

# ***Proliferative Capacities of Tissues***

**DR. AYSER HAMEED**

**LEC.5**

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 replicative 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 nonproliferative 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 (ES) cells**. As mentioned above, stem cells are normally present in proliferative tissues and generate cell lineages specific for the tissue. However, it is now recognized that stem cells with the capacity to generate multiple lineages are present in the bone marrow and several other tissues of adult individuals. These cells are called tissue stem cells or **adult stem cells**. Whether tissue stem cells have similar differentiation capacity (differentiation plasticity) as ES cells remains the subject of active research and much dispute. Bone marrow stem cells have the ability to generate fat, cartilage, bone, endothelium, and muscle.

The new field of **regenerative medicine** has a main objective of regeneration and repopulation of damaged organs using ES or adult stem cells. One of the most exciting prospects in this field is the type of stem cell therapy known as **therapeutic cloning**. The main steps of this procedure are illustrated in (**Figure 4-3**). Other potential therapeutic strategies using stem cells involve transplanting stem cells into areas of injury, mobilization of stem cells from the bone marrow into injured tissue, and the use of stem cell culture systems to produce large amounts of differentiated cells for transplantation into injured tissue.

## **GROWTH FACTORS**

Cell proliferation can be triggered by:

1. Growth factors.
2. Hormones.
3. Cytokines.
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 & 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 protooncogenes (so named because mutations in them lead to unrestrained cell

proliferation characteristic of neoplasia (oncogenesis). 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.

### **Signaling Mechanisms of Growth Factor Receptors:-**

The major intracellular signaling pathways induced by growth factor receptors are similar to those of many other cellular receptors that recognize extracellular ligands. The binding of a ligand 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. Signaling may occur directly in the same cell (autocrine signaling e.g. lymphocyte proliferation induced by cytokines in some immune responses), between adjacent cells (paracrine signaling e.g. recruiting inflammatory cells to the site of infection & in wound healing), or over greater distances (endocrine signaling e.g. a hormone, is released into the bloodstream and acts on target cells at a distance) (**Fig. 4-4**).

The binding of a ligand to its cell surface receptor leads to a cascade of secondary intracellular events that culminate in transcription factor activation or repression, leading to cellular responses. Transcription factors bind to gene promoters and enhancers to trigger or inhibit transcription.

### **EXTRACELLULAR MATRIX (ECM) AND CELL-MATRIX INTERACTIONS**

Tissue repair depends not only on growth factor activity but also on interactions between cells and ECM components. The ECM is a dynamic, constantly remodeling macromolecular complex synthesized locally, which assembles into a network that surrounds cells. It constitutes a significant proportion of any tissue. By supplying a substrate for cell adhesion and serving as a reservoir for growth factors, ECM regulates the proliferation, movement, and differentiation of the cells living within it. Synthesis and degradation of ECM accompanies wound healing & chronic fibrotic processes.

#### **ECM occurs in two basic forms:**

1. Interstitial matrix, which is present in the spaces between mesenchymal (connective tissue) cells, and between epithelium and supportive vascular and smooth muscle structures; it is synthesized by the mesenchymal cells (e.g., fibroblasts). Its major constituents are fibrillar and nonfibrillar collagens, as well as fibronectin, elastin, proteoglycans, hyaluronate, and other elements.

2. Basement membrane, which lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells; it tends to form a platelike "chicken wire" mesh. Its major constituents are amorphous nonfibrillar type IV collagen and laminin.

### **Functions of the ECM**

1. Mechanical support for cell anchorage and migration, and maintenance of cell polarity.
2. Control of cell growth by signaling through cellular receptors of the integrin family.
3. Maintenance of cell differentiation through the type of ECM proteins, also acting largely via cell surface integrins.
4. Scaffolding for tissue renewal: the maintenance of normal tissue structure requires a basement membrane or stromal scaffold. The integrity of the basement membrane or the stroma of the parenchymal cells is critical for the organized regeneration of tissues. It is particularly noteworthy that although labile and stable cells are capable of regeneration, injury to these tissues results in restitution of the normal structure only if the ECM is not damaged. Disruption of these structures leads to collagen deposition and scar formation.
5. Establishment of tissue microenvironments: basement membrane acts as a boundary between epithelium and underlying connective tissue and also forms part of the filtration apparatus in the kidney.
6. Storage and presentation of regulatory molecules. For example, growth factors like FGF is excreted and stored in the ECM in some tissues. This allows the rapid deployment of growth factors after local injury, or during regeneration.

### **Components of the Extracellular Matrix**

There are three basic components of ECM:

1. Fibrous structural proteins (collagens and elastins) that confer tensile strength and recoil.
2. Water-hydrated gels (proteoglycans and hyaluronan), which permit resilience and lubrication.
3. Adhesive glycoproteins that connect the matrix elements to one another and to cells.

### **Collagen**

The collagens are fibrous structural proteins that confer tensile strength; without them human beings would be reduced to a clump of cells connected by neurons. Collagens are composed of three separate polypeptide chains braided into a ropelike triple helix. About 30 collagen types have been identified. Some collagen types (e.g., types I, II, III, and V) form fibrils. The fibrillar collagens form a major proportion of the connective tissue in healing wounds and particularly in scars. The tensile strength of the fibrillar collagens

derives from their cross-linking. This process is dependent on vitamin C; therefore, children with ascorbate deficiency have skeletal deformities, bleed easily because of weak vascular wall basement membrane, and heal poorly. Genetic defects in these collagens cause diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome. Other collagens are nonfibrillar and may form basement membrane (type IV), or be a component of intervertebral discs (type IX) or dermal-epidermal junctions (type VII).

### **Elastin**

The ability of tissues to recoil and return to a baseline structure after physical stress is conferred by elastic tissue. This is especially important in the walls of large vessels (which must accommodate recurrent pulsatile flow of blood), as well as in the uterus, skin, and ligaments. Elastic fibers differ from collagen by having fewer cross-links. The fibrillin meshwork serves as a scaffold for the deposition of elastin and assembly of elastic fibers; defects in fibrillin synthesis lead to skeletal abnormalities and weakened aortic walls (Marfan syndrome).

### **Proteoglycans and Hyaluronan**

Proteoglycans form highly hydrated compressible gels conferring resilience and lubrication (such as in the cartilage in joints). They consist of long polysaccharides called glycosaminoglycans linked to a protein backbone. Hyaluronan, a huge molecule composed of many disaccharide repeats without a protein core, is also an important constituent of the ECM. Because of its ability to bind water, it forms a viscous, gelatin-like matrix. Besides providing compressibility to a tissue, proteoglycans also serve as reservoirs for growth factors secreted into the ECM (e.g., FGF). Proteoglycans can also be integral cell membrane proteins and have roles in cell proliferation, migration, and adhesion.

### **Adhesive Glycoproteins and Adhesion Receptors**

Adhesive glycoproteins and adhesion receptors are structurally diverse molecules involved in cell-to-cell adhesion, the linkage between cells and ECM, and binding between ECM components. The adhesive glycoproteins include fibronectin (major component of the interstitial ECM) and laminin (major constituent of basement membrane).

**The adhesion receptors, also known as cell adhesion molecules (CAMs), are grouped into four families:**

1. Immunoglobulins.
2. Cadherins.
3. Selectins.
4. Integrins.

**Fibronectin** is synthesized by a variety of cells, including fibroblasts, monocytes, and endothelium. Fibronectins have specific domains that bind to a wide spectrum of ECM components. Tissue fibronectin forms fibrillar aggregates at wound healing sites; plasma fibronectin binds to fibrin to form the provisional blood clot of a wound, which serves as a background for ECM deposition and re-epithelialization.

**Laminin** is the most abundant glycoprotein in basement membrane that connects cells to underlying ECM components such as type IV collagen and heparan sulfate. Besides mediating attachment to basement membrane, laminin can also modulate cell proliferation, differentiation, and motility.

**Integrins** are a family of transmembrane glycoproteins composed of  $\alpha$  and  $\beta$  chains that are the main cellular receptors for ECM components, such as fibronectins and laminins. Some integrins are leukocyte surface molecules that mediate firm adhesion and transmigration across endothelium at sites of inflammation, and also play a role in platelet aggregation. Integrins are present in the plasma membrane of most animal cells, with the exception of red blood cells. They bind to many ECM components initiating signaling cascades that can affect cell locomotion, proliferation, and differentiation. Integrin signal transduction utilizes the same intracellular signaling pathways used by growth factor receptors. In this manner, extracellular mechanical forces can be coupled to intracellular synthetic and transcriptional pathways.

## **CELL AND TISSUE REGENERATION**

Cell renewal occurs continuously in labile tissues, such as the bone marrow, gut epithelium, and the skin. Damage to epithelia or an increased loss of blood cells can be corrected by the proliferation and differentiation of stem cells and, in the bone marrow, by proliferation of more differentiated progenitors. The renewal of hematopoietic cells is driven by growth factors called colony-stimulative factors (CSFs), which are produced in response to increased consumption or loss of blood cells.

Tissue regeneration can occur in parenchymal organs with stable cell populations, but with the exception of the liver, this is usually a limited process. The surgical removal of a kidney elicits in the contralateral kidney a compensatory response that consists of both hypertrophy and hyperplasia of proximal duct cells. The regenerative response of the liver that occurs after surgical removal of hepatic tissue is striking. Up to 60% of the liver may be removed in a procedure called living-donor transplantation, in which a portion of the liver is resected from a normal individual and is transplanted into a recipient with end-stage liver disease (**Fig. 4-5**), or after partial hepatectomies performed for tumor removal. In such cases, the tissue resection triggers proliferation of the remaining

hepatocytes (normally quiescent). Experimentally, hepatocyte replication after partial hepatectomy is initiated by cytokines (e.g., tumor necrosis factor [TNF] and interleukin 6 [IL-6]). EGF (epidermal growth factor receptor, or EGFR) with intrinsic tyrosine kinase activity, is mitogenic for hepatocytes and most epithelial cells, including keratinocytes. In cutaneous wound healing EGF is produced by keratinocytes, macrophages, and other inflammatory cells. The main EGFR (referred to as EGFR1) is frequently overexpressed in lung and some brain tumors and is an important therapeutic target for the treatment of these conditions. ERB B2 (also known as HER-2/NEU) has received great attention because of its overexpression in breast cancers, in which it is a target for effective cancer control. It should be emphasized that extensive regeneration or compensatory hyperplasia can occur only if the residual tissue is structurally and functionally intact, as after partial surgical resection. By contrast, if the tissue is damaged by infection or inflammation, regeneration is incomplete and is accompanied by scarring.