Regeneration Biology
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W1L1_What is Signaling?

Hello everyone, it is a new course on regeneration biology and I am sure many of you would have heard about regeneration in your lifetime. You would have seen how a lizard's tail is growing back, how a broken nail in your childhood is growing back. If any damage happens to your fingertip, then the nail will get affected and a new nail grows. And same way if you pluck one hair and if you are careful enough to note the spot, then you see a new hair is growing from that spot from the same root. So, this is nothing but a regeneration. Regeneration of a tissue that is important in your life.

However, when it comes to complex tissue such as brain, spinal cord, heart, kidney, the regeneration is not that efficient in a variety of animals, including us humans. we know after a road accident some people lose their mobility in the lower half of their body it's because of damage to their spinal cord and in rest of their lifetime it do not grow back but all animals are not like that some animals after a damage to their spinal cord or brain like what happens during stroke if there is a stroke in your brain there is a blood supply cut to a given area then based on which area affected some people stop speaking some people can't move their one hand one leg or both hand both leg some people simply pass off so this is because your brain need constant supply of oxygen and nutrients and if it is damaged there is no way you can recover back of course after stroke some people show some recovery because the neurons of the neighborhood take up the function of this damaged area but it's not always possible so what we know from this some tissues in our body has the ability to regenerate whereas others not. But when you think about some animals such as fishes and frogs, they are remarkable in their regenerative capacity. Any tissue in their body, if it is damaged, they regenerate back.

Isn't it a wonderful thing? So the regeneration biology is a fantastic area of research on learning where we try to understand how a tissue regenerates and why it do not happen effectively in some animals such as humans. Of course, our liver has a remarkable capacity to regenerate. We will see them one by one. So, this whole course is mainly to understand how and why Some tissues or some organisms have the ability to regenerate effectively whereas others don't. What is lacking in them? Because we know all animals have somewhat common developmental biology or somewhat common their homeostasis or the maintaining of normalcy of a tissue but when it comes to regeneration some are

better than the other that is why this regeneration biology is quite interesting so this is the first slide that we will be discussing with the basics of regeneration that is different types of regeneration how can we classify regeneration because the regeneration Although we say in a common term bracketed word, it is different from typical wound healing.

It is different from a typical injury response, etc. So we will see how different regeneration or wound healing differs from one another. So injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process. So if there is a damage, the first process has to be to contain it. If there is a cut, there is a blood flow.

So what is the containment procedure? Stop the blood flow. And we know our blood clots, even whether you put a bandage or not. smaller injuries the blood will clot automatically but if there is an injury to your artery you have to apply pressure and put a bandage otherwise the heart will keep pumping blood through the artery and it will continue still it can stop after some time because after some blood is lost the blood pressure will decrease and the flow will decrease and this will eventually lead to a clot so that is the containment procedure this process can be broadly separated into regeneration and repair so once the containment is done based on the species based on the tissue the organism will decide should i go for a regeneration should i go for a repair process slight difference is there between repair and regeneration we will see them one by one so this is a chart where you have different types of regeneration is classified as you can see here the topmost panel topmost writing is the physiological regeneration what does it mean the natural replacement of extruded or worn out cells in our body we know our skin automatically shuts your hair automatically falls and your intestinal epithelium that is your gut lining automatically gets damaged and it gets replaced And every day, whether you go to sunshine or whether you rub your skin, doesn't matter. Your skin is vulnerable for damage. It will reach its lifespan and it will shed off.

Nobody needs to pluck it off and a new skin comes back. So this is called physiological regeneration. And this can happen in different parts of the body. Antler regeneration, you would have seen it like the.

.. many antelopes they will have, during their breeding season the males will have antlers that will grow back and after the breeding season is over it will fall off. Same way you may have seen the feather of the peacock during breeding season now before the breeding season the feather will start growing and during the breeding season the males with the longest tail or beautiful feather will get a chance to mate and once the breeding season is done it's a baggage so it automatically falls off. And the blood replacement your RBC have got a lifespan of 120 days, so after 120 days whether you have an infection you

don't have an infection this cell the RBC red blood cells will die off so new blood has to be replaced and then you have got oocyte regeneration in the case of a lot of animals such as fish and amphibians, and the epithelium, like i already mentioned it can be endothelium which is the lining of your gut or the surface of your skin. And the epithelium can be divided into different categories, epidermis, lining of the gut, shedding of the skin or in the case of snakes and many animals, you know, we call it as molting. So when a snake become bigger, its skin will be removed automatically and many you call it as molting in many insects.

Butterfly you would have seen when it is growing, its skin will be shed off. And many such examples are there. Then comes the second category. These are all physiological regeneration. The second category are reparative regeneration.

That means repairing a damage. Regeneration was not necessary routinely, but now it is necessary because there is a damage. Like nail, you can see a classic example. Usually when a nail is there in your hand, as you grow bigger and bigger, or taller and taller, or.

.. As you develop, your nail also become bigger and bigger. It's not that a small nail falls off and a new nail comes. But your teeth, you know, childhood, you have a tiny teeth. We call it as a milk teeth. And that will fall off and you get a bigger, the proper teeth, which will stay for the rest of your lifetime.

But that teeth goes, you don't get it back. So these are some of, and all of your teeth doesn't go. Only your front line, it will go. It doesn't, your molars with the back teeth doesn't go routinely. and these are all have some sense in the sense that it has to have a demand or we call it as reparative regeneration that means a part of repairing and they are of different category category one is epimorphic regeneration.

What is epimorphic morphic means all of you know it is something morphology if it's a morphology of elephant and morphology of rat means by look itself, external appearance itself, you can distinguish so you can distinguish between a monkey and a human although we know something looks similar but we know monkey is monkey human is human that is appearance that is called morphology epi means surface means appearance on the surface So replacement of complex structures through the mediation of a stem cells or some kind of pluripotent cells called blastema cells are called epimorphic regeneration. So what does it tell you? If there is a damage, you need to have the formation of some unique type of cells called blastema cells. And this is the way in which regeneration happens for the limb, tail and head of various organisms. But remember, mammals cannot do that. This will be mainly done by fishes and frogs.

Then comes in the second category of the reparative regeneration is the tissue regeneration. Organ is not being formed, but the tissue can be replaced. That is replacement of damaged tissues without the mediation of the blastema. So in this case, blastema is not formed, but the tissue can be repaired and replaced. So examples include muscle regeneration, bone regeneration, skin regeneration, and heart regeneration.

In this scenario, you can get the regeneration of these tissues without the formation of a blastema. Remember, this also depends on the extent of damage. If the damage is severe, then definitely you need to have blastema. But if the damage is milder, the damage happened not at organ level but damage happened at the tissue level then you do not need to have the blastema and the third category include cellular regeneration cellular regeneration that means reconstitution of a damaged cell, individual cell, that means neuronal processes say a given neuron Say in your retina, you have got different types of neurons are there. Say photoreceptor is damaged.

You don't need to make all the other neurons. Only photoreceptor need to be replaced. So we have got some dedicated cells underneath the photoreceptor layer and it will replace that photoreceptor. And it is also done in a variety of unicellular organisms such as protozoa. if a given dedicated cell type is damaged they will replace it and then another organism acetabularia also can have this cellular regeneration what does it mean these are simpler organisms where a dedicated area or dedicated cell if gone bad it will replace it Then comes after the reparative regeneration, then the tissue damage when it occurs or loss occurs.

Other way of response is by hypertrophy. Hypertrophy means cell number do not change. The existing cell becomes bigger. so this is what you may have seen it like if a an animal threatens a snake it will spread its hood so it has got ribs on around its head and the skin attached normally when a snake is moving it will look like a cylindrical shape but it will spread its rib and it will look bigger in shape same way if a bird is threatened it will spread its wing and it will show spread and look larger in size our cells also have this capacity and that is called hypertrophy that means a cell let us assume one cell is one ml in size and it will become 5 ml in size now that is number did not change but its volume and the bulk increased but of course it has got some limitation many of you would have seen if you started going to gym gymnasium to build your body Your muscle number is same. Muscle number is not going to change.

Say if you have got thousand muscle in your biceps, even after going to the gym, you still have the thousand only. But before going to gym, your biceps were not visible at all. Now after going to gym for few years, your biceps will become really bulky. But you will think more cells have come.

No. Cell number remains the same. The existing cells became bigger and bigger and bigger by recruiting more of protein or the muscle fibers. Individual protein fibers are recruited inside the cell and that is called hypertrophy. A classic example is bodybuilding. Bodybuilding, you look bigger and bigger because of hypertrophy of individual cells.

They don't become more in number. And this hypertrophy can be of two types. One is compensatory regeneration. What does compensatory mean? That is increase in size of a paired organ after its pair has been damaged or lost. We know our lungs are paired, our kidneys are paired.

We have two to each of this organ. If one of the kidney is damaged, say you donated your kidney or you lost one kidney due to whatsoever reason, the other kidney will become little larger in size to accommodate the demand. And this is called compensatory or becoming larger. Individual cells are becoming larger in size. Kidneys do that and lungs also will do. Sometimes lungs get damaged due to, your lung is like a balloon if it is broken then it is vulnerable for you know leaking of gas etc so doctors will ampute that whole lung so that you can live with the other lung but that other lung will do a compensatory growth And another example, the last example of hypertrophy regeneration is the regenerative response.

What does it mean? Restoration of mass of the damaged internal organs. And this is mainly done by liver and pancreas. So here what happens is not just compensatory growth, but what it does is it will increase in number. Good example to say is, say you have got five fingers in your hand, right? I cut three fingers.

from your hand. Now these two fingers are becoming larger to occupy the space of the other three fingers. And this is not hypertrophy. This is by active cell proliferation. The cell number increases but lost fingers are not coming back. the existing two fingers, say you had only one finger, your five fingers, four fingers are lost, you are left with only one finger and that one finger grows bigger and occupying the space of other fingers and that is what liver does and pancreas does after a damage.

Pancreas have got a limited capacity in the case of human, but liver has got a reasonable regenerative capacity. We have a special dedicated section of liver regeneration that will be coming up. But understand, last part, say a liver was looking like a, let us assume for ease of comparison, a liver was looking like a rat, let us assume, and its head is removed, and its legs are removed, tail is removed. Then actual regeneration, the head should come back, tail should come back, legs should come back.

No, it will not come back. But if the mice was one kilo in size, because of removal of the head, legs and tail, now it became 400 gram. The existing 400 gram now grow by adding 600 gram extra. But it is lost, the head is lost. But for some organ, the functioning depends on the bulk of that organ.

Liver is a classic example. That is why when you donate liver to a patient, then the liver in your body, what they take is very small. So on an average your liver is around 1.5 kilo. So it can grow as small as 150 gram. That means 150 gram of your liver can regenerate back into 1.

5 kilo. Many people suffer from alcoholic liver cirrhosis, non-alcoholic liver cirrhosis. In all this scenario the liver bounce back if the further damage is stopped. in an extreme case you can get a liver donated from a donor but the donor need his liver or her liver so they will take only a small part of the liver and put it into the host or the recipient and there that liver now become 1.5 kilo size what they are taking is a small piece so liver has this remarkable capacity and then comes the last category of regeneration that is morpholaxis Morphylaxis, what does it mean? Reconstitution of form after severe damage by remodeling the body. And this is done by some unique category of animals such as planaria, annelids, hydra, etc.

So what does it mean? If you take this animal and make them into multiple pieces, take a planaria, cut it into 20 pieces. One, two, three. It's a small worm, flat worm. each piece now going to give rise to full animal so one tiny piece of the body is good enough just like you know you may have seen about tissue culture plant tissue culture plant tissue culture all you need is a small tissue if you have that tissue you can happily grow the entire tree out of it or how a seed is growing. So these animals, the morphelaxis is a unique way of regeneration in which a group of tissue or a small segment of the body is capable of giving rise to the entire animal.

So Hydra is a classic example as you can see here in this picture a simple example of regeneration is Hydra and like you can see here this is a big Hydra and from the surrounding you are seeing a new Hydra that is being formed what was done to this Hydra a tiny damage tiny wound was done in this its base of its body and a new Hydra comes just like a tree grows a new branch but having said that every animal cannot do this effectively it is because they are lacking some strategy which these so-called animals that is doing morphelaxis method of regeneration or epimorphic method of regeneration or any other compensatory method there is some difference and the whole world is working on that before going into the details of the regeneration we must understand what is wound healing so in a typical scenario our body is blessed with a bunch of cells

that is we often call it as stem cells or a group of cells they are not committed. In this picture, what you can see here this is a group of cells called stem cells what does stem cells mean stem cells can give rise to any cell type just like a clay if I give you one kilo of clay based on your artistic talent you can make anything you can make a pot you can make a brick you can make a pen you can make a iron box more appearance wise or you can make a face of a person it purely depends on your talent that stem cells are like that stem cells give rise to a baseline cell population And baseline cell population decides whether it should proliferate, it should not proliferate, or it should stay as it is, or it should undergo apoptosis, etc. So when the baseline cell population is maintained, it will give rise to proliferation and increase in number, increase in bulk. And this baseline cell population, they can give rise to new cell type that we call it as tissue differentiation. So it can give rise to neurons, muscles or kidney tissue, lung tissue or any other tissue you name it.

It can give rise to a new cell type called differentiation. Then the same cells can have its own lifespan. The differentiated cell after a few months or a few years, it can die off. Then the body automatically use this baseline cell population to replace it. and no matter in each of this stage they have the vulnerability to undergo apoptosis and if apoptosis occurs to the baseline cell population it compensates by proliferation so what we understand our body has got group of cells pretty much every tissue has got a group of dedicated cells which has the ability to give rise to a given set of cell types.

Say your cells in the bone marrow is capable of giving rise to blood cells. Same way your skin has got some stem cells which is underneath your skin layer. We call it as adult stem cell and they can give rise to only skin. But they all originated from a main group of stem cells right from your development stage. We know we all develop from a zygote and the zygote is the one which is giving rise to stem cell and which eventually give rise to baseline cell population and increase in its bulk and giving rise to a cell type.

So, if you look into tissue repair, repair sometimes called healing. Often used wound healing, wound healing, you would have heard this word multiple times. What does healing mean? Healing simply means the response an organism does to a injury.

That's it. It doesn't mean that it is now problem solved. No. Healing means how it is responding immediately. So healing is a terminology used to understand the response of the body. It can respond in multiple ways based on the damage. refers to the restoration of tissue architecture and function after an injury the healing often leads to restoration of normalcy but the word healing is the response of that tissue by convention the term repair is often used for parenchymal and connective tissue and the healing for the surface epithelia this is what we use it if someone got an injury you say oh is the injury healed

That means we are often referring to a skin damage or a surface damage.

And remember, any organism's ability to repair, like whether it's a bone, muscle, skin, all depends on the organism's survival itself. In other words, if you do not have the ability to repair or regenerate, your organism cannot survive. An organism lives between these extremes. If there is absolute regeneration, no death will happen.

If there is no regeneration, no life will happen. So wound healing is a subsection of the so-called regenerative response. Hence, the critical to the survival of an organism is the ability to repair the damage, toxic insults and inflammation. Say you are eating some food and that food can be toxic and your liver detoxify it but at the cost of liver itself. But if that is the case after a few years liver will be missing. No, liver regenerates back so that you have liver for detoxifying in future.

And many times we know there will be an inflammatory response. If you mosquito bites, there is an inflammation. If you eat very spicy food, you know your lips all will become reddened in color. Your eyes will become reddish. Maybe your tears will start flowing down. All because of some kind of inflammation because the spicy food triggered some response in your body.

And sometimes if there is an infection, some microbes are growing, then there can be an inflammation and the injured tissue often can be easily identified by an inflamed surrounding that is a reddish or a painful surrounding area. not only serves to eliminate these dangers that is microbial dangers that comes to an infected spot but also sets into motion the process of repair so the inflammation is although it is painful although it is helping to protect from the microbes but it also helps in causing the regeneration So repair of damaged tissue occurs by two types of reactions. Your body can respond in multiple ways and one response is called regeneration by proliferation. Proliferation means what? Increasing in number.

Say your building wall is broken. and there is a hole in your house wall. To fix that you need brick for sure, right? So you will purchase it. But cells cannot be purchased from outside. So the existing cell will divide just like the surrounding wall is now proliferating and making new bricks.

That doesn't happen usually but I am giving an example. from the existing residual uninjured cells and the maturation of tissue stem cells. This is what usually happens in a regeneration by proliferation. And then another method is that deposition of the connective tissue. Connective tissue means what? Any tissue that do not have a dedicated function or a dedicated job and they are basically like a cement what you use

for a building's construction what is cement cement is not brick cement is not the baseline of a building but cement is needed without cement you cannot fuse two bricks without cement you cannot anchor a brick to anywhere or you cannot plaster or smoothen the wall it will look unpleasant or ugly so connective tissue can be something similar to that of a cement in a building and the deposition of connective tissue often leads to the appearance of a scar many of you would have seen if you have done an operation then you can count how many stitches have been put. Say someone has done a surgical wound with a surgical suture, you can count even after several years, you can count and tell, okay, five stitches are put in this wound because that gave rise to a scar formation.

Many injury, if it is you have fallen down from cycle or bike or something, you can always have some injury which will give a long lasting mark on your body. And this is what we call it as scar. And this scar is nothing but a way in which your tissue is getting repaired. So keep in mind that the regenerative response and the tissue repair response both are siblings. so much relationship exists between them but they are not the same when the damage is milder when the damage is manageable we often repair it by the deposition of some tissues or the deposition of the existing tissues so that the damaged portion looks okay and more than that if this damage is not healed or the damage is not contained it will often lead to the infection by various microbes etc so keep in mind the tissue regeneration is one of the extreme qualitative response an organism does to the tissue but the tissue repair when you are talking about tissue repair is always about running the show there is a damage so let me fix it let the blood flow is stopped and let me cover it up the injured area with some connective tissue so this is tissue repair and more details of this class or more details on this wound healing we will study in the next lecture. Thank you.