Overview and Integration of Cellular Metabolism

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Lecture 22: Lipoprotein Metabolism (II)

Welcome back to the NPTEL sessions of Overview and Integration of Cellular Metabolism. From the previous class we have started lipoprotein metabolism, we are going to continue the same today. So, in the previous class we have discussed the general structure and composition of lipoproteins. As well as we also have discussed the metabolism of chylomicron and VLDL the two lipoproteins chylomicron and VLDL. Today we are going to discuss another two lipoproteins metabolism that is LDL low density lipoprotein and HDL high density lipoprotein. So, if you remember from the previous class you have to remember because that is the continuation lipoprotein metabolism all the lipoprotein metabolism are basically very much interrelated.

So, before going through this session you need a quick recap of the previous one mind it. So, what we have discussed regarding the VLDL metabolism that VLDL very low density lipoprotein is originated from liver VLDL is basically carrying the endogenously synthesized triacylglycerol endogenously synthesized inside the liver actually. And it is going through different maturation phase that is nascent VHDL nascent VLDL as well as which has been matured to form matured VLDL. Matured VLDL after going through the capillaries is actually hydrolyzed with the help of the enzyme lipoprotein lipase.

So, there is hydrolysis of triacylglycerol with this enzyme. So, finally, which is formed that is a VLDL remnant. The remnant contains less triacylglycerol in comparison to the mature one because the triglyceride is already synthesized. Now we also have discussed the fate of this remnant VLDL that is IDL or intermediate density lipoprotein. Intermediate density lipoprotein can be can enter liver it can there is reuptake of IDL inside the liver as well as it can form another lipoprotein that is low density lipoprotein.

So, we are going to discuss the metabolism synthesis and fate of low density lipoprotein. So, what is low density lipoprotein? You can see lipoprotein this low density lipoprotein is basically the it is formed from the VLDL remnant or IDL. Now in this low density

lipoprotein what is there that is endogenously synthesized cholesterol in huge amount as well as phospholipid and a very minimal quantity of triacylglycerol and as you can see there is one very important apoprotein that is apo B 100. So, this apo B 100 is very specific for low density lipoprotein. Now low density lipoprotein it basically what it does it transport those endogenously synthesized cholesterol from liver to peripheral or extra hepatic tissues.

Now what happens actually this IDL is ideal means it is the VLDL remnant. VLDL remnant again it is constantly targeted or attacked by lipoprotein lipase. So, basically there is a huge depletion of triacylglycerol finally, what is formed is the low density lipoprotein which is cholesterol rich. Now what can what are the fates of this LDL? Now LDL majority like 70 percent of the LDL is basically metabolized inside the liver it it it is it enters liver through LDL receptor. The remaining 30 percent is basically going to extra hepatic tissue it is remember it delivers cholesterol to extra hepatic tissue.

So, this part is very important LDL provides or supplies cholesterol to the extra hepatic tissue and this uptake of LDL say it in liver say it in extra hepatic tissue it occurs through LDL receptor. Now LDL receptor is one very important receptor with respect to cholesterol metabolism. So, we are going to discuss a bit of LDL receptor as well. So, LDL receptor is also known as APOB 100 APOE receptor. So, why it is APOB 100 APOE receptor because basically LDL receptor senses APOB 100 or APOE.

So, this is the signaling molecule for LDL receptor is the basically acting as ligand ligand for this receptor is APOB 100 or APOE. Now this LDL receptor is present in cell surface of different types of cells like liver mainly then peripheral tissues like adrenal glands steroid hormone synthesizing tissues like ovary testes fibroblast smooth muscle cells of vascular endothelium lymphocytes. So, in these cells over the cell surface LDL receptor is present in clathrin coated beads. Now, this LDL receptor as you can see in this diagram that it is a large transmembrane glycoprotein receptor around 115 kilo Dalton molecular weight. Now this receptor has 5 domains and the mature receptor is basically 839 amino acid long receptor containing 5 domains.

So, these are our 5 domains. Now the first domain is the ligand binding domain. The ligand binding domain is the N terminal domain it is situated outside the it is actually protruded outside the cell surface. Definitely ligand binding domain the name indicates that it binds with the ligand that is B 100 or APOE containing lipoproteins. Now in in this ligand binding domain there is a repeat sequence which is known as class A repeat which contains 40 amino acids.

So, there are the repeats are class A repeats containing 40 amino acids. These type of

repeats similar such 7 repeats are actually present in these domain. Now in this domain there is cysteine there are cysteine residues as well as acidic residues and what is that action of this acidic residues acidic means amino acids which are having acidic residues. Now those acidic residues they interact with the basic residues of apoproteins. So, basically there is a interaction there is an interaction between the acidic residues of the LDL receptor with the basic residue of the lipoproteins.

So, this is the reason by which ligand binding occurs. The second type of a ligand is the lipoproteins those lipoproteins which contains once again APOB 100 and APOE ok. So, after that the second domain is EGF precursor homology domain EGF is epidermal growth factor. Now it by the name it is evident that these domain these part of the domain has sequence homology or structural homology with the epidermal growth factor. Now these domain is important for expulsion of the attached LDL inside the cell.

So, once the ligand is bound to the receptor it also needs to deliver the ligand or lipoprotein here to inside the cell. So, these region is basically important for repulsion. So, it extrudes the bound lipoprotein to inside the cell. Next is O linked sugar rich domain ortho linked sugar rich domain. There are multiple O linked glycosidic bonds present in this domain glycosides are attached in this domain.

So, these domain is forming a start is a segment which is actually holding the receptor in such a pattern that it can be expanded outside and can deliver it its proper function. So, it is basically holding the receptor to the outer surface of the cell. Next domain is the membrane spanning domain it is that this part is basically the trans membrane spanning domain then the cytoplasmic tail. Now cytoplasmic tail is the domain which is actually causing endocytosis of the ligand receptor complex. So, these are the 5 domains of LDL receptor once again one domain first domain is important for binding of the ligand or lipoproteins.

Second domain is for important is because it is actually causing expulsion of the ligand or lipoprotein inside the cell. Third domain is important for holding the receptor in such a pattern. So, that it can be bound with the coming ligand then membrane spanning domain and finally, the cytoplasmic tail or cytoplasmic domain which is important for endocytosis of the receptor ligand complex. Now LDL uptake apart from these tissues can be in macrophages as well. Now LDL uptake in macrophages actually forming foam cells which is causing atherosclerosis which is important for heart attacks, myocardial infarction we will discuss this in our next class in details.

So, LDL receptor is important for uptake of LDL inside the cell. Now how this uptake is basically occurring inside the cell? Now remember LDL in a lipo I mean a low density

lipoprotein apo B 100 is the signaling protein which is sensed by the LDL receptor. So, whenever they are whenever the circulating lipoprotein LDL comes in contact with the LDL receptor LDL receptor basically identifies apo B 100. Now definitely there is receptor ligand binding that is here ligand is the LDL remember. So, this ligand is bound to the receptor and that receptor ligand complex is endocytosed by receptor mediated endocytosis.

Remember that LDL receptor is it is actually the surface receptor which and that surface is coated with clathrin. So, those clathrin coated pits are actually responsible for receptor mediated endocytosis. So, after endocytosis what is formed is endosome. So, you can see this is our endosome which contains this is our LDL receptor sorry this is the lipoprotein LDL particle and this part is our receptor. So, the ligand receptor complex is endocytosed within the endosome.

Now this endosome is fused with the lysosome forming endolysosome. Inside the lysosome there are different hydrolases, hydrolases breaks down the cholesterol cholesterol esters inside the lipo LDL particles. Now what happens there is release of you can see there is release of cholesterol as well as fatty acid and also the cholesterol esters are accumulated can be stored inside cholesterol ester droplets. Now the apoprotein part is also hydrolyzed to amino acids different amino acids and released in cytosol and there is amino acid it is basically contributing to the amino acid pool of the cell which is reform further reutilized for other protein synthesis. Now remember the in this receptor ligand complex the ligand or the LDL is only hydrolyzed inside the lysosome whereas, the receptor that is LDL receptor is recycled back to the cell surface for further uptake of LDL particle inside the cell.

Now what is the fate of this cholesterol inside the cell? So cholesterol it has many biochemical properties biosynthetic properties like there are different steroid hormones which are synthesized from cholesterol different vitamins like vitamin D can be synthesized from cholesterol bile acids can be synthesized apart from that it is it is one very important part of cell membrane and also cholesterol is the cholesterol ester is cholesterol cholesterol ester they are they can be stored and can be utilized on requirement. So, this is the fate of cholesterol inside the cell. So you can see that definitely LDL receptor is one very important signal for LDL uptake. Now how this receptor is basically regulated? Remember LDL receptor is regulated through cholesterol concentration inside the cell and as well as in the circulation. Now what happens when there is cholesterol when cholesterol is delivered inside the cell by LDL through the receptor ligand complex that cholesterol can be stored or can be utilized for further different other biosynthetic requirement.

Now when there is circulate when the cholesterol is delivered through circulation the endogenous synthesis of cholesterol is stopped. So, this is a signal that the cell has adequate amount of cholesterol. So, the cell does not need to synthesize more cholesterol endogenously. So, the main enzyme of cholesterol synthesis like HNG coenzyme A reductase is inhibited. So, endogenous cholesterol synthesis is inhibited.

Now there is a transcription factor transcription factor which is known as SREBP sterile responsive element binding protein. So, this sterile responsive element binding protein is influenced with the cellular intracellular concentration of cholesterol. So, when there is high level of intracellular cholesterol which is delivered through LDL it basically is acting in such a way that the endogenous cholesterol synthesizing enzymes are reduced. Similarly, the LDL receptor synthesis is also reduced which indicates that no more uptake of cholesterol is required. So, cholesterol receptor remember cholesterol receptor synthesis is regulated with the and that is signaled by the endogenous cholesterol sorry intracellular cholesterol concentration through a pathway which is influenced by a transcription factor known as sterile responsive element binding protein.

So, next we are moving to the metabolism of HDL or high density lipoprotein. So, if you remember the composition of HDL that HDL is having the highest density amongst the lipoprotein containing the highest amount of protein in the form of apoprotein. So, different types of apoproteins are present in HDL. So, basically HDL is acting as a reservoir for apoproteins in circulation. Now HDL can be synthesized in liver as well as in intestine.

Now intestine contributes for around 30 percent of endogenous HDL synthesis. Now the nascent HDL once again just like VLDL and chylomicron there is a nascent form of HDL and it has two different forms one is hepatic HDL form another is intestinal HDL form. So, hepatic form of HDL contains apo A apoprotein A apoprotein C 2 as well as apoprotein E it is discoidal in shape. Why discoidal in shape? Remember HDL does not have this nascent HDL actually does not have triacylglycerol which forms the lipoprotein core spherical core is formed by cholesterol sorry triacylglycerol, but or phyrophobic lipids.

So, those are not present in HDL. So, nascent HDL is basically discoidal in shape and the surface of this HDL is formed by amphipathic lipids like phospholipids and free cholesterol. Now the intestinal HDL contains only apoprotein A no apo C 2 or apo E basically this apo C 2 and apo E these are synthesized in liver. So, the intestinal HDL nascent HDL form does not have apo C 2 and apo E, but it acquires when it comes to the circulation when the nascent intestinal HDL comes to the circulation it acquires apo C 2 and apo E from the hepatic nascent HDL. So, this is the circulation or metabolism of

HDL in our circulation. So, the nascent HDL or nascent HDL say it intestinal HDL say it hepatic HDL they are mostly released in a form which is known as pre beta HDL.

Now, this pre beta HDL mostly contains apoprotein A A 1. Now what happens initially it contains very meager amount no triacylglycerol and very meager amount of phospholipid and cholesterol. Now this pre beta HDL when comes to circulation it is such a small particle it comes it circulates to the capillary comes in contact with the extra hepatic tissues. Now, from extra hepatic tissues there is transfer of phospholipid and cholesterol mostly cholesterol from extra hepatic tissues to this pre beta HDL you can see pre beta HDL takes rather uptakes cholesterol from extra hepatic tissues through the receptor ABCA 1. So, this is a type of transporter protein ABCA 1 ABC is ABC stands for ABC stands for ATP binding cassette transporter protein and the type is A 1.

So, this ABCA 1 it is responsible for delivery of cholesterols from extra hepatic tissue to pre beta HDL. Now what happens when there is cholesterol and phospholipid accumulated in this pre beta HDL the enzyme LCAT is activated. Now what that LCAT is that is lecithin cholesterol acyltransferase enzyme. Lecithin cholesterol acyltransferase enzyme as it is evident by the name that it transfer transferase means it transfer acyl group from lecithin to cholesterol. So, you can see the this is our LCAT enzyme.

Now in cholesterol it is basically transferring the acyl group or fatty acid basically. So, here this part the acyl group is transferred to cholesterol. So, there is esterification of cholesterol formation of cholesterol ester and lecithin is converted to lysolecithin. So, this is the function of lecithin cholesterol acyltransferase. Now lecithin cholesterol acyltransferase or LCAT is actually associated with HDL and is activated by the apoprotein A 1 mostly also C 1 A 4 they also stimulate the LCAT activity, but most important activator of LCAT is apo A 1.

And remember pre beta HDL contains apo A 1 in huge amount. Now once this pre beta HDL takes up cholesterol from extra hepatic tissues what happens this LCAT is activated by A 1 apo A 1 and cholesterol is esterified to form cholesterol ester which is more hydrophobic than the cholesterol. So, it is basically forming the hydrophobic core of in nascent HDL. So, basically nascent HDL is converted to mature spherical HDL form. Similarly LCAT can also ester if can also converts the cholesterol and phosphatidyl can convert the cholesterol of chylomicron and VLDL remnant to cholesterol ester as well.

Now once again another important protein is there that is cholesterol ester transfer protein known as CETP. Now CETP is another important protein with regard to HDL metabolism and it is important for lipid transfer in between the lipoprotein molecules. How it transfer lipids? Basically CETP transfers triacylglycerol from either VLDL LDL

ideal to HDL. So, basically triacylglycerol is transferred from these to HDL in exchange of cholesterol ester which was in HDL is transferred to VLDL. So, you can see from HDL there is transfer of cholesterol ester to VLDL as well as LDL and what it takes? It takes triacylglycerol from VLDL or from LDL.

So, this CETP or cholesterol ester transfer protein is important for transfer of triacylglycerol in cholesterol in between HDL and VLDL LDL ideal this lipoproteins. Now you can see CETP is important for reduction of cholesterol ester content of HDL. So, cholesterol was up taken from extra hepatic tissue in the pre beta HDL form that cholesterol is converted to cholesterol ester with the help of the enzyme LCAT and that formed cholesterol ester is transferred to VLDL or HDL with the help of the protein CETP. So, basically CETP is reducing the cholesterol ester content of HDL. So, again HDL is ready to uptake more cholesterol from the extra hepatic tissue.

So, basically what you can see that CETP can influence the function of LCAT. So, more CETP acts more cholesterol cholesterol ester reduction from HDL more LCAT is activated to convert the cholesterol to cholesterol ester. Now CETP activity when it is induced CETP basically it transfer the cholesterol ester from HDL to VLDL or LDL and they transferred it to the extra hepatic tissue. So, the requirement of cholesterol in extra hepatic tissue is inducing the CETP to transfer more cholesterol to the extra hepatic tissue. So, this is the function of CETP once again that CETP transfers the triacylglycerin cholesterol ester between HDL and other lipoproteins.

Now what happens for that remember pre beta HDL when it takes up cholesterol ester inside it is it is forming the hydrophobic core. Now there is more maturation of the nascent HDL there because there is more formation of cholesterol ester hydrophobic core which is converting the nascent HDL nascent discoidal HDL to the spherical matured HDL form which is known as HDL 3. Now HDL 3 contains cholesterol ester inside it is core. So, this HDL 3 is basically rich in cholesterol ester, but after CETP activity CETP basically it reduces the cholesterol ester content of the HDL whereas, it increases the triacylglycerol content of the HDL. Now after CETP activity the form of HDL which contains more triacylglycerol and less cholesterol ester is known as HDL 2.

So, these are the isoforms of HDL, HDL 2 and 3 which is and this transformation is basically occurring through the CETP protein. So, once again we are back to the metabolism of HDL. So, you have seen that there is formation of pre beta HDL, pre beta HDL it takes up cholesterol from the extra hepatic tissues with the help of the transporter ABCA 1 and it forms the discoidal nascent HDL form. Nascent HDL it takes up more cholesterol ester from the extra hepatic tissue and cholesterol from the extra hepatic tissue and that cholesterol is esterified with the help of the enzyme LCAT forming the

HDL 3 isoform, HDL 3 form of HDL molecule.

Now HDL 3 remember it is a spherical form. Now HDL 3 is converted to HDL with the help of the protein CETP. So, HDL 2 is a triacylglycerol rich form. Now what is the fate of this triacylglycerol rich HDL 2? It can it enters the liver inside the liver it is uptaken by the receptor SRB 1 scavenger receptor B 1. So, once it is uptaken the triacylglycerol is digested or degraded by the enzyme hepatic lipase remember hepatic lipase lipoprotein lipase needs apo C 2 for its activation hepatic lipase does not. So, hepatic lipase here is degrading the triacylglycerol content of the HDL.

So, once the triacylglycerol content of the HDL 2 is reduced basically it is forming HDL And once the and it continuously circulates through the liver is targeted by the hepatic lipase still there is total depletion of triacylglycerol from the HDL as well as also inside the lysosome there is degradation of cholesterol ester. So, finally, what is formed after action of after depletion of triacylglycerol and cholesterol there is reformation of the pre beta HDL remember which does not have any triacylglycerol or very minimal very very meager amount of cholesterol ester. So, this pre beta HDL is once again form for the cycle. So, you can see this is how cholesterol the HDL functions HDL is synthesized from liver containing apo C 2 A and C apo E and these apo proteins are donated for maturation of nascent chylomicron for maturation of nascent VLDL then also it uptakes cholesterol from the peripheral extra hepatic tissues those cholesterols are converted to cholesterol ester with the help of the enzyme LCAT and there is transfer of this cholesterol ester to VLDL as well as uptake of TG or triacylglycerol with the help of the protein CETP. So, this is the function of HDL it takes up peripheral cholesterol as well as it donates apo protein for maturation of chylomicron and VLDL.

So, this is how the dietary lipid in the form of cholesterol a chylomicron and endogenous lipid in the form of VLDL are circulated which is important for delivering cholesterol to peripheral tissue as well as triacylglycerol to peripheral tissues and this helped in their formation with the help of HDL molecule. So, in this session what we have learned is basically LDL and HDL metabolism. So, LDL is formed from VLDL remnant and it is a cholesterol rich molecule containing apo B 100 remember this is very important apo B apo protein which is in LDL is apo B 100 the uptake of LDL is through LDL receptor and then again HDL metabolism this HDL molecule is a apo protein rich particle which continuously takes cholesterol from the peripheral tissue and it is important for exchange of triacylglycerol and cholesterol in between with other lipoprotein molecules and also it is it HDL acts as the reservoir of different apo proteins.

So, these are my references. Thank you everyone. See you in the next class of lipoprotein metabolism. Thank you.