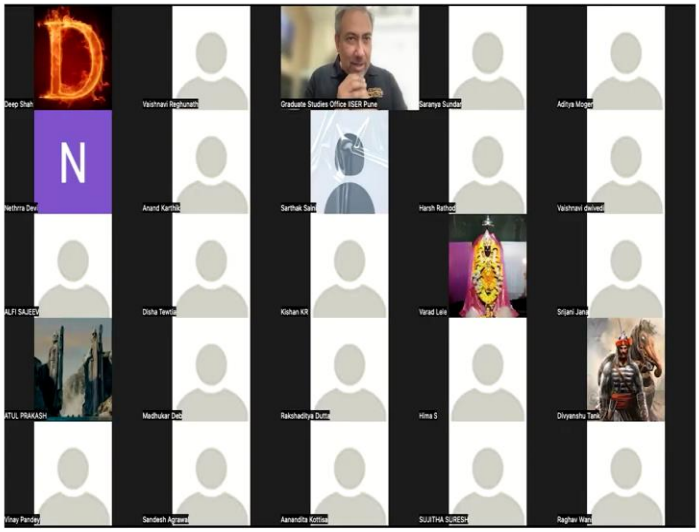
Introduction to Cell Biology
Professor Nagaraj Balasubramanian
Department of Biology
Indian Institute of Science Education and Research, Pune
Lecture 53
Endomembrane System of Cells: Discussion Session 3

(Refer Slide Time: 0:15)



Professor Nagaraj Balasubramanian: So, I will take questions, we will begin with Deep, who has his hand up. Deep go for it.

Deep Shah: Sir, I wanted to ask how does the cell recognize what is damaged or what is not functioning?

Professor Nagaraj Balasubramanian: Good question, Good question that is a important question to ask. So, there are many ways to do this. And it is fairly, it depends on that particular, organelle or tissue, in some cases, there could be certain changes that accrue over a period of time, which means that it is not like it is damaged per se, that is, it is broken in some ways.

But, there could be changes, for example, in the phosphorylation of a protein and this was phosphorylation happens over time. And, over a period of time, a certain percentage of a certain protein is getting phosphorylated in the cell. And that could be a trigger. See, the critical thing here to consider is that there is no, I think, we have a tendency to think that there must be some

kind of a sign or a symbol that says, this is the organelle, that needs to be kind of send for processing through the autophagy pathway.

It is possible that the when these auto phagosomes are being formed, that the proteins that are present that are creating these structures, may also bind to certain things, preferentially, and one of those could be a change like this, on the on to proteins that are present on the surface of an organelle. There could be changes, for example, in the lipid composition that could also contribute to this.

To the best of my knowledge, it is not very clear, if there is like a specific trigger for a specific endocytic sorry, autophagy pathway to be activated. There could be many things that could drive this. But it is an important thought to have saying, what, exactly can flag this. And in many of these situations, these are changes that accumulate over time. I do not know, if you read about telomeres and how telomeres work, and how the age of the cell is determined, in some way.

So if and there is an accruing over every generation. Every time, the cell divides, there are small changes that happen. And after a point you kind of know what the health of the cell is based on these telomeres. So, similarly, there could be small changes, that, for example, mitochondria could accrue over a period of time. And if you are interested, go look this up, some of this is actually known in terms of what proteins are modified, and could be a trigger to send this to the autophagy pathway. Vaishnavi your query.

Vaishnavi Dwivedi: Sir, why do auto phagosomes owns have a double layered membrane?

Professor Nagaraj Balasubramanian: Because they are kind of, they are created within the cell. So they also have a way to kind of, they need to be able to be created within themselves. And that is why they begin. So, it is, essentially, if you think about it, it is actually a vesicle that kind of folds, and then goes this way.

And so there are 2 membranes here. And if you can imagine it that way. And that is just the mechanism that they have evolved with, to the best of my knowledge, there is not a huge advantage to having 2 membranes. It is not like, the membranes, that having one bilayer, and another bilayer actually does something usually important here.

I could be wrong about this. So, look this up, I will also see if I can find something that says that having 2 membranes is actually going to be beneficial in some way. To the best of my knowledge. I do not think so. So, let me check and come back to you as well. And if I find something, I will send it out to the rest of the class as well. Disha your query.

Disha Tewtia: Sir, what is amphisome and how is it different from phagosome?

Professor Nagaraj Balasubramanian: What is a?

Disha Tewtia: Amphisome, sir, it was in the image one of the images.

Professor Nagaraj Balasubramanian: Let me see . So that is essentially the same auto phagosome. But now, it has merged with something that is an endocytic component. And this is, by endocytosis, there is a mechanism called heterophagy, which allows you to pick things up from outside as well. And, and the amphisome is essentially a fusion of both of these. So, there is a something that is coming from the plasma membrane that fuses with the auto phagosome is what creates an amphisome.

So these are essentially all structures that are leading to their fusion with the lysosome, causing, breakup of whatever components they are carrying and the fact that they are brought together in this way, they are named differently in some cases. There are a couple of questions on the chat box that I'll take Sai Chinmayae and I will come back to the hands that are up, Sai Chinmayae has a query saying, How is the functioning of the lysosome is different from the auto phagosome? Does the auto phagosome also release energy as a result of degradation? Is that how it is different?

So the lysosome essentially carries the components for breakup. For chewing everything up and digesting everything. And the auto phagosome is just capturing the component that needs to be broken down. So unless the auto phagosome by itself does not have any lytic enzymes and so the lysosome coming with the auto phagosome is what then allows for the auto phagosome to digest everything that it carries. Kedar has a query.

Student: Sir

Professor Nagaraj Balasubramanian sorry.

Student: So what does the auto phagosome capture?

Professor Nagaraj Balasubramanian: Auto phagosome captures whatever needs to be broken down.

Student: Fine sir.

Professor Nagaraj Balasubramanian: So it is essentially capturing things that need to be digested. Kedar has a query, can we say that the auto phagosome is a kind of lysosome?

Professor Nagaraj Balasubramanian: Sure. See, the thing is, it is not a lysosome, simply because it is a vesicular structure, it is not a lysosome, because for it to be called a lysosome, it has to have lytic enzymes. And the coming together of the lysosome with the auto phagosome is what allows for the lytic enzymes to be part of it. Endosomes and phagosomes. So, endosomes are essentially endocytic vesicles.

And we have not talked about the process of endocytosis, yet, maybe I will speak a little bit next time about endocytic pathways, because so far, we have talked about membranes that are coming in from within the cell. And this is also the endocytic pathway is essentially a way of pinching membranes from the plasma membrane. So, the plasma membrane bends, and then pinches off. And this is a way of regulating the composition of the plasma membrane, it is a way of regulating the amount of receptors that are present on the plasma membrane, it is a way of taking things in and delivering them inside the cell. You know, all of this is done by endocytic pathway.

So, that structure that comes in is an endosome. And that is the difference between a so the difference between an endosome and a phagosome, essentially, would be that when it comes to taking up, it is also phagocytosis is also an endocytic process, but there the component that is taken in is something which is a food particle or something that is harmful to the cell like a bacteria that it wants to take care of.

Endocytic pathways or endosomes are largely working to kind of bring in membrane and receptors that are present on the membrane. Lysosome is basically vesicle lysosome is yes, a vesicle. But it has a vesicle with a very unique pH and a whole bunch of enzymes that can chew a bunch of different things off. And that is why they are different. Anand has his hand up for a while. Anand can you go ahead and ask your question.

Anand Karthik: Yes sir. Sir, I wanted to ask that are there any appreciable differences between the lysosome content within a species? Like for example, I wanted to use the Jacobs disease like different prions, which are actually misfolded proteins. So, it was seen in some drivers tribal's were there, mortal remains of the previous people, and they have got the same disease there like, it got infected in the brains, like there was accumulation of proteins.

So it seems that not all people died because of the disease, like, some were able to maybe digest that protein. And that would be via lysosomes. So, I was thinking, are there any variations in the enzyme content of lysosomes, within a species.

Professor Nagaraj Balasubramanian: That means you and me could have different lytic enzymes.

Anand Karthik: Some were able to digest those.

Professor Nagaraj Balasubramanian: So, some may some of that could also come from the kind of exposure that you had, it could also have to do with other components that are other players that are required for, the coming together of these proteins, because they are essentially aggregates. So the process of aggregation is, could also be influenced by many things, not just one.

And so, the short answer to your query, whether lysosomes. For example, in different cell types, could have different lytic compositions, it is possible, that the composition of the enzymes that are present here, the ratio of the relative enzymes that are present in lysosomes, that are part of a particular organ, could be different from another organ.

I think the fact that individuals have many different cell types and the, not just the lysosomal content, but other content could also be different between individuals. There could be many factors that influence, the nature of these enzymes. And, but I am not sure whether it is known that there could be one or 2 enzymes that, one person may have that another person may not.

Let me know, if you find something, I do not know, if that is really the case. I would not think that that might be the case. Varad has a query on the chat box. The Golgi apparatus does the finishing of proteins, and makes modifications such as lipid modification or glycosylation of proteins? How does the Golgi know that a particular type of protein is needed in a certain

organelle? While making a protein itself, why do not these changes occur? Do all the organelles convey their protein needs directly to the Golgi only?

So these are very interesting questions Varad. Let us, take one at a time. So does the Golgi know that a particular type of protein is needed in a certain organelle? Probably does not. So I think the Golgi does what it does. And this is something to also kind of wrap our heads around. Like, for example, when endocytosis is happening, and this is true for many cellular processes. That is triggered by something that drives endocytosis.

And it is probably not thinking about a lot of other things that are happening in the cell at that point of time, this trigger has happened there is something A that has told it that now endocytosis has to happen it will go into endocytosis, The stuff gets endocytosed and brought in. Then the availability of components inside, what is available, what does it is it in proximity to where exactly this endocytosis has happened, could all be influenced as to what happens to this vesicle

And the same is true for components from the Golgi. The Golgi is taking proteins that are coming from the ER there are times that the amount of protein synthesis may go up the number of vesicles that are coming in are higher the crowding of proteins in the Golgi may be high, the time that an enzyme gets to spend with a protein could get affected. So, the efficiency with which the Golgi works could change, be high or low.

But once the Golgi processes a protein and puts it into a vesicle. Then the vesicle just kind of Bumbles around. If there is a protein, sorry, a motor protein that needs to carry that vesicle that is available immediately there. It goes, captures it. Now this motor protein sits and starts walking with it. Now the vesicle has no clue where it is going. The motor protein kind of knows, you know where it is headed, in some ways.

So a lot of this is not very carefree pre planed. So it is not like, this protein knew right at the beginning that it needs to go bind to this particular motor protein to go to this compartment. The availability of this motor protein, the fact that so, if there is a protein on this vesicle that can bind this motor protein, there might be proteins on this vesicle that bind 7 other motor proteins to.

So, what decides where this vesicle goes to, the factors that could influence this is of the 7 motor proteins that it can bind, which of these motor proteins are available there, maybe 2 are available Now, if 2 are available, what is the relative concentration of these 2? Is one present 5 times more

than the other? The affinity with which they bind. The one that is present 5 times more binds with very poor affinity. So, it will keep binding falling off binding falling off, the one that is less may bind very firmly. And that could influence where this vesicle goes to eventually.

So, as much as some, there is a way for things to be carried to a particular site, it is influenced by many of these immediate decisions that happen. So, I do not think the Golgi is thinking, looks at a protein and says, Aare, this is the protein that, Ye To Apna favourite protein. So, I think the Golgi just looks at the protein and says, Aare, I have a protein, I have to process it, let us look at what signature it has and take care of it.

Does the Golgi keep track of, how many times it has seen that protein? Probably not. Every time it comes, that protein comes it sees there is new and processes it. While making a protein itself, why do not these changes happen? So, the mechanism, the machinery, the conditions that are required for the enzymes that work on this. It is possible that, there could be a glycosylation enzyme that is sitting, next to the ribosomes, one of the considerations here might have been that the ribosomes and are essentially trying to make a protein and have it prepared and sent out.

And they want to do this as efficiently as possible. Having a lysosomal enzyme sits next to there will delay a bunch of things. Because, proteins are being made very rapidly. The glycosylation process is kind of happening at a certain rate. So there is a possibility that keeping them apart allows for things to move at a certain rate and speed here, and at a certain rate and speed here.

The conditions that are required for these enzymes, and the conditions that are required for the ribosomes to function optimally could vary, this could be another reason to kind of keep them apart and separate them as well. Do all the organelles convey their protein needs directly to the Golgi? That is not how this works.

So remember, protein, it is highly possible that there is a signal that is a receptor that is bound to the plasma membrane that talks to the nucleus to tell that it should synthesize, activate the transcription of a particular gene, that now codes for a protein that now is getting made a lot more. And once it gets made, where it gets delivered depends upon that milieu and that environment. So, I do not think organelles per se, are doing this. It may affect the fact that this receptor is bound eventually leads to the delivery to a particular organelle. But did the organelle actually tell the Golgi? I do not think so.

Does autophagy happen in non-dividing cells too, how are they able to replace the organelles that are lost? So, it is a good question. So, there is some autophagy that happens in non dividing cells. I am not sure whether the rates are very radically different. And the synthesis of new organelles, does not is not tied to division. If that is how you are thinking about it neither. It does not have to be that cell has to divide to make new organelles.

So it is possible that, once the components are broken down, that, new organelles are also made in cells that are not dividing. What is the alternate to lysosomes to prokaryotes? So I am not sure there is an equivalent of the lysosome in prokaryotes. And check this up. Let me know if you find something. But to the best of my knowledge. I do not think there is something that does pretty much the same thing. Now yeast obviously have these. But I am not sure whether the prokaryotes you know like bacteria have a lysosomal equivalent or something that actually breaks this down. Let me go look this up as well.

Vaishnavi Dwivedi:: Sir, excuse me, sorry to interrupt, but even I was having the same doubt.

Professor Nagaraj Balasubramanian: Sorry you have to identify. One sec, you have to first identify yourself.

Vaishnavi Dwivedi: So, I am actually Vaishnavi. Even I put that hand up because I was also thinking about the same but I thought it is a silly doubt. Sir.

Professor Nagaraj Balasubramanian: It is nothing called a silly doubt, as you make.

Vaishnavi Dwivedi: Even I was comparing lysosome and amoeba, with that, you showed that slide of processes, endocytosis process and phagocytosis process. They were, on that slide. Professor Nagaraj Balasubramanian: Right.

Vaishnavi Dwivedi: So, I was also thinking the same, even amoeba also taking the food in and also there are vacuoles also there…

Professor Nagaraj Balasubramanian: So amoeba are a different thing. I do not think I think when you say prokaryotes, you are thinking about bacteria. I do not think you are thinking about paramecium or amoeba.

Vaishnavi Dwivedi: I was thinking about unicellular organism microorganism.

Professor Nagaraj Balasubramanian: That is different that is not prokaryotes necessarily. Prokaryotes, if you are thinking about amoeba and paramecium, they have slightly different mechanisms of handling this.

Vaishnavi Dwivedi: Yes.

Professor Nagaraj Balasubramanian: So, bacteria per se, whether they have lysosome like structures, let me look up, I will find out and if what I find that I will let you know.

Vaishnavi Dwivedi: Thank you.

Professor Nagaraj Balasubramanian: Aayush last question.

Aayush: Sir, in the autophagy like the five step process, that was in the scientific American article which you showed, that the first step was like when there is like a signal and all of the signals were, they did not have much to do with like, the damaged mitochondria itself so. Sir my question was, would it be right to say that the autophagy is induced by causes which could damage organelles, rather than the damaged organelles itself.

Professor Nagaraj Balasubramanian: No no autophagy cannot be. See, the thing here is that the autophagy is part of the natural process of the cell as well. So it is something that keeps happening irrespective of whether there is a damage inducing agent or not. Now a damage inducing agent may increase damage and therefore, cause a need for increased autophagy.

But in the normal maintenance of the cell, autophagy is important. And so that creation of an auto phagosome is probably happening at a steady constant rate in all cells. It does not have a lot to eat and process, if damage is not a lot, and this is standard level of processing that it does. But there are situations where there is damage to the cell. And the autophagy process needs to be kind of hastened or sped up, that is also possible. So, both scenarios could exist in that sense.