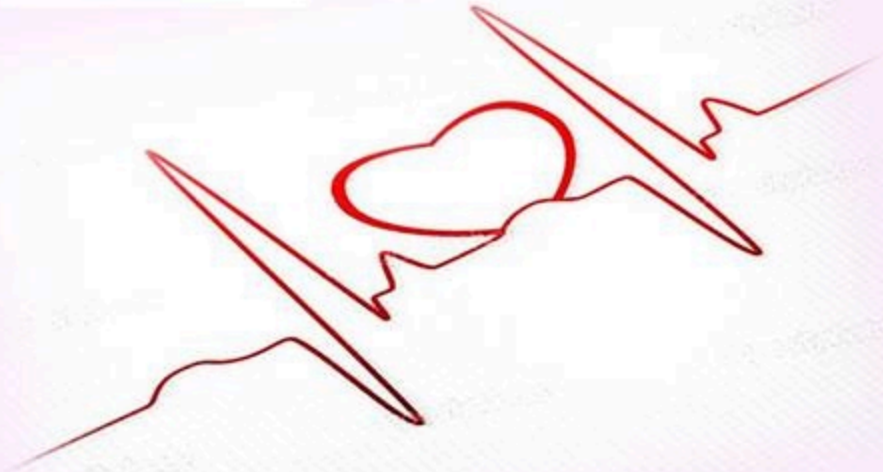
PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE



Lecture Number: 12

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Tissue Repair

This lecture is included in the midterm. The marks in the exam will be distributed equally . Anything placed in a box is **not** in the book. Good luck.

Overview of tissue repair

Tissue repair, or healing, refers to the restoration of tissue architecture and function after an injury.

Tissue repair is divided into two pathways; **regeneration** and **scar formation** ,and both of them contribute in varying degrees to the ultimate repair. Note that scar formation is **not** the same as fibrosis (this will be explained later).

Regeneration is when the tissue replaces the injured cell with the same type of cell, hence, this returns it to the normal state. This means that there should be a proliferative ability for the stem cells or the adult cells that can still replicate to replace the cells that have been injured . This typically occurs in the epithelia of the skin, GI tract, RBC, and one specific dormant (quiescent) tissue which does not usually replicate but has a big regenerative capacity; the liver. (Those are examples for population of cells that are constantly replicating and stay in a steady state) .

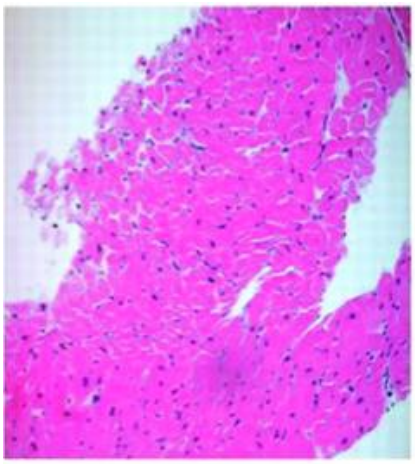
Generally, if you have a mild superficial injury , (more importantly)in a tissue that is labile or stable ,that has a generation capacity ,tissue repair will happen.

However, if the injury is severe, or the tissue can not regenerate ((it's cells are incapable of proliferation ,those tissues are called permanent because they don't have replicating cells or the number of stem cells are not enough to become active and replace the damage ; eg. Heart, neurons. They have found some stem cells in neurons and heart cells but they are not active)), repair will occur by the deposition of connective tissue, which is called scar formation. In scar formation, there will be a potential loss of function. However, enough architecture has returned so that the function will be maintained, although it will be at a limited or reduced capacity.

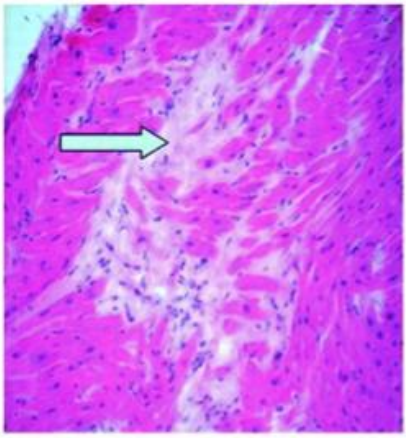
Left ventricular assistance device (LVAD) is given to a heart failure patient to compensate for the inability to provide enough blood to heart. Surprisingly, because these patients are using this device to help the heart to work, they found that some of these patients regained muscle mass, hence retaining some of the heart function. These patients were able to stop using the LVAD. In some stable tissues, there is some minor regeneration capacity, this is where the stem cell therapeutics issue comes from; if we can stimulate or purify these stem cells to replace damaged cells in a tissue that cannot regenerate, it will help in a lot of diseases.

Note that in most injuries there's a combination of both regeneration and scar formation.

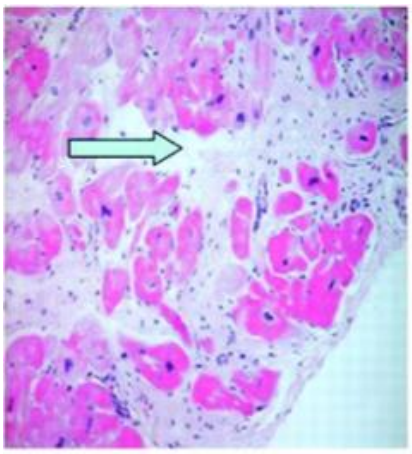
Returning to fibrosis. Fibrosis is when there is extensive deposition of collagen, typically occurring in the kidneys, heart, lungs, and other organs.



This is what a cardiac biopsy should normally look like. There isn't much fiber tissue in there.



Now we're starting to see some fibrous tissue from minor myocardial infarction that has healed. Instead of the cardiac cells being able to regenerate and replace, they cannot, so we get deposition of collagen and scar formation.



If its extensive, we start losing a lot more cardiac function, till the heart completely loses its function.

If, however, there is fibrosis in tissue space (e.g. Peritoneum and pericardium) occupied by an inflammatory exudate, it is called **organization**. Hence, if there is inflammatory exudate in pleural space, part of getting rid of this exudate includes the deposition of collagen, which results in an organized pneumonia. This reduces our ability to take a normal breath.

Cell and Tissue Regeneration

There are two major requirements for healing to occur: cell proliferation, and interaction of those cells with the extracellular matrix. Whether they are endothelial cells, mesenchymal, epithelium cells or any other type of cells, they all have to communicate not only with each other, but with the ECM as well. This will be addressed in the following lecture.

For this lecture, cell proliferation will be addressed.

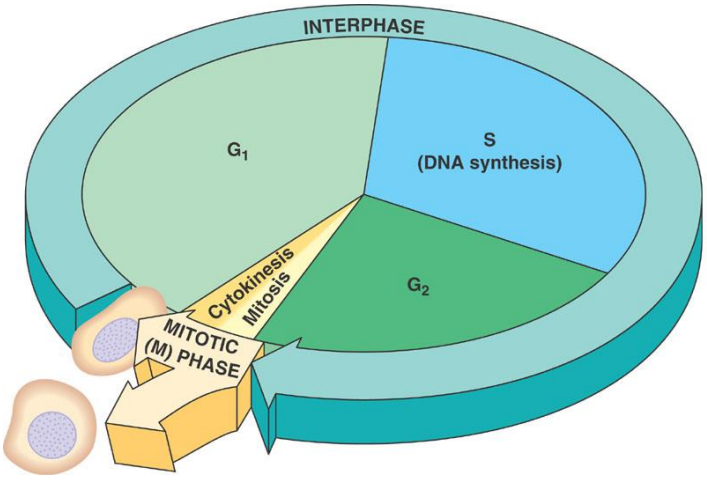
Cell proliferation:

Several cell types proliferate during tissue repair including the inflammatory cells (the remnants of the injured tissue), fibroblasts (which are the source of the fibrous tissue that forms the scar), and if the blood vessels are damaged, then endothelial cells will also proliferate. In the case of the healing of the skin (which is the most commonly used example), then the epithelia will regenerate and the skin will start to heal.

I honestly do not understand what he was trying to say in this part.
Q)What is the difference between (mesoderm, endoderm, and ectoderm) compared to mesenchyme?
In embryonic sense, mesenchyme can give rise to mesoderm , endoderm and ectoderm.
Mesoderm is a specific set of tissue.
* Neoplasia difference between mesenchymal tumors and epithelium tumors.
* Epithelium can be ectoderm or endoderm. Mesenchyme can give rise to all three layers.

Returning to the repair of tissues, is it possible to repair a tissue without repairing the blood vessels? More importantly, are there any tissues that are avascular? The answer would be yes. Cartilage, cornea, and the lens are avascular. Cartilage, for instance, is harder to heal after injury as it is supplied by diffusion. On the other hand, neovascularization of the cornea due to contact lens or diseases gives rise to many problems.
*Note : Cartilage, cornea, and the lens are avascular and they are supplied by diffusion ,because they require less nutrition and oxygen than other tissues and organs that are vascularised .

The normal size of cell populations is determined by a balance among cell proliferation, cell death by apoptosis, and the emergence of new differentiated cells from stem cells. Cell proliferation and the inhibition of apoptosis is a response to growth factors. The key of cell proliferation is DNA replication and mitosis. The sequence of events is controlled by the cell cycle. Remember, the cell cycle consists of G1, S, G2, and M phases. We also want to remember that the DNA will replicate, and it is very important to ensure that there will be no damage to the DNA. There is a critical G1 to S checkpoint, partially controlled by P53, which will repair the damage by inhibitory control. This is regulated by cyclin dependent kinases. This allows the cell to move from one phase to the next



in an orderly fashion without causing any harm to the DNA, and with abundant nutrition to proliferate, resulting in two daughter cells.
*To replenish a limited ability to replicate ,stem cells must be used because they have much better ability to replicate compared to adult cells .

Note that all of this depends on proliferative capacity of a tissue, and the ability of the cell to respond to growth factors. This moves us on to the next part, which is the division of the tissues of the body into three groups based on their proliferative capacities.

Proliferative capacities of tissues:

1) Labile (continuously dividing) tissues
2) Stable tissues
3) Permanent tissues

Labile tissues are called labile because they have higher percentage of labile replicating cells(labile cells are cells that multiply constantly throughout life) i.e. continuous division of mature and stem cells. These tissues can readily regenerate if the stem cells are intact, or as long as the pool of stem cells is preserved. These tissues include the hematopoietic cells in the bone marrow and surface epithelia, such as the stratified squamous of cervix or esophagus , the cuboidal epithelium of bladder, and the columnar epithelium of GI tract. Under physiological conditions, these tissues divide constantly.

Stable tissues are quiescent and are mostly at arrest; there is no wear and tear for them to continuously replicate themselves. They have **minimal** replicative activity in their normal state, but are able to replicate in response to injury(when they are needed). These cells include the endothelial cells, fibroblasts, and smooth muscle cells. They have a limited regenerative capacity, except for the liver. Although the liver is stable organ, it has a massive regeneration capacity.

Permanent tissues have cells that are terminally differentiated and non-proliferative, such as neurons, cardiac, and skeletal muscle cells. Thus, injury to the

brain and heart is irreversible and results in a scar, because neurons and myocytes cannot regenerate. There is evidence that cardiac stem cells may proliferate after myocardial necrosis. Additionally, satellite cells attached to endomysial sheath(fine sheath of connective tissue layer that surrounds (covers) each single muscle fiber) in skeletal muscles provide some regenerative capacity. Nevertheless, it is insufficient to be classified as a stable tissue. Hence, repair of the damage is dominated by scarring.

*Some stem cells have been found in the neurons, cardiac cells and in the cornea, but under physiological conditions they are not able to repair the damage.

*liver is not continuously dividing ,but if it is injured the stem cells in liver have enough regeneration capacity to replace the injured cells with original cells not with deposition of connective tissue ,and that is the difference between the liver and other parenchymal organs(kidney and pancreas) which don't have the liver regeneration capacity .

Stem cells:

It is a cell that can replicate itself, **and** differentiate into many types of cells.

Stem cells can asymmetrically divide; That is, not only it can produce 2 daughter cells(symmetrically), but it can also divide where the stem cell produces two cells: one daughter cell will enter the differentiation pathway and give rise to a mature cell, while the other will remain as an undifferentiated stem cell that retains its self-renewal capacity.

There are 2 types of stem cells: **Embryonic** stem cells, and **Adult (tissue)** stem cells.

The main difference is that embryonic stem cells can replicate indefinitely, and they can differentiate into any type of cell in the body from head to toe (any germ cell layer).

i.e. embryonic stem cell creates you, a human.

Adult tissue stem cells have less ability to self renew. They have shorter telomeres and less telomerase activity than embryonic stem cells . Adult stem cells are further along the differentiation pathway, they don't have the pluripotency of embryonic stem cells. They're usually limited to the organ they are in. Hence, if the adult stem

cell is in the GI tract, it can only differentiate into a globlet cell, columnar cell, or any cell in the GI tract only, but it cannot differentiate into a neuron for example. Adult stem cells are important for homeostasis; for maintaining a steady state in tissues that aren't supposed to wear and tear.
*Pluripotency refers to a stem cell that has the potential to differentiate into any of the three germ layers: endoderm , mesoderm or ectoderm.

In bone marrow there are 2 stem cell populations; mesenchymal stem cells (differentiate in chondrocytes, osteoblasts, myoblasts,etc) and there are hematopoietic stem cells which can give rise to any of the blood cell lineages(سلالات) (red, white, neutrophils, T-cells, etc).

Embryonic stem cells have extensive renewal capacity and can give rise to all cells, so they are ideal for developing specialized cells for therapeutic purposes ;for diseases that require stem cells intervention . However, they are derived from blastocysts ((typically produced from in vitro fertilization ;they bring ovum from a women and sperm from a man then fertilization occur to create an embryo - cell mass- and half of this cell mass is for the male and the second half for the women)), they may cause immunologically mediated rejection by the host, just like organ transplant. Additionally, taking cells from the blastocyst means killing it, which leads to a controversial, ethical issue about killing a human life. Hence, scientists moved to creating embryonic stem cells rather than killing an embryo.

This method was used to make dolly the sheep. They bring an ovum, take out the nucleus, and take stem cells from patient (e.g from the mucosa), and they extract the nucleus and implant it into the ovum, and stimulate the ovum to replicate. Once it reaches the blastocyst stage, they can do the same as they did using the embryonic stem cell. This overcomes the scientific pitfall, but not the ethical, as we are still destroying the blastocyst.

Also called regenerative medicine, it is used to treat Parkinson's disease, nerve injury following a car accident, type I diabetes, etc. This will end a life of suffering or a life of medications.

Adult stem cells are very difficult to purify, except for those in the bone marrow. It is easy to isolate and purify hematopoietic stem cells. The stem cells are extracted

from the bone marrow, and the patient is given a stimulating factor. The cells are taken to a lab to be allowed to proliferate. In the meantime, the patient is given radiotherapy or chemotherapy. Then, you reintroduce the patient's own unmutated cells back into the bone marrow .This is called **bone marrow transplant** from the same patient. It is successful.

As or the **induced pluripotent stem cell,** they are cells that are taken from the skin, fibroblast, or any cells that can normally grow in a dish, and genes that confer stem cell properties are introduced (genes that are expressed only in stem cells, and inhibited in others). Hence, the adult cells are changed into pluripotent stem cells. However, we are artificially introducing genes and manipulating the genetic material of the cell. Hence, it has yet to have any proven efficacy in humans, mainly due to safety as those cells may be changed into cancerous cells. This method is still under research. It's cheaper and quicker (done in 48 hours) than producing blastocyst.

- Note that the images in the slides are very beneficial.

Growth factors

Most growth factors are proteins produced by Lymphocytes, Macrophages, Parenchymal cells and Stromal cells that stimulate the survival and proliferation of particular cells, and may also promote the migration, differentiation and other cellular responses. They induce cell proliferation by binding to a specific receptor, and result in affecting the expression of genes.

Table 2.9, find what is unique. The professor said he does not expect us to memorize it, but to only identify what is unique across multiple types of growth factors. "Fish out the patterns".

There are multiple ways of cataloguing growth factors.

In terms of cell of origin and termination, there are 3 types: **autocrine**, **paracrine**, and **endocrine**. Autocrine is when the growth factor is released from a cell and affects the same cell. Paracrine is when the growth factor released from a cell affects

the neighboring cell. Endocrine is when the growth factor released from a cell travels through the bloodstream to affect another cell.

In terms of the location of the receptor, there are two distinctions: **cell surface** receptor, and **intracellular** receptor. In cell surface receptors, the growth factor must be water-soluble (e.g. insulin, LDL). As for the internal receptor, the growth factor must be lipid-soluble (e.g. steroids, thyroxins, vitamin D).

Finally, on the basis of their major signaling transduction pathways, receptors fall into three main types: **G-protein coupled** receptors, receptors with **intrinsic kinase activity**, and receptors **without intrinsic enzymatic activity.**

EGF, HGF, FGF, and VEGF (**E**pidermal ,Hepatocyte ,Fibroblast and Vascular Endothelial growth factor ,respectively) work through receptor kinases which are on the outside of the cell, and PI3 kinases. They have extracellular, transmembrane, and intracellular domains. They are proteins that have the ability to add a phosphate group to another protein(kinases). We are not expected to memorize the pathways.

In G-protein coupled receptors, they have a G-protein on the inside which is associated with GDP. When the receptor gets a signal, G-proteins replace GDP with GTP. Hence, G-proteins are active, and can transduce the signal.

Finally, in receptors without intrinsic enzymatic activity, ligand interaction induces an intracellular conformational change that allows association with intracellular protein kinases called Janus kinases (JAKS). Phosphorylation of JAKs activates cytoplasmic transcription factors called STATs.

Don't forget to study from the slides. There are images that are not in the book!

Best of luck

Written by Leen Dabbas