Fundamentals of Protein Chemistry
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Module - 09
Membrane Proteins and Transport
Lecture - 41
Membrane Proteins - I

We begin module 9 on membrane proteins and membrane transport. In the first two lectures we will be talking about membrane proteins, their characteristics and what types of proteins are there in membranes. In the following two lectures we will be looking at membrane transport and the specific functionalities and the specific energy associated with transport in the diffusion across the membrane. This will be followed by a lecture on electron transport.

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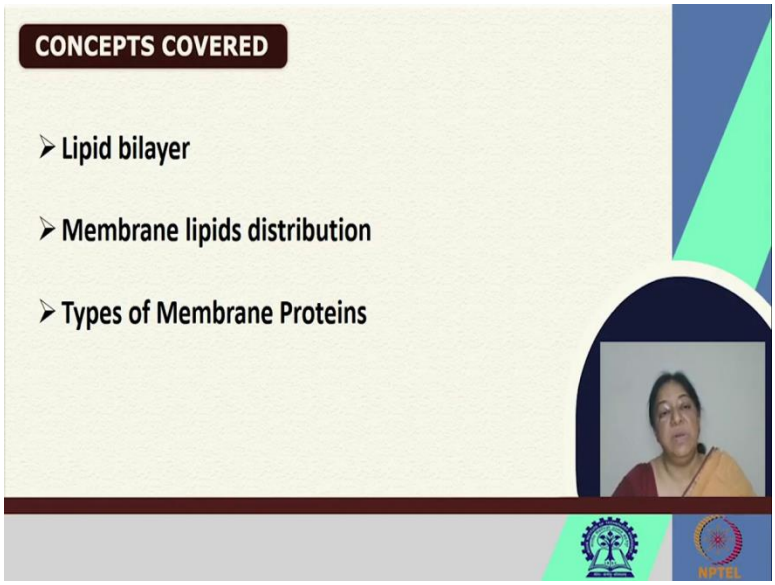

When we look at the specific concept of membranes, the first thing that comes to mind is the lipid bilayer. And what we will be looking at is the specific lipid type distribution in the bilayer, because that is going to decide upon what kind of proteins will interact with these lipids in the

membranes. So, we will also be looking at the lipid distribution in the membranes and the types of membrane proteins.

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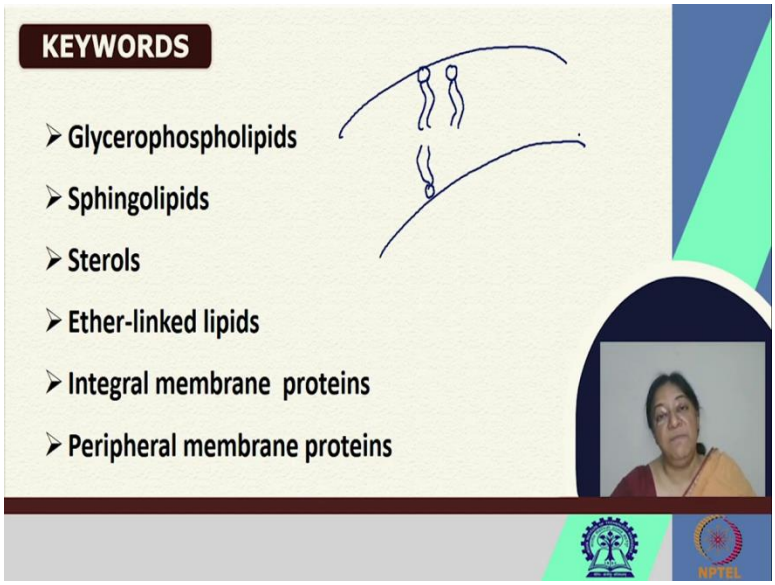

In this we have the specific types of lipids that form the lipid bilayer, which is an extremely important constituent of our cell membrane, where we have our polar head group and the hydrophobic tail. What is the nature of the head group and what is the nature of this hydrophobic tail that will form our cell membrane and based on that, what kind of proteins do we have associated with the membrane.

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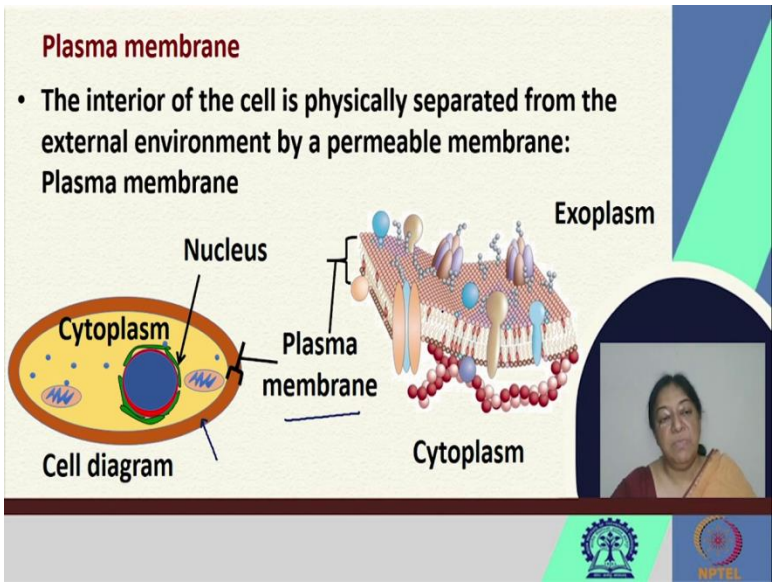

If we look at the plasma membrane, we have this [refer to slide] as our plasma membrane, we have in the cell the cytoplasm, the nucleus and the other cellular organelles. The specific structure of the plasma membrane involves a lot of variations in terms of the types of molecules that are present. So, the interior of the cell is physically separated from the external environment by this permeable membrane, the plasma membrane and in the plasma membrane there are several components that are present.

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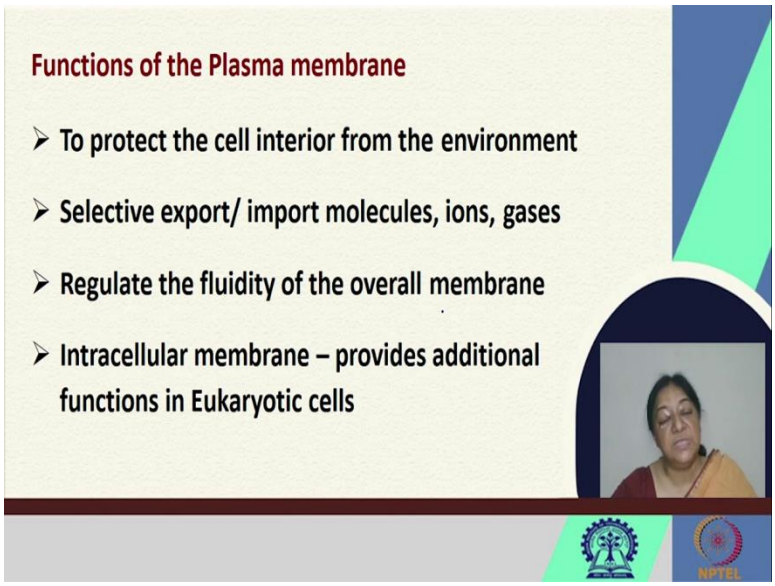

The functions of the plasma membrane are to protect the cell interior from the environment, to selectively export and import molecules, ions, gases to activate the cell in terms of its functionality to bring about biological processes. It also regulates the fluidity of the overall membrane, to allow for this transport and the intracellular membrane provides additional functions in eukaryotic cells and we have the specific types of lipid membranes.

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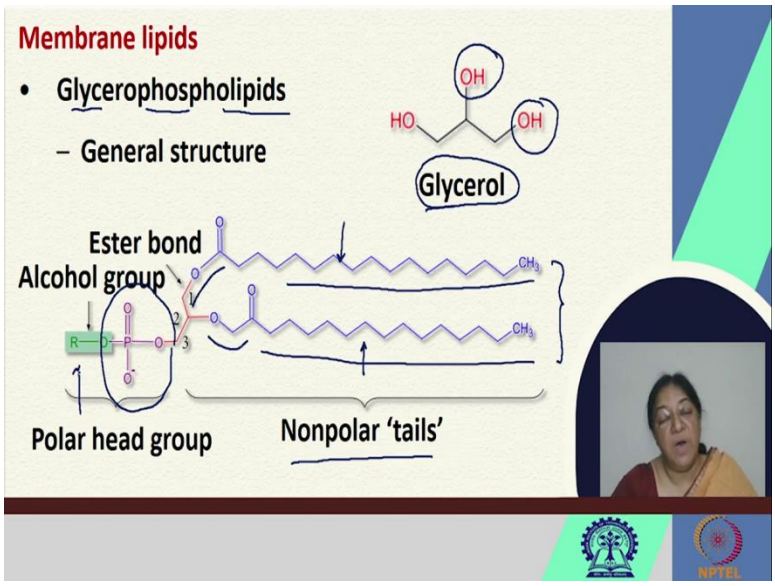

When we consider glycerophospholipids, we understand that these are all derived from glycerol. If we look at the structure of glycerol, in the case of the glycerophospholipids, we have two of these OH interacting or forming two fatty acid chains. These two fatty acid chains are those that form the nonpolar tails, as we see that they are composed mainly of hydrophobic backbone; CH_2CH_2 backbone.

The ester bond that is linked here [refer to slide] and linked here, is what connects this glycerol with the fatty acids in the formation of an ester group. Here we have a phosphate group, which is why these are called glycerophospholipids and there is the presence of an alcohol group here. This alcohol group is the polar head group that forms the polar head of our lipid.

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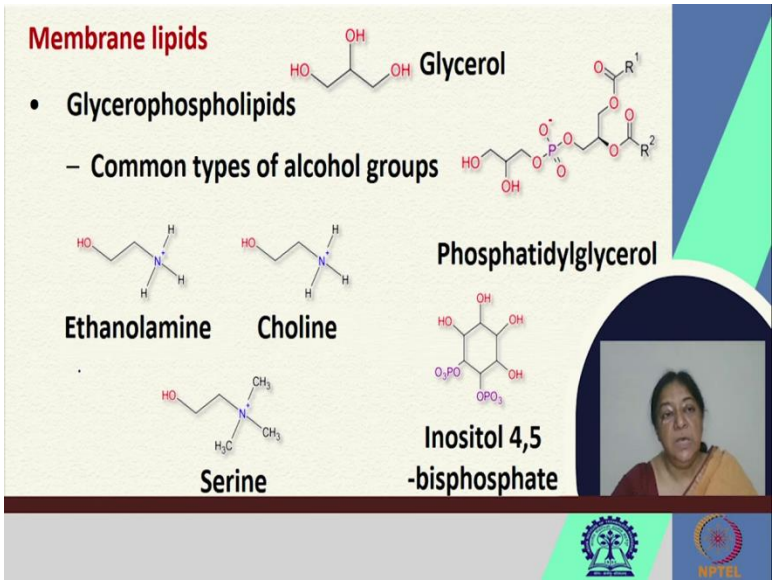

So if we look at the membrane lipids in our glycerophospholipids, where it was derived from glycerol, we have the polar head and the two tails. The polar head group is comprised of specific polarities that give them their specific property in the class of glycerophospholipids.

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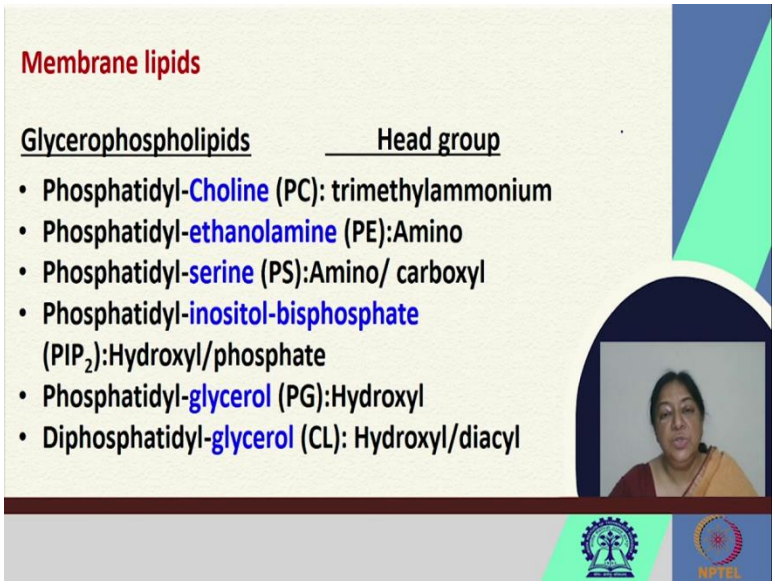

When we look at the glycerophospholipids with their head group according to the alcohol that have they have been derived from, they have specific names. Phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol bisphosphate, phosphatidyl glycerol and diphosphatidyl glycerol. So these different types of head groups give them different properties which is important, the different tails give them properties that are important.

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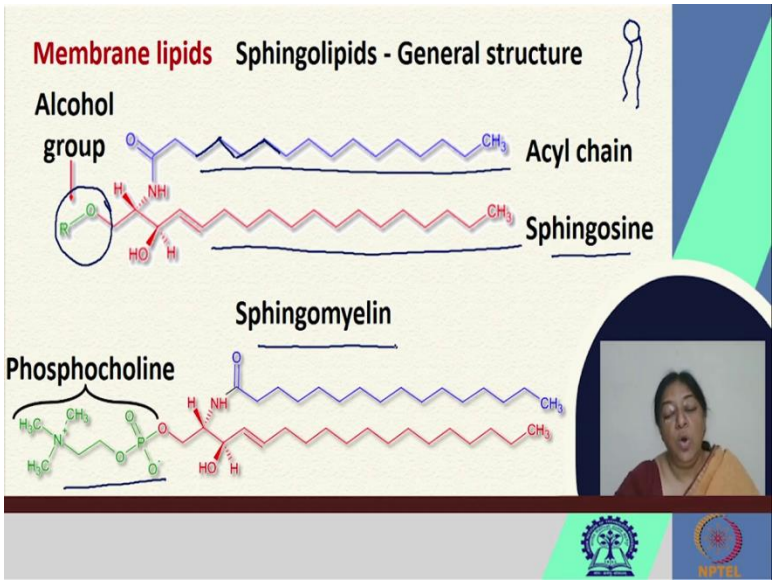

If we look at the sphingolipids here [refer to slide], in this case what happens is, we have one that is an acyl chain the other that is a sphingosine. All based on the fact that we have a polar head group and two hydrophobic tails brought about by the chain of CH_2 moieties that are present. And this again is our alcohol group where we can have a phosphocholine and this is an example of sphingomyelin in the specific type of lipid. So all of these form the parts of the lipids.

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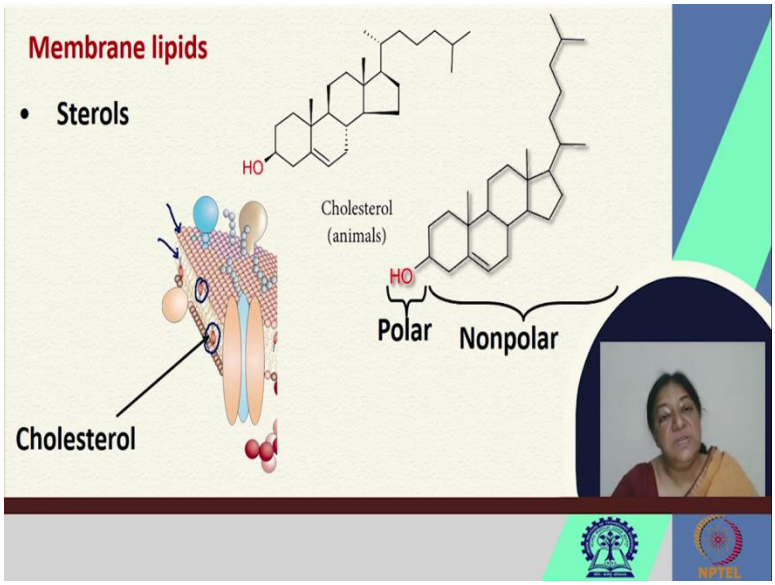

We can look at the sterols that are present also in membranes, which is part of say cholesterol that is part of the lipid membrane, the plasma membrane. Now, the possibility therefore of the plasma membrane to have different types of head groups, different types of tails, results in different types of properties of this.

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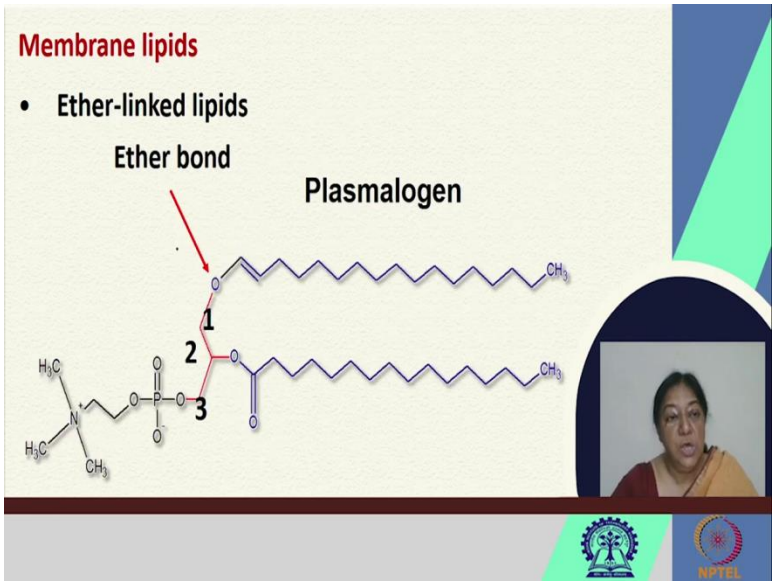

So, we can also have another type which are the ether linked lipids. Again what we notice here is a polar head group with two hydrophobic tails.

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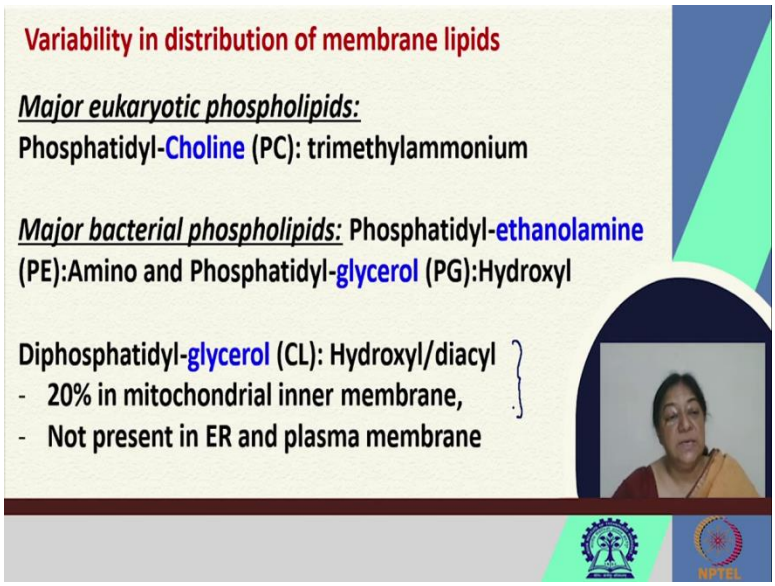

So the variability in the distribution of the membrane lipids, comes from the fact that it is based on the type of fluidity of the membrane, where we have major eukaryotic phospholipids these are phosphatidyl choline mostly mainly. Major bacterial phospholipids are a bit different in that, they could be phosphatidyl ethanolamine or phosphatidyl glycerol. Then we have the other types and the mitochondrial inner membrane has this specific type of lipid.

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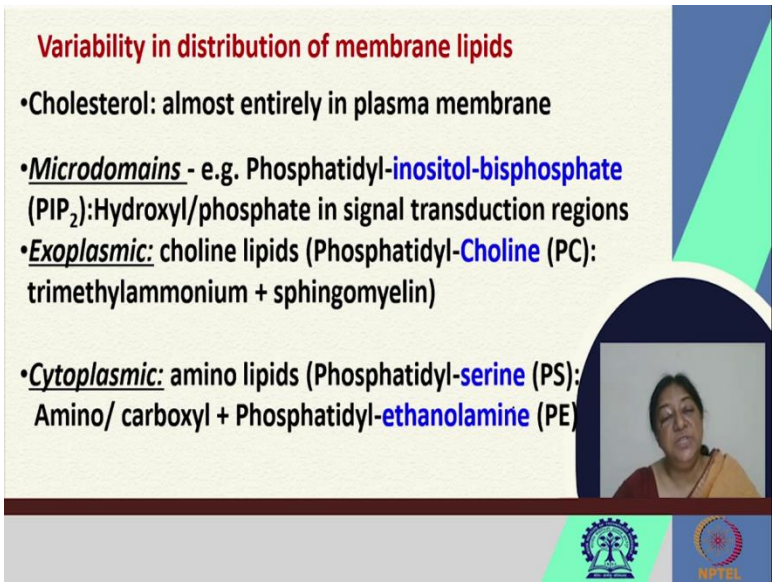

Similarly if we look at the other types, we can have the cholesterol which is almost entirely in the plasma membrane. Then we have the specific microdomains that act as signal transduction regions because we understood that this has a very important role in signal transaction. Then we have the exoplasmic type, that are the choline lipid types and we have the cytoplasmic types that are the amino lipid types. So, when we look at a specific idea of the variability in the distribution of these membrane lipids at the different positions of the membrane, then we will see that these lipid properties affect the membrane in different ways.

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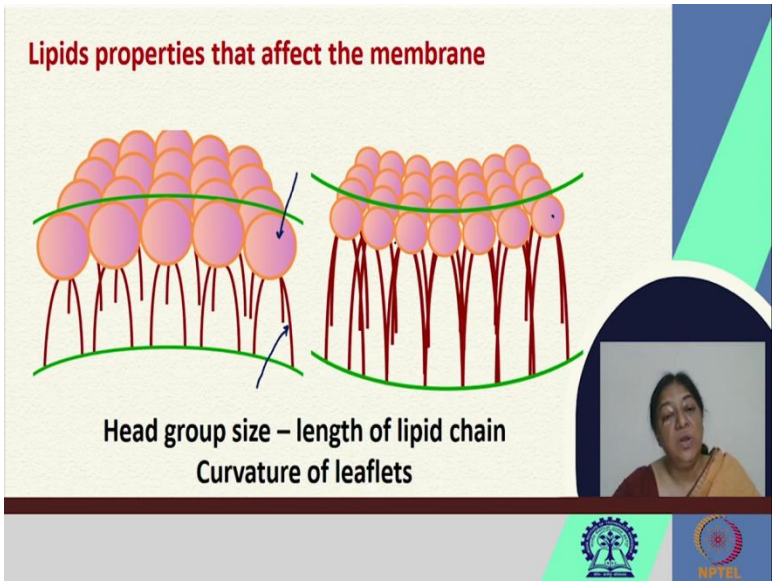

For example, the head group size compared to the length of the chain, is going to give a variation to the structure or what is called the curvature of this specific part. So if we have a smaller head group with a longer chain, the curvature will be different. Based on the head group size and the length of the lipid chain, it is possible to get different types of curvatures associated with what are called the leaflets of the membrane. What are these leaflets?

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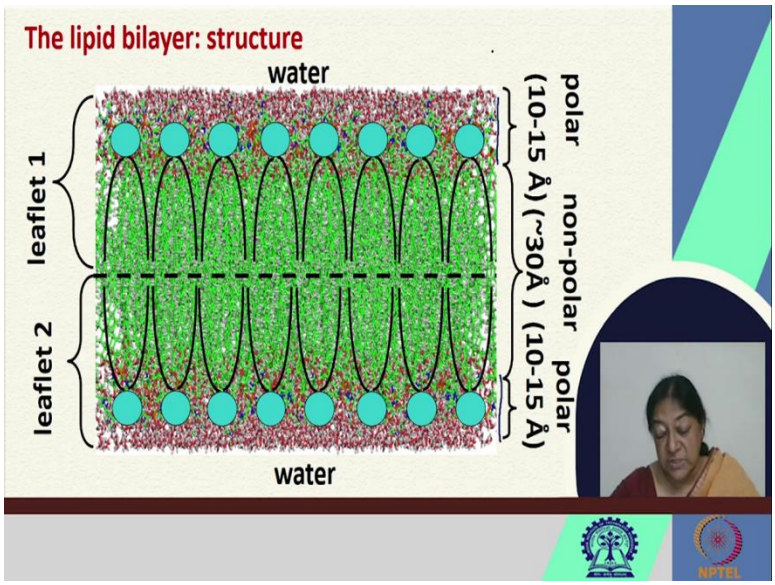

This [refer to slide] is the lipid bilayer structure, a general structure that says that there is water on either side of this lipid bilayer. We have leaflet 1 and leaflet 2 and there are specific associations, in the sense that we have a polar component because of the polar head group that interacts with the water and we have a hydrophobic part, a non-polar part associated with the hydrophobic tails. Given the size of the specific head groups and the length of the chain, we understand that there can be a relative curvature to this, that would result it in forming the plasma membrane.

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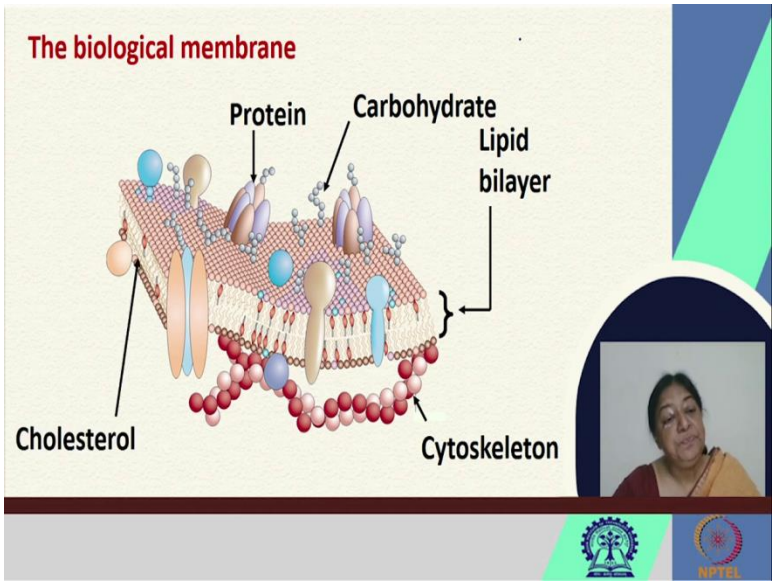

So, if we look at this biological membrane we understand that there are variations in the lipid structure in terms of its head group and its tail, which then results in a specific curvature associated with the membrane. This membrane lipid bilayer, therefore, can have variations depending upon the components that they are comprised of and the components that are present.

This is called a fluid mosaic model because of the different components present on the membrane.

We have the cytoskeleton, we have different proteins on the membrane. These proteins have specific roles to play. We have carbohydrates that are attached to the proteins and we will study about the protein carbohydrate interactions in the following module.

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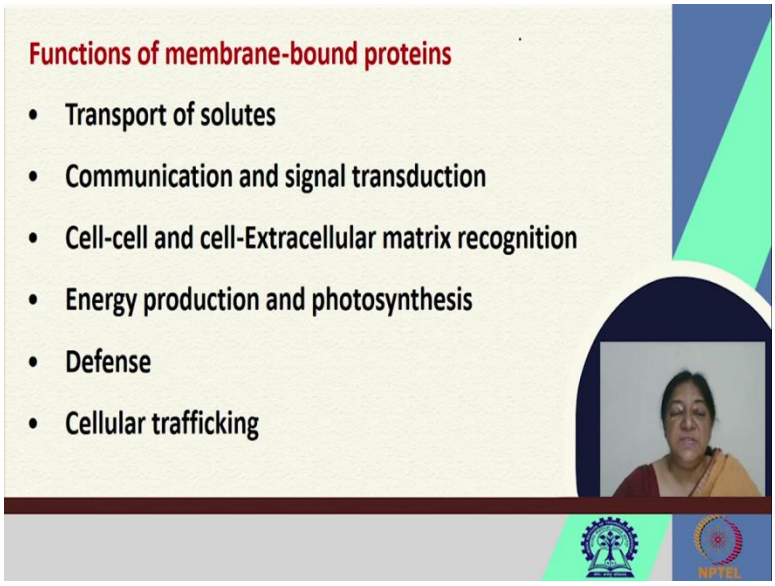

We look at the cholesterol and we have the functions of the membrane-bound proteins. This is involved in the transport of solutes, in the communication and signal transduction, cell-cell and cell-extracellular matrix recognition, energy production and photosynthesis, defense and cellular trafficking.

So, important activities associated with membrane-bound proteins are very evident from the fact that, all the cellular activities in the cytoplasmic region and the transport of material from the inner cytoplasmic region to the extracellular region, are all controlled by the proteins that are present in the membrane.

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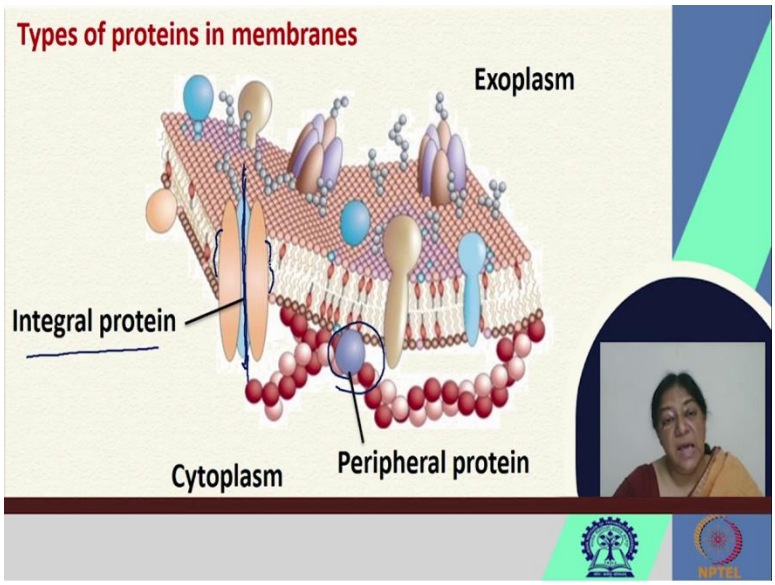

If we look at the types of proteins in the membrane there are two types. One is the integral protein that traverses the membrane, the other is a peripheral protein that is on the surface connected with the lipid. So, it has a protein lipid interaction and this is traversing the membrane in the sense, where the protein lipid interactions are on the surface of this specific protein. We will look at this and the types of residues that are involved in the interactions between the lipid as we go through the lectures.

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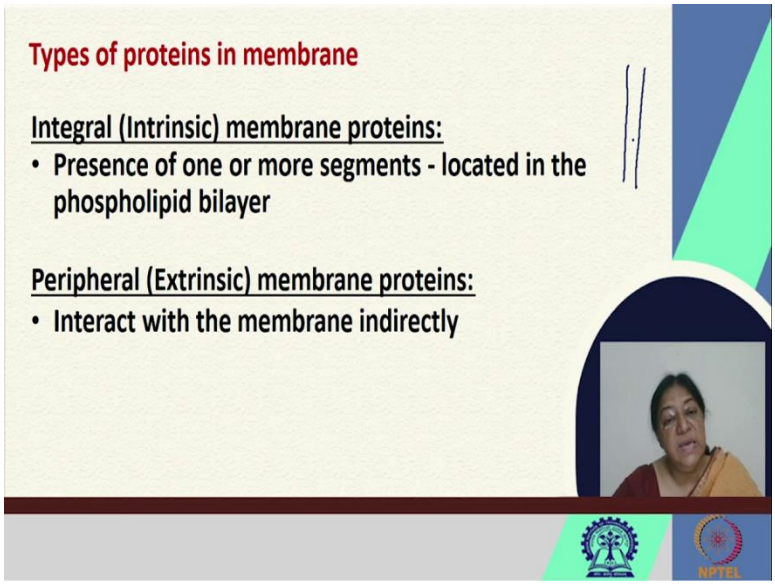

The types of proteins in membranes, are the integral or the intrinsic membrane proteins. They have presence of one or more segments and they traverse the lipid bilayer. We look at the peripheral type, these are the extrinsic membrane proteins that interact with the membrane indirectly.

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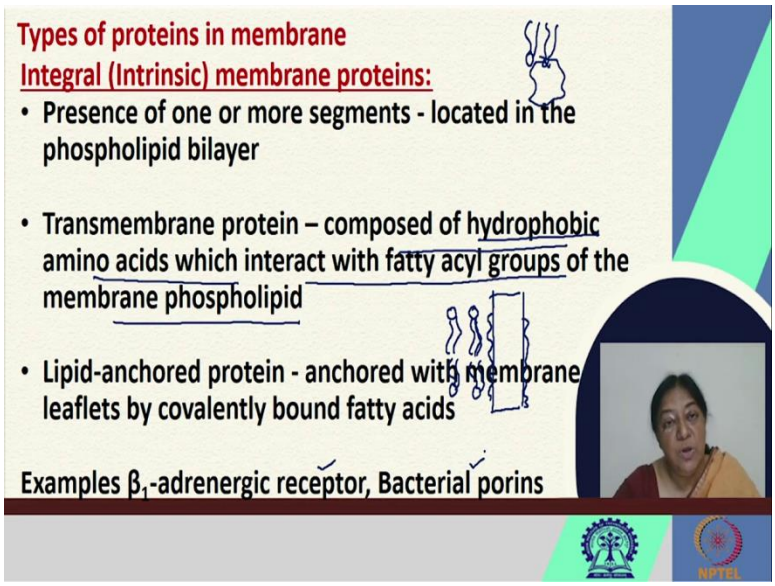

These [refer to slide] are the structures that we have for the lipid bilayer and we would have a protein integrated there, where we would have the interaction with the membrane in a different fashion. When we look at the types of proteins in the membrane, we have this that is located in the phospholipid bilayer. The transmembrane protein is composed of hydrophobic amino acids which interact with the fatty acyl groups of the membrane phospholipid.

This means that when we have our lipid bilayer, we have the polar head group and we have our lipid bilayer. If we have to have a protein that is a transmembrane protein, that traverses the membrane thickness, then the residues on the surface at this [refer to slide] point or at this point would have to have hydrophobic amino acid residues because the tails are hydrophobic in nature.

We have the lipid anchored proteins, where they are anchored with the membrane leaflets by covalently bound fatty acids. These are specific examples of these types of integral proteins.

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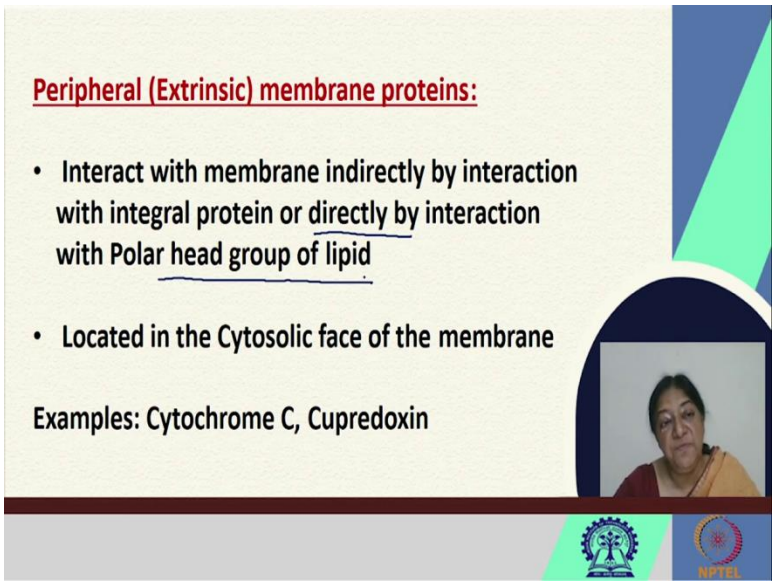

The peripheral extrinsic membrane proteins, they interact with the membrane indirectly by interaction with the integral protein or directly by interaction with the polar head group. So, we have either a protein attached or we have them directly interact with the polar head group of the lipid. They are usually located in the cytosolic face of the membrane and there are specific examples such as cytochrome C and cupredoxin. Their structural components are different than those of the integral proteins.

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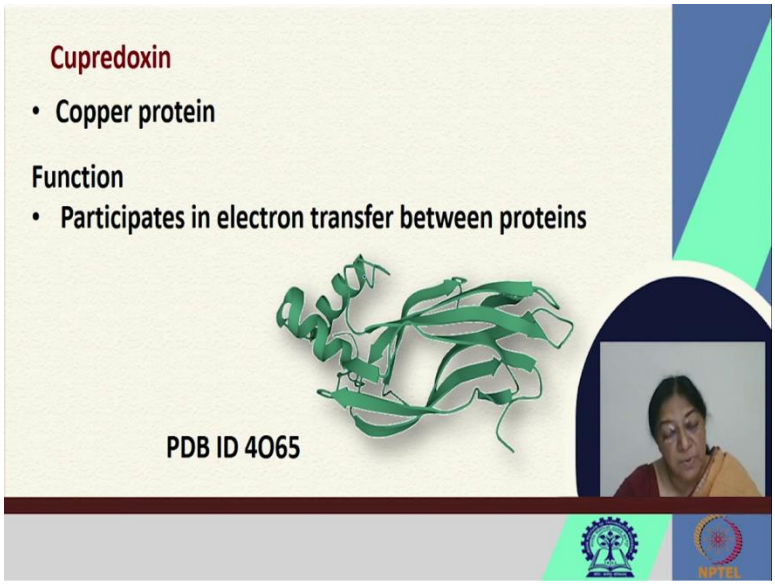

We will look at an example of a peripheral type of protein initially and then look at the integral points. So cupredoxin is a copper protein that participates in electron transfer between proteins and we see that its structural aspects allow it to interact with the surface of the membrane, that is the polar head groups.

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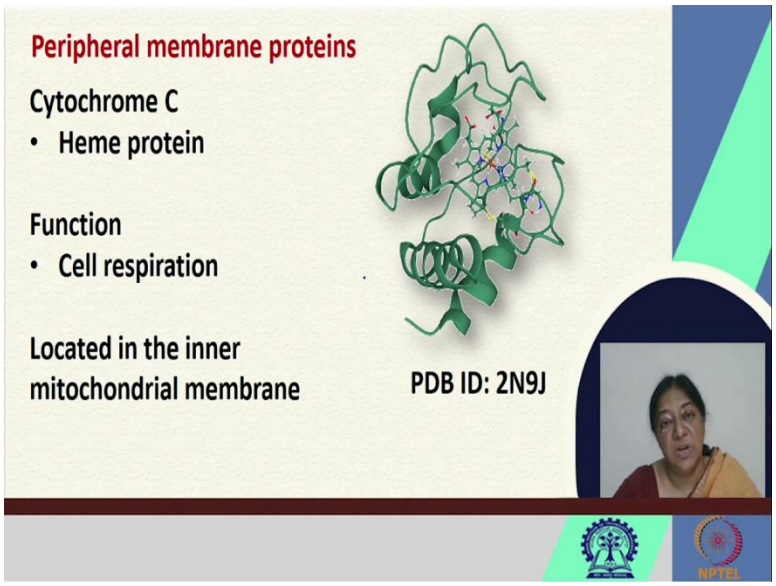

Similarly, in the cytochrome C which is a heme protein the function is cell respiration. This is located in the inner mitochondrial membrane that also has a structure that is distinctly different from the integral membrane protein structures, which we will look at.

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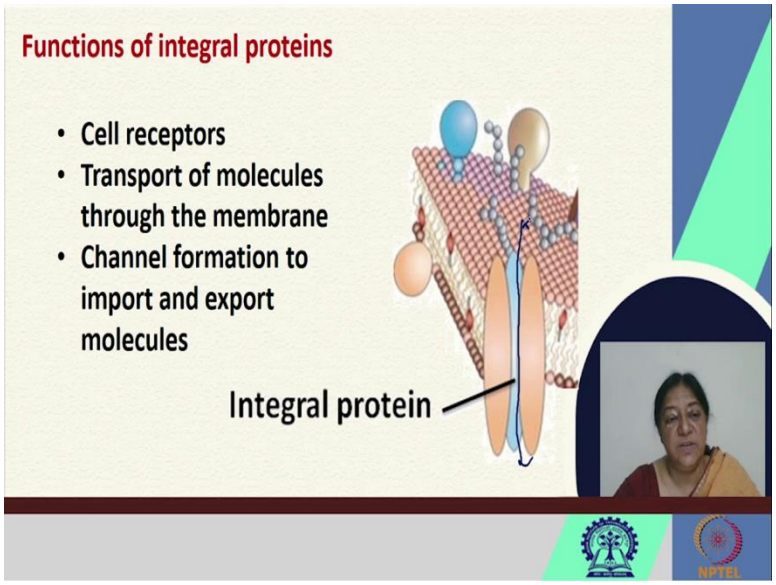

The functions of the integral proteins thus are as cell receptors because they traverse the cell membrane, act as cell receptors. They can transport molecules through the web membrane, which is the most important function that they have and they can form channels to import and export molecules, which is their main purpose of membrane transport.

In the sense that there are specific components, there is a specific membrane potential, that is important for the channel formation and the transport of material from the inside to the outside of the cell and from the outside to the inside of the cell. And we will be looking at this in detail, in our discussions on membrane transport.

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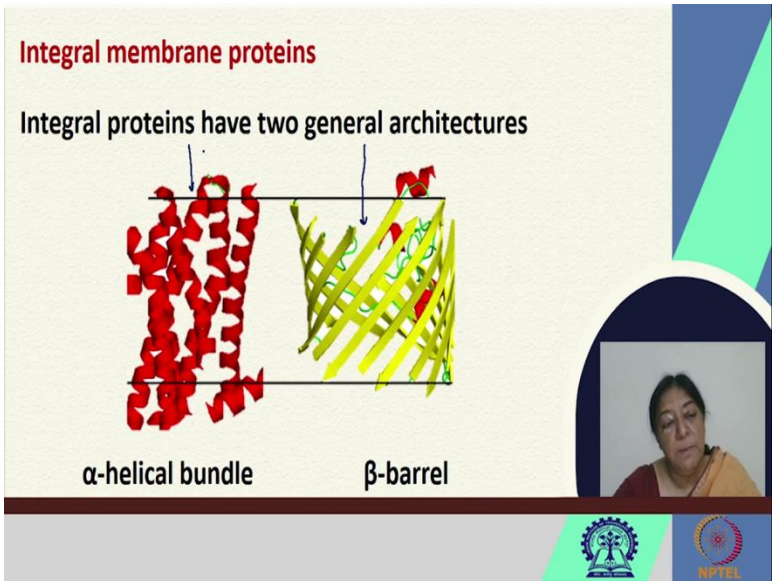

The integral proteins have two general architectures. One is an α-helical bundle type as it is called or a β-barrel. We realize that this is necessary because there has to be a pore whereby the material, whether its small molecules or ions or even larger molecules, would have to be transported through the membrane.

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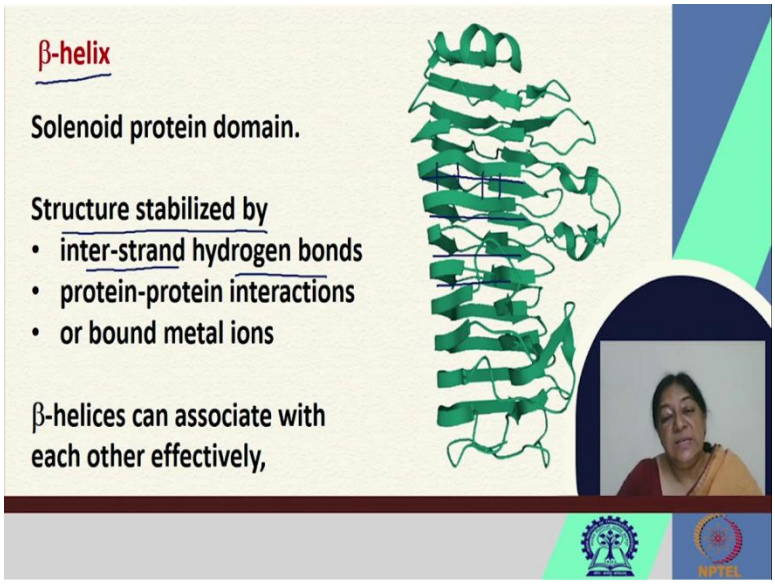

Another type of structure which we have not looked at before, is called a β-helix. This is a kind of solenoid protein domain and these [refer to slide] are the strands that are in this fashion here. So, we have the structure that is stabilized by inter strand hydrogen bonds. These are the hydrogen bonds that stabilize this structure and it also can be stabilized by other protein-protein interactions or metal ions. What they do is, they associate with each other very effectively and they can form a pore by which we can have transport.

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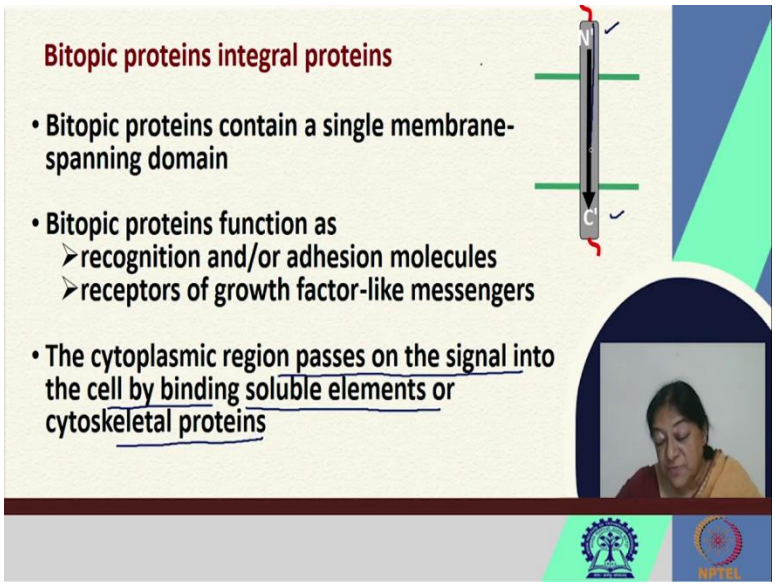

There are bitopic proteins that are integral proteins. They contain a single membrane spanning domain. If this [refer to slide] is our membrane, we would have the N terminal on one side and the C terminal on one side and when we have a single membrane spanning domain, this is called a bitopic domain. They can function as recognition or adhesion molecules, as receptors of growth factor like messengers and the cytoplasmic region passes on the signal into the cell, by binding the soluble elements or cytoskeletal proteins.

So what happens is, if we have the transfer in this direction to the cytoplasmic region, then the signal is passed on through other molecules to the specific location or the target where the signal has to go.

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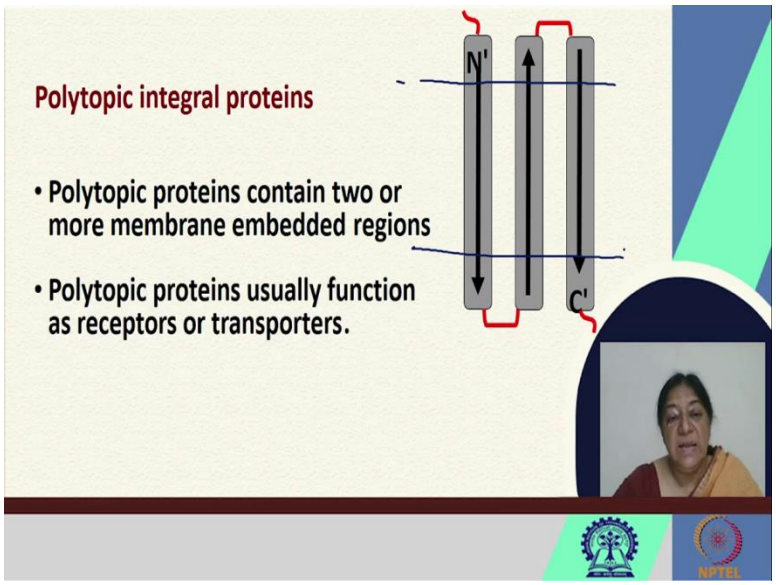

There are polytopic integral proteins, which have their variations. This [refer to slide] is where they traverse the membrane a number of times. So, they contain two or more membrane embedded regions and they usually function as receptors or transporters and the functionality we see is dependent upon the structure of the protein.

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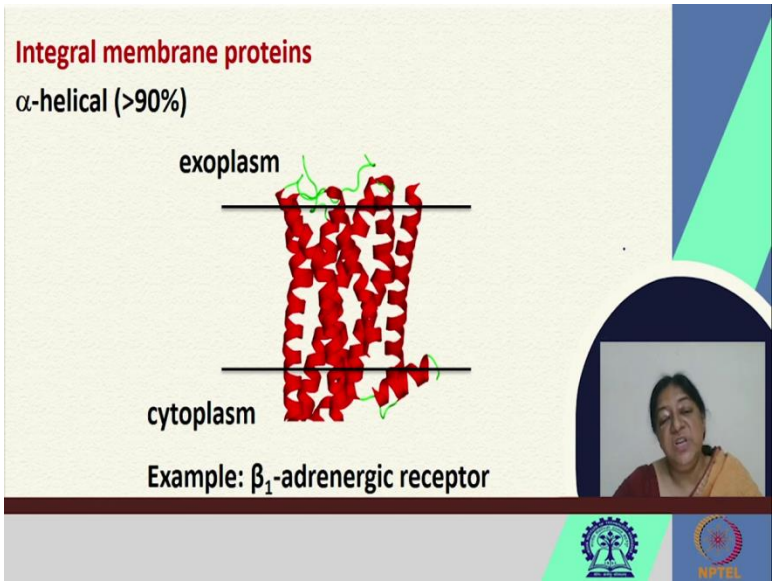

If we look at the integral membrane proteins which have over 90% α-helical structure, this is an example where we have the adrenergic receptor, that acts as an integral membrane protein.

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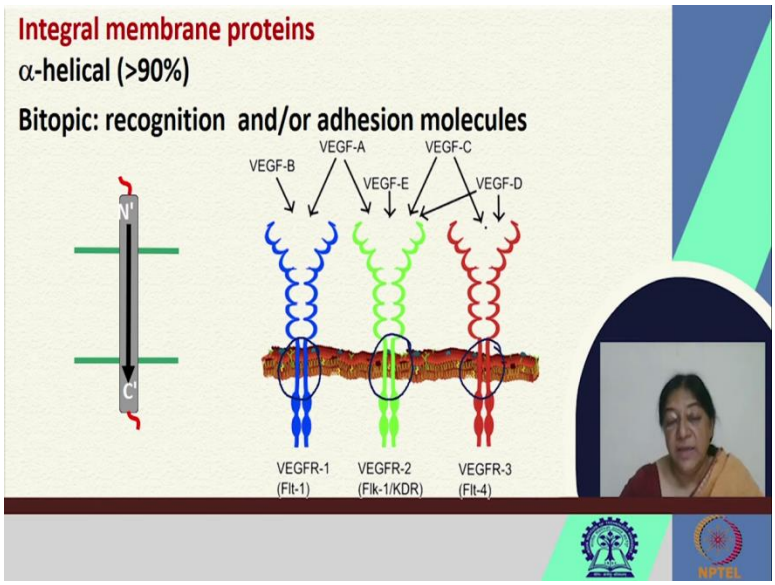

Other examples include the biotopic that is the recognition of adhesion molecules, where we have a specific type of traversing of the membrane and a specific recognition site, that recognizes a molecule or for cell - cell adhesion also, that would result in the transport of material.

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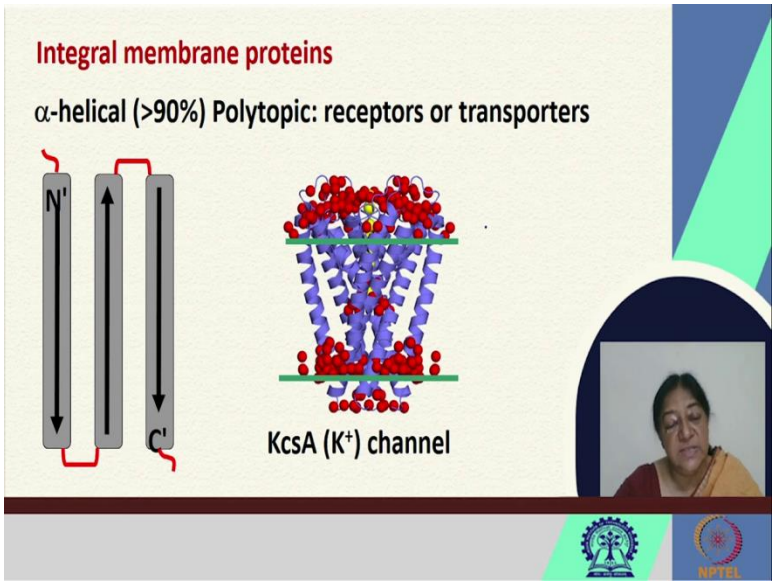

In the polytopic receptors or transporters we can have an example like the K^+ channel, that involves the transport of ions. We will be seeing the membrane transport in greater detail in the subsequent lectures.

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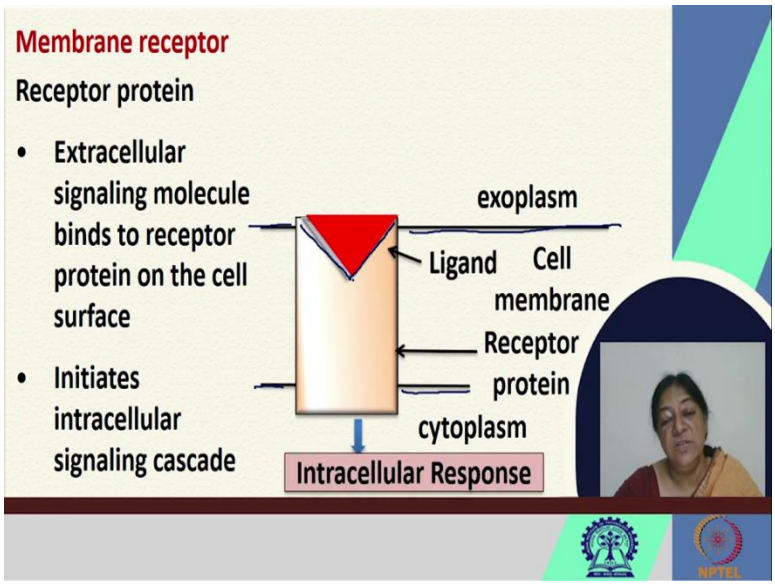

When we look now at a transfer of the membrane, we have our exoplasm, we have our cytoplasm and an integral protein that is a specific receptor protein. This receptor protein can be an extracellular signaling molecule that binds to the receptor protein on the cell surface. So, this binding occurs and when this binding occurs, this initiates an intracellular signaling cascade. These receptor proteins are very important in their structure-function relationships, so that the specific binding is going to trigger this signaling cascade. So, then there is an intracellular response once the binding occurs.

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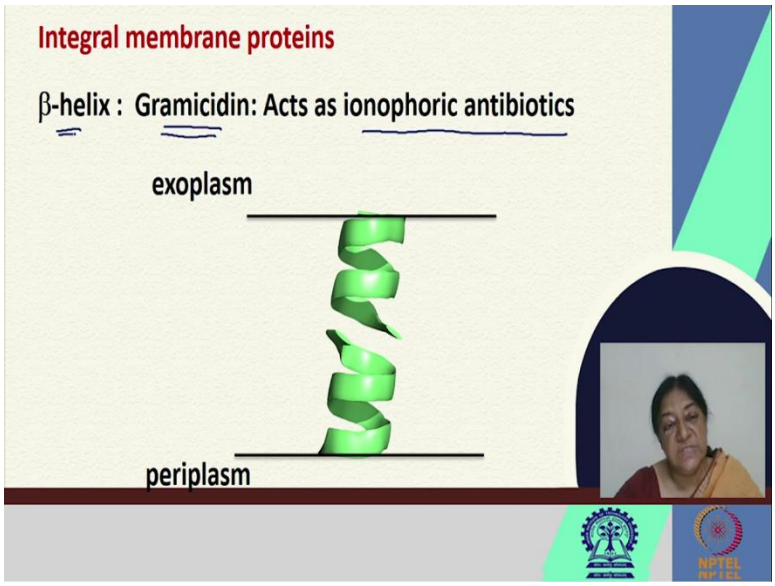

An example of an ionophoric antibiotic, is gramicidin. This gramicidin is an example also of a β-helix type protein and we have the exoplasm, the periplasm and the transport of material across the cell, across the membrane. This is extremely important as we understand, for the functioning of the cell, for the transport of material to maintain the cell.

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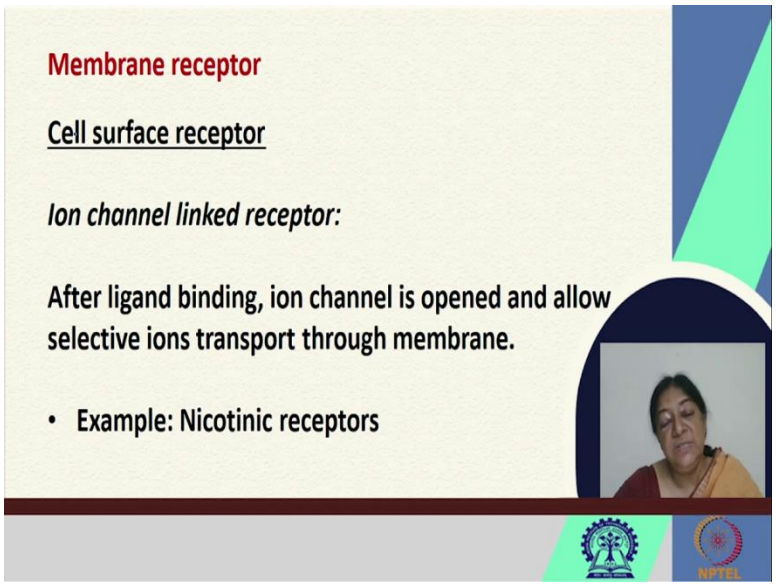

The cell surface receptor therefore can act as an ion channel linked receptor, where after ligand binding, the ion channel is open and it allows selective ions to transport through the membrane. So this membrane potential which we will look at, is important in allowing the binding of the receptor that is going to open the channel, to allow the ion to be transported.

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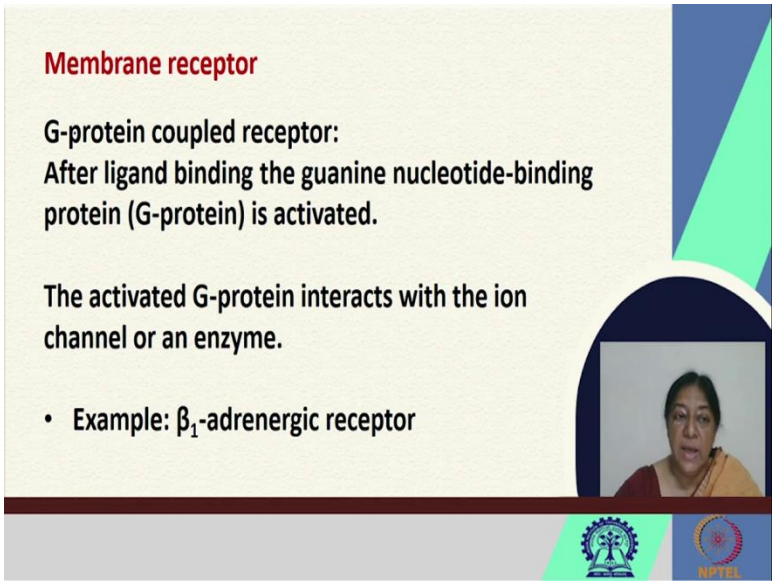

We have another example, a G-protein coupled receptor. After ligand binding the guanine nucleotide-binding protein, the G-protein is activated and once it is activated, it interacts with the ion channel or an enzyme.

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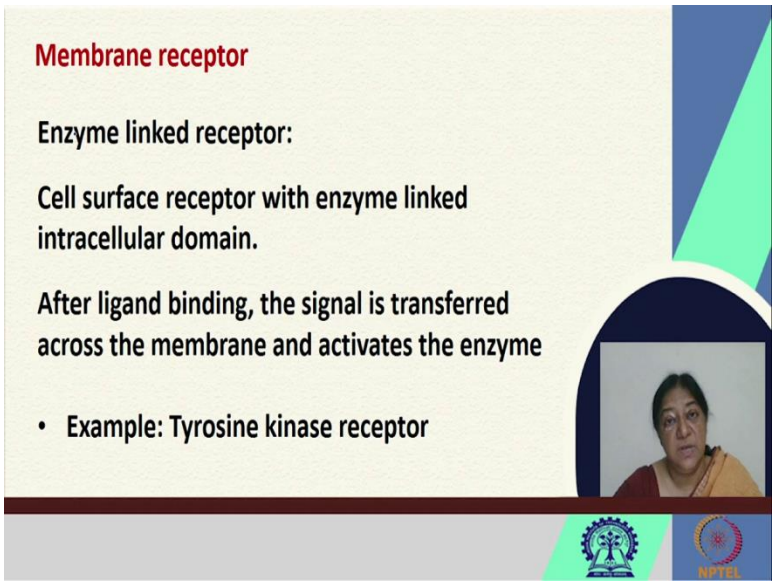

Another type, is where we have an enzyme linked receptor, where the cell surface receptor has an enzyme linked intracellular domain. After ligand binding, the signal is transferred across the membrane and this activates the enzyme into performing its function. An example is tyrosine kinase receptor, where there would be a phosphate transfer involved.

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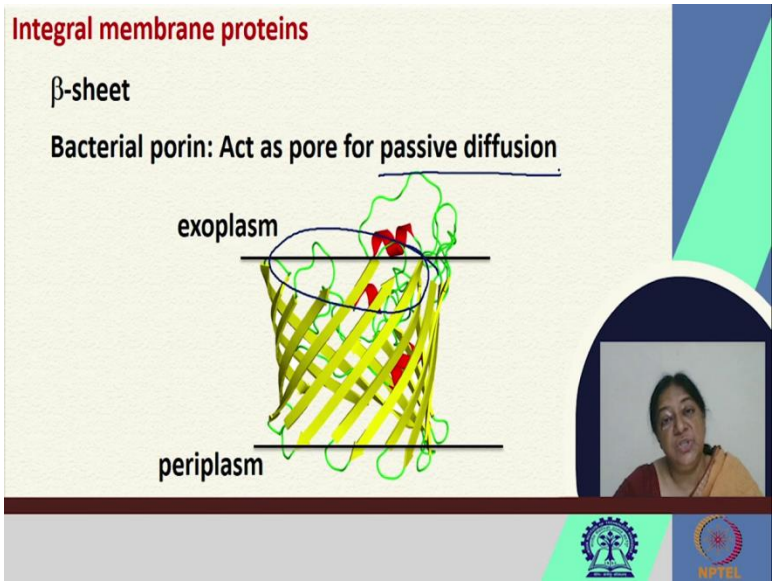

This [refer to slide] is a β-sheet, where this is the formation of a large pore, a porin type molecule and the size of the molecule that it is transferring, is important. We will see what we mean by active and passive diffusion, in our lectures on membrane transport.

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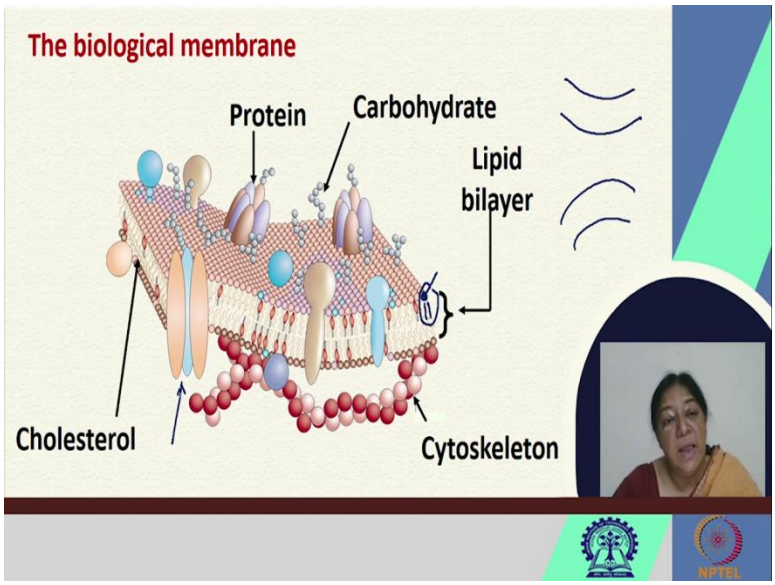

So we looked at the biological membrane, we understood the components of the lipid bilayer, the cytoskeleton, the specific proteins involved; the integral type proteins and the peripheral type proteins and why they would adopt the specific structural components that they are comprised off. We have the carbohydrate attached, the protein carbohydrate interactions and we have the cholesterol that due to its presence maintains a fluidity.

We learned that the lipid head group size and the length of the chain helps to adopt a different structure and a different curvature. For the integral proteins there are specific type of structural aspects that we are looking at, whether they are forming an α-helix bundle or a β-sheet type, a β-barrel structure that would be a porin or they can form a β-helix that looks like a solenoid type structure.

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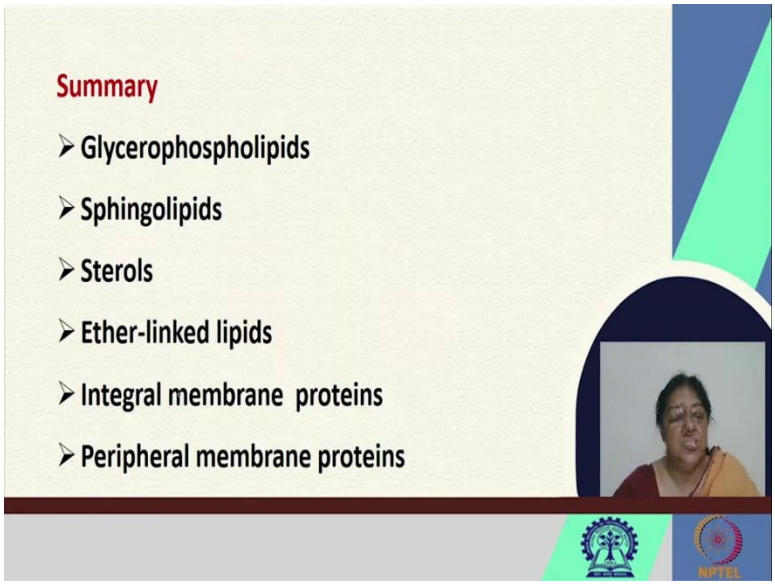

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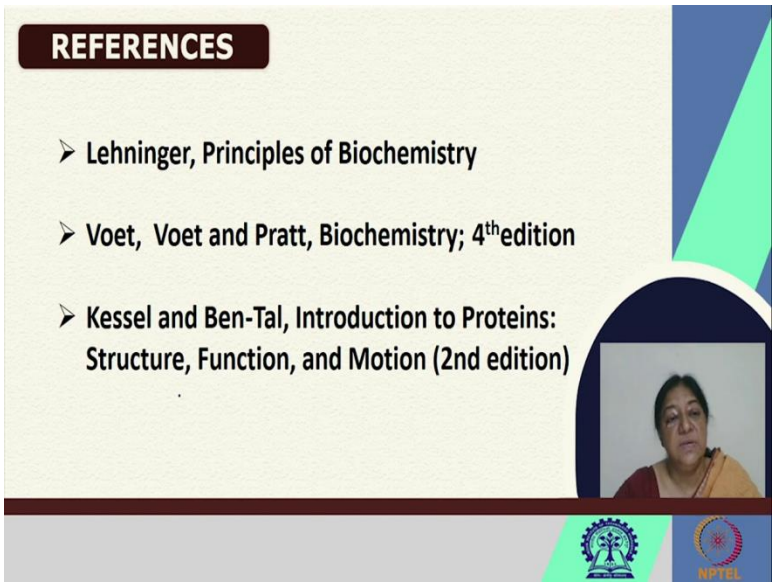

So what we looked at is the glycerophospholipids, the sphingolipids, the sterols, the ether linked lipids, integral and peripheral membrane proteins.

These [refer to slide] are the references.

Thank you.