Introduction to Cell Biology
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Lecture 50
Endomembrane system of Cells: Part 2

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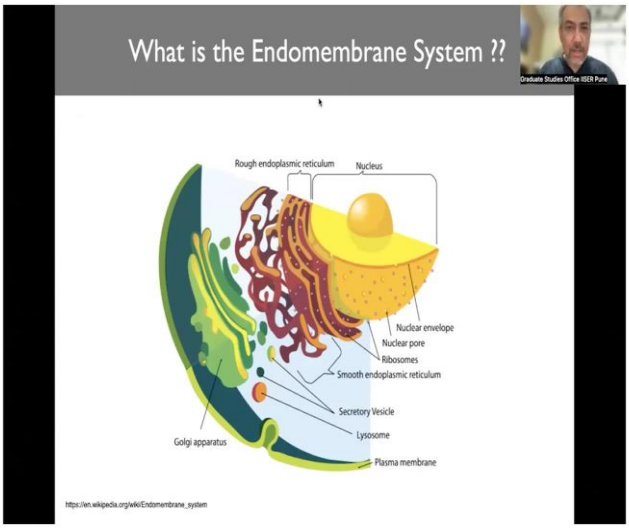

We will start today's lecture with a small recap of what we were discussing last time and then we will dwell into 2 of the major players of the endomembrane system today. We are going to look at the endoplasmic reticulum. And we are going to trying look at the Golgi and see how they are assembled and what we know about it, these are very interesting systems. The endomembrane system as I mentioned earlier, is a system that is put in place which connects the protein synthesis machinery at one end to the delivery of processing and delivery of proteins to different parts of the cell including the plasma membrane.

And the fact that the plasma membrane is made up of lipids this network is also made up of lipid membranes. And that allows for proteins to travel in a milieu of lipids to be modified, functionalized in this milieu of lipids, because eventually they have to function in a milieu of lipids. So, that is the delivery mechanism that these endomembrane systems allow for, and starting from the nuclear. Nucleus the first component of the endomembrane system is the rough endoplasmic reticulum which is where a large amount of the protein synthesis happens, because of ribosomes that are attached to the endoplasmic reticulum. Which then, transitions into a smooth endoplasmic reticulum where the density of these ribosomes is reduced.

This is more where the packaging of these proteins that have been synthesized in the rough endoplasmic reticulum happens and then stuff delivered gets delivered to the Golgi.

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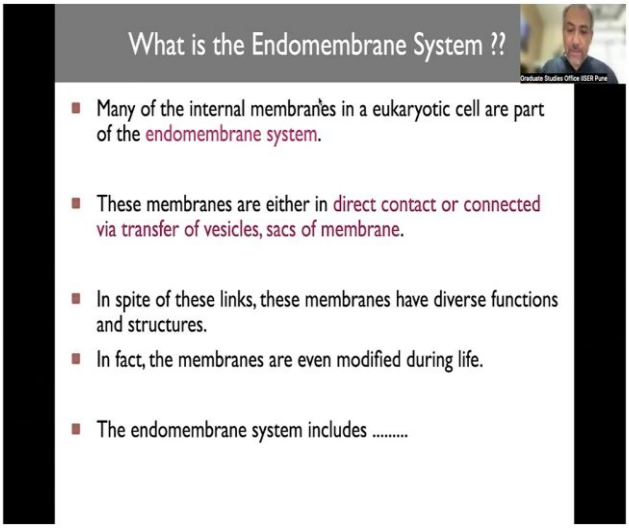

So, it is these 3 components that we are going to look at today. And we looked at, or we briefly talked about the endomembrane system and how the endomembrane system is put together, and how these vesicles are transported from one compartment to the other. We also spoke a little bit about the fact that the composition processing capability of each of these components could be different. So, when we look at the Golgi, for example, we will talk about how there are different enzymes that could be present in different Golgi compartments, and how proteins, for example, can be modified as they make it through these compartments as well.

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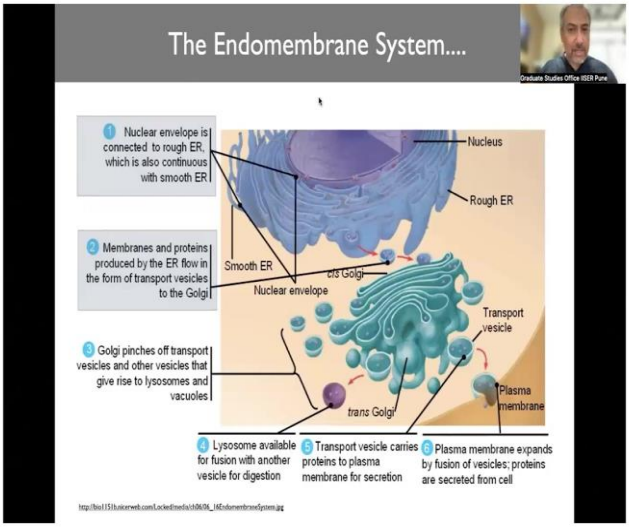

The endomembrane system, as I said, begins from the nucleus to the smooth, rough and the smooth ER to Golgi. And then, all the vesicles, the transport vesicles that deliver stuff to the plasma membrane and other sites inside the cell.

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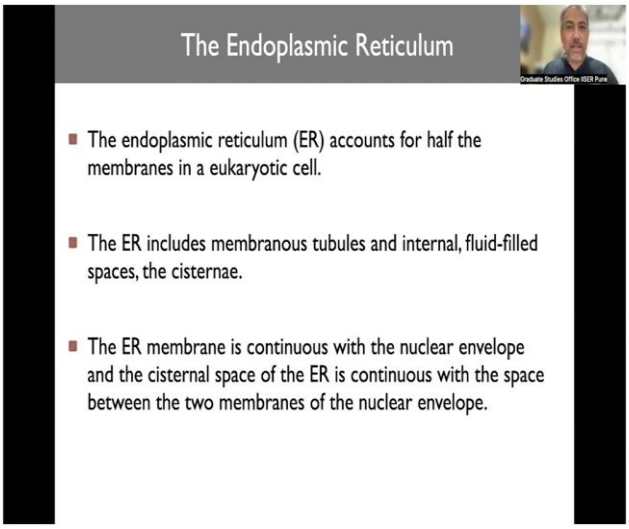

The endoplasmic reticulum accounts for half the membranes in a eukaryotic cell. And this is an interesting point to remember that when you see diagrams in textbooks, the endoplasmic reticulum is presented as a sheet around the nucleus. But remember, this is distributed throughout the cell. I will show you some images that we have taken in the lab later as well, that shows you how extensively distributed this network is.

So, it is a mesh almost like the cytoskeleton network is present throughout the cell. The endoplasmic reticulum also is present pretty much throughout the cell. It includes membranous tubules and an internal fluid will space which are called the cisternae. The ER membrane is continuous with the nuclear envelope. So, if you ever get asked whether the nucleus and the ER talk to each other the answer is yes. And that happens at the level of their membranes.

And the cisternal space of the ER is in continual continuous is continuous with the space between the 2 membranes of the nuclear envelope. This also allows for the initial steps of protein synthesis that has to be facilitated on the ribosomes to happen on the rough endoplasmic reticulum.

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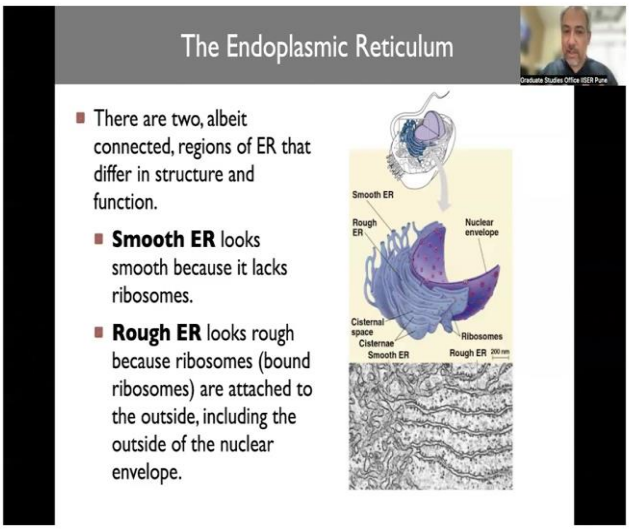

There are, as I said, 2 kinds of endoplasmic reticulum and rough and smooth is just on the basis of the texture that they have. And the smooth endoplasmic reticulum looks smooth because it lacks ribosomes. And the rough endoplasmic reticulum looks rough because ribosomes are bound to the membrane of this architecture. So, the ribosomes sit on the on this membrane and you can see this image here, where you can see these tiny dots which are the ribosomes that are present on the membrane.

And if you remember the movie the “inner life of the cell” you will remember that there is this image of a ribosome synthesizing a protein that then gets integrated into the membrane. And that is what is happening here on the rough endoplasmic reticulum.

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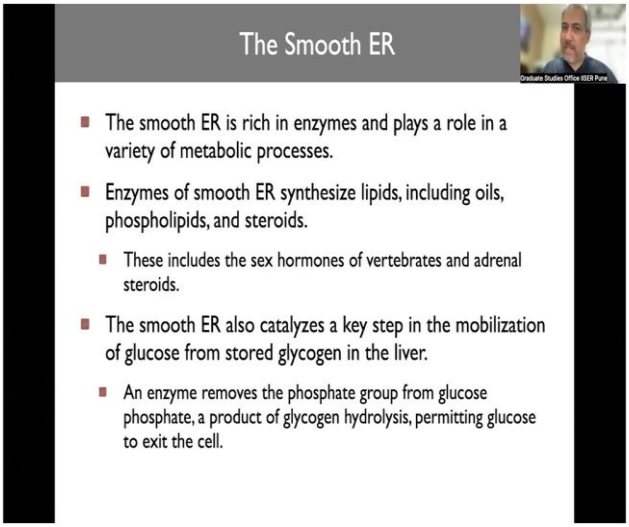

The smooth endoplasmic reticulum is rich in enzymes and plays a role in a variety of metabolic processes. Enzymes of smooth endoplasmic reticulum synthesize lipids including oils, phospholipids, and steroids. These include many hormones the smooth endoplasmic reticulum also catalyzes a key step in the mobilization of glucose from stored glycogen in the liver. And enzyme removes the phosphate group from glucose phosphate, a product of glycogen hydrolysis permitting loads of glucose to exit the cell.

So, this is just to illustrate the fact that there are many things that are happening at the level of the smooth endoplasmic reticulum. As I said the synthesis of lipids is rather important, because a lot of the milieu in the cell is made up of lipids and a lot of the reactions that are taking place, interactions that are taking place are happening on lipids. And so, the lipid architecture composition of the cell is vital to the functioning of the cell. And the smooth endoplasmic reticulum is contributing very directly to that.

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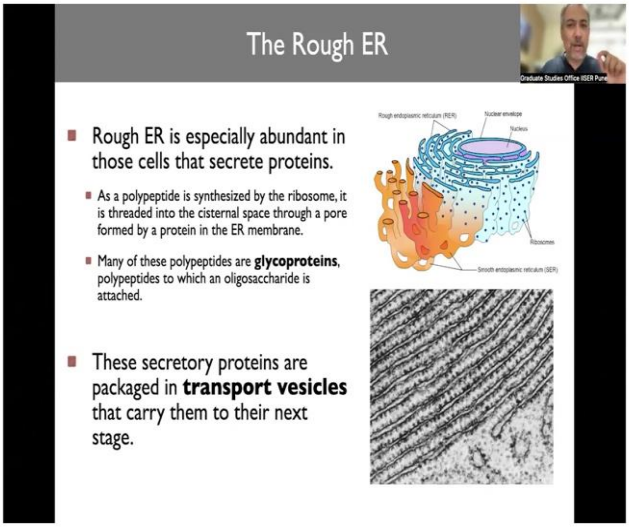

The rough endoplasmic reticulum as we just talked about, is rich in ribosomes and so, it is the site where the synthesis is taking place. So, these are the protein factories of the cell. And once the protein is synthesized the fact that the ribosomes are sitting on a membrane allows for the protein to then now directly be passed on to the membrane. And that is an important step in this process, because the movement of these proteins from the rough endoplasmic reticulum they are packaging and processing in the smooth endoplasmic reticulum delivery to the Golgi processing in the Golgi all of this is happening on the membrane.

So, the ability of the protein to be made and integrated into the membrane is very vital. Another important point that we spoke about last time is the fact that the eventual delivery of these vesicles where the protein is presented to the plasma membrane requires for these vesicles to open inside out which means if the protein if this is the protein and that is the top and the inside. And in the cell membrane this is how the protein has to be presented where this is outside and this is inside the cell. Then, in the vesicle this has to be inverted.

So, in the vesicle, the head of the protein in this case, for example, the receptor should be inside. So eventually, when it gets delivered and fuses with the plasma membrane the orientation becomes the way it is. So, this is also interesting point to remember that the proteins that are being synthesized and integrated into the rough endoplasmic reticulum. Remember that that synthesis accounts for this and ensures that the protein integration happens in this orientation such that their eventual functional orientation is like this. And that is an important element to how synthesis and integration is taking place.

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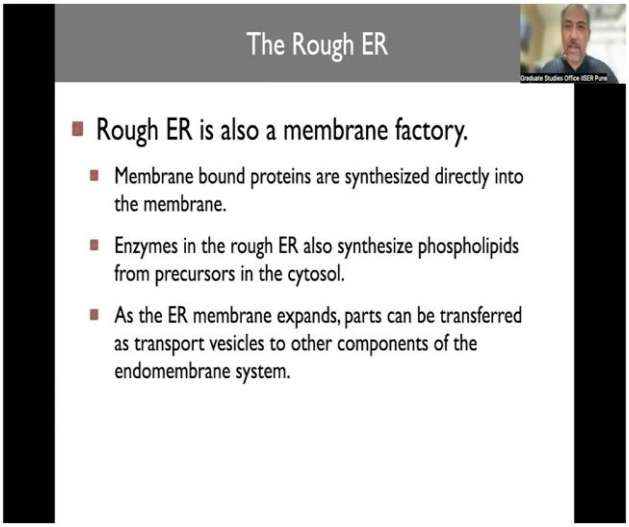

As I said it is the rough endoplasmic reticulum is also the place where membranes are being made. And membrane bound proteins are synthesized directly in that membrane. Enzymes in the rough endoplasmic reticulum also synthesized phospholipids that are from big precursors in the cytosol as the endoplasmic membrane expands. Parts can be transferred as vesicles to other components of the endomembrane system and that includes the smooth endoplasmic reticulum and from the smooth endoplasmic reticulum to the Golgi.

We are not spending a lot of time discussing the mechanism of this delivery, because you are just trying to kind of scratch the surface and understand that there is a series of steps here. At a later point of time, you will read about the delivery mechanism. And there are very intricate proteins that are required for taking a vesicle and ensuring it gets delivered to a very specific site in the next compartment.

And so, stuff gets moved along from one it is like a conveyor belt. It goes from one compartment to the next to the next to the next and eventually to the site where it needs to be function.

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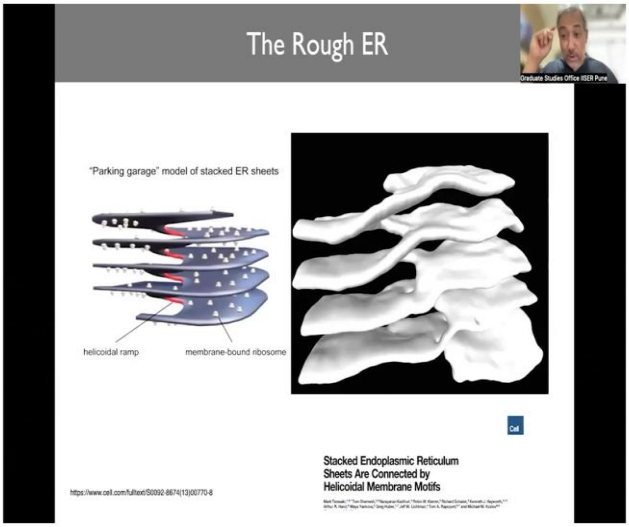

The rough endoplasmic reticulum architecture has very interesting has now, we have had some very interesting insights. And there is this very interesting paper that was published a few years ago that essentially said that the architecture of the rough endoplasmic reticulum could have this parking garage model. And I do not know, if you have used a parking garage, how you are able to kind of move up the parking garage in this manner. And that arrangement allows for things to be moved around, at the same time optimizing the area of the endoplasmic reticulum.

So, it is packed very interestingly and this is known about the rough endoplasmic reticulum whether the Golgi has a similar architecture we at this point of time do not know. And this was a very seminal paper that essentially looked at and modeled used EM images to model the architecture that the rough endoplasmic reticulum could have. So, this is an interesting arrangement to allow for processing to take place and also for things to get carried along.

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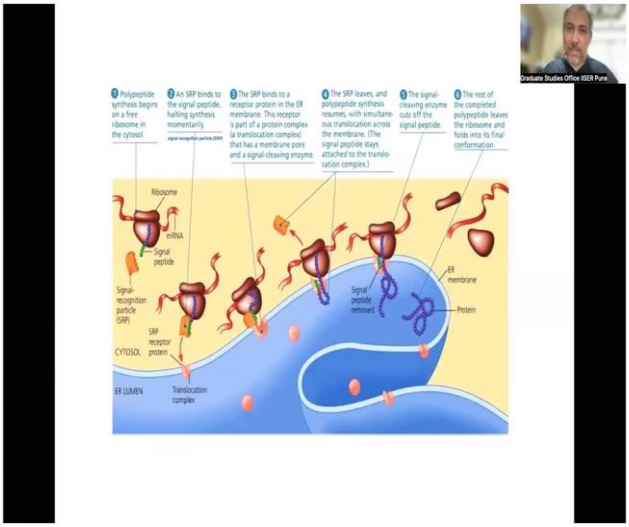

As I said the synthesis of proteins happens through ribosomes on this compartment. And we spoke about this as well. When we looked at the inner life of the cell movie where ribosomes come and attach to the ER membrane and proteins could be synthesized either into the lumen or integrated into the plasma membrane it depends on what kind of protein you are trying to make. And the mechanism of protein synthesis is not something that we are covering at this point here.

So, all you are need to understand from this is that the ribosome comes and attaches to the ER and spends time on the ER and allows for synthesis of proteins that either get secreted inside or get integrated into the plasma membrane both possible scenarios exist.

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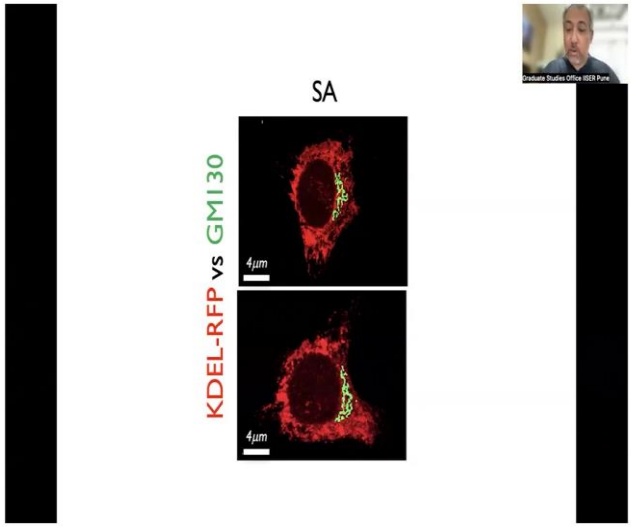

These, for example, are images taken in the lab where we are staining for an ER marker called KDEL. And the Golgi is labeled with a marker called GM130. And the Golgi is in green, the ER is in red and the point that I wanted to make more than anything else is that even though the images that we run into show the ER as being the small network of membranes around the wall around the nucleus.

Remember that the ER is essentially spread throughout the cell so, the ribosomes and the rough ER is closer to the nucleus this big empty space that you see in the center is actually the nucleus. And so, the Golgi is sitting next to the nucleus. So, you now know that depending upon where the Golgi is sitting, you also know that the microtubule organizing center is supposed to be somewhere there.

So, the microtubules are likely to be present in that particular region around the Golgi. And what is interesting is how the ER is distributed throughout the cell and it goes to all corners of the cell. And so now, there is a far greater understanding of what the ER could do by itself as well. And for a long time, we thought everything that the ER does needs to go through the Golgi or other compartments. And it is possible that that need not always be the case. And so there could be a role for ER in the way it is distributed here as well.

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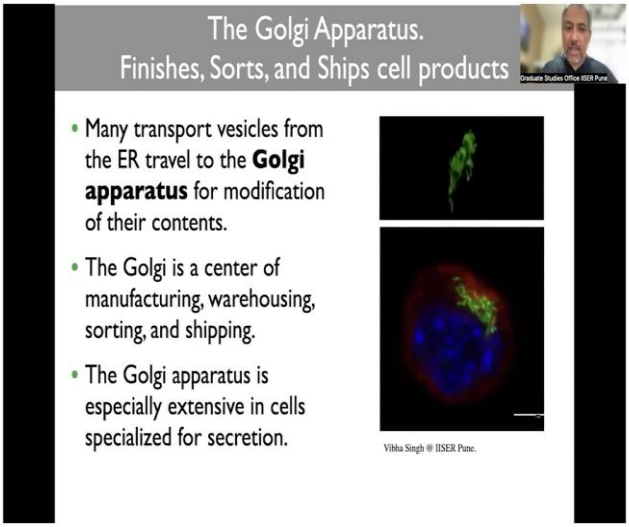

The Golgi apparatus which comes which lies next to the ER and does a significant part of the processing essentially finishes the protein. And when I say finishing it is like it gets the protein in a crude form it looks at the protein from all sides besides what else needs to be attached to it. Modifies it in that way, that allows for the protein to now be fully functional and then sends the protein on its way.

So, transport vesicles from the ER carry components to the Golgi. So, remember the that these are big bags of lipid that have proteins either inside or on their membrane and they come and stick to the Golgi compartment. And now the Golgi takes up these components and now processes them. It is so the architecture of the Golgi and the way the Golgi is assembled is very vital to how this processing takes place.

So, if you change the architecture of the Golgi, you dramatically change the way proteins are being processed and the Golgi is constantly working so, in cells in our body now at any given point of time, for example, as we are all trying to pay attention in class and focus your neurons in your brain are constantly firing. And there is modification of proteins delivery of proteins to synaptic vesicles, through synaptic vesicles to the synapse all of this is happening as we speak and it is a continuous process and the Golgi is very vital in mediating this.

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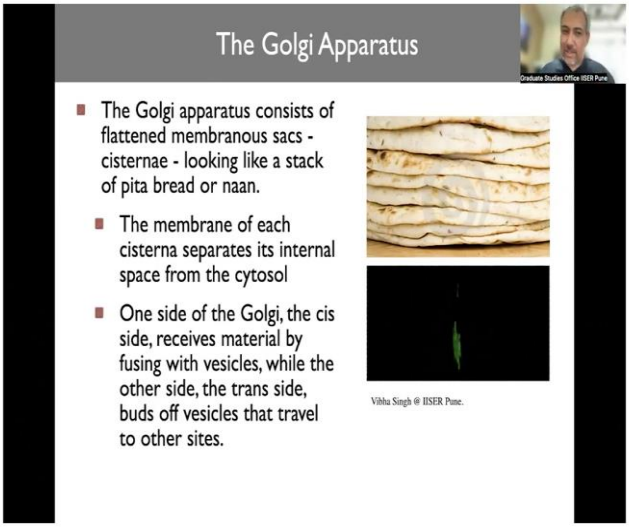

So, it has a stack of lipids and as I showed you with the ER, we do not know whether the Golgi stack also has this parking lot appearance. It is possible that it does, because one of the challenges has been in being able to open the Golgi and look at it. So, the ER at least has a fairly opened up architecture.

The Golgi is a more compact structure and it is a stack of membranes one above the other and that is meant that it would be really nice if we can hold and somehow pull the Golgi apart and then, start looking at how these membranes are all connected. It is thought that these membranes or these *parathas* that are line one above the other, are connected by membrane connections. So, it is not like they are kind of separate from each other.

And the presence of these connections, the architecture of that connection, if any, is still not clear to us. The Golgi again, has very distinct even though it is one structure. It has very distinct architecture inside it. It is like we have a campus of IISER, all of the stuff that is inside the campuse is IISER but within that campus you have different buildings that do different things. And that is kind of the distinction that we have. So, externally, all of these membranes make up the Golgi but if you look carefully depending upon the kind of enzymes that are present there is some classification that is taking place.

The important thing to consider here is this classification could be fluid that there are 3 major Golgi compartments the cis, medial, the trans Golgi, and then there is something called the trans Golgi network which kind of is from where vesicles are budded off and taken out. And

the cis medial trans compartments their boundaries are a bit fluid. So, remember yes, this might be the cis compartment this is where the medial compartment begins.

But is there a boundary that is always very sharp? No, this boundary is kind of getting mixed. So, there is cis, cis, cis and then cis medial, cis medial stuff coming in and then medial, medial, medial and so, and that is how this architecture is arranged. Remember, there is a this is a fairly fluid structure and is not very rigid. The separation of these enzymes and that is an interesting thing there I told you. There are proteins and enzymes that are uniquely cis and there are proteins and enzymes that are uniquely medial and then, those that are uniquely trans.

And it is thought that the organization the membrane lipid organization of these compartments is what is allowing for some enzymes to be enriched and kept in one compartment and some to be kept in the other. So, the enzymes could have a tendency to move from one compartment to the other but the fact that is difficult for them to do because of the architecture of the or the lipids that are present, is what ensures that they are enriched in one compartment versus the other.

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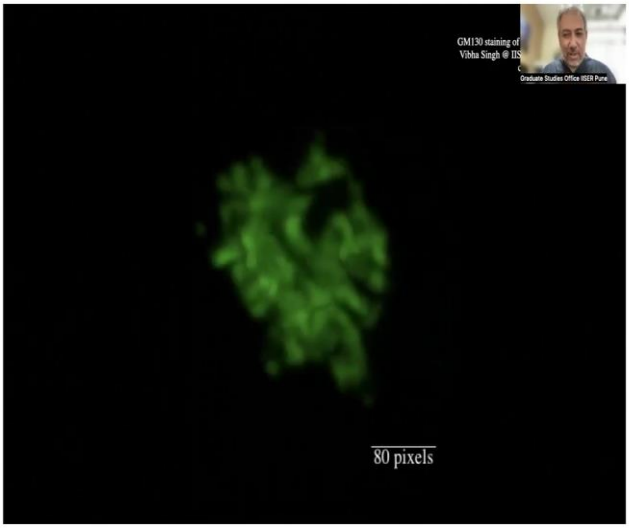

So, this, for example, is an image that is taken in my lab where we are looking at this GM130 and you are looking at the Golgi stack in a cell that is adherent. And you can see this is one marker called GM130 which actually marks the cis Golgi. I will show you some images where we have looked at the cis and the trans Golgi. And in the, when the cell is adherent the cis and the trans compartments are right next to each other. And there are some unique

circumstances where the architecture of the Golgi undergoes change where you can actually see these 2 compartments separated from each other.

This is again, a cis Golgi compartment that is in a cell. These are images taken using a confocal microscope. And if you remember, I when we talked about microscopy, we talked about taking sections and then, putting them together and that is what we have done. So, these are like these bread slices that was sliced and then, each image was taken and then, a composite image was created. And you can see that there are gaps in the architecture you can see that these are indeed tubular structures.

And remember, there is a certain resolution that the microscope allows which is why you can see this architecture, the see this architecture the way you do. You go to an electron microscope you will see a significant number of membranes that are put together in each of these stacks that you are seeing here.

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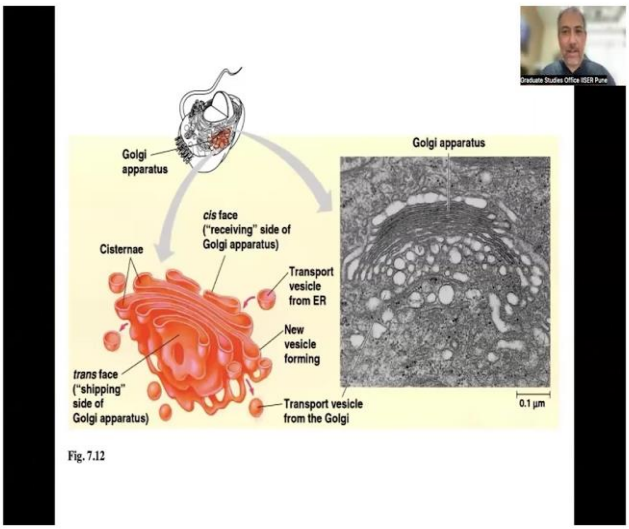

And that is how things look and the way they are organized. So, essentially membrane upon membrane upon membrane, and stuff coming in from one end from the ER, and then leaving at the other end after it has gone through all these compartments. And has been processed accordingly.

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Among the things during this transit from the cis to the trans end of the Golgi things that come from the ER are modified as I said and reach their kind of final functional state. Among the modifications are addition of the sugars oligosaccharides which are added to proteins to particularly make glycoproteins which are sugar modified proteins. And the glycosylation of proteins is one of the major changes with time now we have understood that many proteins carry glycosylation changes and these glycosylation changes are very vital to the functionality of these proteins.

So, 2 things that the Golgi accomplishes is 1 changing or modifying the protein in such a way that the functionality of the protein is optimized. And second also ensuring that it has all the pieces that are required to deliver the protein to very specific sites and inside the cell. The Golgi can also manufacture its own macromolecules including pectin and other non cellulose polysaccharides. During processing material is moved from cisternae a to cisternae so, each of those *parathas* is a cisterna.

And these are essentially an elongated sac of a lipid membrane and things move from one cisterna to the other. And there are different models that are thought to describe how this movement can take place. In one model, suggest that things leave from this compartment and just fuse with the next compartment and then, go through fuse this one and then, fuse to the next and then just go through. One model suggests that no, no from this cisterna to this cisterna, if you have to move a vesicle comes out of it and then, goes and binds here, and then from here to the next, and then from there to the next.

We still clearly do not know entirely how or which module is actually, the module that the cells use. Is it possible that they use more than one mechanism to do this moving forward of the cargo it is possible. So, the Golgi, tags, sorts, and packages materials into transport vesicles. And now, like envelopes or letters that carry content in them these vesicles are sent out and they go bind things as they are required to bind and then are delivered to very specific components inside the set.

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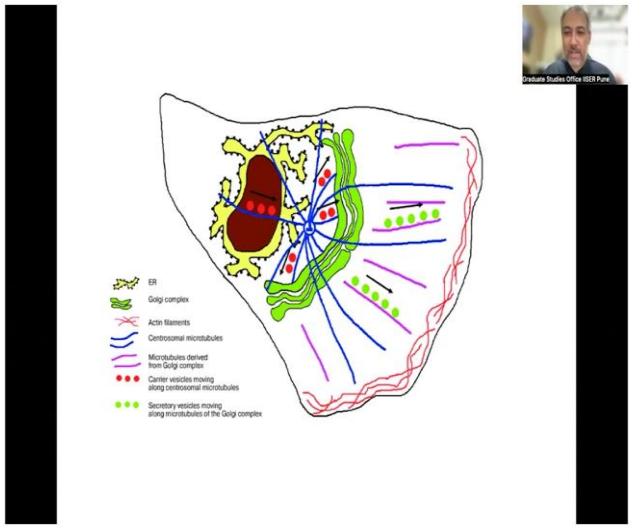

A lot of this architecture of the Golgi as I said, is maintained by the cytoskeleton so, this is the kind of movement that we are talking about. And you know that the Golgi compartment sits around the MTOC so, a lot of the microtubules are in very close proximity in contact with the Golgi. They are actually important for this kind of architecture the nice packed architecture of the Golgi to also be maintained.

So, a lot of the microtubules are kind of holding the Golgi around. And just as a matter of information I am telling you that there are many Golgi compartments that actually bind motor proteins. And so, the motor proteins that are touching and walking on the microtubules are in turn attached to Golgi membranes. And so, the relative movement of these motor proteins also ensure that the Golgi compartment is kept where it is.

And there are times where the Golgi actually has to get broken up. And one very interesting time is when the cell undergoes division and at the very end of our lecture series we will look at the cell process of cell division briefly to kind of highlight all these players in the context of cell division. And cell division is interesting, because as the cell divides this Golgi which

is a nice compact packed structure has to get distributed between the 2 daughter cells. And the way it does it is that the Golgi actually breaks up.

So, everything that is kind of keeping the Golgi together, the microtubules, the motor proteins all get rearranged during cell division. And when that happens, there are other proteins that are required for Golgi architecture that also come into play. And what they eventually do is that they allow for the Golgi to break up and the Golgi actually distributes throughout the cell completely breaks up and distributes throughout the cell.

And then, now the cell divides. And once the cell divides pieces of Golgi here, pieces of Golgi here. And once the division is complete, and the cell attaches and spreads, this Golgi pieces that were all floating around along the microtubules, are brought back into a compact Golgi for this cell and this cell.

And it is a really wonderful mechanism that the endomembrane system along with all the other players that are in the cell, is able to work and do this.

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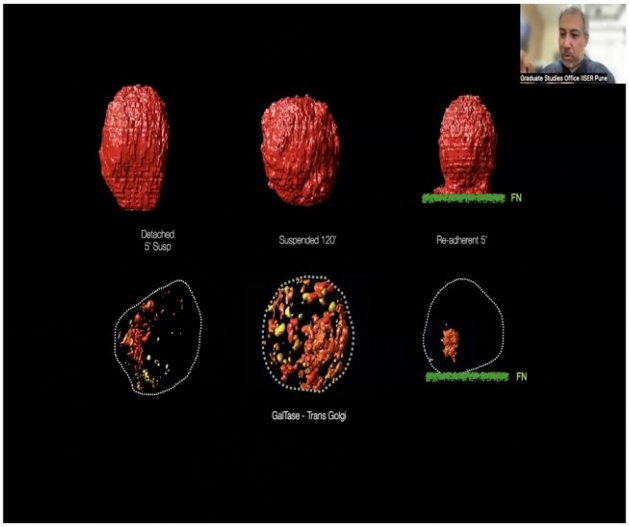

And this mechanism of the breakup of the Golgi we study in the lab I am just showing you some images of the Golgi in a cell that is actually detached. So, when I told you that during cell division, the cell actually rounds up. And because the cell rounds up our hypothesis was that could trigger the Golgi to break up. And that is what we see that when you take a cell and detach it you can see the Golgi which is here.

We are looking at the trans Golgi. The Golgi is actually broken up and distributed throughout the cell. If I take this cell, and now plate it on back on matrix and the cell attaches and it is just attached it is still around. The Golgi goes and becomes a compact structure. And this taking apart and coming back happens along the microtubules. And it is dependent on motor proteins, the way these images are taken is, again, these are confocal images, these are stacks, which are then processed using a very special software that does something called Deconvolution.

And then, they are surface rendered. So, you can see the shiny objects, because of the way the images have been processed. But they all are actually originally images that are taken on the confocal stacks that are then kind of put together and then processed further.

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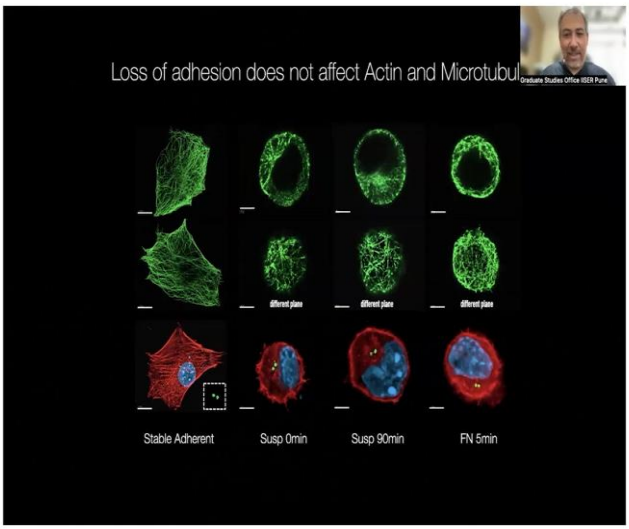

The architecture of the cytoskeleton in these cells that are detached, is still I told you this moves out and in along the microtubules. And you can see that architecture is pretty much retained. It is a mesh even though these are suspended cells, these big hollow structures are actually the nucleus in the in the cell.

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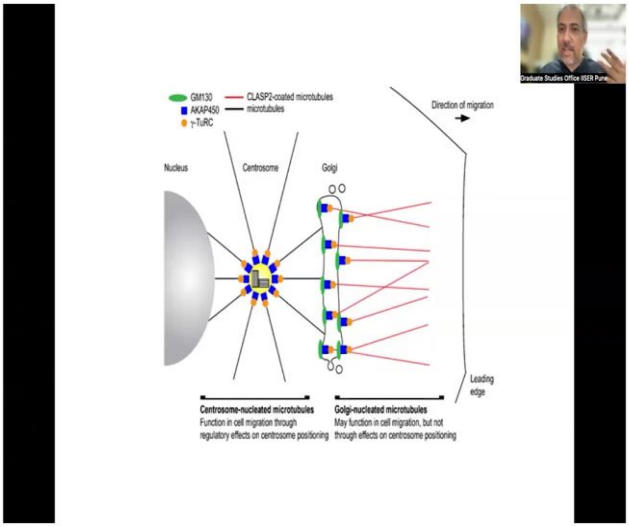

Another very interesting facet about the Golgi that has been discovered in the last maybe 5 or 10 years, is that the Golgi sits around the centrosome. So, the centrosome is where the microtubules are originating. But now there is enough evidence to suggest that the Golgi could also act as a place from where microtubules can originate. So, there are a class of microtubules that are Golgi nucleated microtubules that is they originate from the Golgi.

And this is another role that the Golgi is now known to be playing, which the Golgi was discovered so many many years ago, it is only now 5 years ago that we have identified it has this capability as well. So, there could be other things the Golgi does that we do not fully understand and will take time for us to also discover.

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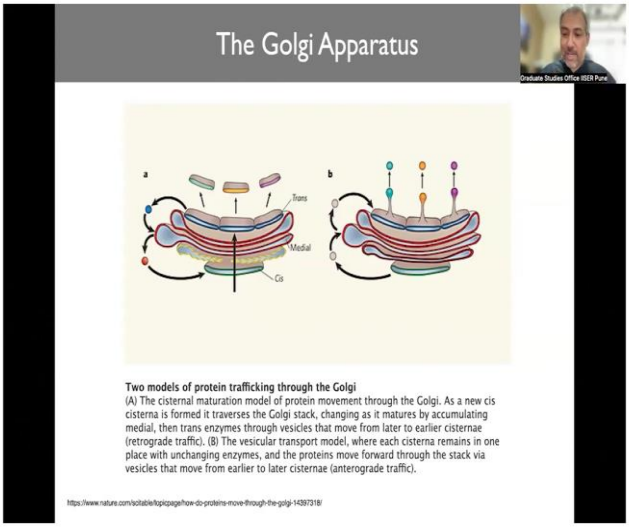

As I said the processing of the Golgi this movement of vesicles that are happening and along with the fact that the vesicles can move in the front, there is thought that the vesicles can also go backwards. So, there is a movement forward and a movement backward and that keeps the balance of how proteins are being processed. And depending upon how these movements are regulated the way processing takes place, changes. Remember one important thing that a time a protein spends inside the Golgi in each compartment has some influence on the architecture of the protein eventually.

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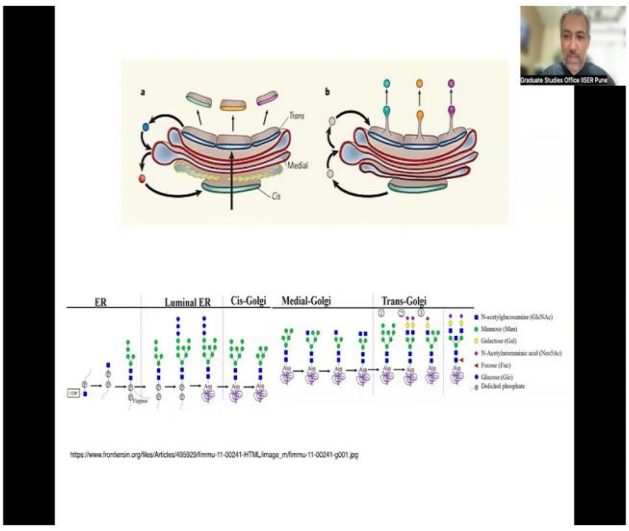

And one of these major changes that proteins undergo is the addition of these polysaccharides, and I am just showing an example of a protein that as it moves from the ER

to the luminal, ER to the cis Golgi, to the medial, to the trans Golgi. These blue and green dots that you see are different sugars that get added to the to the protein. And that is the final protein that comes out as a very elaborate sugar signature. And that sugar signature is very vital to where the protein is targeted and how it functions.

And this just gives you a flavor of how movement through these compartments. Each individual sugar unit gets added and these additions are made mediated by enzymes that are sitting in each of these compartments. And the time that a protein spends in a compartment in the presence of an enzyme is going to determine how that modification takes place and how well it made it is made.

Now imagine a protein has to go through all these compartments and come out in a fully functional form. These little things they all have to work with and ensure that all the changes that are required are taking place such that the protein now gets delivered in a particular form. The change in the sugar composition of that sugar modification of the protein can affect the localization and the functionality of the protein. So, the cell can at times use this processing machinery to change how the protein functions and where it works.

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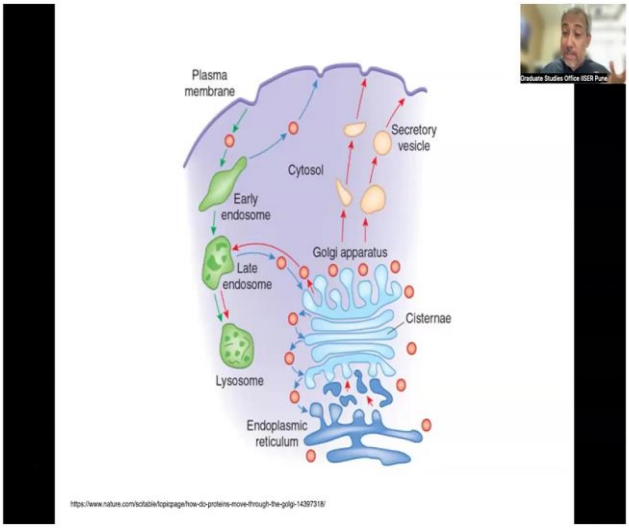

And that is also a remarkable thought here, this is the mechanism of processing as I said along with the Golgi and ER through secretory vesicles things are carried to the plasma membrane and then, there are early endosomes, late endosomes lysosomes, that we will talk about next time which are all different components and things from the Golgi can get move to one or more of these compartments.

And these compartments can also talk to other compartments that are present there. But remember, all these are lipid filled sacs, and they have vesicles that come in stick to them, fuse with them, do things with them, and then vesicles that pinch off and go. And these vesicles are really interesting structures.

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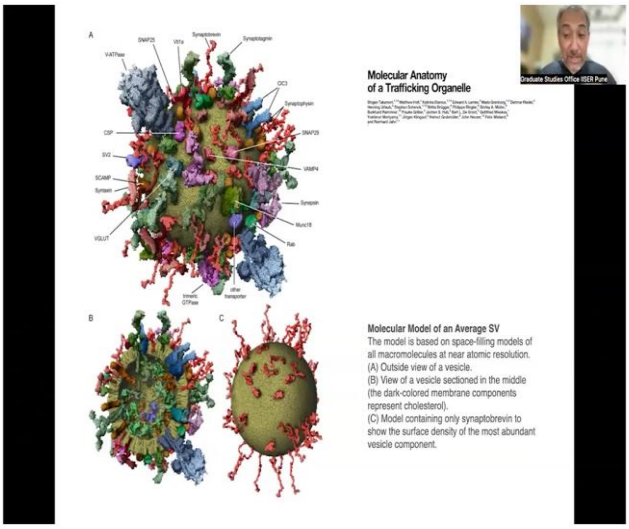

And this is actually, I just wanted to show you this, because it gives you a sense of how what is the kind of crowding that a vesicle can expect. This is a synaptic vesicle, and this is a synaptic vesicle with all the different proteins that it could carry. It is a model these are not real images but the proteins that are put on them are real, because that is the architecture of the protein. You can see a cross section of that vesicle, you can see there are some proteins that are transmembrane, some that are only on the outside, but look at the kind of crowding that a synaptic vesicle could have this image.

See here, is containing one particular protein that is distributed on the vesicle, which is synaptobrevin. And so, if you look at one protein and it is confirmations that present that are present on the vesicle. And then now all the other proteins that are coming through that are brought in and these synaptic vesicles are what move along neurons and will reach synaptic vesicles and are delivered to do to communicate, create communications between 2 synaptic vesicles.

Look at the density of things that are on the vesicle. And it is important to keep that in mind, because you are imagining a vesicle, you should not be thinking this has three proteins on it, very unlikely.

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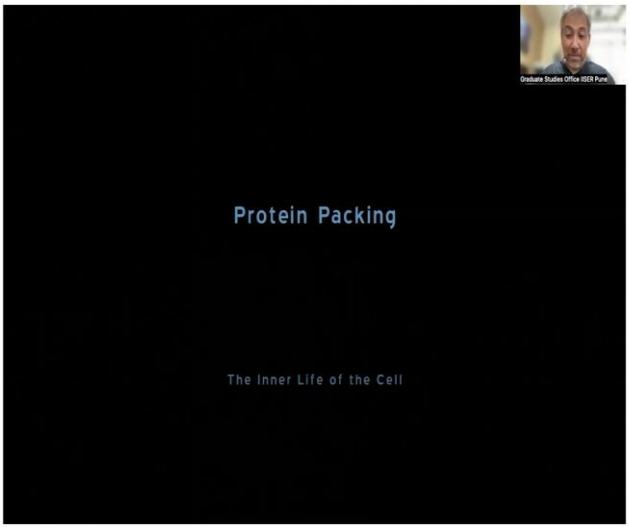

I am going to play a small part of this inner life of a cell, which is a new video that was made a couple of years ago which is a modification of what they had earlier. And I am only playing that portion where they talk about a vesicle. And how vesicle is looks. The things that I want you to pay attention to is, of course, the vesicle and what the components are. Again, remember how this is all moving around in the cytosol in the cell. You will see microtubules you will see motor proteins as they are walking with a vesicle along the microtubules.

Look at the crowding the density of things right inside the cell as well. So, remember the ER, the Golgi, the vesicle compartments that are talking to each other, the microtubules, the centrosomes all this is packed into a very in a very dense manner inside the cell. And still, they are all able to talk to each other communicate and function ideally to allow for the cell to do what it needs to do at every given point of time.

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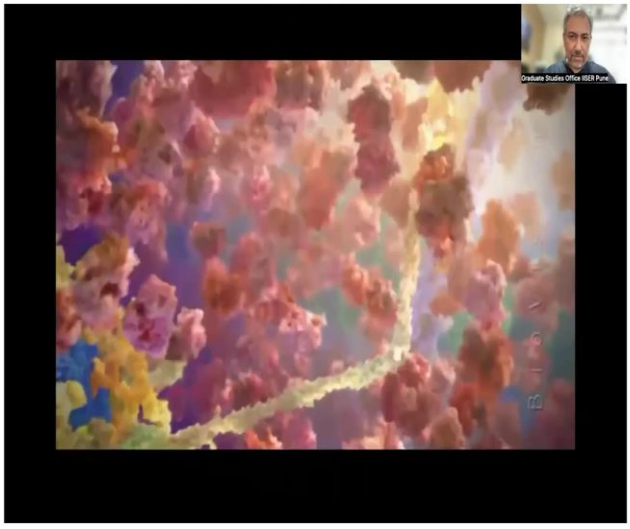

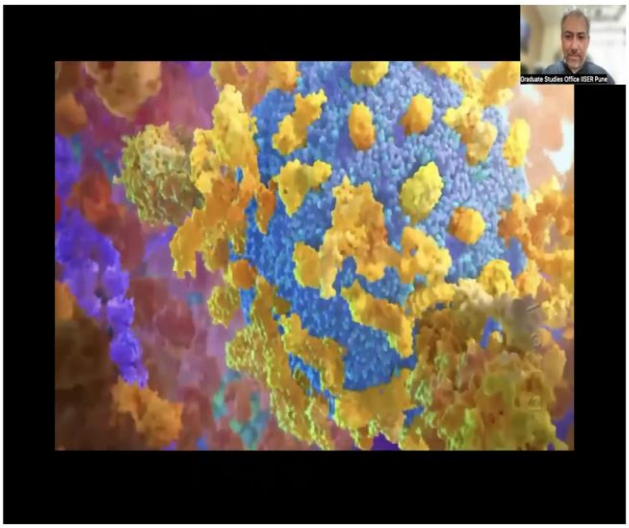

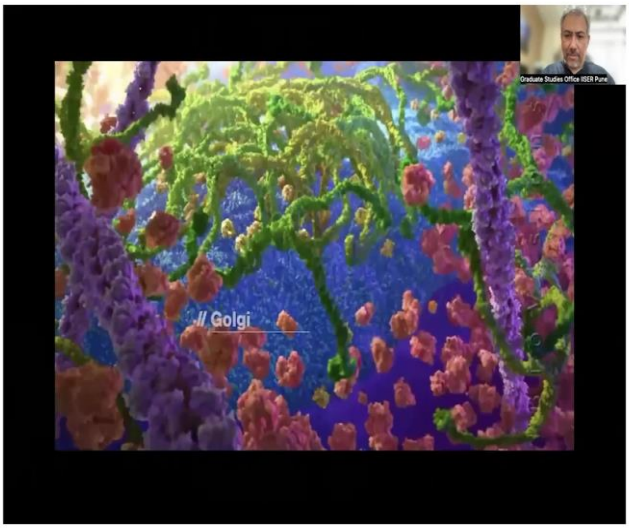

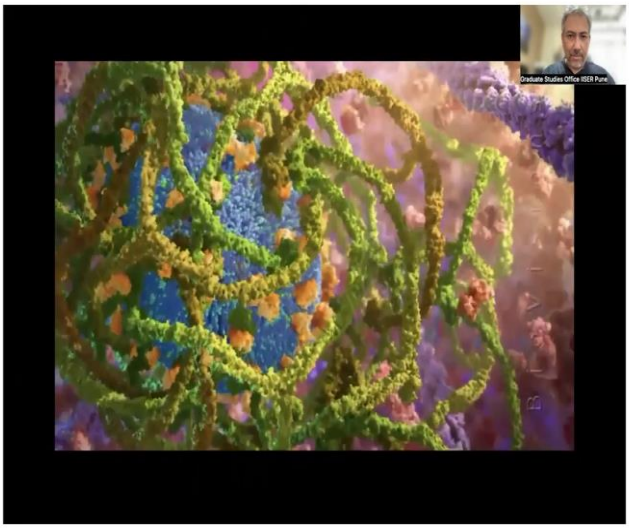
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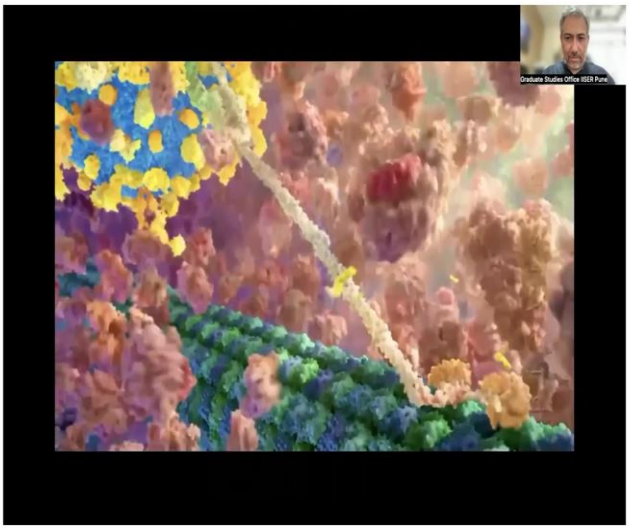
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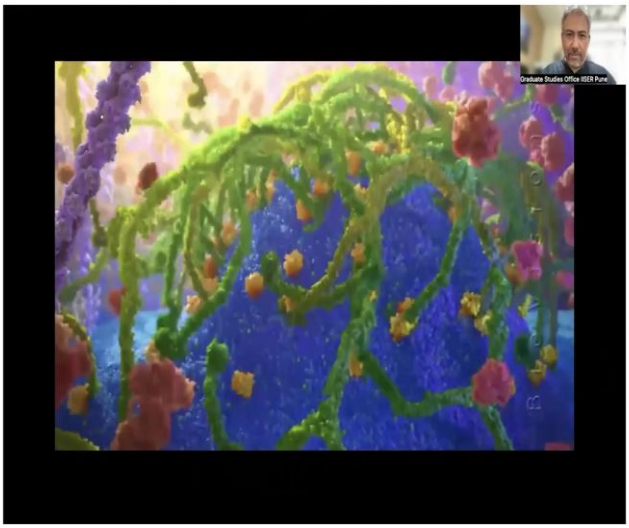
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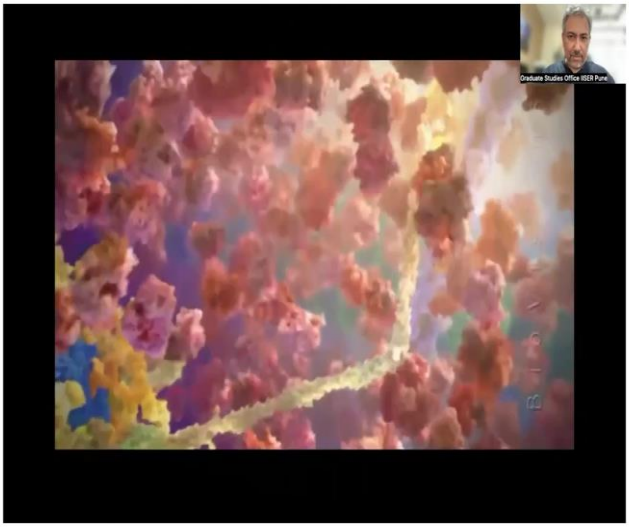
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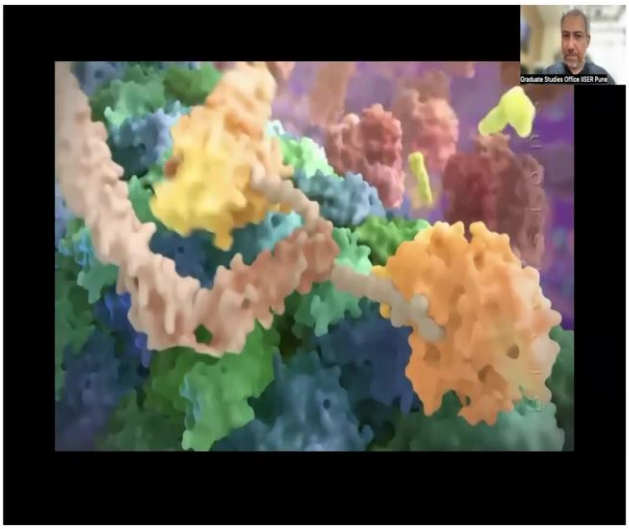
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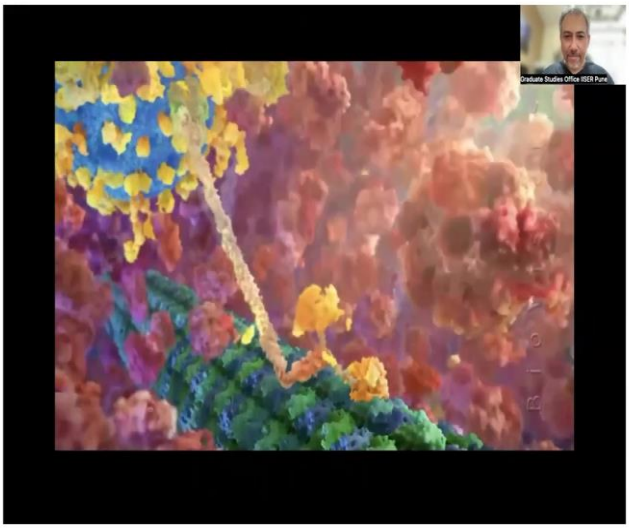

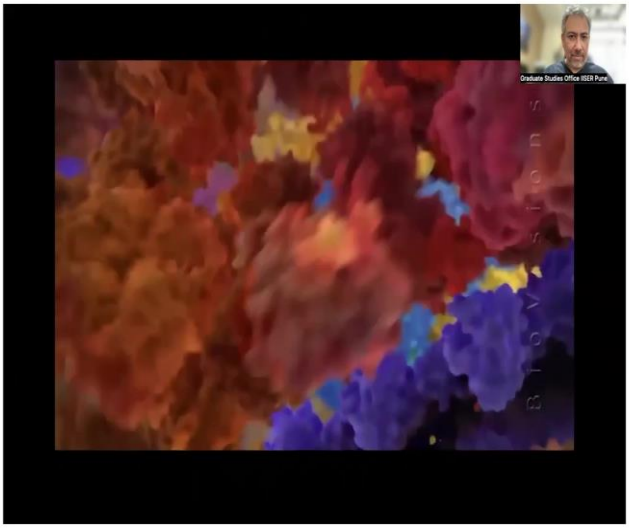

So, let us listen in here, the nation secreted proteins, membrane proteins, and proteins targeted to intracellular organelles, for example, vesicles destined to late endosomes are formed at the surface of Golgi stacks. With the help of clathrin molecules that assemble into coat, promoting the curvature of the Golgi membrane. Shortly after they release, the vesicles shed their clathrin coat and adapter proteins. Synaptic vesicles undertake a long journey along axons to overcome limited diffusion caused by molecular crowding, motor proteins, transport vesicles, on long fibrous proteins called microtubules. You can see motors move each synaptic vesicle toward the plus end of microtubules.

Free kinesin adopts an inactive folded conformation. Upon binding with the vesicle, the kinesins stock region unfolds and the 2 kinesin heads are free to interact with a microtubule. The ATP dependent switch between microtubule bound and free states leads to the

alternating swing of the heads that characterizes the hand over hand walk of kinesin. Conformational changes and electrostatic steering, remote unidirectional movements of vesicles. And any given time one kinesin head is attached to a microtubule thus favoring long range uninterrupted vesicle transport.

If a vesicle detaches, its very limited diffusion increases the probability for fast free attachment. In the crowded environment of the cell mutations altering protein folding increase the risk of aggregate accumulations which play a key role in the pathogenesis of many neurodegenerative diseases.

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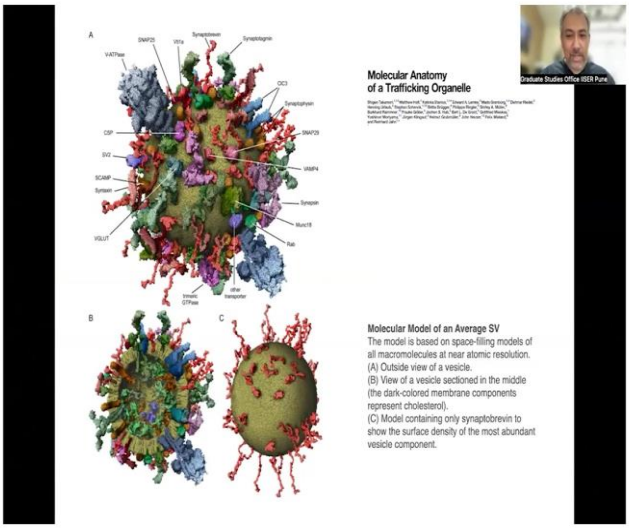

So, this movie is largely about talks about how neurodegenerative diseases are created. But this portion is interesting because of what we just talked about in the last few lectures. So, that is that kind of crowding despite that the fact that these architectures are maintained and transport and delivery to very specific sites in the in the cell are being done, is truly wonderful and remarkable you know, if you consider that.