Course Name: I Think Biology

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W4L21_Cell Cycle Control

Hello. In today's lecture of the "I Think Biology", NPTEL course, we will be discussing cell cycle control. So, in the previous class, we talked about the cell cycle, what is involved in the cell cycle, we talked about cell division, we talked about the different phases of mitosis, and we also covered sort of unusual kinds of cell divisions, right.

Today, we will discuss really what is the outcome of cell division and why do cells divide in the first place? What purpose do they serve for biological function? So why don't you think about that question, while we discuss really those those two main outcomes. The first will emerge as you view this video.

This is the embryo of a C. elegans, Caenorhabditis elegans, which is a roundworm. And it started off as a fertilized zygote. And you see that it's gone from a single cell to two cells, to four cells, and now you see cell divisions taking place, right.

What is the outcome of these cell divisions? I think you will start to see as this video progresses that you are going from a single cell to being a multicellular organism, where those cells actually take on sort of different functions, right. They start to differentiate. And this process where you go from a single cell to a multicellular organism with varied kinds of functional tissue that have specific functions is really called development, right. So I just fast forward this video a little bit so that you start to see that there are more and more cell divisions. Now you start to see that these cells are you know, pinching off in between. And remember that the ultimate outcome of this sets of cell divisions, what you really want to get is a worm, right. This almost starts to look like very familiar, like a fetus, human fetus, but you will see that this actually ends up being very much a worm, right. So these cell divisions have led really to the formation of a roundworm, over the you know to the process of development.

And then you will very soon see that this single celled organism emerges from its egg shell and

you have a worm, right. So development is the first outcome of cell division often. The other is growth, right. So you start off from being a small organism to one where you're much larger. And usually this growth in most organisms, it's not always the case, growth occurs by cell division. So it's not that your cells themselves are growing much larger, but rather that they are multiplying in number. So it's more cell proliferation than cell growth itself that leads to organismal growth.

Okay. So the two things that we really want to think about is cell is development and growth. These are the reasons why you would want cells to divide in the first place, right. okay. So one of the things you would have may have noticed in the first video with the worm is that cell divisions seem to be triggered at a precise time. And not only that, the duration is really very, very well regulated.

So it is not that a cell during the course of development can divide whenever it wants to, right. It is precisely timed through the course of development. And even during the process of growth in an organism, a cell has to divide when the environment is favorable, right. There's no point in dividing if there aren't enough nutrients available in the environment for example, to support a larger number of cells. So what is the process through which this happens, right?

So we talked about in the last lecture, the process of cell division, we said that mitosis is really the, which is the M, also called the M phase, shown in blue here, is the process where cells actually ultimately divide after cytokinesis. And the G1, S and G2 phases are really phases where the cell is preparing to divide, right. And so these phases G1, S and G2 are what we refer to as interphase.

Okay the M phase is mitosis. And what you will see is in mitosis, what you must realize that in mitosis, cells actually split apart, right. You recall this from our previous lecture. And they split apart through a process called cytokinesis. So what are the things, imagine you were a cell, what is the thing you would want to check for before you say, okay, this is time, I have everything I need for the two cells to split apart. So you might want to check that the DNA is replicated properly.

You might want to check that you have two copies of every chromosome that you need to form daughter cells that are identical, right. And so this point, right, before cytokinesis might be what you might call a checkpoint. This is where you want to check that everything is okay and cells can split apart, at after anaphase to the telophase, right. Okay, another point where you might want to check if things are going okay, and you are actually ready to duplicate your DNA is just before the S phase, right, where DNA is replicated, right. So what are the kinds of things you would want to check for, right. You might want to check if the environment is favorable, right? You might want to check that the existing cell that you actually, the cell that you are, everything is in order before you divide. Again, just after the G2 phase, before you enter into mitosis and

you start actually splitting the cell in two, you might want to check again that the environment is favorable for cell division, right? So this is also a checkpoint.

All right, so I use the word checkpoint deliberately because this is in fact what they're called if they're called cell cycle checkpoints, right. And depending on the organism that we are looking at, whether we look at yeast or human cell lines, check there are different checkpoints, right. There can be more or less, but the idea is really that these checkpoints serve to ensure that cells are replicated properly and at the right time. So how do we study cell division in this kind of a form? So as we just discussed, cell division happens a lot during development, right.

So this image shows you the development of a frog. So from the oocyte stage, right, this is the oocyte. From the oocyte stage all the way, so this is where the oocyte is growing. This is the first stage. After this, the oocyte and the egg, the sperm come together and fertilization occurs. And it's following this in the third phase that cells start to divide. And this division is referred to as cleavage.

And what you can see, as is written here, over the course of just seven hours following fertilization, you go from being a single cell to having 4,096 cells, just in seven hours, right. And once these cell divisions take place, you then see dramatic changes in shape and morphology through which gives rise to a tadpole. And then there's metamorphosis, you get a frog, the frog in turn lays eggs and the cycle continues, right. So this cell division in the cleavage, the cleavage portion of frog development is very interesting because it also allows us to study not only cell division, but the process of development, right. So how is the division of cells linked to how these cells eventually specialize and form this functional organism, the tadpole itself. So this is really interesting to study the juxtaposition or the overlap of division and development. But suppose you wanted to study something much simpler where you don't really want this overlap, then perhaps you might return to a slightly simple organism. And this is what is pictured here.

These are two different techniques of imaging the same cell. And these are Schizosaccharomyces pombe. So these are called fission yeast, also colloquially called fission yeast, because they really go through fission and they split into two and that's what you see here. So fission yeast are really nice to study because they are unicellular and they give rise to two cells that are about the same size and they don't need to specialize the way that cells do during development and fission yeast, Schizosaccharomyces pombe, have been really instrumental in us understanding cell cycle checkpoints.

OK, so these stars that I've drawn here are the checkpoints that I referred to earlier. But let's try to understand a little bit how checkpoints work, right. If you were a cell and a cell is essentially the sort of biochemical reactor with a set of instructions in the form of DNA,right. How might you think about checkpoints? How might you say, OK, now you can go ahead or you can't? What are the different mechanisms through which a cell may pass a checkpoint?

So the key sort of molecules that are involved in these in these checkpoints are what are called cyclin-dependent kinases. What you may already know are that kinases are enzymes that phosphorylate other proteins.

And what these kinases do is, they are present throughout the cell cycle and that's what's pictured here. So in black are the CDKs, the cell cycle, the cyclin-dependent kinases. And they're present throughout the life, the cell cycle. But what actually happens is during certain phases of the cell cycle right, there are proteins called cyclins. And these kinases, the ones shown in black, are dependent on the kinases for their activity, hence the name CDKs, right. Cyclin-dependent kinases.

And what you see here, for example, if you look at the M-cyclin protein, right, M-cyclin is synthesized just before the M phase. And when M-cyclin binds to the cyclin-dependent kinase, the kinase activity is switched on, right. Once mitosis is ending, M-cyclin is destroyed. That's what you see here, right. M-cyclin is degraded. And that means then that the CDK is no longer active.

The same is true when you're entering the S phase. There's another protein called the S-cyclin, which starts to be expressed and produced in the cell. And when this happens, the S-cyclin binds to the cyclin-dependent kinase that activates the CDK and allows its function. And it allows it to cross through this checkpoint.

Once it's crossed and the S phase is completed, the S-cyclin gets degraded. And now the cyclin-dependent kinase is no longer active. So another way to sort of picture this would be to say, as the S phase begins, let me draw it here. S-cyclin gets produced and then slowly falls off, right.

This is S-cyclin. And then in the case of M-cyclin, you would see production increasing and then dropping off towards the end of the M phase, M cycle. So you can also see why these are called cyclins because their production in the cell is cyclical. Ok, so this is already kind of a pretty fascinating mechanism,right. And it turns out that it's even more complicated than this.

So the CDK, which is shown in black here, and it's labeled CDK, is when bound to the cyclin is active. And it has one phosphate group attached to it. Now this complex can be inactivated in the presence of other proteins. So for example, when a protein called V1 is present, it phosphorylates another domain on this CDK-cyclin complex. And that renders this whole complex inactive, ok. On the other hand, if there is another protein, another phosphorylase, actually, phosphatase protein, another enzyme called CDC25, what it can do is it will dephosphorylate this complex and render it active.

So there are enzymes, both V1 and CDC25, that act antagonistically, right. And they result in either the activation or inactivation of this protein complex. So let me show you how and and in

fact, it was the fact that there were, as Bombay, in the fission yeast, the people who were studying the cell cycle actually found differences in the size of cells when they had a mutation in V1. So that meant that when V1 was present in much smaller quantities or in inactive forms, the enzyme was rendered, this enzyme complex was rendered inactive. And that meant that the cells divided earlier than they should. And so cells overall were much smaller. So let's have a look at how this might function. This is a regular fission yeast cell.

It's growing. And as it grows, there is a protein called POM1. And because the cell is expanding, as this happens, the POM1 expression is lowest in the center. And because it's really low, because of this concentration gradient in the center of the cell,right, POM1 is no longer able to inhibit enzymes that it normally inhibits, right CDR1 and CDR2. And what this means is because CDR1 and CDR2 are present, they actually inactivate this protein called V1.

That's what we've seen here right. Because they inactivated, this enzyme complex becomes active. And that allows, it's an active CDK, right. It becomes active. And that allows then the trigger into the next phase of the cell cycle, and it crosses the checkpoint, right. On the other hand, when V1 is present in the cell, what happens is that this POM1, sorry, V1 is present in the cell or rather active in the cell when POM1 concentrations are fairly high.

So when they are high, these proteins CDR1 and CDR2 are inhibited. This means V1 is active, which means then the enzyme complex that we've just talked about becomes inactive and the cell does not divide, right. So it does not go through that checkpoint. So I think this is a really fascinating process through which you see multiple enzymes or multiple proteins signaling and coming together to actually decide when a cell should divide, right. These kinds of CDKs are present throughout the cell cycle. And they interact with cyclins to allow basically passage through these checkpoints that we just talked about.

Okay, so it's interesting to study the mechanism. But why is the cell cycle so important? So one thing that we just talked about with the V1 mutant right, is the cell cycle helps determine cell size, right. And you can imagine that this is quite important, right. You can't have cells of really randomly different sizes. You have to have some sort of regulation for a function, for a tissue to remain functional.

Of course, it's fundamentally important for us to understand how cells divide, right. Because this then leads us to understanding how growth occurs, right. It also helps us to understand how development occurs, which is what we talked about. The outcome of cell division is really one of these two things. The cell cycle is also important because when it is impaired, it can lead to all kinds of diseases.

And in this case, because of these discoveries, basically of the studies into the cell cycle and the discoveries of the cyclins, the Nobel Prize was awarded to three scientists in 2001. So

Leland H. Hartwell had identified many proteins that were involved in the cell cycle. Tim Hunt identified specifically the cyclins. And Paul Nurse identified the interactions between these cyclins and CDKs that then eventually led to passage through these checkpoints. And he also identified the fact that cell cycle checkpoints are actually quite universal.

And wherever there is cell division, pretty much there are cell cycle checkpoints. So I want to further highlight the importance of these of these discoveries by showing you several examples where the CDKs and the cell cycle have been shown to be important for disease. So this is an example where you see that cyclin-dependent kinase 1 is important for muscle regeneration. So whenever there is muscle, injury to muscle, the regeneration of muscle can only occur if CDK1 is present and is not damaged in some way or mutated in some way.

So another example is that cell cycle deficits are important for neurodegenerative disorders. So this ranges from Alzheimer's disease to dementia and even actually schizophrenia. So uncovering the mechanisms of why cell cycle deficits are important are really important for neurodegenerative diseases as well. One more example is referring to Parkinson's disease, right. So dysfunction in the G1, S cell cycle checkpoint has been shown to be important in Parkinson's disease.

Next and finally, the cell cycle is controlled often by oncogenes. So these are oncogenes basically code for proteins that promote cell proliferation and if they are not controlled, they may then lead to cancer. The cell cycle is also controlled by tumor suppressors. So tumor suppressors suppress cell division. So as you can imagine, they may also help suppress tumors, right. So if the cell cycle is not regulated properly, it can drive the transformation of normal cells into cancerous cells.

And so basically the focus of our next two lectures will actually be on cancer and the cell cycle and really how, what cancer really is and its role in our understanding of cell biology. So I want to end by summarizing what we talked about. We talked about cell division. We went again over the different phases of interphase and mitosis. We talked about when and how a cell cycle should take place.

Why should we have checkpoints in the first place, right? So a cell might want to check whether the DNA is replicated properly. It might want to check if the environment is favorable. It might want to check if once the DNA is replicated, are chromosomes going to segregate properly by attaching to the spindle? So there are multiple questions the cell would want to ask itself at different points along the cell cycle and that's what checkpoints are for. We talked about how these checkpoints are controlled via the expression of cyclins which bind cyclin-dependent kinases.

So cyclins have the cyclical expression. This expression pattern then leads to basically cyclical

activation of CDK proteins which are involved in the passage from one stage of the cell cycle together. And finally we finished by talking about the importance of these cell cycle checkpoints, especially by highlighting sort of the wide variety of diseases that arise when cell cycle checkpoints are dysregulated.