Introduction to Complex Biological Systems
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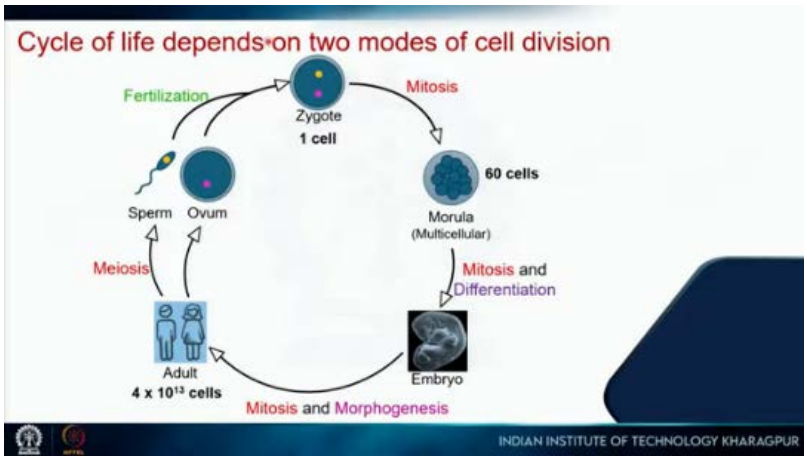
Lecture 24
Stem Cells

Welcome to the fourth lecture of week 5. Today, I am going to talk about stem cells. So, life starts as a single cell. We have already seen this in the last lecture. So, this is a zygote, and from this, it divides into some cells.



So, this will be around 60 cells. This is called the morula. So, this is for a multicellular organism. At this point in time, all these cells are very similar to each other, and then these cells, while dividing, start to differentiate. So, we have seen that there are two types of cell divisions. One of them is mitosis, and the other one is meiosis.

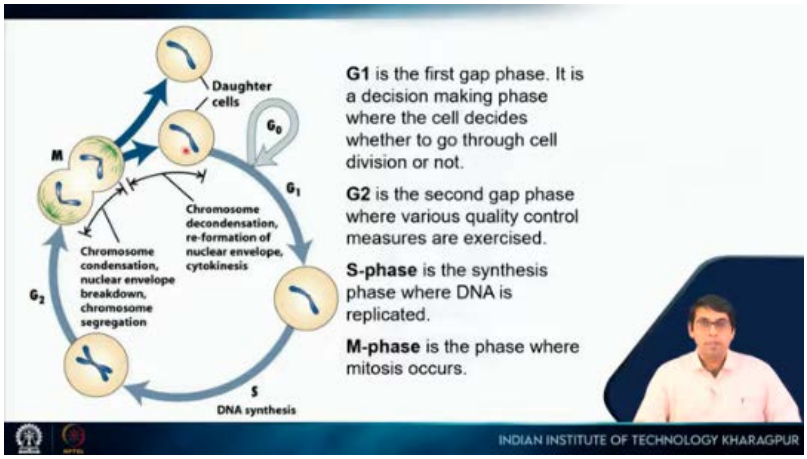
So, in the case of mitosis, the genetic information remains exactly the same. What we are going to see today is that even though these cells divide by mitosis, the daughter cells are not exactly the same. So, the two daughter cells can be different from each other, or the daughter cells can be different from the parent cells. So, this is called differentiation. So, while this happens, the organism grows.

There is also something called morphogenesis, where different organs are developed and finally, we have the adult organism. So, all these divisions are mitosis, where the genetic information is preserved. There is also another division that we saw, which is meiosis, where reduction division occurs. So, 46 chromosomes become 23 chromosomes, and we get these germ cells, which are the sperm and the ovum, and the fertilization of these two gives rise to a new life, which is a zygote.

So, this is the cycle of life, and it depends on two modes of cell division. So, just a recapitulation, we saw there are two types of cell division. One is mitosis and this one is mitosis. So, from the parent cell, the two daughter cells are produced, and they have the exact same genetic information as the parent cell.

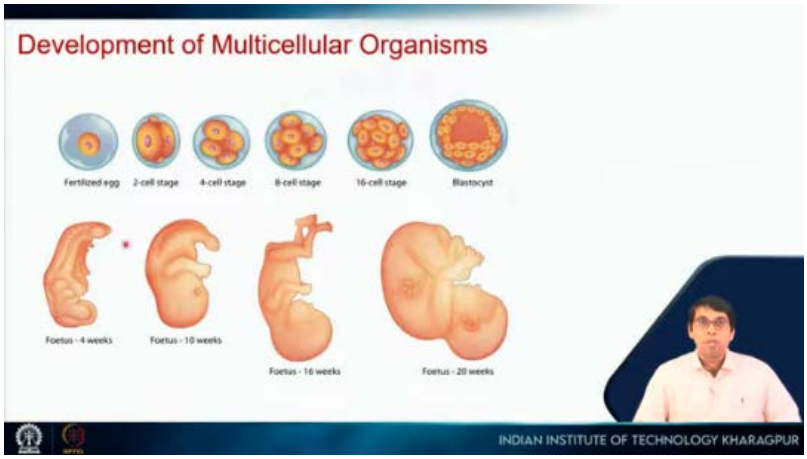
In the case of meiosis, two rounds of division happen. So, the first round segregates the homologous chromosomes. So, they pair up, and then the second one segregates the sister chromatids. So, you end up with four cells from one parent cell, and these are all haploids. So, you have 2n number of chromosomes here, and you have n number of chromosomes here.

So, this is only for the gametes. For all other cell types, the ones that we are going to discuss today, they will all undergo mitosis. So, the genetic information is not going to change, and the number of chromosomes will also remain exactly the same. Then we saw that cells have the cell cycle, so there is this first gap phase where it decides whether the cell wants to go through this cell division process. Once it commits to that, then it goes into the S phase, which stands for DNA synthesis, so the amount of DNA is doubled. Then there is another gap phase where it assembles all the mitotic machinery, and finally, it goes into mitosis or the M phase and then we get these two daughter cells. However, this type of diagram gives us the impression that the parent cell, which goes through this division, giving rise to these two daughter cells, they are all exactly the same.



Now, this is true when we talk about the DNA, but this is not true when we talk about the whole cell. That is what we are going to see today. So, this is the development of a multicellular organism. So, it starts with this zygote, and then it divides, so we get 2 cells, 4 cells, 8 cells, and then finally we get this blastocyst. Up to this point, all the cells are very similar, but then we start getting something called morphogenesis, so the cells will

start differentiating. The cells which are in this region will be different from the cells in this region, which will be different from the cells in this region and slowly, you can see that different parts of the body are getting developed. So the cells here are called stem cells, and the cells that are present here are called differentiated cells. So, most of the cells will be differentiated cells; however, there will be some stem cells still present. So, what is a stem cell? Stem cells are undifferentiated cells in multicellular organisms. So, again, we are talking about multicellular organisms where you have different cell types. So, stem cells are undifferentiated cells which can proliferate indefinitely, which means that they can divide indefinitely and generate multiple cell types.

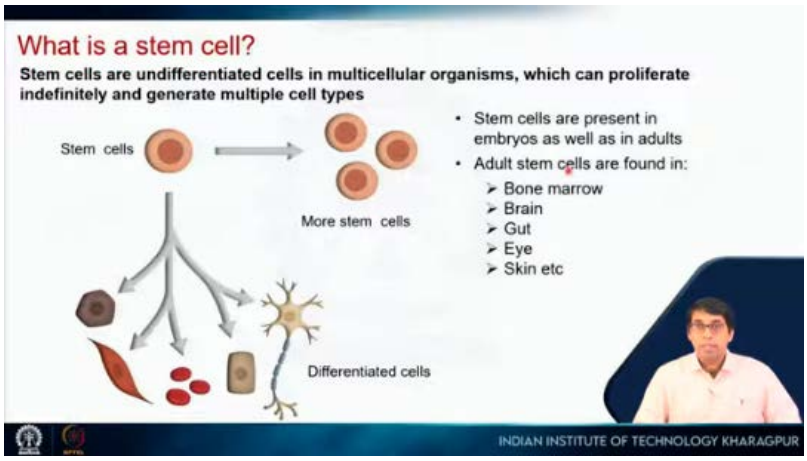


So, these stem cells can divide to generate more and more stem cells, or they can differentiate to generate these different cell types. So, we see here a neuronal cell, this is a red blood cell, and this is a muscle cell. So, we have all these different cell types that are there. So, stem cells are present in embryos as well as in adults. So, we saw the zygote and then the first few stages; those are the embryonic stem cells.

However, when we become adults, we still have stem cells, but these are more specialized stem cells. For example, there are adult stem cells which are present in our bone marrow, and they will give rise to different types of blood cells. There are stem cells present in our brain, gut, eye, skin, etc. For example, your skin has to be replenished.

So, more and more new skin cells have to be generated, and they come from the stem cells which are present in the skin. Similarly, blood cells have to be regenerated. I have already discussed this. If you think about the red blood cell, its lifespan is 120 days. So, new red blood cells have to be generated, and it turns out that we generate almost a million red blood cells every second in an adult. So, they come from these stem cells. The stem cells will divide and differentiate into these different blood cell types. So, this is an

example of this different cell differentiation, and here we have taken up the example of blood cells. So, the stem cells that produce blood cells are called hematopoietic stem cells, and these are present in the bone marrow. So, these types of stem cells are multipotent stem cells.



Multipotent means that they can give rise to all these different types of cells which are present in our blood. So, this is an erythrocyte, which is the red blood cell, but apart from that, we also have these other different blood cell types. So, all of these can be generated from this hematopoietic stem cell; hence, it is called a multipotent stem cell. However, it can produce only these cells. It cannot produce a liver cell, it cannot produce a muscle cell, or it cannot produce a neuronal cell.

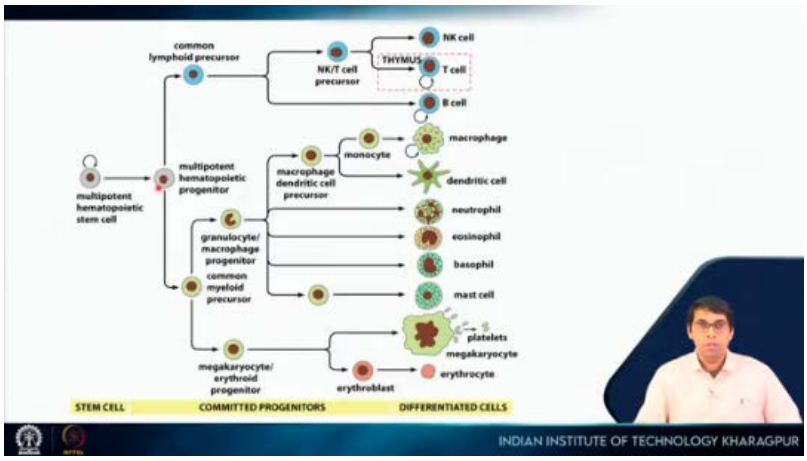
For those, there are other stem cells. So, that is what happens in an adult. But an embryonic stem cell can produce a liver cell, it can produce a blood cell, and it can produce a muscle cell. So, it can produce all those cells. So, we will see that even in stem cells, there are different types of stem cells.

So, let us go through this diagram properly. So, this is a stem cell; it's a multipotent stem cell, and all the cells which are listed on this right-hand side are differentiated cells. So, they cannot divide on their own. So, these are the terminal cells, and they perform their function. For example, a red blood cell carries oxygen; we have these natural killer cells, T cells, B cells, which are very important in our immune system.

So, we will talk about these cells, the macrophages and the dendritic cells. We will discuss these different cell types when we explore our immune system in later lectures. So, the stem cell can regenerate itself, which is shown by this arrow. So, it will be producing itself, and it can also produce other cell types. So, this will be a multipotent

hematopoietic progenitor. So, it's slightly different from this and then it gives rise to two different stem cells or two different cell types. One is a lymphoid precursor, and the other one is a myeloid precursor. So, it turns out that blood cells can be grouped into these two major groups, the lymphoid cells and the myeloid cells. And then these lymphoid cells will give rise to these cell types, and this myeloid precursor will give rise to all these different cell types. So, you can see that there is a progressive change.

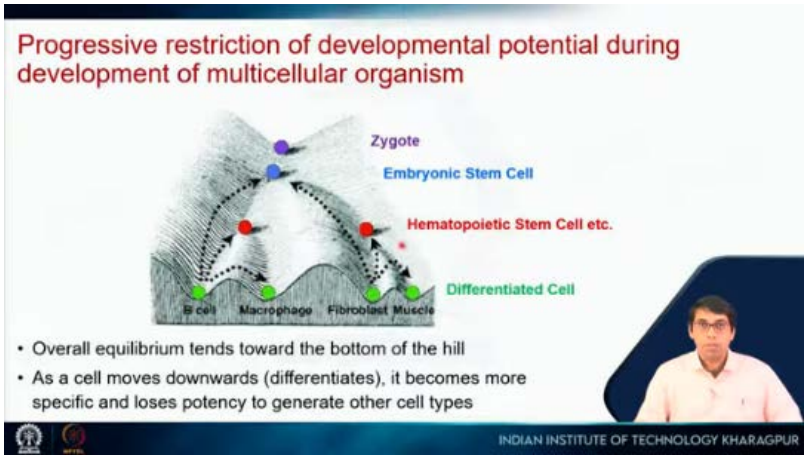
So, this will not directly produce this cell. So, it will go through these different intermediate cells, and as these cells progress from this direction to this direction, they lose their potency. So, they become more and more differentiated, finally leading to this type of completely differentiated cell. So, this can be shown in a diagram like this. So, at the top of the hill, we have the zygote, which can produce any cell type.



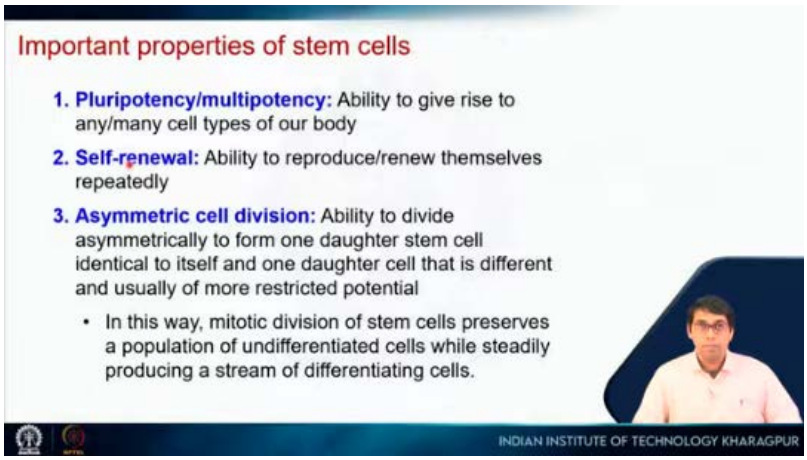
So, zygote and the embryonic stem cells can produce any cell type. But then, as an organism matures and becomes an adult, there are stem cells which have lower potency compared to these cell types. So, there are hematopoietic stem cells which can produce only blood cells, stem cells which can produce only liver cells, and stem cells which can produce only neuronal cells, and so on and so forth. So, overall, this equilibrium tends towards the bottom of the hill.

So, these cells progress towards this cell, and finally, we have the differentiated cells here. A cell moves downhill, so it becomes differentiated. It becomes more specific and loses its potency to generate other cell types. So, hematopoietic stem cells can only generate blood cells. Liver stem cells can only produce liver cells. So, these are some of the properties of stem cells. The first one is called pluripotency or multipotency, which means it is the ability to give rise to any or many cell types of our body. So, for embryonic stem cells, it will be any cell type. So, they can produce any cell type in the

body, but for hematopoietic stem cells, it will be many. So, they can produce many cell types which are all blood cells, but they cannot produce liver cells or neuronal cells. So, this is pluripotency or multipotency.

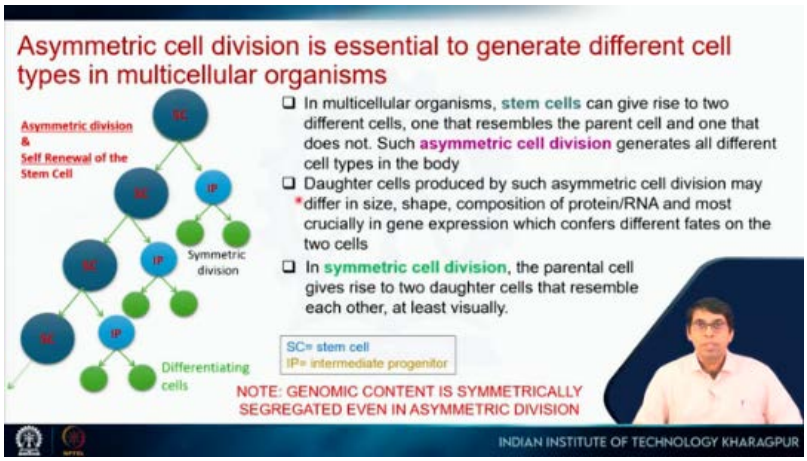


So, embryonic stem cells are pluripotent, and hematopoietic stem cells are multipotent. The second important property that these stem cells have is the ability to self-renew. So, they can regenerate themselves. So, they can reproduce and renew themselves repeatedly and the third one is their ability to undergo asymmetric cell division. So, it's the ability to asymmetrically form one daughter cell, which will be a stem cell, so it regenerates itself, and the other one will be a differentiated cell, so, in this way, even though it's a mitotic cell division, asymmetric division will give rise to two different types of daughter cells. So, it is shown pictorially here. So, we have a stem cell here. It undergoes asymmetric cell division. So, it produces two cells.



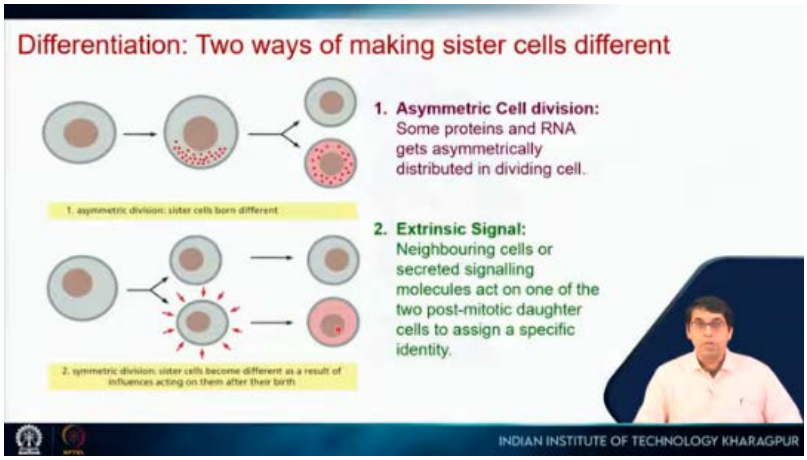
This one is a stem cell. So, it is exactly the same as this. So, this cell will be exactly the same as this. However, this one is an intermediate progenitor. So, this is slightly different from this. Now, this cell can again undergo division and it can produce two daughter cells which will be

differentiated cells. So, from the stem cell, we get this differentiated cell via this intermediate progenitor, and the stem cell will keep on regenerating itself. So, these daughter cells are produced by asymmetric cell division. So, how do we get this asymmetric cell division? There are two ways; again, there are many different mechanisms, but these are the two broad mechanisms by which we can get asymmetric cell division.



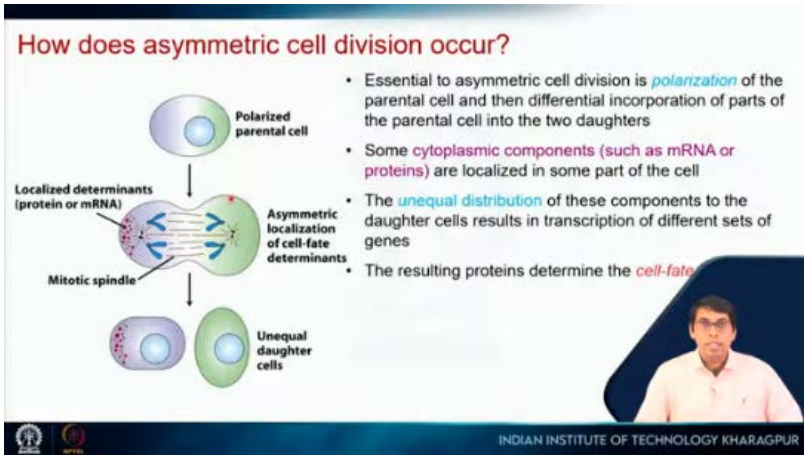
So, let us say we have this stem cell, and it produces these two daughter cells, and you can see that these two daughter cells are different from each other. So, how do we get that? We have this stem cell; now, there are some proteins or RNA, so this can be protein or messenger RNA, which are localized on one part of the cell. Now, if mitosis happens and the cell divides like this, then all these proteins or the RNA will be transferred to only one cell, one of the two daughter cells, so this other daughter cell will not get any of these proteins or the RNA. Now, once this protein and RNA are here, they can induce the production of other proteins which will not be induced here. So, this cell will have different characteristics compared to this cell.

So, this is asymmetric cell division due to the asymmetric division of these proteins or RNA. Another way this can be done is the cell divides symmetrically. So, you produce two cells which are similar to each other. However, they migrate to different locations. In the tissue or the organ and the neighboring cells will then produce signaling molecules, which will induce this cell to produce certain proteins that will change the characteristics of this cell. So, this cell remains the same, but this cell becomes different. So, the ultimate outcome is that the two daughter cells are different from each other. So, this is based on extrinsic signals, and this is based on internal molecules, which result in the differentiation. So, it is shown; the first one is shown like this.



So, we have a cell, and we can call it a polarized cell because the two ends of the cell are not similar. So, there are these proteins or messenger RNAs, which are localized to this part of the cell and this localization can be done by anchoring these molecules to the cell membrane. So, if we can anchor these molecules in the cell membrane, then they will not diffuse; they will remain on this part. So, they will not diffuse throughout the cell.

Now, cell division happens; mitosis happens and you have cytokinesis, so the cell division happens. This daughter cell will not have any of these proteins or RNAs. So, its characteristics will be different from this daughter cell. So I have already shown you the example of hematopoietic stem cells; there this is another example. So, this is the lumen of our gut is present in our small intestine. So, the cells of our intestinal epithelium, which are the cells that line the epithelium, line this particular organ. So, they have to continuously regenerate from stem cells because these cells, when we digest food, undergo a lot of mechanical wear and tear. So, typically, the lifetime of these cells is one day. So, within a day, they will get destroyed.

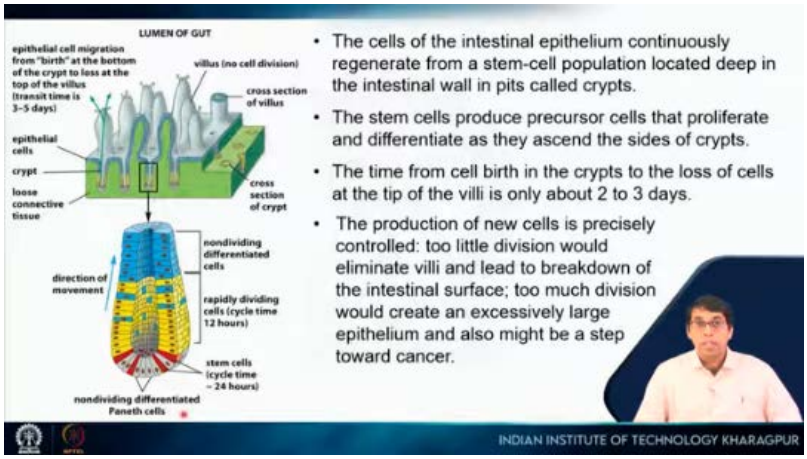


So, they have to be regenerated. So, there are stem cells that are present in these crypts. So, these are called villi. So, they increase the surface area so that they can absorb nutrients very efficiently and in these pit-like structures of the crypts, the stem cells are present.

So, these stem cells produce precursor cells that proliferate and differentiate as they ascend the sides of the crypts. So, the stem cells will divide, and then these differentiated cells will keep moving up and will replenish or remove the cells that get damaged or die in this top part. The time from birth in the crypts to the loss of cells at the tip of the villi is only about two to three days. Once it divides, it will go up and then perform its function here. These are the non-differentiated cells, these are the differentiated cells, the non-dividing cells, and then finally, they will die.

So, this whole process takes 2 to 3 days. Now, there is a very delicate balance that has to be maintained. The production of new cells is precisely controlled. Too little division would eliminate villi and lead to the breakdown of the intestinal surface. So, if the cell division is too slow, then the cells up here will die faster, which will result in the loss of this structure.

So, it can cause ulcers. On the other hand, if the division is too fast, too much division will create an excessively large epithelium. So, these villi, this epithelium can become bigger, so that will create a lot of problems. Also, it can be a step towards cancer because you have unregulated cell division, so that can lead to cancer. So, very slow division is a problem, very fast division is a problem, and this type of division is again very tightly controlled. That is the control of our cell cycle. So, what is the molecular basis of this cell division?



So, if we think about the zygote or if we think about any of these differentiated cells, they have the exact same genetic composition. The DNA is exactly the same. Well, in the case of RBCs, the nucleus is thrown out. So, there is no DNA in the final mature RBC, but when it forms, the nucleus is there. So, the DNA there versus the DNA here versus the DNA here is exactly the same.

So how come we have these different cells, the cells which look so different from each other and perform functions which are so different? That is because of the presence of proteins or the proteins which are expressed differently in these different cells. So we know that there are around 20,000 or 21,000 genes in our body, which will produce these 20 or 21,000 different types of proteins. Now, all these proteins are not expressed in all these cells.

So let's say a muscle cell will produce around 15,000 out of 21,000 genes or 15,000 proteins out of 21,000 proteins. Neuronal cells will also produce, let us say, 15,000 out of 21,000 proteins. But these 15,000 versus these 15,000 will not be exactly the same. So some proteins will be exactly the same and those types of proteins are called housekeeping proteins or housekeeping genes.

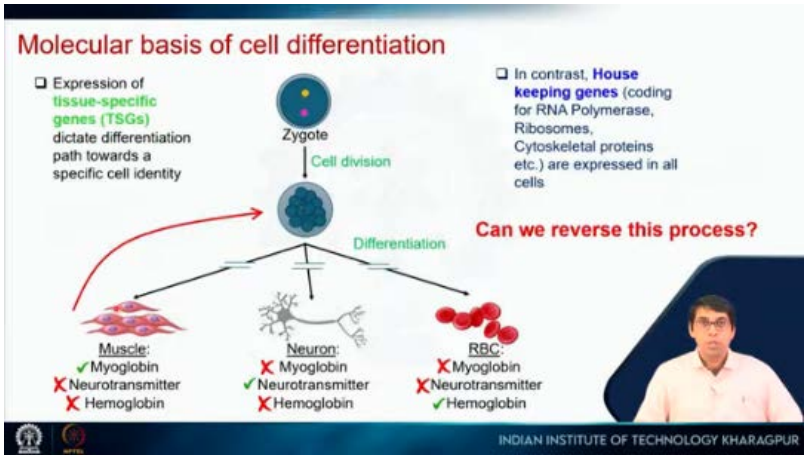
For example, they can be RNA polymerase, they can be ribosomes, and they can be the cytoskeletal proteins like microtubules, actin filaments, and intermediate filaments. So, these types of proteins are needed for all cell types. So, there will be a set of proteins which will be common in all these different cell types, and these are called housekeeping genes. So, all the cells need them to perform some common functions. However, there will be certain other proteins which will be very specific to these cell types or the tissue types.

These are called tissue-specific genes. So, these tissue-specific genes will produce the tissue-specific proteins, and we can see some examples here. So, these three proteins: myoglobin, a neurotransmitter, and hemoglobin. Let us look at these three. So, in muscle cells, myoglobin is present.

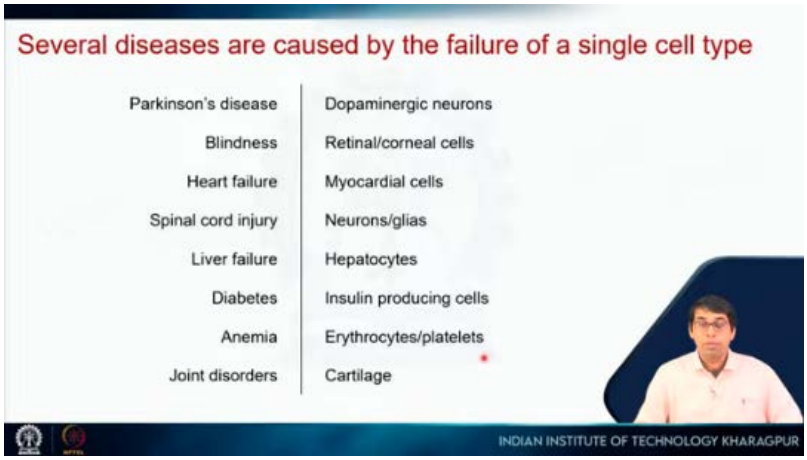
It is not present in neuronal cells, and it is not present in RBCs. Neurotransmitters are not present in the muscle cells, but this neurotransmitter is present in the neuronal cells, and again, it is not present in RBCs. Hemoglobin is present in RBCs; it is not present in neuronal cells, and it is not present in muscle cells. So, these proteins will be tissue-specific proteins, and they will result in the particular characteristics and the functions

that these cells perform, so the characteristics of these cells and the functions that they perform.

So, it is the expression, the different expression of different proteins, that results in these different cell types. So, if we understand this molecular basis, there is a very important question that we can ask that if different expression of different proteins can result in these different cell types then can we reverse this process? Meaning, can we express certain proteins so that our differentiated cell, like this, can go back to a stem cell, like this. So, can we reverse this process? This is exactly, so this is something that is very important because it turns out that there are several diseases—not all diseases, but many diseases—are caused by the failure of a single cell type. So, this is a list of some of such diseases; for example, Parkinson's disease is caused by the loss of dopaminergic neurons. These are neuronal cells. Blindness can be caused by the loss of retinal cells or corneal cells, heart failure due to myocardial cells and the spinal cord injury due to damage in neurons or glial cells.

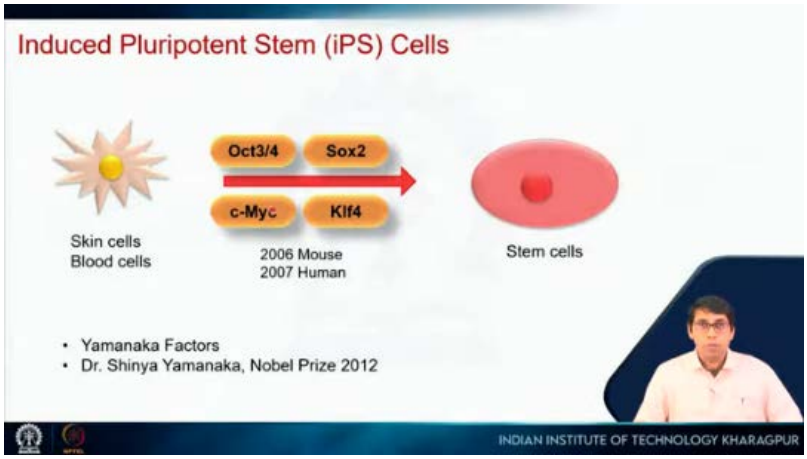


Liver failure is due to damage in hepatocytes, diabetes due to reduction in insulin-producing cells, anemia due to reduction in erythrocytes or platelets, joint disorders due to damage in cartilage. So these are all single cell types. So, if we can produce a stem cell, we can then differentiate it to produce these cell types. So, if we can produce a stem cell and then differentiate it to produce dopaminergic neurons, we can transplant these neurons to a Parkinson's patient so that the patient can produce these neurons and overcome the disease.



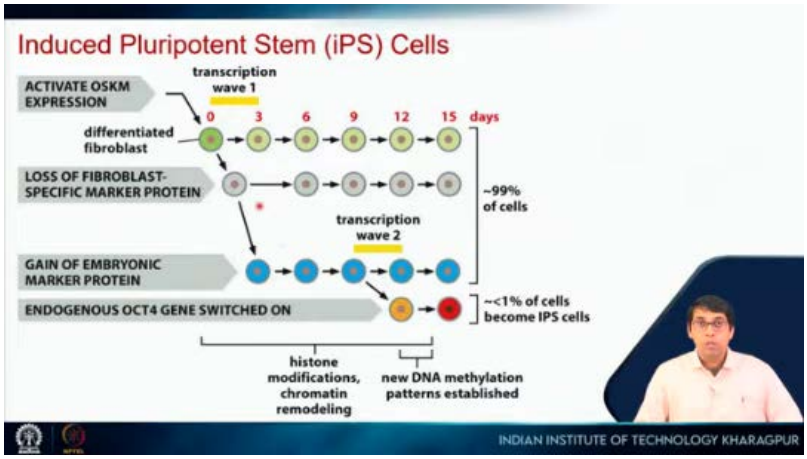
So, this is exactly what was done by Professor Shinya Yamanaka. So, in 2006, he showed in mouse cells and in 2007 in human cells that you can take a differentiated cell, like a skin cell or a blood cell (again, not a red blood cell but some other blood cell). If you add these four proteins, they are OCT, Sox2, Klf4, and c-Myc. So, if you add these four proteins, you can convert a differentiated cell into a stem cell and these types of stem cells are called induced pluripotent stem cells because we are inducing the formation of these stem cells by adding these factors. These are pluripotent, which means that you can produce any cell type from these stem cells. So this is fantastic and because of this fantastic discovery, Professor Yamanaka won the Nobel Prize in 2012.

So, these four proteins are often called Yamanaka factors, or you will also see in textbooks that they are referred to as OSKM factors, so just taking the initials of these four proteins, OSKM. So, this is briefly the process that happens. So, let us say we take a differentiated cell, which is a fibroblast. So, activate the expression of these four proteins, the OSKM proteins.



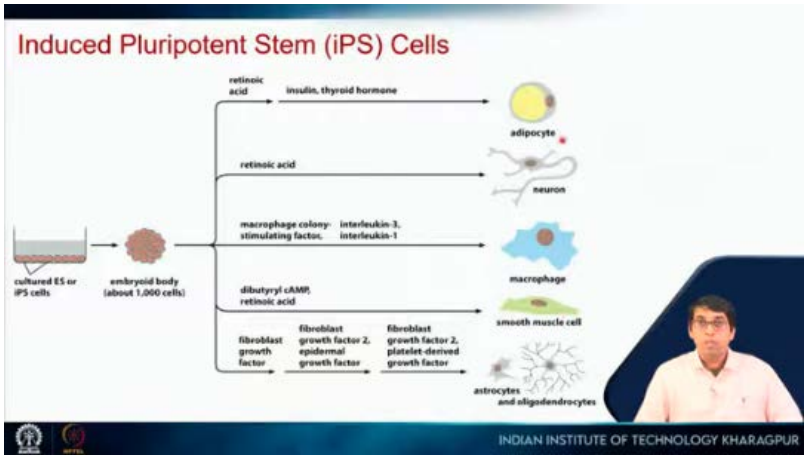
So this is day 0. So these proteins are activated, and many cells will remain in this stage. But some cells will show a loss of fibroblast-specific marker proteins. So, there are certain proteins which are produced by this fibroblast, and you will see that those proteins are slowly disappearing, which means that this cell is losing its characteristics. So, it was a differentiated cell and it is slowly losing its characteristics and then, over time, you will see that many cells will remain in this particular stage. A very small subset of these cells will then gain embryonic marker proteins. So, they will become more stem cell-like. So, they are producing proteins which are produced in embryonic cells and again, over time, some of them will remain like this, but a few of them will start producing some more proteins.

Finally, they will attain this stem cell-like characteristic. So, if you start with, let us say, 1000 cells and you treat them through this, you will get maybe 3 or 4 cells, a few cells which will become induced pluripotent stem cells but that is good enough because we can then culture these cells and produce more and more iPS cells because they have the property of self-renewal. So when this happens, a lot of things happen. There are different transcriptions that happen.



So the transcription pattern changes, different proteins are produced, histones are modified, and DNA methylation happens so all of these things happen. So ultimately, we get a few stem cells from thousands of these types of cells. But now, once we have these stem cells, we can culture them. So we can culture them and produce a large body of cells, and then we can add these other factors which can differentiate them. So, we can add factors that will make them neuronal cells, and we can add some other factors that will make macrophages. So, this is present in our blood; it is very important for our defense system, the immune system. We can add certain factors to produce smooth

muscle cells. So, we can produce all these differentiated cells by adding these different factors.



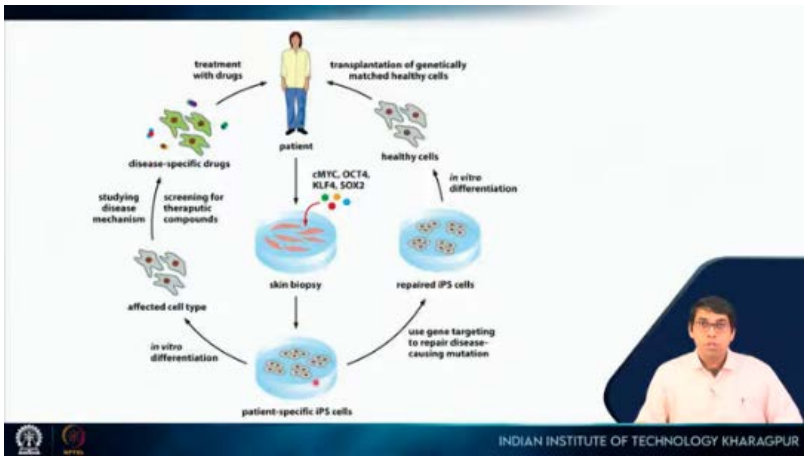
So, we take a differentiated cell, add the Yamanaka factors to produce the induced pluripotent stem cell, and then we add these other factors to produce these differentiated cells. So, why would you do that? Let us see an example of an application. So, let us say this particular patient has some illness. So, we want to replenish, let us say, Parkinson's disease, and we want to replenish these dopaminergic neurons.

If you take neurons from some other person, most probably this person will reject it; the body of this person will reject it because there is something that our immune system can distinguish, that okay, this is coming from our own body or this is coming from a different person or different organism. So, it can differentiate between self and foreign. But that problem can be overcome if we, let us say, take a skin cell from this person, add the Yamanaka factors, and produce these induced pluripotent stem cells. Now, since this is taken from this person, it will have exactly the same genetic makeup. So, the immune system will not differentiate it as foreign; it will identify it as self.

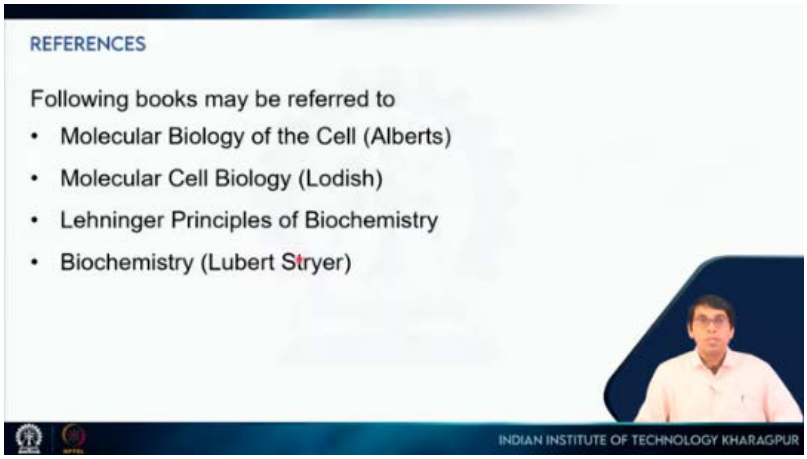
Then we can use certain gene editing methods to repair whatever the problem is with this cell. So maybe there is some mutation, and we can remove that mutation. So we can repair that using technology like CRISPR. Now, you have these repaired stem cells, then differentiation can happen and can be induced to produce healthy cells, and those healthy cells can be transplanted into this person. So, the cells are taken from this, and then they are put back; the body will not reject it, and you are putting back healthy cells.

So, this is one application; the other application can be that instead of repairing it, we can produce the defective cells. So we can produce the defective cells. We can then tease apart what is wrong in this cell. We can figure out the mechanism of the disease.

So that will be the research or we can use these cells to screen various therapeutic molecules and then we can use those therapeutic molecules to treat the disease. So treatment can be via this path or treatment can be via this path. In all those, these induced pluripotent stem cells will play a major role.



So, these are the books that you can refer to for this particular lecture.



Thank you.