differentiated cells from stem cells

***2-Stable Tissues: (Quiescent cells)***

Cells of these tissues are quiescent and have only minimal proliferative activity in their normal state. However, these cells are capable of proliferating in response to injury or loss of tissue mass.

Stable cells constitute:-

1. The parenchyma of most solid tissues (liver, kidney, and pancreas).

2. The endothelial cells.

3. The fibroblasts.

4. The smooth muscle cells.

With the exception of liver, stable tissues have a limited capacity to regenerate after injury.

***3-Permanent Tissues: (Non dividing cells)***

The cells of these tissues are considered to be terminally differentiated and non-proliferative in postnatal life ex. **Neurons** and **cardiac muscle** cells. Thus, injury to the brain or the heart is irreversible and results in a scar formation. **Skeletal muscle** is usually classified as a permanent tissue, but satellite cells attached to the endomysial sheath provide some regenerative capacity for this tissue

***Cells involved in repair: -***

1- The remnants of the injured tissue

2- Vascular endothelial cells to create new vessels (nutrition).

3- Fibroblasts which are the source of the fibrous tissue that forms the scar

***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 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.

***Mechanism of action of growth factors:***

1- They stimulate the function of growth control genes, many of which are called **proto-oncogenes** because mutations in these genes lead to uncontrolled cell proliferation that is the characteristic of cancer (oncogenesis).

2- They stimulate proliferation of some cells and inhibit proliferation of others.

3- They can have opposite effects on the same cell depending on its concentration. An example of such a growth factor is transforming growth factor-β (TGF-β)

Growth factors act as extracellular signals that will bind receptors located on the cell surface or intracellularly. The activation of the receptor will trigger a series of events leading to stimulation or repression of gene expression and cell division.