Tissue repair

Regeneration ***Scar***

Repair: sometimes called healing, refers to the restoration of tissue architecture and function after an injury. It occurs by two types of reactions: regeneration of the injured tissue and scar formation by the deposition of connective tissue

Regeneration. Able the tissues to replace the damaged cells and essentially return to a normal state; this process is called regeneration. And occurs by proliferation of residual (uninjured) cells that retain the capacity to divide, and by replacement from tissue stem cells. It is the typical response to injury in the rapidly dividing epithelia of the skin and intestines, and some parenchymal organs, notably the liver.

Scar formation. repair occurs by modulate of connective (fibrous) tissue, a process that results in scar formation. If the injured tissues are incapable of regeneration, or if the supporting structures of the tissue are severely damaged,

fibrosis is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction).

If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called <u>organization</u> (as in organizing pneumonia affecting the lung).

1- Cell and tissue regeneration

The regeneration of injured cells and tissues involves **cell proliferation**, which is driven by **growth factors** and is dependent on the integrity of the extracellular matrix.

We must understand the following

1- describing examples of repair by regeneration,
2-discuss the general principles of cell proliferation
3- functions of the ECM in this process.

The Control of Cell Proliferation

Several cell types proliferate during tissue repair. These include the remnants of

a-the injured tissue (which attempt to restore normal structure),

b-vascular endothelial cells (to create new vessels that provide the nutrients needed for the repair process)

c-fibroblasts (the source of the fibrous tissue that forms the scar to fill defects that cannot be corrected by regeneration).

The proliferation of these cell types is driven by proteins called *growth factors.* The production of polypeptide growth factors and the ability of cells to divide in response to these factors are important determinants the repair process.

The key processes in the proliferation of cells are DNA replication and mitosis. The sequence of events that control these two processes is known as the ***cell cycle***

1-the nondividing cells are in cell cycle arrest in the G1 phase or have exited the cycle and are in the G0 phase.
2- Growth factors stimulate cells to transition from G0 into the G1 phase and then into DNA synthesis (S), G2, and mitosis (M) phases. Progression is regulated by cyclins, whose activity is controlled by cyclindependent kinases. Once cells enter the S phase, their DNA is replicated and they progress through G2 and mitosis.

the tissues of the body are divided into three groups their intrinsic proliferative capacity.

- ***Labile (continuously dividing) 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, such as the stratified squamous surfaces of the skin, oral cavity, vagina, and cervix; the cuboidal epithelia of the ducts draining exocrine organs (e.g., **salivary glands, pancreas, biliary tract**); the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; and the transitional epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.

- ***Stable tissues.*** Cells of these tissues are quiescent 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, and pancreas**. 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.

- ***Permanent tissues.*** The cells of these tissues are considered to be terminally differentiated and nonproliferative in postnatal life.

Permanent **cell Most neurons and cardiac muscle** cells belong to this category. Thus, injury to brain or heart is irreversible and results in a scar, because neurons and cardiac myocytes cannot regenerate. Limited stem cell replication and differentiation occur in some areas of the adult brain, and there is some evidence that cardiac stem cells may proliferate after myocardial necrosis. Nevertheless, whatever proliferative capacity may exist in these tissues, it is insufficient to produce tissue regeneration after injury. Skeletal muscle is usually classified as a permanent tissue, but satellite cells attached to the endomysial sheath provide some regenerative capacity for this tissue. In permanent tissues, repair is typically dominated by scar formation.

SUMMARY

Cell Proliferation, the Cell Cycle, and Stem Cells

• Regeneration of tissues is driven by proliferation of uninjured (residual) cells and replacement from stem cells.

• Cell proliferation occurs when quiescent cells enter the cell cycle. The cell cycle is tightly regulated by stimulators and inhibitors and contains intrinsic checkpoint controls to prevent replication of abnormal cells.

• Tissues are divided into labile, stable, and permanent, according to the proliferative capacity of their cells.

• Continuously dividing tissues (labile tissues) contain mature cells that are capable of dividing and stem cells that differentiate to replenish lost cells.

• Stem cells from embryos (ES cells) are pluripotent; adult tissues, particularly the bone marrow, contain adult stem cells capable of generating multiple cell lineages.

• Induced pluripotent stem cells (iPS cells) are derived by introducing into mature cells genes that are characteristic of ES cells. iPS cells acquire many characteristics of stem cells.

Growth Factors, Receptors, and Signal Transduction Growth Factors, Receptors, and Signal Transduction

• Polypeptide growth factors act in autocrine, paracrine, or endocrine manner. Growth factors are produced transiently in response to an external stimulus and act by binding to cellular receptors.

Different classes of growth factor receptors include receptors with intrinsic kinase activity, G protein–coupled receptors and receptors without intrinsic kinase activity.

• Growth factors such as epidermal growth factor (EGF) and hepatocyte growth factor (HGF) bind to receptors with intrinsic kinase activity, triggering a cascade of phosphorylating events through MAP kinases, which culminate in transcription factor activation and DNA replication.

• G protein–coupled receptors produce multiple effects via the cAMP and Ca2+ pathways. Chemokines utilize such receptors.

• Cytokines generally bind to receptors without kinase activity; such receptors interact with cytoplasmic transcription factors that move into the nucleus.

• Most growth factors have multiple effects, such as cell migration, differentiation, stimulation of angiogenesis, and fibrogenesis, in addition to cell proliferation.

Role of the Extracellular Matrix in Tissue Repair

Tissue repair depends not only on **growth factor activity** but also on interactions between cells and ECM components.

The ECM is a complex of several proteins that assembles into a network that surrounds cells and constitutes a significant proportion of any tissue.

Function OR ROL (IMPORTANT)THE ECM
1-ECM sequesters water, providing turgor to soft tissues,
2- minerals, giving rigidity to bone.
3- regulates the proliferation, movement, and differentiation of the cells living within it, by supplying a substrate for cell adhesion and migration and serving as a reservoir for growth factors.
4-The ECM is constantly being remodeled; its synthesis and degradation accompany morphogenesis, wound healing, chronic fibrosis, and tumor invasion and metastasis.

ECM occurs in two basic forms: interstitial matrix and basement membrane

• *Interstitial matrix:* This form of ECM is present in the spaces between cells in connective tissue, and between epithelium and supportive vascular and smooth muscle structures. It is synthesized by mesenchymal cells (e.g., fibroblasts) and tends to form a three-dimensional, amorphous gel. Its major constituents are fibrillar and nonfibrillar collagens, as well as fibronectin, elastin, proteoglycans, hyaluronate, and other elements (described later).

• *Basement membrane:* The random array of interstitial matrix in connective tissues becomes highly organized around epithelial cells, endothelial cells, and smooth muscle cells, forming the specialized basement membrane. The basement membrane lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells; it tends to form a plate like “chicken wire” mesh. Its major constituents are amorphous nonfibrillar type IV collagen and laminin

SUMMARY
Extracellular Matrix and Tissue Repair
• The ECM consists of the *interstitial matrix* between cells, made up of collagens and several glycoproteins, and *basement membranes* underlying

epithelia and surrounding vessels, made up of nonfibrillar collagen and laminin.

- **The ECM serves several important functions:**

· It provides mechanical support to tissues; this is the role of collagens and elastin.

· It acts as a substrate for cell growth and the formation of tissue microenvironments.

· It regulates cell proliferation and differentiation; proteoglycans bind growth factors and display them at high concentration, and fibronectin and laminin stimulate cells through cellular integrin receptors.

- An intact ECM is required for tissue regeneration, and if the ECM is damaged, repair can be accomplished only by scar formation.