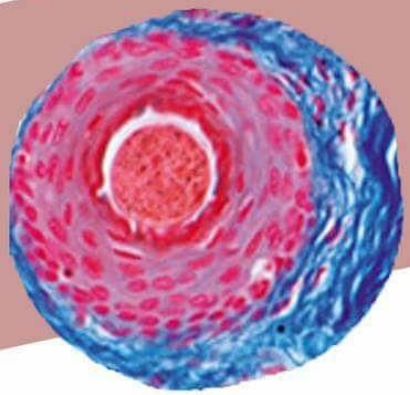
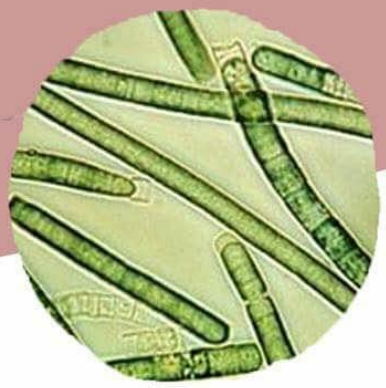
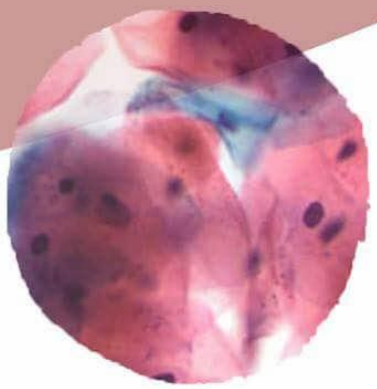
INTRODUCTION TO PATHOLOGY

Done by Dana AF

Corrected by Asem Hizzani

Sheet# 12

Repair

Previously, we discussed inflammation, in this and the next lecture we will discuss “Repair of Inflammation “, so let’s go ☺

We should know that when inflammation starts, repair starts too.(so they are related).

Q. What do we mean by tissue repair?
It means restoration of tissue’s architecture and function after an injury. So, if there is an injury, we need structure and function to go back to normal, this is called repair.

Types of repair:

1- Regeneration：(things going back to normal)
It means the replacement of the damaged cells and restoration of normal function. This happens if the injury and the tissue destruction are mild.

How does regeneration occur? Damaged cells are replaced by:

A- Proliferation of tissue remnants (residual or uninjured cells): if the skin becomes injured, it will regenerate its cells by proliferation of epithelial cells, hair follicle cells, fibroblasts, etc. ... (all the cells that found in the area of injury).
B- Stem cells

2-Scar Formation:
repair by laying down of connective (fibrous) tissue resulting in scar formation.

Which cells replicate during scar formation?
- Fibroblasts which produce collagen and other components of the ECM for scar formation.

Notice that this happens if the inflammation is severe and the injury is extensive to the tissues. And if, the injured tissues cannot replicate themselves .

Scar cannot perform the function of the lost tissue so if we replace an injured area of the skin by skin it will function normally; but if, we replace it by fibrous tissue and scar; it will not function normally but the scar will support it. Although, there is no restoration by function, there will be structural a support.

Note: a student asked, if there is sensation in the region of the scar?
The doctor said: “That depends on the nerves, if you lose a nerve end, you will lose sensation as well.”

Note: in the majority of injuries, both (regeneration and scar) play a role in repair, meaning that part of the cells will be regenerated and the rest which cannot regenerate are filled by fibrous tissue
Now we will discuss regeneration more and more: The Control of Cell Proliferation:

Q. Which cells replicate during repair?
A-Remnant cells
B-Stem cells
C- Endothelial cells; to return the vascularity to the area of injury. We don't want a non-vascularized tissue; Why? Because this tissue will need nutrients and oxygen; so we need to restore blood vessels as well.
D- Fibroblasts; to make fibrosis.

Note: the proliferation of all these cells is controlled by certain chemical mediators called GROWTH FACTORS. (some are stimulatory growth factors and some are inhibitory growth factors)

Note: So in any part of our body, injured or uninjured, there is a homeostasis in the size of the tissue; which means there is a normal size of the tissue, and it cannot increase and shouldn't decrease (for example; in the GI tract we change the epithelium of the GI tract very continuously). There should be a balance between cell death and cell regeneration; this balance is controlled by growth factors and apoptosis. So, some cells will die by apoptosis and others will grow instead of them.

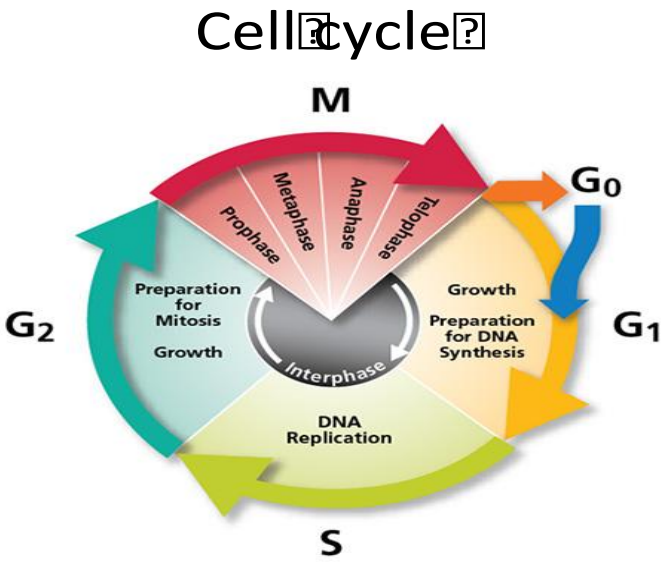
If we lost 10 cells for example, the body will regenerate 10 cells, otherwise a cancer will occur (if the number of cells that proliferate is more than the number of cells lost, cancer happens)

Terminology:
Repair: healing (regeneration and scarring).
Fibrosis and organization is basically the same thing.
Fibrosis: a term for solid organs. e.g. Injury in the liver/pancreas results in fibrous tissue.
Organization: in a cavity. So, inflammation in the lung cavity results in fibrous tissue
Ex: Organizing Pneumonia; a patient has inflammation in the lungs, a cavity is formed, and then it's filled with fibrous tissue.

So, we said that in order to have Repair, we need the cells to proliferate and proliferation is controlled by growth factors and represented by the cell cycle (G0, G1, S phases).

How do cells regenerate and enter the cell cycle?
As we remember the cell cycle, the G0 phase has cells that are NOT replicating, they are stable. They enter the cell cycle if we need them to replicate; by transition to G1 phase (G stands for Gap originally, but it means Growth). There is a growth; so proteins and enzymes increase in number.

- G1 phase: increases proteins synthesis and preparation for DNA synthesis.
- S phase means synthesis phase, DNA replication occurs in this phase.
- G2 phase another growth phase.
- Then mitosis



So tissues in our body are divided into 3 types depending on their ability to replicate:

1- Labile cells : continuously divide like: skin, mucosal membrane, hematopoietic cells → continuously lost and replaced by proliferation of mature cells and maturation of stem cells

2 - Stable cells: Quiescent, inactive cells. Have minimal replicative activity in normal state but can proliferate in response to injury. Except for the liver; these cells have limited capacity to regenerate. Examples: Parenchyma of solid organs, endothelial cells, fibroblasts, smooth muscle cells

3 - Permanent cells: cannot replicate; they are always in the G0 phase, and will never be able to replicate. Ex: neurons and cardiac muscle. (And also skeletal muscle can be classified as a permanent tissue.)

Remember:
Labile cells are always shredded and teared, they need a constant replacement.
Permanent cells are just the three examples given.
Anything else is a stable cell.

Growth factors that work on liver give it a high regenerative capacity, they are:
- Hepatocyte growth factor HGF (specially for the liver).
- Epidermal growth factor EGF family. (transforming growth factor α is a member of this family)

Growth factors are protein molecules that do the growth, make the cell enter the cell cycle and replicate.

Note: neuronal stem cells, cardiac stem cells alongside with a certain satellite cells which present in the skeletal muscle have a very limited capacity to replicate. (We say that permanent tissues -never replicate- but in medicine "never" is a wrong term because there are some exceptions). *This capacity can be minimal and negligible.

Note: so the cells that can replicate are the normal cells and the stem cells

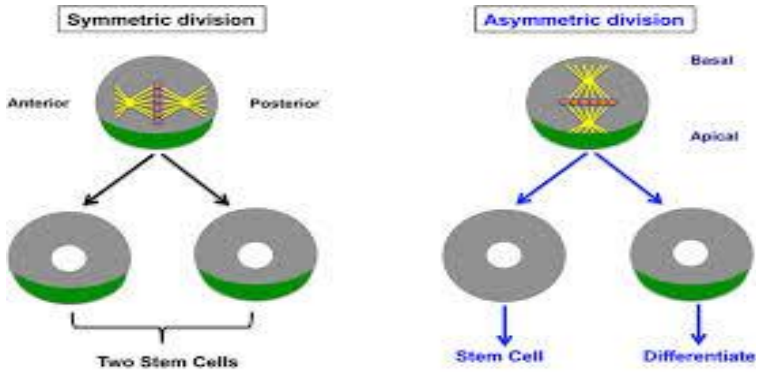
A student asked, if the liver can regenerate itself why does scarring and fibrosis occur?
It is about the extent of injury and the tissue (even skin which is labile can form scar). In the liver if the injury is severe, the architecture is damaged and it affects the fibrous tissue (the stroma), we will end up with fibrosis **instead of** regeneration.

Stem Cells
are also responsible for renewal.
Stem cells: undifferentiated cells in our body which have two characteristics:

1- Self-renewal capacity ---- so they can renew themselves (they can replicate)
2- Asymmetric replication ---- when the cell divides and gives 2 different type of cells (the two daughter cells are different from each other (not exact) --One becomes a stem cell to preserve the number of stem cells and the other becomes a mature differentiated cell.

Note: in the symmetric replication --- the cell is divided to 2 daughter cells which are the same (exact).

Asymmetric replication



Types of Stem Cells

•Embryonic stem cells (ES cells) are the most undifferentiated stem cells. They are present in the inner cell mass of the blastocyst and have extensive

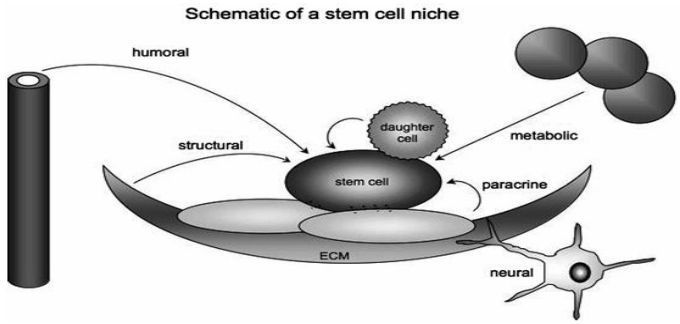
cell renewal capacity. Hence, they can be maintained in culture for over a year without differentiating. Under appropriate culture conditions, ES cells can be induced to form specialized cells of all three germ cell layers, including neurons, cardiac muscle, liver cells, and pancreatic islet cells.

• Adult stem cells, also called tissue stem cells, are less undifferentiated than ES cells and are found among differentiated cells within an organ or tissue. Although, like ES cells, they also have self-renewal capacity, this property is much more limited. In addition, their lineage potential (ability to give rise to specialized cells) is restricted to some or all of the differentiated cells of the tissue or organ in which they are found.

Note: whereas the normal function of ES cells is to give rise to all cells of the body, adult stem cells are involved in tissue homeostasis.

**Stem cell research (stem cell uses in medicine):
There are difficulties in working with the adult stem cells because it is difficult to isolate them to purity, as they are already rare in our bodies.
So, to take an isolated stem cell (pure) from the skin without the rounded cells is difficult because isolating the stem cells to purity is difficult (except the hematopoietic stem cells (the only successfully isolated stem cells)).
Also, stem cells are present in our bodies in “niches”.
Stem cell niches: is the microenvironment where the stem cell lives.
- This microenvironment includes hormones, nutrients, blood vessels and other things that will help stem cells and tell them when to divide and when not. For example, in the skin, stem cells are found mainly around hair follicles, so when you cut the hair from the follicle you lose the stem cells.
The importance of niches: when you make isolation of stem cells from the body you are isolating them from their niches; thus, they might not function properly.

Stem cell niches



To sum up:
- There are two problems with stem cells in clinical treatment:
1-They cannot be isolated to purity.
2- When you take them from the body, you separate them from their environment; thus, they cannot do their function properly.
So, using stem cells in medicine is very difficult.

**regenerative medicine --- when there is an injury in our body, we can regenerate out tissues by using stem cells.

Note: tissue stem cells mean that you take a sample of stem cells from the same person so there is no problem with rejection. Embryonic stem cells can make better regeneration because they can differentiate into any cell type if they are placed in the proper environment, but the problem is the rejection because these embryonic stem cells are not extracted from the same patient.

Note: stem cells of the skin are found around the hair follicles (if a cut affect a hair follicle, there will be scarring).

Even though tissue stem cells are hard to use, still some of them can be used.

Blood stem cells are in the bone marrow:

It is easier to isolate and purify them.

They are more abundant.

To take tissue stem cells from bone marrow we need to:

Increase their numbers by using growth factors (colony stimulating factors).

They're used to treat lymphoma and leukemia.

Bone marrow also contains mesenchymal (stromal) cells that can be isolated and can differentiate into cartilage and bone.

From bone marrow we can take:

-Hematologic stem cells (stem cells of RBCs and WBCs and so on).

-Mesenchymal stem cells.

It is not just bone marrow that we can take stem cells from, we can take from the blood as well. If we give a lot of growth factors, stem cells will increase in number and then they will be shifted from the bone marrow to the peripheral blood before their complete differentiation (maturation), and so, it is easy to isolate them, and this process is easier than taking them from the bone marrow.

To solve the rejection problem, there is a new type of cells (induced pluripotent stem cells).

Induced pluripotent stem cells: During this process, the gene responsible for making embryonic stem cells replicate is placed inside mature cells, which in turn are converted to stem cells that have the characteristics of ES cells --- these new cells are called “induced pluripotent stem cells”

- We compare the genes of our mature cells with the genes of ES cells. We will notice that some genes of ES cells are responsible for “Stem-cell-ness”.

If we introduce these genes to the mature cell, it will acquire the characteristics of ES cells. These mature cells that are now having self-renewal capacity are called induced pluripotent stem cells.

- These cells will not be rejected by the patient because they are taken from him.

- Stem-cell-ness: being a stem cell.
- induced → because transforming into a stem cell is induced by introducing new genes to the mature cell.

***growth factors:** *P*roteins which stimulate cell survival, proliferation, migration, and differentiation and other cellular responses.

From where these growth factors come?
Macrophages, endothelial cells, mesenchymal cells and several other types.

Note: Examples of growth factor (not to memorize just to be familiar with):
1-epidermal GF
2-transforming GF
3-hepatocyte GF--- very important for the regeneration of the liver
4-PDGF
5- vascular epithelial GF

Growth factors cause growth of cells (some stimulate growth, while others inhibit growth.)

So, how do the growth stimulatory growth factors work?
- They promote the entry to the cell cycle. When a cell is in G0 phase, it enters the G1 phase under the effect of the growth factor.
- They relieve blocks on the cell cycle progression (there is a certain check point between phases in the cell cycle which prevents the cell from proceeding freely from G0 to G1 and so on).
- Prevent apoptosis (prevent cell death).
- Increase protein synthesis during G1 and G2 phases → to make the cell ready to divide and give two daughter cells.

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

How do they do this???
By certain signaling mechanisms.
GFs have receptors on the cell surface or inside the cytoplasm (in case of lipid-soluble GFs).
- And these receptors (when the GFs bind to their receptors) send signals to the nucleus (mitogenic signals) to stimulate proliferation, to increase protein synthesis, to stimulate DNA replication and so on.

Note: the effect of the GF can be:
-autocrine – affect the same cell which releases the GF
-paracrine – affects the near cells
-endocrine – circulating in the blood

*So let us talk about the mechanism of GF in more details ☺ :
When growth factors bind to their receptor, there are 3 pathways to activate the receptor, so there are 3 types of receptors (they will be explained later):
1-receptors with intrinsic kinase activity
2- G protein coupled receptors
3- receptors without intrinsic kinase activity

So:
GF binds to the receptor _____phosphorylation of the receptor which in turn will be activated _____ active receptor transfers the message to the nucleus.

How does phosphorylation occur?
By 3 mechanisms:
1- The receptor itself is a kinase—like tyrosine kinase. (when the GF binds to the receptor → dimerization → phosphorylation of tyrosine → the receptor binds to and activates several intracellular proteins → second messenger mechanisms → cell proliferation and induction of transcription.
2- Within the G protein --- seven-helix receptor which is attached to a G protein inside the cell --- G protein is normally bound to GDP --- when the ligand binds to the receptor, the GDP is exchanged with GTP and thus activated.
3- No intrinsic kinase nor G protein, but the binding between the GF and the receptor activates a cytoplasmic kinase ---- when the ligand binds to the receptor --- conformational change will occur which activates an intracytoplasmic receptor JAK-1 (a kinase) and this transfers the signal by a second messenger called STAT (JAKs –STATS system).

STAT = Signal Transducer and Activator of Transcription protein.