Introduction to Complex Biological Systems
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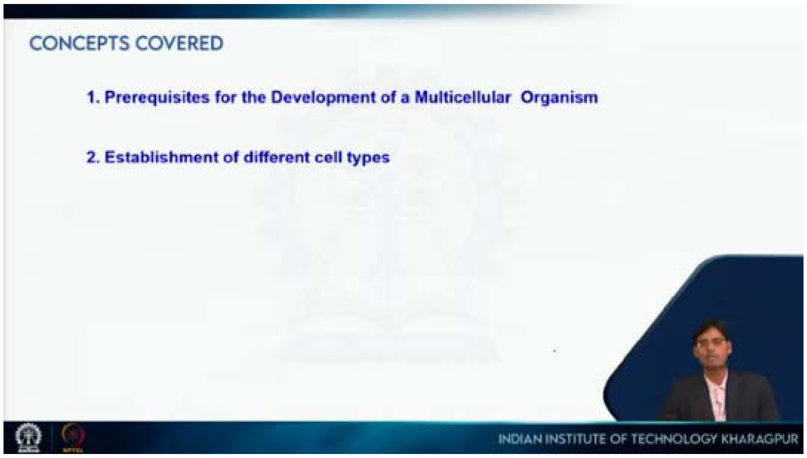
Lecture 26
Overview of the development of multicellular organization

Welcome back to the online NPTEL course on Introduction to Complex Biological Systems. Now, we are in module 6, where we are going to discuss cells, tissues, and organs, particularly the complex architecture of living systems. So, in module 5, Professor De discussed the cell, the smallest unit of life. But here we will go into more complex topics, such as how multicellular organisms develop.

So, let us start. So, today, particularly, I will be discussing the prerequisites for the development of a multicellular organism and then the establishment of different cell types. As you know, in multicellular organisms, for example, in humans, we have different types of cells in our body. So, how those cells are generated will mostly be introduced in this discussion. So, here I am showing the life cycle of a multicellular organism. So, as you can see, if I start from here, this is the zygote.

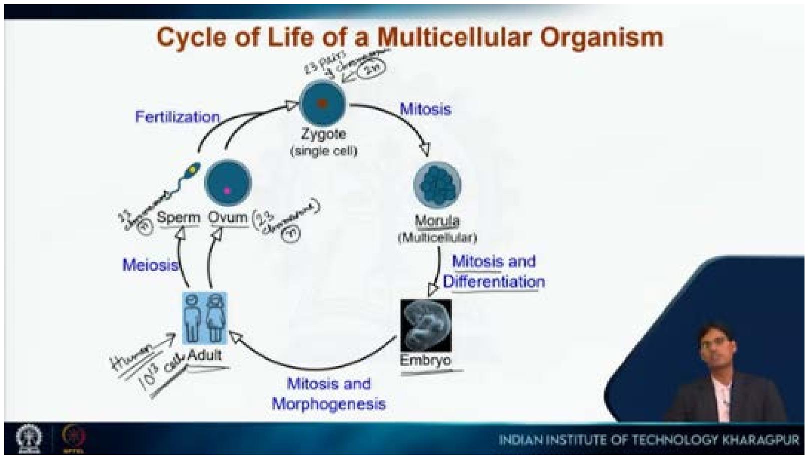


So, just after the fertilization of sperm and ovum, it forms the zygote. So, if I am talking about the human system, then here we have all the chromosomes that should be present. So, in this case, 23 pairs of chromosomes are present in the zygote, and now it will undergo mitosis and form a morula. So, at this stage, as you can see here, only a few cells are present, and these cells have the property of being called stem cells. You already know this from your module 5 lectures.

So, now, these stem cells have the potential to make different types of cells in our body. So, as a result of that, it will undergo mitosis again and it will differentiate into different types of cells as well as form some organs and finally, we will have the embryo. So, these are the early developmental stages. All these things are happening because of mitosis, as you already know that there are two major types of cell divisions, they are mitosis and meiosis.

So, as you can see, all these processes are happening because of mitosis. Now again, from the embryo, mitosis will continue, and morphogenesis will occur, and finally, after some time, we will have an adult individual, as you can see, we are just using the example of a human here. So, as you know, in an adult, there are approximately 10^{13} cells present in a human. So now, those cells are being produced because of mitosis, and as you can see, in a complex body plan, we have specialized organs, everything is in its proper place, and that will help us. So now, in adults, meiosis is also occurring, and because of meiosis, some specialized cells, germ cells, will form sperm in the case of a male individual and ovum in the case of a female individual and finally, after fertilization, we will have the zygote again. So, in the ovum, in that case, we have half of the chromosomes, which means just 23 chromosomes, not 23 pairs, just 23 chromosomes. Similarly, here, 23 chromosomes in the sperm. So, we say this is the n number, and this is n, and finally, in the zygote, we have $2n$ number of chromosomes.

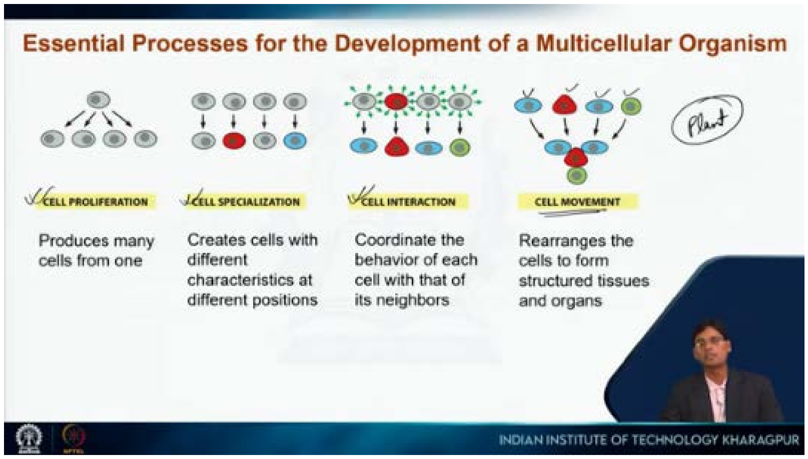
So, this is kind of the cycle of life in a multicellular organism because, in the case of unicellular organisms, for example, bacteria, the system is completely different. So, from one bacterium, just its chromosome will be replicated, and then the cell will divide into two, but they will not stay together. Those two cells will be different. They will be different individuals because they are unicellular organisms. But in the case of multicellular organisms like plants, animals, including humans, we have a lot of complex organization and complex processes, and I am going to discuss a few of those things today. So, these are the essential processes for the development of a multicellular organism. As you know, one important thing is cell proliferation here. So, that produces many cells from one cell, as I already mentioned that, for example, every individual, like a human, for example, we started from just one cell, from just a zygote, and an adult individual, I just told that approximately 10^{13} cells are present.



So, as a result of that, you can understand that cell proliferation is a very important thing that will produce many cells from just one cell. Now, here, the next thing is cell specialization. So, this is creating cells with different characteristics at different positions. For example, as you know, our nerve cells have their unique features and unique functions. On the other hand, some cells present in the liver, or pancreas, are also busy doing their specialized functions.

So, cells need to be specialized over time during development, which is also an essential step during the development of a multicellular organism and very importantly, number three is cell-cell interaction, or just say cell interaction. Coordinate the behavior of each cell with that of its neighbor. The thing is, although we have many cells in our body, they are kind of regulated; they coordinate with each other, they influence each other, so that they can help in different types of specific functions in our body. So, this is absolutely important for a multicellular organism and then, cell movement, as you can see here, we are showing that, four different types of cells, as you can see, this one, this one. We are just marking with different colors, but you can see here that those cells are moving in a specific pattern.

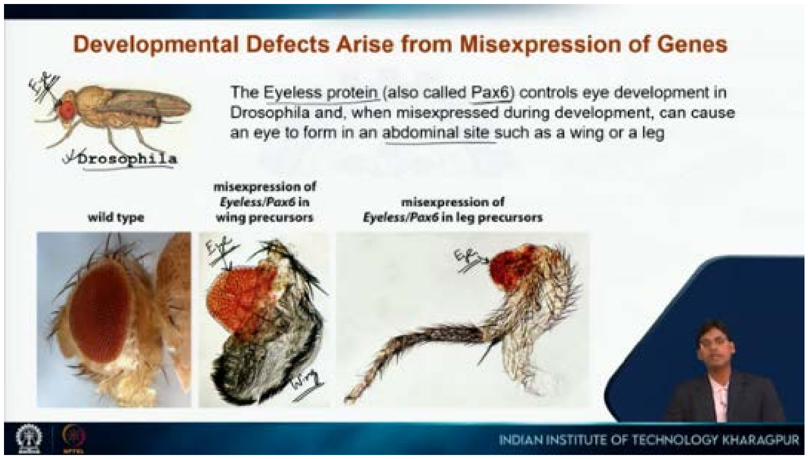
So, they can rearrange to form different types of structured tissues and organs during the developmental processes. So, this cell movement is, I would say, a very unique feature in the case of animal development. As you can see in the case of plants, in plant development, this cell movement is almost nonexistent because in the case of plants, those cells have cell walls, which are very hard structures, and those cell walls kind of cement those cells in the surrounding region, so they cannot freely move here and there. So, as a result, this is a major difference in cell movement between animal development and plant development.



So, these are the four important prerequisites for the development of a multicellular organism. Here, I am just introducing that developmental defects arise from the mis-expression of genes. Whatever four steps I mentioned in the previous slide, if some dysregulation happens, some problem occurs, maybe because of some genetic-level issue, then it will result in some developmental defects. So, here we are showing one fly, Drosophila. So, as you can see, this is the eye of Drosophila.

Now, there are many genes involved in the development of the eye in Drosophila. One of the important genes here is the eyeless protein, which is also known as Pax6. This is the product of some gene that controls eye development in Drosophila, but when it gets mis-expressed, its expression is not controlled properly and is mis-expressed, then we can see the development of the eye in the abdominal side. For example, as you can see, here is an eye-like structure, you can see that eye here, where this is just a wing. So, the mis-expression of eyeless or Pax6 in the wing precursor produces an eye in a different location, which is not the normal location. Similarly, here you can see the development of an eye on the leg of this Drosophila.

This is again because of the mis-expression of this protein. Now, the question is not just the mis-expression of this eyeless protein in Drosophila. Scientists observed that the homolog of this protein, I would say the same or I would say the similar gene, which is responsible for the development of the eye in other animals, and if that is mis-expressed in a transgenic fly, this will also result in a similar scenario. So, therefore, this kind of thing is very much conserved also. The expression should be strictly regulated; the mis-expression will result in developmental defects, but fortunately most of the time everything is going properly in our body, which is why we are healthy and happy.

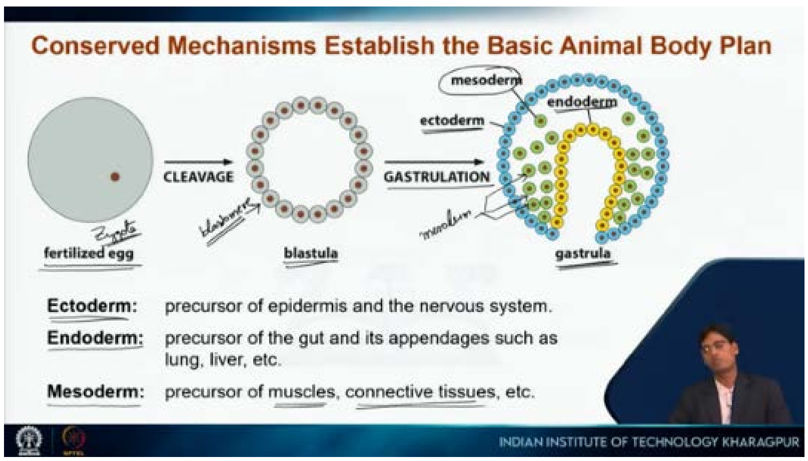


Now, I will start with an overview of development. Here, a conserved mechanism that establishes the basic body plan, so particularly here, whatever I am trying to explain, this is related to the development of an animal. So as you can see, this is a fertilized egg, or we can say this is the same thing, a zygote, a fertilized egg, and after cleavage or several rounds of initial division, it will form a blastula, and these cells present here are called blastomeres. These are kind of epithelial cells, and they are blastomeres, and now it will undergo another process called gastrulation. This is a complex process, and during this gastrulation process, as you can see, we are showing cells with different colors in here; this is a gastrula.

So, now you can see whatever cells are present here in the blastula; after this stage, after gastrulation, some of those cells are stuck inside. So, as you can see, these green cells are stuck inside. So, these green cells are called here, in this diagram, they are mesoderm. As already mentioned in this figure, this is mesoderm. While we are showing these cells on the outside in blue color, they are epidermis or I would say ectoderm, here ectoderm, and cells which are going inside, shown in yellow color here, that is endoderm.

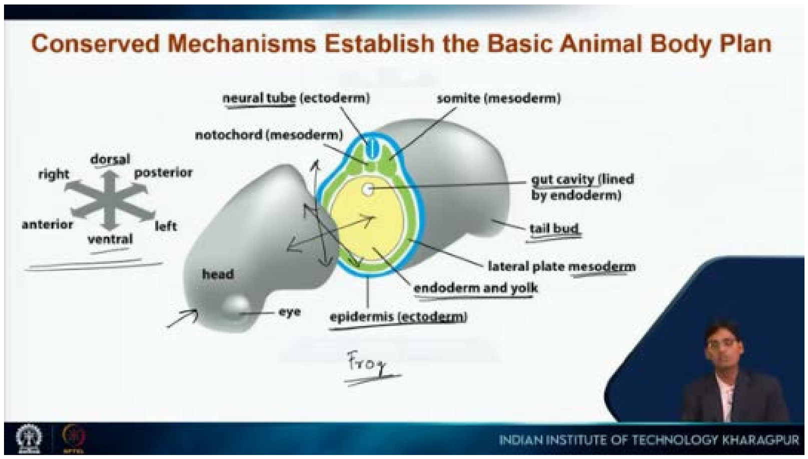
So, as a result of that, what I am trying to explain is that during gastrulation, some of the cells get stuck inside and they form three different layers. On the periphery, we have the ectoderm, and inside, we have the endoderm, and the mesoderm is kind of sandwiched between the endoderm and ectoderm. And more importantly, I would like to mention here that the ectoderm is the precursor of the epidermis, for example, the skin layer. This is the precursor of the skin as well as the whole nervous system, which is also produced from the ectoderm and this overall idea is true for every animal, I would say, in humans and in frogs. So, this is mostly based on experiments on frogs, but this is a kind of conserved body plan.

Now, the endoderm, whatever I told at the inside, at the core, this is the precursor of the gut and its appendages, such as the lung, liver, pancreas. All those organs are formed from this endoderm and the mesoderm, which is sandwiched between the endoderm and ectoderm, is called the mesoderm. This is the precursor of muscles and connective tissues. For example, our blood cells, blood vessels, all are produced from the mesoderm. So, as a result of that, you can understand that at the very early stage of development, those things are getting decided from this position and patterning of the ectoderm, mesoderm, and endoderm, which will form different complex systems and organs as the development progresses. So, here, as you can see, the conserved mechanism establishes the basic animal body plan. Whatever I was discussing here, we are showing an early stage of an embryo, and this is again an example taken from a frog. Frog embryo.



So, and now here, on the left side, as you can see, we are trying to explain different planes, I would say, here the dorsal side and the ventral side. So, if I see here, like I am trying to show here. So, this is the dorsal side, and this is the ventral side. This is ventral and dorsal, and then we have posterior, this is posterior, and this is anterior, the front part and the back part, and then we have right and left, this is right and this is left.

So, this way for our discussion, we are just mentioning in this way, but this anterior-posterior determination, dorsal-ventral determination, this is very important for the development; otherwise, everything will be skewed up. So, as you can see, if we just make a cross-section through this embryo, as you can see, on the outer surface, we have the layer which is shown in blue color; that is the ectoderm that forms the epidermis, and as I already mentioned, that ectoderm is also playing an important role for the formation of the nervous system. The neural tube formation takes place from the ectoderm itself, and now, at the very middle here, we have the endoderm and yolk. So this shown in yellow color, endoderm, and inside the endoderm, you can see some hollow cavity-like structure here; we are saying that gut cavity here, which is lined by endoderm. Now, mesoderm is just the layer in between endoderm and ectoderm, as we already discussed, and this part is the head, and this is the tail. So, as a result of that, after a certain time of development, it will be very much clear that this is the head, and this is the tail, and then other organs will form progressively.



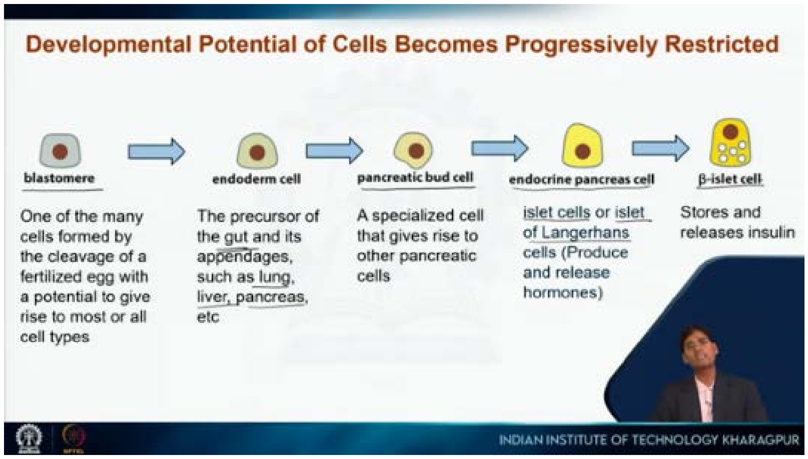
Now, whatever I told that was kind of a little bit of introduction; if I take a specific example here, that is how these different types of cells or organs develop. In this case, whatever I mentioned, this is because of at the beginning, for example, the zygote it has huge potential; it is kind of a stem cell. So, the zygote can divide into multiple cells, those are called blastomeres. But they are stem cells; they have the potential to make different types of cells in our body and, after gastrulation, when we have the epidermis or the, I would say, the ectoderm, endoderm, and mesoderm, now they have some kind of restricted potential that mesoderm will form blood tissue or those kinds of tissues, connective tissue, but mesoderm will not form nerve cell, for example, because that is already restricted.

So, this is the point here that the developmental potential of cells becomes progressively restricted over time during development. So, here, blastomere, this is, as you can see, one of the many cells formed by the cleavage of a fertilized egg with the potential to give rise to most or all cell types, as I already mentioned. Now, in the next step, when it is forming endoderm cells, then it has some limited options, it cannot make everything; it has the potential to make the gut and some other appendages in our body, such as the lung, liver, pancreas. So still it has the potential to make different types of organs in our body during this stage. Now, if I go a little bit more, for example, in the next stage, as you can see, this endoderm cell is forming now the next cell type, that is, pancreatic beta cell; now, this is a kind of specialized cell that will give rise to other pancreatic cells.

So, that means this is now confined to the pancreas only. It will not be able to make lung, liver, or gut. This is kind of already going into the pancreatic line. Again, after some division, it can make endocrine pancreas cells. So, in the pancreas, there are many types of cells.

Some of those cells are endocrine cells. They are producing hormones for us. For example, islet cells, also called islets of Langerhans cells that produce and release hormones like insulin and glucagon. Those are the hormones that are very essential for our body, and those are produced from the islets of Langerhans. So, as a result of that, when this blastomere, through these processes reach into this stage, like endocrine pancreas cells, that means their fate is to produce hormones inside the pancreas. Now they can again be specialized, and they can form the beta cells in the islets of Langerhans. Langerhans beta cells in the islets of Langerhans, as you know, that beta cells in the islets of Langerhans.

They produce insulin for us. So now they are not even able to produce glucagon, the other hormone. So they are very much specialized, and they are forming and storing insulin for us. So this way progressively, our stem cells can be converted into more and more specialized cells, and with, like, specialized cells with specific functions, as we explained in the case of this. pancreatic beta cells, which produce insulin for us. Now, why are these things happening? Because we must consider that all those cells, even during the gastrulation process, I told you that there are three major different types of cells, those are ectoderm, endoderm, and mesoderm, but all those cells, they have same set of information. They have the same DNA, but still, they are behaving differently. They are going into different, different options, and they are making specialized cells and organs in our body. So, because each cell type expresses a unique subset of the genome and that product means here, the RNA and protein, give the cell types their unique function. And because of that, the control of gene expression is very, very important. Although we have the same information in every cell, but how those genes are getting expressed, that is very crucial for this different type of cell fate.



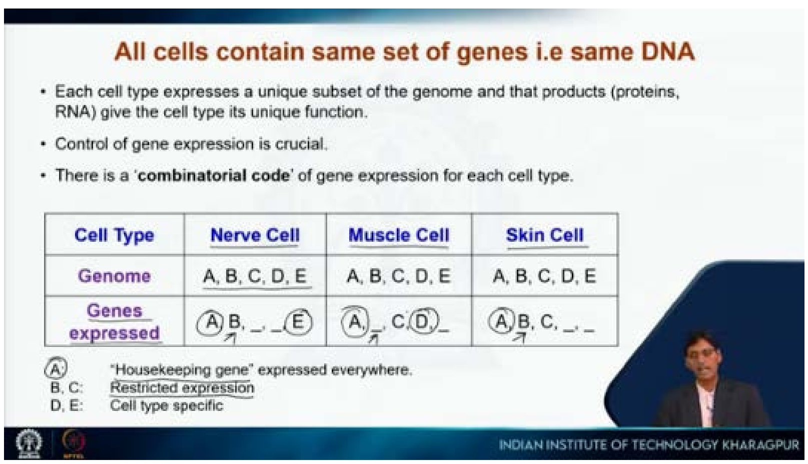
There is a combinatorial code of gene expression for each cell type. I mentioned, in some discussions, that we have around 20,000 different protein-coding genes, but they have a very complex combinatorial code. Some genes are constantly expressed in all cells in our body, while some genes are not expressed at all in certain cells and tissues. So, as a result of that, it is a very complex process that determines the production of different types of cells in our body. Here, very simply, I am going to discuss what this means, that is the combinatorial code of gene expression.

So, here, if you see, I am trying to explain three different types of cells. One is a nerve cell, the next one is a muscle cell, and the last one is a skin cell. So, those three cells have different locations in our body, they have different functions, and they are completely specialized for their functions, but if you see, their genome is the same. In their genome, they have, as I mentioned, 20,000 protein-coding genes, all of which are present. But here, for clarification and explanation, I am just mentioning five genes. Those are A, B, C, D, and E, that are present in all these cells, the nerve cell, muscle cell, and the skin cell. Now, out of these five genes, as you can see, gene A is present and it is expressed. So, here we are showing gene expressed.

So, gene A is expressed in nerve cell, muscle cell, and skin cell. We are showing just three different cell types. Maybe if we include more cells, like liver cells and pancreas cells, we will see that A is getting expressed everywhere. So, as a result of that, I would say that gene A is a housekeeping gene that is expressed everywhere. The next ones, genes B and C, have restricted expression. So, as you can see, gene B is present or gene B is getting expressed in nerve cell and in skin cell.

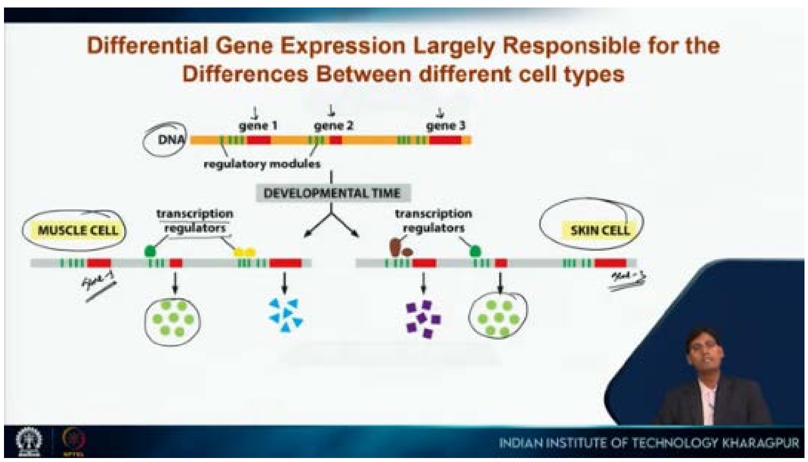
So, both are originated from ectoderm, but gene B is absent here in muscle cell; muscle cell is produced from mesoderm. So, as you can see, they have some kind of restricted expression. So, that is why this gene B and gene C have restricted expression.

If you see gene D and gene E, they are cell-type specific, as you can see gene E is only getting expressed in nerve cell, and that is giving unique features to nerve cell. While gene D is only getting expressed in muscle cell and providing unique features to muscle cell. So, these cell-type specific genes, although we are saying just gene E in nerve cell, but we might have many other genes also that are specific to nerve cell, but this is a very simplistic view of this combinatorial code of gene expression. Therefore, you can understand how it can regulate or it can determine different types of cells with their specific function. Now, this differential gene expression is largely responsible for the differences between different cell types, as I already mentioned. But why are these different genes getting expressed in different types of cells, although the information is present everywhere? All this is happening because of the regulatory modules and the regulation of gene expression.



As you can see, I am showing here this DNA and in this DNA, I am just concentrating on three genes here, the gene 1, gene 2, and the gene 3. Those three genes are actually present in both muscle cell and skin cell, as I already mentioned and the information is the same everywhere. Now, at a certain point of time during developmental time, as you can see, in muscle cell, somehow the gene 1, this is our gene 1, shown here is not making any product because of some kind of regulation. On the other hand, you can see that gene 3 here, gene 3 in skin cells, is also not making any product. So, therefore, as you can see, only gene 2 is getting expressed in both cases, in skin cells as well as in muscle cells, but gene 1 and 3 they are kind of differentially expressed in two different types of cells, muscle cells and skin cells. This is because of the availability of this transcription regulated by some other proteins.

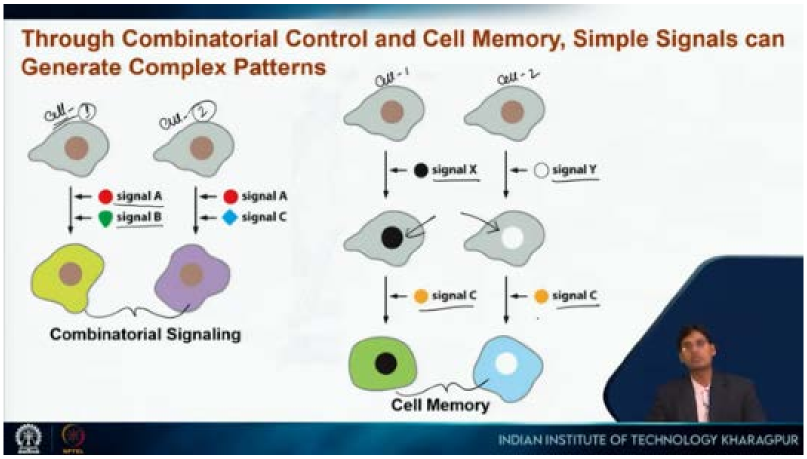
They are controlling the expression of this gene, and that actually determines the fate of this cell, what kind of product they will make, and accordingly, they will make different types of cells in our body. So, also, through combinatorial control and cell memory, sometimes simple signals can generate complex patterns, as you can see. Instead of specifying that particular gene 1, gene 2, gene 3, whatever I discussed before, here I am trying to explain in a defined way. So, as you can see, these two cells, here the cell number 1 and the cell number 2. They have the same properties, that is why we are showing the same color, same shape, everything. So, I would say that they are kind of the same cell. Now, combinatorial control means when these cells are getting divided or when these cells are undergoing developmental processes.



So, as you can see, in cell 1 here, we have some signal A and signal B they are influencing the fate of this cell 1. If I say this is cell 1, this signal A and signal B are influencing the fate of this cell 1, while in the case of cell 2 here we have the signal A, same, but signal C is different, some other signal. Signal means here it can be some protein, some hormone, or any other chemical found in our body that can be some kind of signal. So, this signal A and signal C are also influencing cell 2. So, as a result of that, now these two cells, you can see are different. So, here these two cells are getting different.

Their property will be slightly different also. So, as a result of that, this is what I am trying to explain to you, the combinatorial control. And on the other hand, here this is even more complex, that control at the level of cell memory. So, that means, here again if I mention this is cell 1 and this is cell 2, and when we are providing two different types of signals, I would say some kind of two different types of influences like signal X and signal Y. So, as a result of that, those two signals actually alter those two cells. They can remember, those two cells can remember that they received two different types of signals, and that is why I just changed their color, the nucleus color here, as you can see.

So, this is a different signal that they can somehow remember. On top of that, when they are getting the same signal, signal C, by these two cells, again you can see two different types of cells are getting generated. Here, what is the difference between this left side and right side? So here, at the end, signal C is the same in both cases, but still, because those cells previously received two different signals, signal X and Y, and they are staying as memory in those cells, So, as a result of that, upon receiving signal C, they are giving you some different types of cells in our body. Apart from that, I would also like to mention that a small number of conserved cell signaling pathways coordinate some kind of patterning in our body. This is very important.

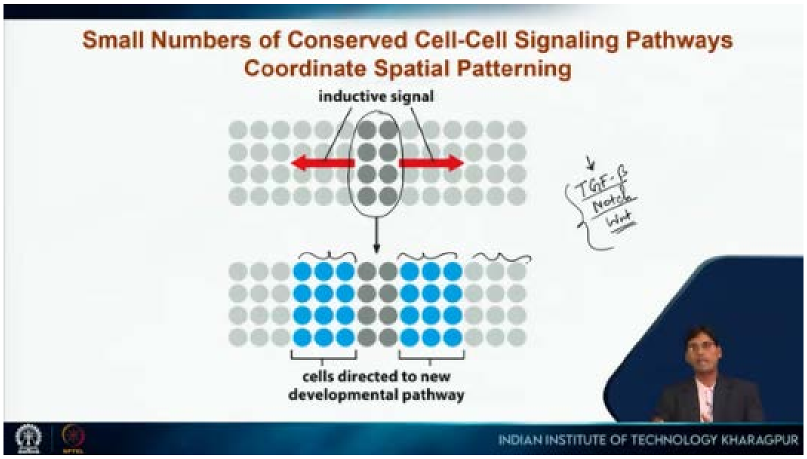


Although we are very defined, for example, one Drosophila, one worm, or I would say one bird, human, we look very much different, but we have a few conserved cell signaling pathways. For example, I would say like TGF beta notch signaling. So, these are very common signaling pathways that are conserved in many animals. So, now, what is this inductive signal?

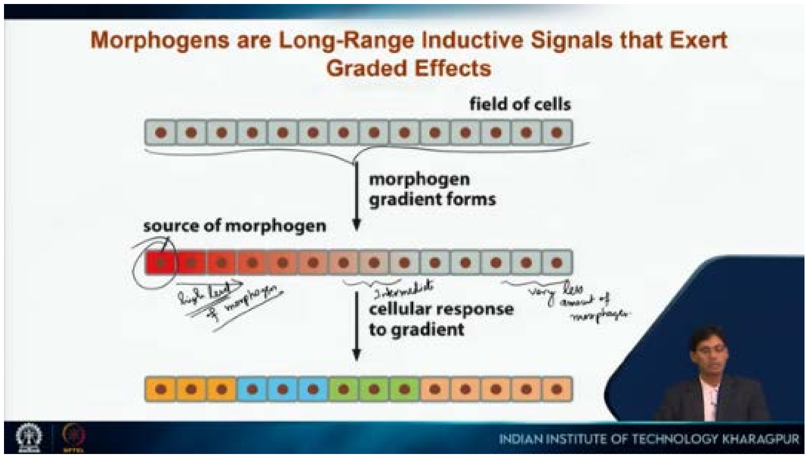
As you can see, these cells here, we are just putting, cells one after another here. So, now, this cell at the center might produce some kind of signal. For example, this TGF beta, TGF beta stands for transforming growth factor beta. So, this TGF beta will induce surrounding cells to develop into different types of behavior, different types of cells, as you can see, because of this signaling effect, these cells are now getting changed from the surrounding cells.

So, as a result of that, these cells are directed to a new developmental pathway because of these inductive signals and this signal can travel through different methods, for example, when cells are close by, cells are interacting with each other. So, two cells are getting attached by some kind of cell-cell junction. So, as a result of that, nearby cells will receive these signals. Also, it is possible that some of these signaling molecules can travel, they can diffuse over a long distance, and they can also modulate the function of those particular cells.

Then how will it happen? Because maybe the receptor of those particular signaling molecules is present on those cells which are receiving. Although they are present a little bit away from the source, but they have the receptor which will bind to this signal, for example, TGF beta. TGF beta will bind to its receptor present on some other cell, it might be a little away, but still, it will give rise and it will help to change the fate of those cells because of this signal. Here, the morphogens, they are particularly long-range inductive signals that exert a graded effect, as you can see. So, we are showing in two dimensions only, as you can see, those cells are just present in this way, but although we are showing here, you can also understand in three dimensions that everywhere cells are present and maybe this is the source cell which is producing some kind of morphogen. So, it will diffuse from the source like this. So, as a result of that, as you can see, if it is diffusion, then the nearby cells will have more concentration of this morphogen, but here we will have an intermediate level of morphogen, and here very less amount of morphogen, and this is intermediate, and this is a high level of morphogen.



So finally, that will make those cells different, and they will have some kind of specialized property in those cells. So, as a result of that, this morphogen also helps to determine the specific function of specific cells present in the surrounding. Here, this is the last concept for the generation of different types of cells here. So, as you can see, the asymmetric cell division can also generate different types of cells. So, here this is a stem cell.

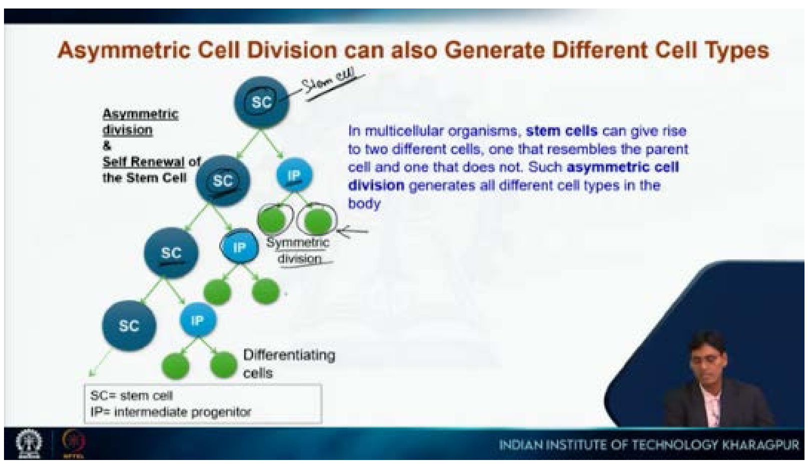


So, this is a stem cell, this is a stem cell. So, as I already mentioned, in blastula, those blastomeres are the stem cells, as they have the potential to make different types of cells. But I would also like to mention that adult individuals also have some stem cells. For example, in our bone marrow, we have stem cells.

So, from there, we are constantly getting different types of blood cells. So, as a result of that, although during the early developmental stage we have a huge amount of stem cells, they have a huge potential to make different types of cells. But in adults, they also preserve some stem cells for specific functions. Now, as we can see, this stem cell, when it gets divided. So, if the stem cell gets divided and it is not forming a stem cell again, then we will not have the stem cell when we grow, and I just mentioned that even in adult individuals, they have stem cells.

So, as a result of that, when the stem cell is getting divided, those stem cells somehow have maintained some kind of lineage. Some stem cells need to be preserved, right? That is happening because of the asymmetric cell division, as you can see. When these stem cells get divided, they will make one of these cells called intermediate progenitor cells (IP), so here intermediate progenitor cells, and one stem cell again. These intermediate progenitor cells will divide again, and that division can be symmetric division. Because of the symmetric division, it will make some identical cells, as you can see here that is because of the symmetric division. Now, after symmetric division, these cells, because of differential gene expression, some inductive signals, and so many things, can again alter the fate of these cells. But somehow, these stem cells are maintaining this stem cell line again. When this stem cell divides again, it will make intermediate progenitor cells and it will keep some stem cell line. So, this is the beauty of asymmetric cell division. So, therefore, they can maintain the stem cell lineage and they can also produce differentiated cells here. So, now this is very important for the development of different cell types. As you can see, you might get different types of cells here from this IP.

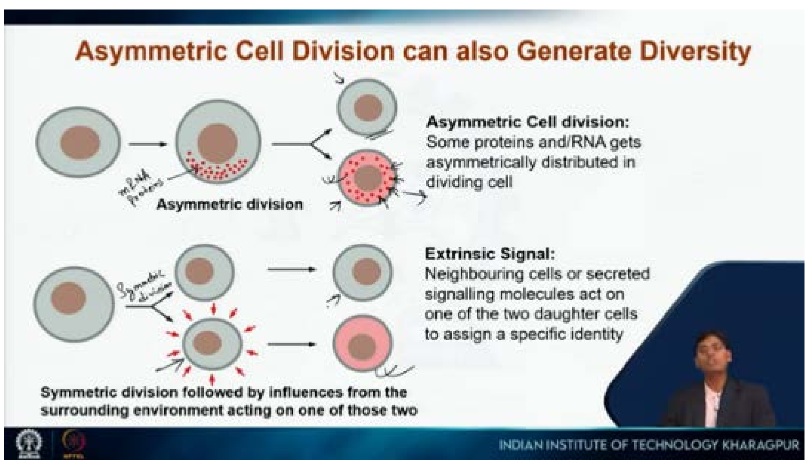
Similarly, here you can get different types of cells from this IP or intermediate progenitor cells. Now, what is the fundamental basis of this asymmetric division? Because when the division is happening, for example, this is showing asymmetric division, you have to be very careful here. Although this asymmetric division is happening here, the genome, the information, is the same in both cells here. This cell and this cell have the same set of information, the same genomic content. Genome-wise, they are not different, but somehow they are still making different types of cells, different types of fate in our body. That is because during asymmetric division, what happens is that some of those important products, I am not going into the details during this lecture, in the next lecture, I will discuss in more detail. So, here, for example, this might be specific RNA.



It can be particularly mRNA, or it can be a specific type of protein. They are somehow getting segregated to one pole of the cell, to one side of the cell. So, as a result of that, after division, as you can see here, these cells are now receiving those special molecules. Whatever those are, mRNA or protein, that does not matter here, but they are getting those special products, and that will influence this particular cell to make some different types of cells compared to the cells I am showing on the top. But they are not receiving those special molecules, which are the determining factor here. So, this is asymmetric cell division, and because of that, from the same cell, you are getting two different types of cells, and gradually they will make completely different types of cells.

Right. Another thing here is very important. Sometimes symmetric division, although I just mentioned asymmetric division, but sometimes symmetric division, as you can see here, is going on here. Two cells are the same. But after division, this cell at the bottom, I am showing here, this one, is getting some extrinsic signal from the surrounding. As a result of that, it will give rise to a different type of cell compared to the top cell here. So, this is another way that two cells are getting different.

This extrinsic signal can be some kind of whatever I told you that some inductive signaling or some other kind of signal, and that also results in two different types of cells. So, all those things define types of gene expression, combinatorial gene expression, as well as asymmetric cell division. All sorts of things actually determine or decide the fate of different types of cell types; they produce different types of cell types. And, from there, as we progress during development, it will make complex organs in our body, and this is very important for the development of multicellular organisms. So, this is all for today and, mostly for this part, you can refer to Molecular Biology of the Cell by Alberts et al., and, like many of those, the figures are actually taken from this textbook, and that is all.



Thank you very much.