Introduction to Complex Biological Systems
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Lecture 28
Cell division, cell death and tissue homeostasis

Welcome to the NPTEL online course on Introduction to Complex Biological Systems. Today, I am going to discuss cell division, cell death, and tissue homeostasis. So, over the last two lectures, I mostly discussed cell division in the context of how a zygote can develop into a complex multicellular organization. In Particular, I discussed pattern formation, growth, and development. So, for today's lecture, I will mostly cover two different aspects: cell division as well as cell death.

Both are key factors for the growth and development of organs and tissue homeostasis. Following that, I will also discuss programmed cell death, known as apoptosis. Finally, I will discuss how controlled cell division and cell death regulate growth and development in multicellular organisms. So, here, division and death refer to cell division and cell death, which are key factors for the growth and development of multicellular organisms, especially for the formation of organs and tissue homeostasis. So, if you see here, cell division, which is discussed in much more detail in Module 5 by Professor Soumya De, so I am just bringing a few keywords related to cell division. As you can see here, for example, mitosis and meiosis.

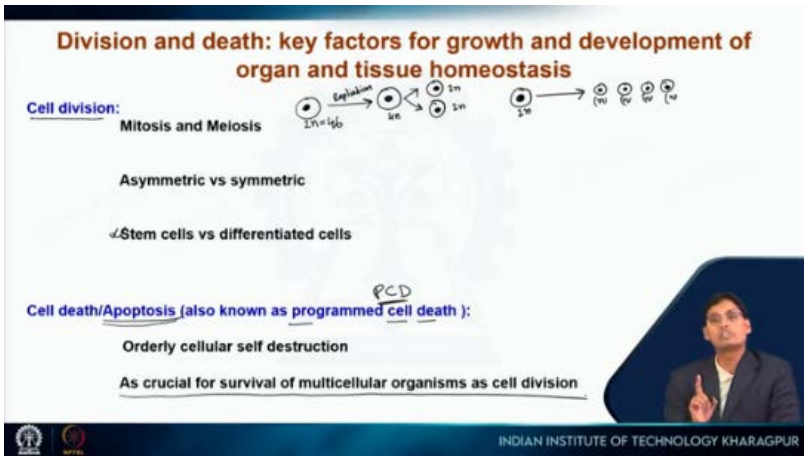
So, all of us know that mitosis means, for example, if I consider a human cell. So, just a somatic cell. So, I would say if this is the cell and this is the nucleus, then what will be the ploidy number? So, this should be $2n$ because it is a body cell or somatic cell. So, $2n$ means here $2n$ equals 46 for humans and now through mitosis, what will happen initially? First, there will be replication of DNA. As a result of that, now you will have that the total number of chromosomes will increase. So, the total DNA content will be doubled. So, that is why this is $4n$ in this test, but just after this replication process, this cell will divide into 2. So, now again, you have 2 cells here, and these 2 cells should have $2n$ number of chromosomes.

But in the case of meiosis, this is different. Here, there will be another round of division without replication. So, as a result of that, through meiosis, at the end, for example, from this cell, if this is $2n$, after meiosis, we will get a total number of 4 cells, and all of them should be n. Their genomic content should be n, which means half of the chromosomes should be present there. So, for example, in our germ cells, like egg and sperm, they have n number of chromosomes.

So, this is mitosis and meiosis and then, if I talk about asymmetric and symmetric division, I also discussed a little bit about these two things in this module. Sometimes, a cell might undergo asymmetric division. For example, during that time, some of the material present inside the cell, especially some mRNA and protein, will be distributed asymmetrically in two cells, and therefore, the fate of those two cells will be different. Particularly, stem cell division goes through this kind of asymmetric division. The last point here I am mentioning is the stem cells versus differentiated cells. Stem cells have the potential to make different types of cells. On the other hand, differentiated cells are already differentiated. So, generally speaking, differentiated cells will not divide anymore. But in a few cases, they can divide. They still have some potential for division, but they cannot make different types of cells. They can only produce the same type of cells. Those are the differentiated cells.

Now, if I like to explain this slide again, the title of this slide is division and death. So, based on our previous experience in the last two lectures, if you see, division is very important, and I just summarize different types of cell division and the associated processes. But what I want to mention here is that cell death, particularly I would say

apoptosis, is very important. It is also known as programmed cell death (PCD). So, programmed cell death is very important for growth and development, particularly for multicellular organisms. That is why I am mentioning here that it is as crucial for the survival of multicellular organisms as cell division. So, cell division and apoptosis both are very important for the formation of organs as well as overall development.



This cell division, when I was going through it, just came to my mind. In cell biology, this cell division is only what I would say the division where the division and multiplications are the same. Anywhere you cannot say the same thing is completely different. All of us know, but sometimes we say cell division, sometimes we are saying the multiplication of cells is the same. Division and multiplication in the context of cell biology. This is just an interesting fact. Now, if I go to the slightly more complex aspect of this thing, that is how this tissue homeostasis happens. In the previous slide, I was trying to explain that cell division and cell death both are equally important. But here, particularly, I will emphasize why it is important and how it is important. Over the last few minutes, I am going to discuss that. So, now, if you see, the lining of the small intestine is continually renewed through cell proliferation in the crypt. So, the interesting aspect is that in the adult body, most of the cells are differentiated cells.

For example, I have repeatedly mentioned that in an adult human, approximately they have 10^{13} cells. So, 10^{13} cells are approximately present in an adult human. So, now, most of those cells are differentiated cells. But still, we have some stem cells, and they are doing their own job. That is why we are doing fine. So, there are many examples, but one very

beautiful example, and it is some kind of model organ, we have a lot of information about this, is the lining of the small intestine.

A lot of stem cells are present in the epithelial layer of the small intestine, and that helps a lot. The particular reason is, if I try to explain to you, the intestine is a part of our digestive system, and particularly this long tube-like structure, and inside this a lot of digestion is going on, and those cells, particularly in the inner lining of this intestine are continuously doing work, mostly like absorption and so many other types of work. They are always trying to digest food and take digested food inside our body. So a lot of wear and tear is going on. As a result of that, those cells also don't survive for long. So as a result of that, we have a very good system to continuously replace those cells in the epithelium, particularly the lining of the small intestine. So, in humans and mice, approximately, I would say, those cells survive for 4 to 6 days and within 4 to 6 days, those cells are gone, and then again, new cells are getting generated. But I will be going through it carefully and in more detail. Let us see. So, I would say, if this is part of our small intestine, we have a very long tube-like small intestine.

Now, if we make a cross-section, this is a cross-section, we will get something like this. So, this is the tube here, what I am trying to say, inside here, you can see these small appendages. Those appendages are called villi. The membrane is folded inside, and they are forming finger-like structures. These are called villi. So now, if I just zoom this part here, it looks like this. So, this is like an actual micrograph. So, we can explain many things here in this picture, like in this micrograph.

So, here what you can see is that this is villi, but in singular form, this is villus, the same thing, and as I mentioned. So, this is a finger-like structure, but why is this present? Because it increases the surface so that the absorption can happen in a very efficient way. So, if we increase the surface, then the absorption will be very efficient. So, this is one of the most important reasons for this.

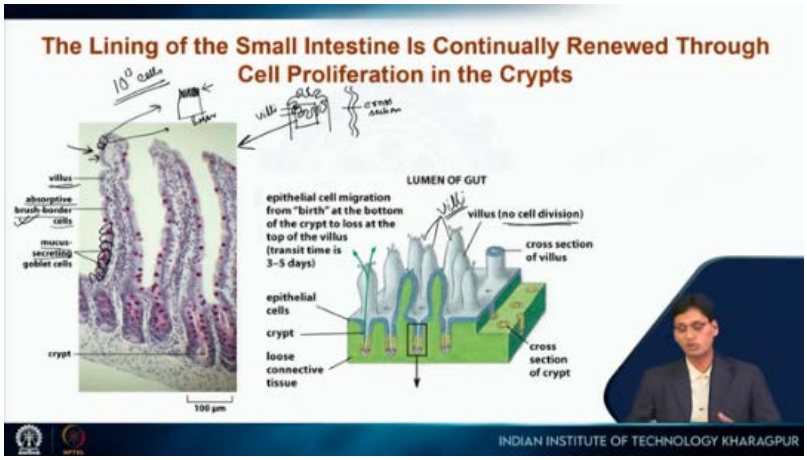
Now, if you see here in this intestine, this epithelium is just one cell layer. This layer is made up of one cell, one cell layer where cells are continuously present. Now, for example, if you look at this one cell here and another cell here, these cells form a single cell layer

and now, particularly in this diagram, as you can see, some of those cells are mentioned as absorptive brush border cells. From the name, you can understand that absorptive cells absorb. Whatever nutrients we need, they absorb, and in addition to that, brush border cells.

So, I mentioned that they have these villi, finger-like structures that actually increase the surface area. In addition to that, particularly this cell, for example, here one cell, two cells, if those are absorptive. If you see, this is the basal surface, that means this part, and this is the apical surface, which is actually facing the lumen of the intestine. So, there you will see small structures. One is the presence of villi, and next, every cell in there, on the apical surface. They have this kind of brush-like structure. Again, it is increasing the surface area so that absorption can be even more efficient.

So, that is why the name is brush border cell, as you can see here. Other major types of cells are called mucus-secreting cells or goblet cells. So, their function is to secrete mucus. So, they maintain a mucus layer inside our intestine, which is very important in terms of physiology. Now, this diagram, if we can make it a little bit, is a real micrograph, but now this is a kind of model diagram.

So, as you can see here, these finger-like appendages, those are the villi, and here on top of these cells like these villi, these cells are actually differentiated cells. That is why you can see no cell division there, and I mentioned that these cells last only for 5 or 6 days, something like that. So, then, from where are the cells coming? So, as you can see just here beside these appendages, you have some kind of dispersion. Also, some cell layer is coming down that forms the crypt or the base of these villi, and now at the base, we have stem cells. I am going to discuss this in more detail. This is connective tissue present here and this part, particularly the crypt part, if we explain it in more detail, then you will find something like this.

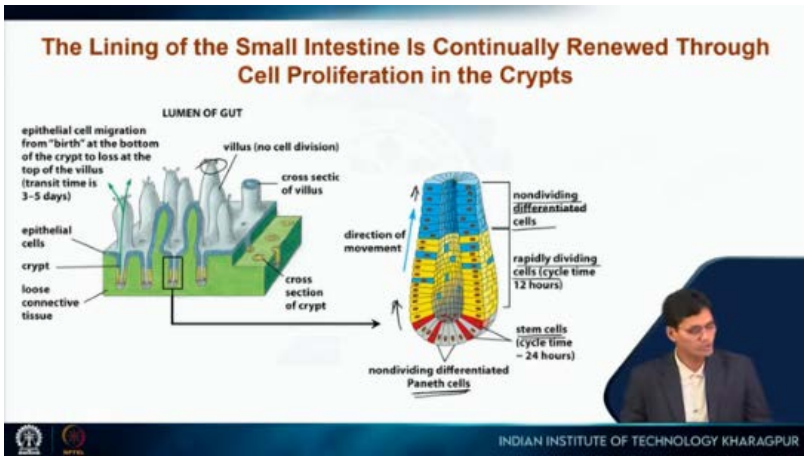


So, here, if we zoom in on this part at the base of these villi, particularly, we say this is the crypt. So, you can see a lot of different types of cells which are labeled by different colors in this diagram. And as you are going upward through this crypt, like the crypt going upward, you will be getting these non-dividing cells at the top. But at the base, we have two important cell populations, one of them is stem cells, and the other one important thing is the Paneth cells. So, although Paneth cells are differentiated cells, they stay at the crypt, and they play an important role in maintaining the stem cells.

So, now, these stem cells have the potential to divide again and again, and they will form different types of differentiated cells, and they will be going in this upward direction, and as you can see, these yellow-colored cells here are the rapidly dividing cells, but although they are already getting differentiated from stem cells, and when they are again dividing and dividing, finally, they will form non-dividing differentiated cells, and by 3 to 5 days, they will reach the top of this, the top of this villus, and then they will set some kind of cell death mechanism. Because we have to understand here that in order to maintain proper physiology, this cell division, particularly from these stem cells, whatever these cells are getting formed, and cells from the tip of the villus which are getting away. So, there should be some kind of balance in order to maintain tissue homeostasis. Otherwise, this villus size and all those things will not be maintained properly.

So, that is why tissue homeostasis is very important. That is, cell division and cell death should be very much controlled and very important for this purpose. So, now if we look into differentiated cells which are particularly present in this region, right in the villus, I

would say the majority of cells are absorptive cells; their main job is to absorb nutrients. You can see here by this direction that these are the apical surface here, the apical surface, and at the bottom, these are the basal surface. That means, those are the apical surface; they are facing the lumen of the intestine. So, as you can see, these absorptive cells have this brush border, whatever I mentioned here, to increase the surface area even more, and that the nutrients intake in this direction.

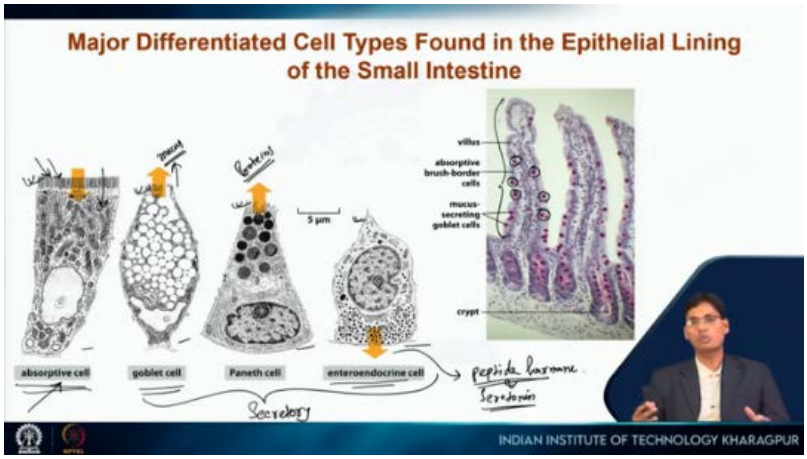


So, they are coming inside the cell. On the contrary, if you see goblet cells, that is also present here, particularly I would say here. If you see these cells, they stand by some dye. So, that the goblet cells are in red color here; these are the goblet cells present in the villus. So, their secretion pattern, see, this is going outward because I already mentioned what the function of goblet cells is that they secrete mucus.

So, here, whatever the major differentiated cells present in the intestinal epithelium, out of those three cells, they are secretory in nature. That means they secrete something, and this is different; their function is absorptive, the first one being absorptive cells. So, I already mentioned that goblet cells secrete mucus, and then the paneth cells also secrete some kind of protein and they also play an important role in innate immune response. So, these proteins actually fight against bacterial infection. So, which I am going to discuss in more detail during the immunology lectures.

So, paneth cells secrete some kind of proteins. On the other hand, these enteroendocrine cells, as you can see, are secreting different types of peptide hormones. Serotonin and many other things are very important to maintain the physiology of the intestine and also help in

the digestion process. So, altogether, these differentiated cells actually make the process of nutrient uptake as well as related physiology more efficient. But at the bottom of the crypt, those stem cells that are constantly dividing and forming these differentiated cells. Now, I am going to discuss how these stem cells maintain their stem cell line at the crypt because we should always have that; otherwise, our intestine will not be functional, and we will suffer from various diseases. So, these stem cells play a very important role. So, here, if you see, these stem cells present at the crypt, particularly as we are showing here in red color, and some paneth cells are also present. So, together, these paneth cells and stem cells at the bottom form the stem cell niche. So, now, if you see, these stem cells are multipotent. So, they are multipotent.



So, as a result of that, that is why I told you that from these stem cells, they are making all these kinds of differentiated cells. But multipotent means they will make different types of cells which are related to this organ only in the context of the intestine. So, these cells are forming absorptive cells as well as goblet cells, paneth cells, and enteroendocrine cells. So, they have some kind of potential, but they cannot make everything. But on the contrary, if you try to remember, if we say embryonic stem cells, embryonic stem cells are pluripotent. What is the meaning of pluripotent? That means they have the ability to make everything present in our body. For example, a zygote just after fertilization in the case of mammals, and again the first few divisions when we have only around 8 to 16 to 32 cells stage, during that time, cells are very much pluripotent. They have the potential to make everything, but here we are talking about these multipotent stem cells which are present in the crypt of the intestinal epithelium. Stem cells which are present in the crypt of the intestinal epithelium.

Now, one big question is how these stem cell lines are maintained because embryonic stem cells are gone, but in adult stem cells, for example, stem cells present in the crypt. So, these are called adult stem cells. Also, another example, if I say our skin layer, like if you see the skin layer, those are also epithelial cells, but the major difference here is in the intestinal epithelium there is just a single layer of cells. The epithelium layer is just one layer of cells, but in our skin, we have multiple layers of epithelial cells and at the bottom, we have more like stem cells, and they are getting divided and differentiated, and the cells are coming up and up, and at the top level, that is called the dermis layer, where those cells are mostly getting died after some time, and they will fall off. That is all, but whatever I started about this intestinal epithelium and these stem cells.

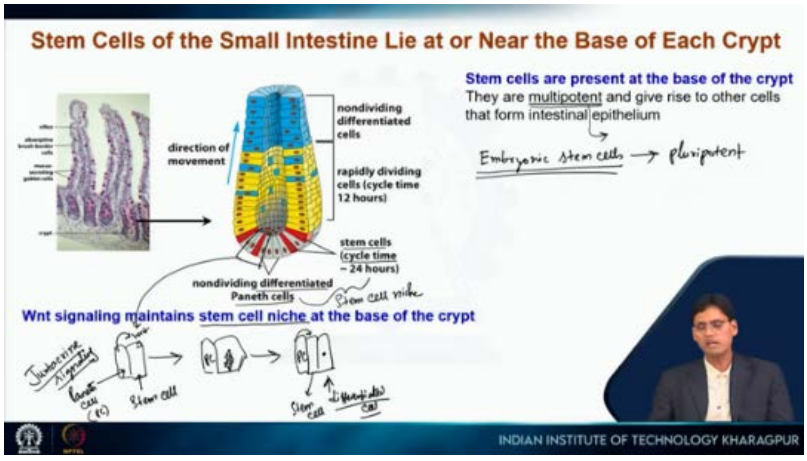
Let us see. So now, if I try to explain this part, like here. For example, you have one cell here like this. So, just a cartoon diagram, this is our managed cell, and this is our stem cell, as I already mentioned that paneth cell and stem cell, they form some kind of stem cell niche. Stem cell niche at the base.

So, now, what is the mechanism? How are these stem cells staying there for a long time, like years after years as we live? So, now, these paneth cells, they secrete some kind of ligand, which is called Wnt ligand. In this module, I discussed that some signaling molecules are very much conserved in our body, like in invertebrates, for example, one of those is the Wnt signaling pathway. So, these paneth cells, they secrete some ligand that is called Wnt ligand and these stem cells just adjacent, they have some receptor here, and that receptor is called Wnt receptor. So because of this Wnt ligand binding to the Wnt receptor this stem cell will start dividing. So in the next step, if I draw like this. So, in this cell, I am just showing that the chromosomes are getting separated.

So, this cell, this is again, I am saying that PC paneth cells. This is PC, and this stem cell is getting divided. In the next step, what will happen? This Paneth cell should be there, and now we have two cells because of the division, but now see. The cells which are adjacent to the paneth cell are getting this Wnt signaling, but not the cells which are going away because of the division. Now, these cells, these are the cells that are away from this paneth cell, and this signaling mechanism is called juxtacrine signaling.

That means, when these cells are adjacent, when this stem cell is just adjacent to these paneth cells, and it secretes this Wnt ligand. Only that cell will receive that signal, and it will do whatever it should do. So in this case, cell division. Now, particularly, this cell is now going away from this paneth cell. As a result of that, it is not a stem cell anymore. So I will say this is stem cells, particularly intestinal stem cells (ISC), and these are now differentiated cells. I hope you understand this basic mechanism. So, at the bottom of this villus or at the crypt region, this paneth cell and the stem cell population, they form this kind of stem cell niche, and that is getting maintained over time, and they are continuously forming some kind of differentiated cells, and they are going upward. Through the villus and another kind of differentiation, they form this kind of four different types of differentiated cells, and there should be some more complex mechanism of how those cells are making different types of differentiated cells.

Now, if we go just beside discussing the stem cells present in the intestine, I already mentioned that stem cells are also present in our skin layer. Similarly, I must mention here that stem cells are also present in our bone marrow. It is very important, for example, almost all blood cells are produced from our bone marrow. So, bone marrow is a kind of stem cell, but a multipotent stem cell, and it forms only different types of blood cells and immune cells, that is all. Similarly, some interesting facts are that sometimes tissue renewal does not depend on stem cells. Although this is not very common, in this case I will give you at least one example that is the liver. Inside our liver, we have cells which are called hepatocytes, and hepatocytes, although they are differentiated cells, can still divide and make hepatocytes inside the liver.



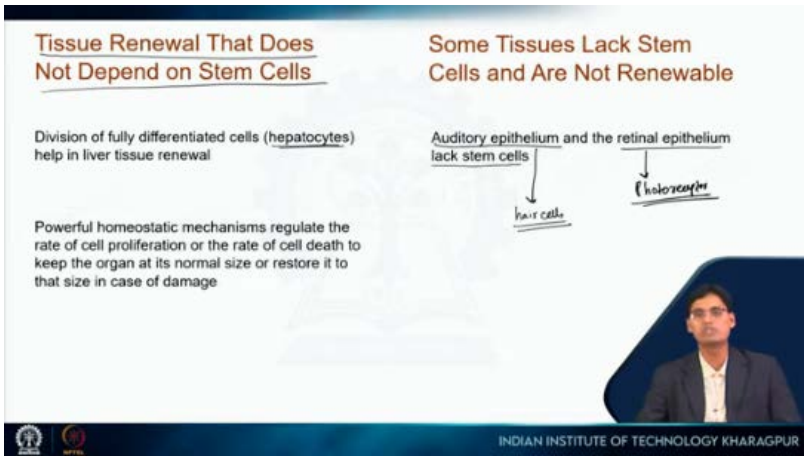
But there should be a very powerful mechanism to control this; otherwise, if it divides again and again, the liver will enlarge a lot, which is not a good sign. As a result, there should be a very tight mechanism to control this division and proliferation. In general, liver cells grow very slowly; it takes almost one year or more for their turnover number. But in addition to that, scientists did experiments, for example, particularly in the rat model. If they removed two-thirds of the liver from a rat, then within a few weeks, 2 to 3 weeks, the normal size liver developed again. So, as a result, that suggests again that hepatocytes can divide and make hepatocytes again. So, now I will give you another example here. Some tissues lack stem cells and are not renewable.

So, in the liver, what I told is that stem cells are not dependent on stem cells. Hepatocytes themselves can divide; there should be a much more complex mechanism, but for this course, I am just discussing the major point here. Some tissues lack stem cells and are not renewable. One example you can see is the auditory epithelium, which is related to our hearing process inside our ear and also the retinal epithelium. Epithelium that lacks stem cells. So, now, if you see the auditory epithelium particularly and the retinal epithelium, they have fully differentiated cells. As a result, if some injury, for example, a very loud sound, destroys some of those important auditory cells.

So, that will not be generated anymore. So that particular person will not be able to hear. I must mention here, the hair cells present in our inner ear, inside our cochlea, if they are getting damaged, then it is a problem. So, they cannot divide again. So, because they are not renewable. Similarly, the retinal epithelium, which is present in the retina, means it is present in our eye, and in the retina, we have cells which are photoreceptor cells. Photoreceptor cells are also very important. For example, if some laser beam hits someone's eye for a long time and if it destroys this photoreceptor, it is a big problem. As a result, in current times, a lot of research is going on to develop some kind of stem cell therapy so that we can rectify this issue. Rectify means we can generate photoreceptor cells so that person can see again. So, this is a very emerging field of research in current times.

Now, I will mention something particularly about this tissue homeostasis in the intestine and the liver also, and how the stem cell line is maintained in the intestine, but now when the cells are getting divided, I mentioned that cells should die also otherwise, it is a

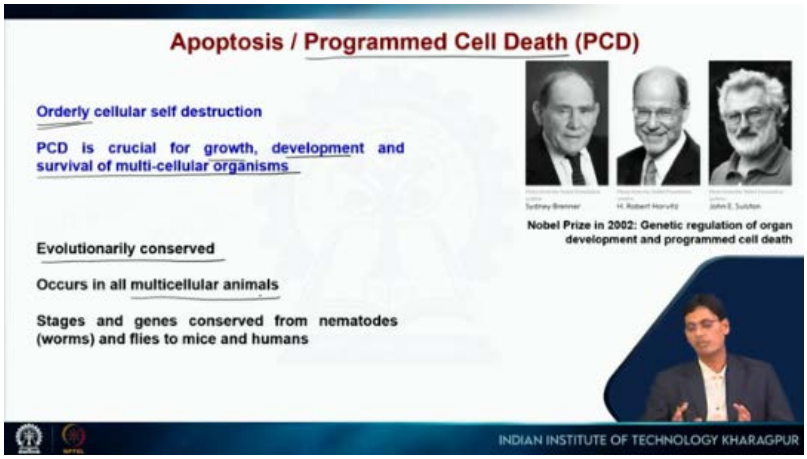
problem. We cannot keep this balance; homeostasis should not be there if the balance is not there. So, here comes this process called programmed cell death. So, from that name itself, you can see this is programmed and I would say that some kind of programme is already there. So, that means this is orderly cellular self-destruction; this is not something random. There is some kind of order, some kind of fixed mechanism there.



So, programmed cell death is very important for growth, development, and survival of multicellular organisms, and also, this is very much conserved in terms of evolution. I must say that programmed cell death, typical programmed cell death is majorly found in animal cells. In plant cells, some kind of apoptosis is also present, but this is much different from what we are going to discuss now. So, one is evolutionarily conserved, this process, and then it occurs in all multicellular animals, which is why I particularly mentioned that multicellular animals and particularly stages and genes are conserved from nematodes, for example, worms. So initial studies were mostly done in C. elegans, which is a nematode worm, C. elegans and from flies to mice and humans, everywhere these genes and the basic process are very much conserved, and for their beautiful work, and this is very much related to therapeutics also. Apoptosis is very important. For their work, Sydney Brenner, Robert Horvitz, and also John Sulston received the Nobel Prize in 2002, particularly for their work on genetic regulation of organ development and programmed cell death.

So now, what are the features of apoptosis? So, apoptosis is one type of cell death in which a suicidal program is activated within a cell and leads to rapid cell death. So, as I already mentioned, this is from inside itself, meaning that it is already programmed because of

some reason that the cell should die, and then the apoptotic cell, the cell which is undergoing apoptosis is called an apoptotic cell. They shrink, condense, and the cytoskeleton collapses, followed by condensation of the nucleus and the fragmentation of chromatin or DNA. Cytoskeleton means, you already studied in the previous module that we have an actin cytoskeleton, we have microtubules, and we have intermediate filaments. So, all those cytoskeletons are very important, but at this stage, when cells are undergoing apoptosis, their cytoskeleton collapses, and finally, their nucleus also gets fragmented, and now This is a very essential and critically important process for organism growth, development, and continues into adulthood, maturity.



For example, in the case of the intestine, what I told you is very much true during the adult phase as well. All the time, it's happening, cell division as well as the cell death. In contrast to apoptosis, cells that die accidentally in response to some acute injury, for example, a lack of blood supply, some kind of trauma, or some kind of pathogenic infection, that is called necrosis. So, this is the difference between apoptosis and necrosis. Now, a few important biochemical properties are there which are recognizable in an apoptotic cell. Particularly, I would say, chromosomal DNA gets fragmented and that is very important. And then, another important thing is phosphatidylserine. This is a negatively charged phospholipid which is normally located in the inner leaflet of the lipid bilayer. You know that in membranes like the cell membrane, we have a lipid bilayer, and this phosphatidylserine is generally associated with the inner leaflet, in the inner layer.

But in an apoptotic cell, something happens so that it flips. As a result of that, now in the upper leaflet, we have this phosphatidylserine. So, this is kind of a signal to other cells that this cell is undergoing apoptosis because when cells are dying, then what will happen? Somehow, it should be cleared from the body otherwise if the apoptotic cells are staying in our body, it will create a problem. So, as a result of that, we have either the neighboring cells or we have very specialized phagocytic cells.

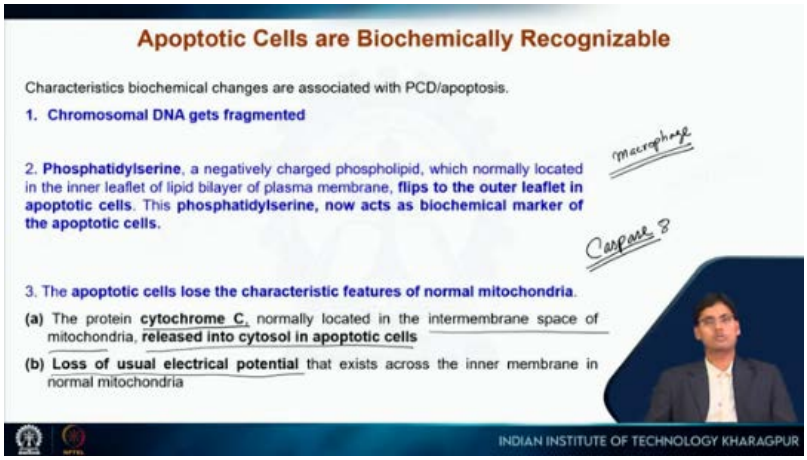
For example, I would say macrophages. Macrophages, which are important cells in our immune system. So, macrophages have one very good property that is called phagocytosis. So, they will take those debris, particularly these apoptotic cells so that they will clear them from the site. So, this is very important. But this recognition will be much better if the phosphatidylserine is present on the upper leaflet.

Now the apoptotic cells lose the characteristic features of normal mitochondria. So, what is the function of mitochondria? The major function is to generate energy or ATP. Now if you see a protein called cytochrome C is present in the intermembrane space of mitochondria, and this is very important for the electron transport chain. The electron transport chain is associated with cellular respiration, which you will learn in more detail in the next module.

So, now if cytochrome C is released into the cytosol, then the electron transport chain will not be as efficient, and as a result, there will be some loss of the usual electrical potential that exists across the inner membrane in normal mitochondria. Those are the major biochemical properties of an apoptotic cell, and then finally, the cell will undergo apoptosis. So, now when this is happening, how is it happening? What is the mechanism? So, as I mentioned, this is very much concerning.

For example, an important enzyme family called caspase. This is some kind of proteolytic enzyme. So, caspase, particularly caspase 8, for example, plays a very important role in the apoptosis process. So, there are many different types of caspase present, and they play important roles, and there are many complex mechanisms behind this programmed cell death, but this is very concerning in our system. Now I would like to particularly focus on

as I already mentioned some of those things. What is the necessity or function of this programmed cell death?



So, programmed cell death eliminates unwanted cells during organ formation or early development. So, whatever I mention in the case of the intestine or intestinal epithelium, that is happening all the time, but this is during early development or during organ formation. This point I am trying to explain, for example, if you see our hand. This is our palm, so as you can see, we have five fingers here. But if I try to explain when we are growing up even before our birth. So for example if this is the part of this portion, like this portion, it will grow up and it will make this palm. So, what will happen? So, this is growing.

So, now if this grows like this, then it will grow in all dimensions, then we will not get this kind of set, and this five-finger digit. So, as a result of that, there should be some mechanism which is happening in a very beautiful way, in a very controlled way, so that we are always getting this kind of structure. So, that is very much proven scientifically also, as you can see here in this figure. So, digit formation in mouse paw during embryonic development. So, for example, here what will happen?

I was going to discuss the human hand. So, if a few cells are dying here, dying here, dying here, then those cells are growing. They are growing over time, and then we will get our finger. So, here we are showing, see, these cells are undergoing programmed cell death. So, as a result of that, here you can see more kinds of this digit formation take place.

So, that is why this is just one example I have taken because this example is very easy to explain, but the thing is this is very much true for different types of organ formation in our body. Also, another interesting example is if you see the removal of the tail as a tadpole changes into a frog. So all of us know that tadpoles have a big tail here. This is the tail, but now for a mature frog, the tail should go away.

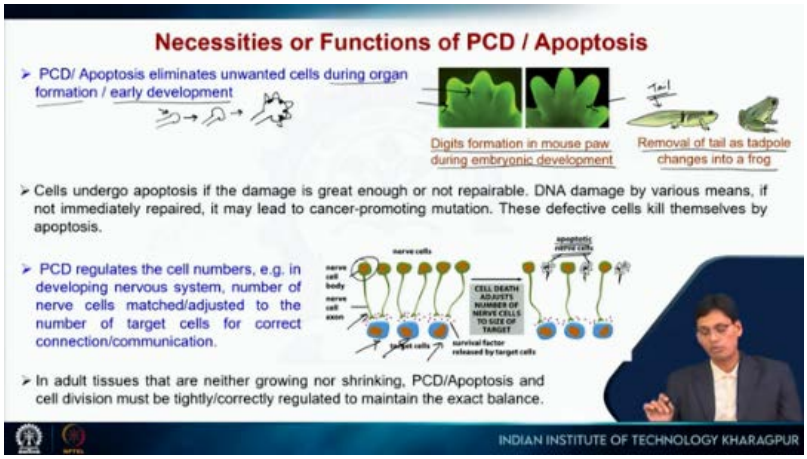
So, here also apoptosis is going on, and finally, the cells will die, and now mature frogs do not have the tail. The tail is required at the very beginning because they start their life in water and now cells undergo apoptosis if the damage is great enough or not repairable, particularly DNA damage by various means. If not immediately repaired, it may lead to cancer-promoting mutations. You already went through the cancer topic, as you can see, a mutation is one major reason for cancer, and the accumulation of mutations will create more and more problems.

So some mutations, for example, during replication, if some wrong nucleotides get incorporated, that should be rectified by the polymerase itself, like we have proofreading activity during replication, but if this is not happening properly or for some other reason, some ionizing radiation or other things that actually cause the mutation, some kind of changes in DNA, and that cannot be repaired, then it is better for those cells to go through programmed cell death because if they stay and if they somehow get divided, they will make more and more mutation-promoting cells, which will lead to more and more mutations and finally lead to cancer. So, this is one of the very important aspects of programmed cell death. Those cells should die, and that programmed cell death also regulates the cell number. For example, here if you see ah. In the developing nervous system, the number of nerve cells is matched or adjusted to the number of target cells for correct connection and communication. What is this? So, if you see here, these are the target cells.

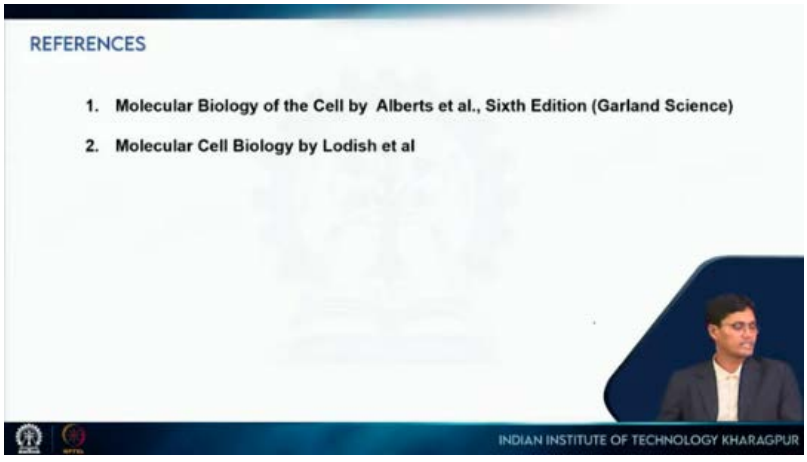
So, for example, if we pinch somewhere here in our skin, immediately we understand why because in the surrounding we have nerve endings, we have nerve cells. But now in one target cell, if you have many, many nerve cells, then there will be a problem in communication. So, what you can see here is that these are the nerve cell bodies, and this is the action of nerve cells. As you can see here, multiple actions are actually present in

one target cell, but at a certain point in time, you can see that some of those nerve cells are undergoing apoptosis to make the proper connection. Now, we have the correct ratio of target cells and nerve cells. This is also done by programmed cell death.

So, that is why I told you it is very important for growth and development and in adult tissues that are neither growing nor shrinking. Programmed cell death and cell division must be tightly regulated to maintain the exact balance.



One example is intestinal epithelium and these are the references, you can go through any of these two textbooks for more detail and you will learn more.



Thank you very much.