PATHOLOGY

◉ Sheets ○ Slides

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و من لم يذق مر التعلم ساعـة ... تـجرع ذل الجهل طـول حياتـه

Repair

We talked before about inflammation and in this lecture and the next one we will talk about "repair of inflammation " so lets go ☺

You should know that when inflammation starts, repair will start .(so they are related).

Q.What do you mean by tissue repair ?

It means restoration of tissue architecture and function after an injury. So, if there is an injury, we need things to go back to normal in terms of structure and function and this is called repair .

Types of repair :

1-regeneration : (things will go back to normal)

It means replacement of damaged cells and restoration of normal function, so everything goes back to normal and this happens if the injury is mild and the tissue destruction is also 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 , fibroblast ... (all the cells that found in the area of injury).

B- stem cells

2-scar formation :

It means repair by laying down of connective (fibrous) tissue resulting in scar formation.

Which cells replicate during scar?

- **Fibroblasts which produce collagen and other components of the ECM for scar formation.**

Notice that this happens if the inflammation is severe , 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 I replace an injured area of the skin by skin it will function normally but if I replace it by fibrous tissue and scar, it will not function normally but the scar will support. Although there is no restoration by function, there will be structural support .

Note : student ask the doctor if there is a sensation in the region of the scar ?

The doctor said, " No , and that depends on the nerves , if you lose a nerve , you will lose sensation as well."

Note : in the majority of injuries both (regeneration and scar) play a role in repair that mean part of the cells will be regenerated and the rest which cannot do regenerate is filled by fibrous tissue

Now we will talk about regeneration more and more :

<u>The Control of Cell Proliferation:</u>

Q. Which cells make replication during repair ?

A-remnant cells

B-stem cells

C- endothelial cells : to return the vascularity to the area of injury because we don't want to return tissue which is not vascularized … Why ?
because this tissue will need nutrients and oxygen so I need to restore blood vessels as well .

D-fibroblast :to make fibrosis

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

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

If I lost 10 cells, I will regenerate 10 cell , otherwise cancer will occur (if the number of cells that proliferate is more than the number of cells lost , cancer will occur))

Note : when we study neoplasia with Dr.Mazin later on, we will show that cancer cells are not affected by growth factors, so they don't have inhibitory signals and that's why the number cancer cells increases uncontrollably.

So we said that in order to have repair, we need the cells to proliferate and proliferation as we know is controlled by growth factors and represented by the cell cycle (G0 , G1 , S).
- Certain cells are in G0 phase → these are non-dividing ,and some stay in G1 phase(resting) which contain growth and replication , and then cells enter the S phase and then G2 phase and then the mitosis phase .

Note : the details about the cell cycle we will study it later but you should know that non dividing cells are either in the G1 phase or they exit the cell cycle in the G0 phase .

So you divided the tissues in our body to 3 types of tissues depending on their ability to replicate :

1-labile cells : the cells which continuously divide like : skin , mucosal membrane ,hematopoietic→ these cells are continuously replicated.

2-stable cells : usually their replication is inactive (they are quiescent cells) , they don't divide in the normal state however these cells can replicate if injured (يعني راكزين ما دام ما حدا داسلهم على طرف)

So if injured, they replicate but they have a <u>limited capacity to replicate</u> except the liver , so on stable tissues can't go back to normal completely if injured.--> there will be some fibrosis except the liver which has a good capacity to replicate (if someone loses a good part of his liver, the remaining part will replicate)

3-permanent cells : they cannot replicate , they are in the G0 phase and nothing will take them from G1 phase , they will never be able to replicate.
Ex : neurons and cardiac muscle.
- and also skeletal muscle can be classified as a permanent tissue.

Note : neuronal stem cells and cardiac stem cells have a very limited capacity to replicate and certain stem late cells which are present in the skeletal muscle can replicate . (we always say that permanent tissues -never replicate- but in medicine "never" is a wrong term because there is some exceptions) .
- this capacity can be minimal and neglegtable.

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

<u>Stem cells</u>

They are also responsible for renewal.

Stem cells : undifferentiated cells in our body which have two charactaristics :

1-self renewal capacity ---- so they can renew themselves (they can replicate)

2-asymmetric replication ---- when the cell divide give 2 different type of cell (the two daughter cells are different from each other (not twins)

--One becomes a stem cell to preserve the number of stem cells and the other one becomes a mature differentiated cell.

Note : symmetric replication --- the cell divided and give 2 daughter cell which are the same (twins)

<u>Types of stem cell :</u>

1-embryonic stem cells : the most undifferentiated cells and they have an extensive cell renewal capacity, so they can differentiate to any organ (to the three germ cell layers)

2-adult stem cell (tissue stem cells) : less undifferentiated , they can differentiate only to the tissues in the vicinity , for example a stem cell in the skin can differentiate to simple squamous epithelium of skin or can differentiate to endothelium to give blood vessels in the skin.

****Stem cell research (stem cell uses in medicine) :**

There is a problem to work with the adult stem cells because it is difficult to isolate them to purity because they are already rare in our bodies.

So to take isolated stem cell (pure) from skin without the rounded cell it is really difficult to isolate them to purity (except the hematopoietic stem cells (the only successful isolated)).

Also stem cells are present in our body in" niches" (بالزبط مثل عيشة السنافر جوا الفطر :))

Stem cell niches : 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 ex. 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 actually having them out of their niches ,so they might not function properly.

To sum up :

- there are two problems with stem cells in clinical treatment :

1-that cannot be isolated to purity.

2- when you take it from the body you separate them from their environment so 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. we can regenerated.**

- this is used mainly in treatment of diabetes (experimentally).

Note : tissue stem cells means 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 you put it in the proper environment but the problem is the rejection because we don't take it from the same patient .

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

Induced pluripotent stem cells : mature cells where they put the gene inside it (this gene which makes the embryonic stem cell replicate) that means we convert a mature cell from a patient to a stem cell that has 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 being 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 : ex. 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 are growth inhibitory and some are growth stimulatory)

so how the growth stimulatory work ?

- **They promote the entry to the cell cycle.**
  when a cell is in G0 phase, it enter 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 prevent 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.**

The strong question is – how do they do this ???
By certain signaling mechanisms.
GF 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 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 lets 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 on) :
1-receptors with intrinsic kinase activity
2- G protein coupled receptors
3- receptors without intrinsic kinase activity
So :
GF bind the receptor _____phosphorylation of the receptor to 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 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 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.

وذات الفتى والله بالعلم والتقى ... إذا لم يكونا لا اعتبار لذاته

Sorry for any mistake

GOOD LUCK ☺