Regeneration Biology
Rajesh Ramachandran
Department of Biological Sciences
IISER Mohali
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W1L2_Regeneration, Wound Healing and Scar Formation in Different Regenerative Capacity

Hello, good evening everyone. Welcome to another session of regeneration biology. We will continue with the topic we covered in the first class, and we will also try to understand how regeneration is different from wound healing. Sometimes during wound healing, you end up with a scar that forms in the tissue. So, today's topic is regeneration, wound healing, and scar formation in different regenerative capacities. I had shown this slide in the previous class, but.

.. I feel that there could have been some crop. Therefore, I am showing it again for your easy understanding.

So, tissue repair is basically the way in which your body responds to an injury and how cellular proliferation contributes to regeneration. So, this slide we discussed. So I will not go into detail. So regeneration often results in the complete restitution of the lost or damaged tissues. So this is the beauty of regeneration.

However, the repair, what we call the milder version of regeneration, is capable of restoring some original structures but can cause structural derangements. Say, for example, if a person's bone is fractured, if the orthopedist does not set the bone, stretch it, and put it in the right position, you will end up with a bent bone; instead of healing straight, it will heal in that direction. Therefore, the structural derangement has to be properly addressed, as healthy tissue healing occurs in the form of regeneration or repair after any insult. Causes tissue destruction and is essential for the survival of the organism. As I told you, if you do not have regenerative ability, it is very difficult to retain the functionality of a tissue or even an organ.

So regeneration refers to the proliferation of cells and tissues to replace lost structures, such as the growth of an amputated limb in amphibians. We all know that if a limb is amputated, it grows back; if a tail is broken, a new tail comes back. However, in mammals, this is different. Restricted quite, restricted the whole organs and complex tissues rarely regenerate after an injury, and the term is usually applied to a process such as liver growth after partial resection or necrosis, but these processes consist of compensatory growth rather than regeneration, like we saw in the previous class: a different category of regeneration, the compensatory growth. It basically means the function is restored, but the structure is not properly restored.

So in this picture, you can see the ways in which an injured tissue responds soon after injury. There is a cellular and vascular response, and soon after the stimulus is removed in the case of an acute injury—acute means a sudden injury—the parenchymal cell death occurs. That is, the intact cell matrix or the matrix of a given tissue is what we refer to as parenchyma. It happens in many cases of superficial wounds. Some inflammatory responses are triggered by an acute injury.

So, in a properly regenerating organism, regeneration is basically the restoration of the normal structure. Some examples include liver regeneration after partial hepatectomy. If you remove completely the liver, new liver cannot form from there. Superficial skin wounds, such as a tiny knife wound or something on your skin surface, heal, and the resorption of exudate in lobular pneumonia; in many cases, pneumonia causes damage to the respiratory epithelium of the lungs, which regenerates. When there is parenchymal cell death, it's associated with the tissue framework, which means, basically, the deep wounds, as you can see here.

Responded by a process called healing, there is no proper regeneration; rather, it heals, and there is definitely a scar that is formed, which we call scar formation. Here, the organization of exudate exists, meaning the organ is now very prominent due to the damage, and it does not look like it has regenerated properly. Some examples include deep accessional wounds and myocardial infarction. When the blood supply is stopped to the heart muscles, we call it myocardial infarction. Those kinds of wounds often lead to A healing response is associated with scar formation; scar formation means it is junk tissue that fills in that area, but functionality is not restored, although the structure is somewhat retained.

Then comes persistent tissue damage. When there is persistent tissue damage, it is like people who are eating, you know, paan, gutka, those kinds of things. When you put something in your mouth, you are constantly damaging your mouth epithelium. So this is not a wound but rather constant erosion of the tissue, and this also leads to constant inflammation. In such situations, the body responds with a process called fibrosis, where the tissue scar is very prominent.

Examples include chronic inflammatory diseases like liver cirrhosis. Chronic pancreatitis, pulmonary fibrosis, etc. If you are living in a highly polluted environment, your lung epithelium is constantly under pressure, so it can lead to a fibrotic response, which we often refer to as fibrosis. If you look into different types of cells, we all know that we are derived from a zygote, and the zygote is basically a The initial starting point of a living organism gives rise to a blastula or blastocyst, and the blastocyst contains many cells that we call pluripotent stem cells. This means they can give rise to any cell type of interest, and they differentiate slightly to become multipotent stem cells, which means they have moved away from pluripotency but still have the ability to give rise to a variety of cells.

Then come these multipotent cells, which give rise to lineage-committed cells. They have moved away from the multipotent status. Now they have committed to give rise to a group of cells. Classic examples include your bone marrow stem cells, which can give rise only to the RBCs and WBCs, red blood cells and white blood cells. It does not give rise to skin cells or muscle cells or something.

It can give rise to only those cells. Below your skin, you have skin stem cells. That can give rise to only the skin cells; it cannot give rise to any other cells in your body, and they are called lineage-committed cells. These lineage-committed cells give rise to differentiated cells, such as skin, bone, or any other adult cells. Endoderm-derived, mesoderm-derived, and ectoderm-derived are the main three groups; these are all the primary germ layers we are talking about: ectoderm, endoderm, and mesoderm.

So they give rise to these cell types. And you can culture these pluripotent stem cells, and they can give rise to any type, like pancreatic cells, hematopoietic cells, cardiomyocytes, neurons, and hepatocytes. All cells can be derived from these embryonic stem cells, and not only that, adult tissues have got. A resident population of stem cells underneath, like a classic example, is your skin. You know your skin has hair shafts that come out; you also have sweat glands and sebaceous glands.

All these things are located on your skin, which has an epidermis and a dermis. You can see here that there are different dedicated cells, and there is also a distribution of epidermal stem cells. What do they do? They can give rise to the epidermis whenever there is skin damage, which happens constantly. You are losing your skin every day, but it is being replaced by these stem cells. And if you look into your intestine the same way, your endoderm intestinal lining has also got severe wear and tear due to the movement of digested materials from your buccal cavity, and there are also different types of cells: goblet cells for secreting mucus and absorptive enterocytes.

Enteroendocrine cells release hormones, and they also have crypt cells, which are often referred to as stem cells, and there are also paneth cells. So these stem cells constantly enter the cell cycle to replace the damaged tissue. In the same way, you have liver cells that can constantly regenerate as your liver undergoes damage. And these liver stem cells can give rise to a new liver cell type. That is why even after liver damage, the liver bounces back.

And this is part of your eye. You know, in your eye, the white portion is called the conjunctiva. The black portion, when you look into an eye, is normally layered by the cornea. So if there is any damage to your cornea, you can go blind. In between this white portion and the dark portion, there is a boundary called the limbus, and the limbus is the one that can give rise to the cornea.

So if you can collect these corneal stem cells or these limbal stem cells, you can culture corneas in the petri dish, and people are doing that for surgical transplantation as well. So

regeneration is something that some tissues are able to use to replace the damaged components and essentially return to a normal state. This process is called regeneration. So regeneration occurs by the proliferation of cells that survived the injury, but this is in the neighborhood of the cells, and they retain the capacity to proliferate in the rapidly dividing epithelia of the skin and intestine, as well as in some parenchymal cell glands. Mainly the liver and other organ tissue stem cells, as shown in the previous picture, may contribute to the restoration of damaged tissues; however, in mammals, they have a very limited capacity to regenerate damaged tissues and organs.

The liver is an exception, but the majority of them have a limited capacity to regenerate tissues with a high proliferative capacity, such as the hematopoietic system and the epithelia of the skin and gastrointestinal tract, which renew themselves continuously because that is the way. They leave because there is constantly damage, and they have to replace it; they can regenerate after injury as long as the stem cells of these tissues are not destroyed. So the connective tissue deposition, or scar formation, occurs when there is an injury; after it is healed, you can see a mark that allows you to identify, even after several years, that there was an injury. This is called scar formation if the injured tissues are capable of complete restitution or if the supporting structures of the tissues are severely damaged. Repair occurs by the laying down of connective or fibrous tissue by a process called scar formation.

Although the fibrous scar is not normal, it is sufficient to provide structural stability so that the injured organ is able to function. If your table is wobbling, what you'll do is take a cardboard piece or a plywood piece and put it below one of the moving legs so that the table is now stable. The same process is scar formation. The term fibrosis is most often used to describe the extensive deposition of collagen that occurs in the lungs. Once the scar formation becomes too haywire or too dominant, we call it fibrosis; this can occur in the lungs, liver, kidneys, and other organs as a consequence of chronic inflammation.

Inflammation means the reddening; like if a mosquito bite is on your skin or you have a pimple on your hand, you will see some reddening around that injury spot, and that is called inflammation. However, chronic inflammation can happen in your body because of various allergens, pollutants, and toxins, etc. Can happen in the myocardium after extensive ischemic necrosis, which is called infarction if the blood supply to the heart muscles is compromised. Then there is partial damage; once the damage becomes severe, the contraction of the heart can be affected, and we use the term heart attack or myocardial infarction. In all these conditions, there is involvement of fibrosis.

If fibrosis develops in a tissue space occupied by an inflammatory exudate, this is called organization. Organization means. There is not any particular organ that is being formed. It basically created a stable structure in that organ, which is derived from the fibrotic tissue or the scar-forming tissue. Especially organizing pneumonia that affects the lungs.

During a fixation, several cell types proliferate to aid in tissue repair. These include the remnants of injured tissue that attempt to restore the normal structure, and a good example includes vascular endothelial cells. Endothelium means, you know, the lining of your blood vessels. You know blood capillaries, arteries, veins, etc., are there in the lining of that vascular tissue we often refer to as endothelial cells, and keep in mind that for the blood vessels to form, you need to have this endothelium multiplication and tubular structure formation, etc.

This helps in creating new blood vessels that provide nutrients. That is needed for the repair process; you know for an injury response you need nutrition, oxygen, glucose, etc. Who will supply that? That has to come through your blood system, and the blood will flow only if there are blood capillaries. The second category includes the fibroblasts; the endothelial cells have to come for blood vasculature formation, and the fibroblasts are needed to fill the gap. They are the source of fibrous tissue that forms the scar to fill the defects that cannot be corrected by regeneration.

So when this scar is formed, if the organ is not able to regenerate... Then the scar forms because the body is filling the gap or the damaged area of the organ with so-called junk tissue that is called fibroblast. When we call it junk tissue, it doesn't mean that it is useless; however, it does not have a defined organ-specific function.

So, fibroblast deposited in the liver will not perform liver functions; if it is deposited in the kidney, it will not perform kidney functions; if deposited in the lung, it will not perform lung functions. However, it will fill the gap. So it is like if the tiles in your house are broken, you can replace them with exactly the same tile if you have stock. But if you don't have something of a similar color, you can replace it. If you don't have tile, then what will you do? You will fill it with cement, and this is car formation, so you can easily identify, "Oh, tile was here and it is broken now; they filled it with cement.

" It will look ugly, but at least the wall will look okay. The wall will not get damaged, and the floor is not looking really affected. Cell proliferation can be stimulated by physiological and pathological conditions. Pathology refers to any kind of infection. For example, the proliferation of endometrial cells under estrogen stimulation during the menstrual cycle and thyroid-stimulating hormone-mediated replication of thyroid cells enlarges the gland during pregnancy because this occurs due to the need for more thyroid hormone.

Physiological stimuli, for example, may become excessive, creating pathologic conditions such as BPH resulting from dihydrotestosterone stimulation and the development of nodular goiters in the thyroid as a consequence of increased serum levels of TSH; thus, these are all conditions in which you can end up with sudden nodules and fibrosis. Though cell proliferation is largely controlled by signals from the microenvironment that either stimulate or inhibit proliferation. Just like a car. Your car needs to have an accelerator and a brake. What if your car has only one of them? That car is useless.

So you should have stimulation and inhibition as well. An excess of stimulators or a deficiency of inhibitors leads to net growth, overgrowth. You don't know when to stop. In the case of cancer, uncontrolled cell growth occurs. Say you have a wound and that wound has to heal by cell proliferation.

What if proliferation doesn't stop? So, it will lead to cancer. So normally it doesn't happen because the inhibitory signals are working well. The tissues of the body are divided into three groups on the basis of the proliferative activity of their cells: they are three categories: continuously dividing ones, which we call labile tissues; quiescent ones, or stable tissues; and the non-dividing ones, or permanent tissues. They are broadly categorized into these three. So you can see, many of you have seen this in your intermediate or school class textbook; this is called the cell cycle.

Cell cycle: what does it mean? A given cell can be in one of the phases of the cell cycle. The act of a given cell dividing into two is called cell division. So that normally happens during mitosis. So a new cell is born soon after mitosis, binary fission, or cell division, and this newly formed cell has multiple options. One option is to stay in its G1 phase, the first phase of the cell cycle, G1 phase, which is the growth phase 1.

Many cells, which are permanent cells, will arrest in this G1 phase, and we often refer to them as permanent cells. That means they never get into the G1 phase at all. Soon after multiplication, they become permanent cells. Examples include neurons and cardiac myocytes. That means they never explore the possibilities of becoming 2, 4, or 8.

So those that have the potential to enter the cell cycle will get into the G1 phase, and they are called quiescent stable cells. That means they have exited the cell cycle. We often refer to them as G0. That means they are basically G1 only, but they have no plans for change. Getting into the cell cycle, however, if the stimulation is proper, they tend to enter into the cell cycle; that is what this dotted arrow shows.

They will enter into the cell cycle, and it will get into G1. Of course, it has to pass through the restriction point, and DNA replication and every checkpoint have to be passed. Then there is a synthetic phase. The S phase and the continually dividing or cycling labile cells are in this cycling phase, which includes G1, S, and G2 phases; they will constantly keep on dividing, like your epidermal cells and the gastrointestinal tract epithelium; they will not arrest in G0 or this permanent phase; they will be in their cycling phase. And these cells, once they have passed the S phase, will enter the G2 phase and then, once they have passed this checkpoint, the G2M checkpoint, they will enter mitosis.

So this will continue for the continuously dividing cells, and some partially exited ones will be quiescent cells, such as hepatocytes, while the permanent cells include neurons and cardiomyocytes. The labile cells continuously dividing in these tissues are constantly being

lost and replaced as they divide; this is due to the proliferation of stem cells and mature cells. The labile cells include hematopoietic cells of the bone marrow, which means there is a constant supply of blood needed, including red blood cells and white blood cells, as the bone marrow keeps producing blood cells in the majority of the surface epithelia. Have these features, such as the stratified squamous epithelia of the skin, oral cavity, vagina, and cervix, and the cuboidal epithelia of ducts draining the exocrine organs like the salivary glands, pancreas, and biliary tract, etc. The columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes provides many examples where labile tissues exist.

These tissues can readily regenerate after injury as long as the pool of stem cells is preserved. In old age, what happens is that the stem cells can deplete for various reasons, leading to a decrease in your stem cell population; hence, the labile cell population will also decrease. In continuously dividing tissues, cells proliferate throughout life, replacing those that are destroyed. These tissues include surface epithelia, the columnar epithelium of the GI tract and uterus, the transitional epithelium of the urinary tract, the cells of the bone marrow, and hematopoietic tissues. In most of these tissues, mature cells are derived from adult stem cells.

The intestine, skin, etc. have adult stem cells that have a tremendous capacity to proliferate, and whose progeny may differentiate into several kinds of cells; based on the tissue you are talking about, those stem cells can give rise to a minimal set of cell types. When you come to the stable tissues, the cells of these tissues are quiescent, which is the G0 arrested stage of the cell cycle, and have only minimal proliferative capacity in their normal situation. These cells are capable of dividing in response to injury or loss of tissue mass. So, table cells constitute the parenchyma of most solid tissues, such as the liver, kidney, and pancreas. Also, the mesenchymal cells, such as fibroblasts, smooth muscle cells, vascular endothelial cells, lymphocytes, and leukocytes, all come under these stable tissues.

They also include endothelial cells, fibroblasts, and smooth muscle cells. The proliferation of these cells is particularly important for wound healing purposes. With the exception of the liver, stable tissues have limited capacity to regenerate after an injury. Whereas the liver can replace damaged tissue and restore function. When you look into permanent tissues, these cells are present in the tissues that are considered terminally differentiated and non-proliferative.

That means they cannot even think of proliferating postnatal lives. They can divide during prenatal life, not during postnatal life. The majority of the neurons and cardiac muscle come under this category. Thus, the injury to the brain or heart is irreversible and results in a scar because neurons and cardiomyocytes cannot regenerate; limited stem cell replication and differentiation occur in some areas of the adult brain. If neurons of the central nervous system are destroyed, the tissue is generally replaced by the proliferation of supportive cells called glial cells. There is some evidence that the heart muscle cells may proliferate after myocardial necrosis, and this is followed by scar formation, but it is not powerful

enough to restore the damaged area; nonetheless, whatever proliferative capacity may exist in these tissues, it is insufficient to produce a proper regenerative response.

Skeletal muscles, a classic example of your body's muscles, are usually classified as permanent tissue, but the satellite cells attached to the endomysial sheath provide some regenerative capacity for the muscle. In permanent tissues, repair is typically dominated by scar formation. Repair most often consists of a combination of regeneration and scar formation. It's not just one or the other when it comes to the deposition of collagen. What is collagen? Collagen is an extracellular matrix protein, and the relative contribution of regeneration and scarring in tissue repair depends on the ability of the tissue to regenerate and the extent of injury; therefore, the scar formed or the regenerative response depends on the extent of damage.

For example, a superficial skin wound heals through the regeneration of the surface epithelium because there are stem cells available; however, Scar formation is the predominant healing process that occurs when the extracellular matrix framework is damaged by a severe or deep injury. The damaged ECM can attract immune cells that contribute to the repair. This is very important for us to understand. But we also talked about chronic inflammation. Chronic inflammation is something that happens in your body due to various reasons.

Especially in old age, your body is more vulnerable to inflammation. Of course, credit goes to your WBCs, macrophages, and various neutrophils that are contributing to this. Pro-inflammatory responses that accompany persistent injury and chronic inflammation can occur due to persistent injury and also in the case of diabetic ulcers, which also stimulate scar formation because of local production of growth factors and cytokines. Growth factors are what help cells replicate, or the proliferation of cells happens because of growth factors, and cytokines are what can be pro-inflammatory or anti-inflammatory. That promote fibroblast proliferation and collagen synthesis, because without growth factors and cytokines, you cannot have either of them. The ECM components are essential for wound healing because they provide the framework for cell migration.

Without extracellular matrix, the newly formed cells cannot move from one place to another. They are almost like railway tracks. Without railway tracks, trains cannot go anywhere. So how important is railway track for trains? That extracellular matrix, or ECM, network is important for the cell to migrate. They maintain the correct cell polarity for the reassembly of multilayer structures, and they also participate in the formation of new blood vessels called angiogenesis.

So what we have seen so far is how and when a regenerative response occurs in a given tissue based on the availability of stem cells or the extent of damage, to which the cells respond, facilitated by growth factors and cytokines, leading to the production of Proper extracellular matrix formation is necessary; if there is too much deposition of collagen, then

a severe scar will form, and there may not be enough cells. However, if the injury is in a manageable state, it will give rise to a properly healed wound. And healed wound here, what we mean is something that has the proper maturation of the tissue, and it will often lead to the polarity of the structures, and it participates in the formation of new blood vessels, and that is referred to as angiogenesis. So I will end this class now and see you in the next class. Thank you.