Overview and Integration of Cellular Metabolism

Prof. Aritri Bir

Dr. B.C. Roy Multi-Speciality Medical Research Centre

Indian Institute of Technology Kharagpur

Week 05

Lecture 21: Lipoprotein Metabolism (I)

Hello everyone, welcome back to the NPTEL classes of Overview and Integration of Cellular Metabolism. We were actually in lipid metabolism which have been which is started from the previous class. Today we will proceed to lipoprotein metabolism. In this class we will discuss the general structure and composition of lipoprotein, then what are the different types of lipoprotein and their specific biochemical properties. Then how these different types of lipoproteins are actually formed inside our body and also metabolized inside the body. And finally, their clinical or metabolic importance how different disorders can be raised from their metabolic defect.

So, in human body how transportation of lipids occur because as we have discussed in our previous class that lipid is actually hydrophobic. So, they are not soluble in the aqueous medium of plasma and remember all the enzymes are working in aqueous phase. So, for transportation as well as metabolism these lipid particle has to be made water soluble by formation of lipoprotein. So, basically lipoproteins are the solubilized form of lipid by which they can be transported and metabolized in the aqueous medium of blood or plasma.

So, what are lipoproteins? Lipoproteins once again is a conjugated lipid conjugation between lipid and protein and here in lipoprotein the protein part is known as apoproteins. So, you can see in lipoprotein lipids can be either hydrophobic lipids that is triglycerides and cholesterol esters or some amphipathic lipids like phospholipids or cholesterol. Remember cholesterol cholesterol is more hydrophilic in comparison to cholesterol ester where a lot of fatty where fatty acids are attached. Then protein part contains apoproteins as well as other protein. In apoproteins there are multiples apoprotein apo A apo B apo C E D different apoproteins are there which we will discuss for in our further discussion.

Now in the structure of lipoprotein you can see that the those hydrophobic part of lipoprotein hydrophobic lipids they are located in the central core away from the aqueous

phase. Whereas, the peripheral part which is in contact with the aqueous phase are mostly formed by different polar materials like amphipathic lipids like glycerophospholipids, phospholipids glycerophospholipids cholesterol as well as apoproteins. So, the outer shell is formed by polar polar molecules polar parts of the amphipathic lipids or proteins. Now in proteins remember there are two types of proteins in lipoprotein one is integral protein another is peripheral protein. Now integral proteins are those proteins which are attached in the core part of the lipoprotein.

And if you separate those integral protein the basic structure of the lipoprotein will be lost. Whereas, peripheral proteins are loosely attached in the periphery and their detachment will not hamper the basic biochemical structure of the lipoprotein. Now we will discuss this peripheral and integral lipoprotein in our further discussions. So, basically lipoproteins function is like a transport vesicle it contains the insoluble form of lipid helps in their transportation being the dietary source exogenous source being the endogenous source the lipids which are formed inside our body all are transported through lipoprotein. And it is important for not only from for transfer transport rather it transfers lipids from one organ to another.

Now there are few specific characteristics of lipoprotein we will highlight like site where these lipoproteins are synthesized. Then different lipid contents and their types different apoproteins their types and contents the size and density of different lipoprotein where they are transported their transport destination and their ultra centrifugation and electrophoretic pattern. So, here is a composite list of lipoprotein. So, you can see there are different types of lipoprotein like chylomicron VLDL stands for very low density lipoprotein IDL stands for intermediate density lipoprotein LDL stands for low density lipoprotein and HDL stands for high density lipoprotein. So, you see in the name of different types of lipoprotein what is highlighted is the density.

So, based on the increasing or decreasing density these lipoproteins are named. So, you can see the least density the lipoprotein which is having least density is chylomicron. Then VLDL then IDL intermediate density lipoprotein then LDL low density lipoprotein and finally, the highest density is present in HDL that is why the name is high density lipoprotein, but it is just the opposite of the size of the lipoproteins. So, you can see the largest lipoprotein is chylomicron and this chylomicron is having the least density. Then the size decreases in very low density lipoprotein further decreases in IDL further decreases in LDL finally, the smallest one is the high density lipoprotein.

Now, if we consider the contents of these different types of lipoprotein you can see in chylomicron the major part 98 to 99 percent of the constituents are actually lipid. What lipid the dietary triacylglycerol and only 1 to 2 percent of the contents are actually

proteins apoproteins like all these A 1 A 2 etcetera. So, only 1 to 2 percent of the content of chylomicron is protein apoproteins. Now, in case of VLDL once again there is lipid content there is lipid which is 90 to 93 percent a lesser content of triacylglycerol which type of triacylglycerol in VLDL the triacylglycerol is basically endogenously synthesized triacylglycerol. And here in VLDL the protein content is slightly increase in comparison to chylomicron that is 7 to 10 percent with the apoprotein B 100 apoprotein different C's.

Then intermediate density lipoprotein which contains triacylglycerol and more cholesterol in comparison to VLDL and also apoproteins like B 100 and apo E. Then comes LDL or low density lipoprotein which is rich in cholesterol as well as 21 percent protein is there in LDL and that is apo B 100. Then comes HDL, HDL is the high density lipoprotein with highest density of proteins present there different types of apoproteins are concentrated in high density lipoprotein and a very small amount of lipid like phospholipid and cholesterol are present in HDL. So, you can see there is very negligible amount of triacylglycerol which is present in HDL no triacylglycerol to negligible amount of triacylglycerol. So, this is how the lipoproteins are classified based on their density they are increasing or decreasing density you can see that density is increasing from chylomicron to HDL whereas, the size is just running to the opposite.

So, here is another representation of the contents density and diameter of the lipoprotein. So, you can see chylomicron is having the largest size, but the lowest density with highest level of triacylglycerol which is actually dietary triacylglycerol. Then comes VLDL smaller in size, but more in more dense particle with lesser amount of triacylglycerol, but more amount of cholesterol content which finally, you can further you can see ideal LDL intermediate density lipoprotein low density lipoprotein their density are actually increasing, but the sizes are decreasing. Finally, the densest one most dense is the high density lipoprotein which contains least amount of triacylglycerol and more amount of proteins concentrated with apoproteins different types of apoproteins. So, this is the electrophoretic pattern of lipoprotein where you can see on electrophore if it is if the lipoprotein mixture is run in a electrophoresis what will happen the larger one is the least dense one.

So, chylomicron will remain at the site of origin whereas, based on the density there will be accumulation of LDL which is known as the beta particle or beta lipoprotein then V VLDL the pre beta lipoprotein. And finally, the farthest running one is the HDL or alpha particle which will be located more towards anode. Remember why because anode anode is the positive one and HDL contains protein containing more negative charges. So, this is the lipoprotein the pattern of lipoprotein electrophoresis. So, plasma lipoproteins where triglycerides are mostly carried the triglyceride rich lipoproteins are actually chylomicron where triglyceride is of dietary origin and the endogenously

synthesized triacylglycerol is carried by VLDL.

Whereas, the cholesterol rich particles are LDL and in HDL there is esterified cholesterol. Then these are the important organs where we will discuss lipoprotein metabolism like intestine, liver then extrepatic tissues importantly adipose tissue. And here is a list of enzymes and proteins related to lipoprotein metabolism just remember the names just I mean just remember this list one by one we will discuss with the respective metabolism part. So, lipoprotein, lipase, hepatic lipase, LCAT, lecithin cholesterol acyltransferase, CETP cholesterol ester transfer protein along with various types of apoproteins and receptors we are going to highlight and discuss in the metabolism of lipoproteins. So, let us come to the first one first lipoprotein chylomicron.

So, what is chylomicron? This is the largest, but lowest density chyl lipoprotein it is assembled in the intestinal mucosal cells remember it is that it is carrying the dietary triacylglycerol. If you remember from the previous class basically the absorbed lipid which lipid forms which were in the enterocytes they were they re synthesize the complex form and these complex form are actually forming chylomicron and they are released from the basolateral part of the intestinal mucosa or enterocytes. It the chylomicron the contents of chylomicron is actually 99 percent lipid and one only 1 percent in protein and the highest concentration of triacylglycerol present in chylomicron which is of dietary origin. Now, chylomicron is actually carrying this triacylglycerol from intestine to liver as well as it is delivering the contents free fatty acids glycerol etcetera to the peripheral tissue. And it has very quick digestion within 2 hours of meal the chylomicron is actually digested and it gives a physiological milky appearance of the plasma.

Now this is the very important part to remember that apoprotein which is very much specific for chylomicron is apoB 48. This is the characteristic apoprotein which is located in chylomicron if you separate this apoB 48 from the chylomicron the biochemical structure will be dissolved. So, basically this is this apoB 48 protein is the integral protein in case of chylomicron. Now, what happens after re synthesize re synthesize of the complex lipid inside the enterocyte what happens there is assembly of this complex lipid with the apoprotein. Now those apoproteins are actually synthesized inside the rough endoplasmic reticulum after synthesis those apoproteins are assembled with the complex lipid inside the smooth endoplasmic reticulum which finally, enters Golgi bodies for glycosylation or other modification.

So, basically there is formation of a nascent chylomicron molecule inside enterocyte which where there is apoB 48 mandatory which is actually the specific apoprotein for chylomicron. So, this is the whole chylomicron metabolism let us see what is happening

here. So, basically from small intestine it is absorbed through the lactase enters in the lymphatics comes in the circulation as nascent chylomicron. Nascent chylomicron contains B 48 mandatorily this is the integral protein of chylomicron along with that there is a small amount of apoprotein A which is attached to the chylomicron. Now chylomicron while going through the circulation it takes different other apoproteins from the apoprotein rich particle which is HDL.

So, HDL contains all types of apoprotein. Now nascent chylomicron takes up apoprotein C as well as apoprotein E from nascent chylomicron takes up these two apoproteins from HDL and forms mature chylomicron. Now this mature chylomicron while going through the circulation reaches the extra hepatic tissue in the peripheral capillaries it is metabolized with the help of the enzyme lipoprotein lipase. Now remember in the previous class I told you there are two different enzymes lipoprotein lipase and hepatic lipase now we are going to discuss lipoprotein lipase. Now lipoprotein lipase is present in the endothelial lining of blood vessels or capillaries and how it is attached it is the extracellular enzyme it is attached to by heparan sulfate to the endothelial lining.

It is predominant in tissues like peripheral tissues like adipose tissue, heart, skeletal muscle. Now there are different activating and inactivating factor you need to remember most important activating factor of lipoprotein lipase is apo C 2 as well as phospholipid. Whereas, apo C 3 and apoprotein A 2 are the two inactivating factors for lipoprotein lipase. Now what lipoprotein lipase does it is lipase. So, basically it breaks down triacylglycerol to produce glycerol and free fatty acids it is stimulated in presence of the hormone insulin.

So, once again we are going back to the metabolism of kylo micron. Now kylo micron mature kylo micron reaches the peripheral tissue comes to comes in contact with the capillary. Now remember kylo micron is actually carrying apo C 2 apo C 2 which has been taken up from the HDL and apo C 2 remember it was the activating factor for lipoprotein lipase. So, whenever kylo micron comes in contact with the lipoprotein lipase the apo C 2 part activates as well as the phospholipid very low amount of phospholipid is there in kylo micron actually. They activate lipoprotein lipase lipoprotein lipase breaks down kylo micron to triacylglycerol and fatty acid constant circulation of kylo micron in the capillaries and constant breakdown of triacylglycerol.

So, what happens the triacylglycerol content of the kylo micron is basically depleting. So, what will be the effect on it is diameter and density definitely density will be increased and the diameter will be decreased. So, there will be a smaller version of kylo micron after the action of lipoprotein lipase which has very low amount of triacylglycerol and definitely the triacylglycerol cholesterol ratio is decreased means if

you compare the ratio then the cholesterol content in comparison to the previous mature kylo micron one is actually increased here. So, these version of kylo micron is known as kylo micron remnant. So, kylo micron remnant is the catabolized version of kylo mature kylo micron where triacylglycerol content is very low along with that there are few there are release of few apoproteins like apo A and apo C these apoproteins are given back returned back to the HDL particle what remains is apo B apo B 48 and apo E.

Now why these two are important remember apo B 48 is the signature of kylo micron. So, it has to be there and apo E is the signaling molecule for its uptake to when in liver. So, what happens what is the fate of this kylo micron remnant this kylo micron remnant is taken up by liver with the receptors receptor which is apo E apo E sensitive receptor those are known as remnant receptor or apo E receptor or LRP LRP stands for LDL receptor related protein. So, these kylo micron remnants are taken up inside the liver with the help of these apo E dependent receptors inside the liver whatever triacylglycerol are present inside the kylo micron remnant is digested with the help of hepatic lipase. So, there is another lipase that is hepatic lipase which is present in the liver it breaks down triacylglycerol which are directed inside the liver.

So, kylo micron the the low amount of triacylglycerol which is present in kylo micron remnant is broken down by hepatic lipase as well as there are other lysosomal hydrolysis which finally, breaks down the protein and conjugate conjugation releasing apo proteins inside the circulation in the form of HDL. So, basically this is the total catabolism of kylo micron. Next we will move to the metabolism of VLDL very low density lipoprotein. So, remember very low density lipoprotein contains triacylglycerol which is endogenously derived triacylglycerol.

Endogenous means inside the body. So, inside the body where this is synthesized in hepatocytes and a very short amount of triacylglycerol is internally synthesized in intestinal mucosal cell as well. Now here the signature apoprotein is apo B 100. So, once again this is the integral protein for VLDL. Remember the integral protein for kylo micron used to be apo B 100 apo B 48 for kylo micron whereas, for VLDL that is apo B 100. So, these are the integral proteins if you detach this protein the characteristics of the lipoprotein will be lost.

Whereas, all the other apoproteins they are located in the periphery like apo C 2 apo E those are located in the peripheries and they are detachable and on their detachment the characteristics will not be lost. So, those are the peripheral proteins. Now VLDL it basically facilitates the mobilization of endogenously synthesized triacylglycerol from liver to other extra hepatic tissues. Now let us see what happens in the metabolism of VLDL once again the metabolism of VLDL is very much similar with the metabolism of

kylo micron. Now you can see there is formation of nascent VLDL just like the formation of nascent kylo micron.

So, in the nascent kylo VLDL what is there the signature apoprotein that is apo B 100 along with that a very small quantity of apo E and apo C. Just like kylo microns maturation maturation the maturation of VLDL occurs by taking up some other apoproteins like apo C and apo E from HDL mature VLDL reaches the peripheral capillaries and is acted upon by lipoprotein lipase. Remember VLDL on maturation also have taken up that apo C 2 and whenever this VLDL is coming in contact with the periphery peripheral capillaries in contact with the lipoprotein lipase it is actually activating the lipoprotein lipase. So, lipoprotein lipase it what it does it digests it breaks down the triacylglycerol into free fatty acids and glycerol. This free fatty acids are taken up by the extra hepatic tissues for further processing further metabolization of fatty acids what remains once again is a remnant that is VLDL remnant.

Now, in that remnant what will be there once again there will be lesser amount of triacylglycerol because most of the triacylglycerol is already broken down by lipoprotein lipase. So, there is lesser amount of triacylglycerol. So, because there is leaving I mean there is releasing or breaking down of triacylglycerol the size will be decreased. So, the VLDL remnant is a smaller molecule in comparison to the mature one. Again there is returning of some apoproteins to HDL which is apo C.

So, what remains the signature apoprotein that is apo B 100 along with that apo E which is basically sensitizing the receptors like remnant receptor apo E receptor LDL receptor like all these receptors are sensitive to apo E. So, what happens the finally, after catabolism of VLDL with the help of lipoprotein lipase there is formation of a VLDL remnant and this VLDL remnant is actually known as intermediate density lipoprotein. Now, what is the fate of this intermediate density lipoprotein? It can be taken up directly by liver inside the liver the fate is just like chylomicron whatever remaining triacylglycerol is there those will be metabolized with the help of hepatic lipases then further there will be action of lysosomal hydrolysis which will separate the lipid parts as well as the protein part protein parts will be re circulated in HDL. Now, apart from uptake by liver IDL have IDL has another fate that is formation of low density lipoprotein.

So, this is low density lipoprotein. So, you can see IDL has 2 fates it can directly enter liver can be can there can be reuptake inside the liver as well as there can be formation of low density lipoprotein. So, low density lipoprotein is one very important lipoprotein we will discuss about the metabolism of low density lipoprotein in our next class as well as the fate of low density lipoprotein. So, at the end of today's session these are the key

points which we have discussed in this session that is the structural composition biochemical composition and biochemical characteristics of lipoprotein in general. Then specific composition of chylomicron and VLDL they are synthesis and they are catabolism as well as characteristics of one very specific enzyme related to lipoprotein metabolism that is lipoprotein lipase.

So, these are my references. Thank you all see you in the next class.