Overview and Integration of Cellular Metabolism

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Lecture 23: Lipoprotein metabolism (III)

Hello everyone. Welcome back to the NPTEL session of Overview and Integration of Cellular Metabolism. So, we were discussing in our last two classes lipoprotein metabolism. This class is about lipoprotein metabolism once again, this is the last class of lipoprotein metabolism. So, to recapitulate the previous classes that we have discussed the general structure, biochemical properties of different lipoproteins, then the metabolism of different lipoproteins like chylomicron, VLDL, HLDL, HDL. Now today we are going to discuss two important topic, one is reverse cholesterol transport, another is disorders related to lipoprotein metabolism.

So, reverse cholesterol transport is important with regards to HDL function or high density lipoprotein function. So, if you remember the metabolism of HDL that the nascent HDL say it intestinal HDL or nascent hepatic HDL, they are initially they are initially secreted as pre beta HDL and this pre beta HDL takes cholesterol from extra hepatic tissues. Then it forms the discoidal nascent HDL. Now, this discoidal nascent HDL if you remember is forming spherical matured HDL 3.

How by up taking cholesterol and cholesterol esters from the peripheral tissue. So, this part is known as reverse cholesterol transport. Why? Now, remember cholesterol endogenous cholesterol in very low amount or sorry exogenous cholesterol which is through ingested through diet that is very low in amount and also endogenously mainly endogenously synthesized cholesterol, they are delivered to extra hepatic tissues with the help of the lipoprotein particles like VLDL most important is LDL low density lipoprotein. So, this is how cholesterol is transported from liver to extra hepatic tissues, liver is the synthesizing organ in off cholesterol. So, this is cholesterol transport the reverse one is basically transporting or transferring back of cholesterol from extra hepatic tissue to liver.

So, this is known as reverse cholesterol transport and these reverse cholesterol transport is done by HDL. Now in this regard there are two very important receptors that is

playing the those are playing the main role in reverse cholesterol transport. So, one is SRB1 if you remember we have named these two receptors in our previous class SRB1 stands for scavenger receptor B1 and ABC transporter protein ABC stands for ATP binding cassette transporter proteins. So, these two groups of receptors are very important in reverse cholesterol transport. Now SRB1 plays dual role if you remember once again you can see in the previous slide that in the previous slide as we have discussed that HDL 2 is basically up taken with the help of the in receptor SRB1 in liver.

So, through SRB1 receptor the hepatic SRB1 receptor HDL is basically transferring the cholesterol or basically there is transfer of cholesterol from HDL to liver. So, SRB1 is playing the role of taking cholesterol from HDL inside the liver that is one role. Another role of SRB1 is basically delivering of cholesterol from extra hepatic tissue to HDL. So, in extra hepatic tissue the role of SRB1 is basically transferring the intracellular cholesterol to HDL. So, remember SRB1 receptor or transporter it plays dual role HDL uptakes peripheral cholesterol through SRB1 as well as it delivers its own cholesterol to liver through SRB1 transporter.

Now, the other one ABC transporter protein or ATP binding cassette transporter protein it is basically one ATP dependent transporter. So, there is one ATP attached on binding with the ligand these transporters the bound ATP is hydrolyzed the energy is the reason by which there is delivery of intracellular cholesterol from the cell to the HDL. So, ABC transporter protein now ABC transporter protein are of different types it can be ABC A 1 can be ABC G 1. Now remember ABC A 1 is important for delivering of cholesterol to the pre beta HDL. So, once again if we go to the previous slide.

So, you can see that ABC A 1 is important for delivering cholesterol to the pre beta HDL whereas, ABC G 1 transporter is important for delivering cholesterol to the discoidal HDL as well as to the matured HDL 3. So, this is important for reverse cholesterol transport. So, you can see pre beta HDL is the cholesterol poor triacylglycerol depleted particles. So, it has the maximum tendency of uptake of cholesterol from the endogenous extrahepatic tissues then HDL 3 are also HDL 3 molecules are also important for uptake of peripheral cholesterol. So, these two important receptors are there which are actually important for reverse cholesterol transport.

Apart from that another enzyme that is LCAT if you remember lecithin cholesterol acyl transferase is also important. So, basically the transferred cholesterol the transferred cholesterol which is transferred from extrahepatic tissue to the HDL is actually converted to cholesterol ester with the help of the enzyme LCAT forming the hydrophobic core. So, basically the content of cholesterol is reduced in HDL similarly

another protein is there that is CETP. So, CETP what it is causing? CETP is delivering the cholesterol ester from HDL to the other lipoproteins like VLD and LDL. So, basically these two LCAT as well as CETP they are reducing the cholesterol content in HDL.

So, cholesterol depleted HDL form when it circulates through the extrahepatic tissues the gradients difference of cholesterol between HDL and extrahepatic tissue is the main reason of cholesterol transfer from extrahepatic tissue to HDL. So, basically whenever there is cholesterol poor HDL is circulating through the extrahepatic tissues which contains high amount of cholesterol there is reverse cholesterol transport through the receptor SRB1 as well as ABC transporter protein. So, now we are going to discuss different clinical conditions related to lipoprotein metabolism they are mostly related to lipoprotein synthesis lipoprotein transport or lipoprotein degradation remember these are the primary defects in lipoprotein metabolism. So, basically these are the inherited condition similarly different other acquired conditions are there where lipoprotein contents are increased or decreased importantly diabetes mellitus atherosclerosis kidney disorder like nephrotic syndrome those are the acquired condition where lipoprotein concentration is increased in the circulation. But today we are going to discuss the familial condition or inherited conditions these are known as the primary dys lipoproteinemias.

So, this dys lipoproteinemia can be hypolipoproteinemia can be hyperlipoproteinemia. So, hypolipoproteinemia are basically where the lipoprotein concentrations are low hypo whereas, hyper stands for increased. So, hyperlipoproteinemias are basically where the lipoprotein concentrations are increased. So, these are the two important primary hypolipoproteinemias one is A beta lipoproteinemia. So, A beta lipoproteinemia is basically associated with a defect in synthesize synthesis of apo B beta lipoprotein is related to apo B apoprotein B.

Now, the problem in synthesis of apo B and if you remember apo B 100 is linked with LDL and apo B 48 is linked with VLDL. So, what will happen if there is sorry apo B 48 is basically related to chylomicron sorry VLDL and LDL they are linked with apo B 100. So, what will happen there is reduced there will be reduced concentration of chylomicron VLDL and LDL because there is no apoproteins no apoprotein B is there. So, what will happen in blood acylglycerol concentrations will be very low. So, there will be accumulation of those lipids or acylglycerols to those organs from where chylomicron and VLDL were synthesized.

So, chylomicron were synthesized in intestine and VLDL were synthesized in liver. So, those trials are glycerol because they cannot come in the circulation through chylomicron

or VLDL. So, they will be accumulated inside intestine and liver. So, there will be intestinal malabsorption those lipids cannot be absorbed and cannot be circulate cannot enter the circulation. So, there will be intestinal malabsorption.

And if you remember that dietary lipid is important for transfer of lipid soluble vitamins like vitamin A D E K. So, there will be severe vitamin these fat soluble vitamin deficiencies and the early death can be avoided by administration of those fat soluble vitamins in large doses particularly vitamin E in this regard is very important. So, this is about beta lipoprotein deficiency. Then we are coming to the alpha lipoprotein deficiency alpha lipoprotein is related to HDL. So, there are 3 primary alpha lipoprotein deficiency one is tanger's disease, then there is fish eye disease and finally, APO A 1 deficiency.

Now what happens in tanger's disease these transporter synthesis is defective. So, if you remember ABC A 1 transporter why it was important remember pre beta HDL the nascent very nascent HDL which is secreted from ah intestine or liver it was pre beta HDL and pre beta HDL takes up the peripheral or extra hepatic cholesterol with the help of the transporter ABC A 1 to form the nascent discoidal shaped HDL which is finally, forming the other forms of HDL that is HDL 3 or HDL 2. Now in absence of this ABC A 1 transporter what will happen HDL remain in HDL will remain in the form of pre beta HDL. So, there will be no discoidal HDL no matured HDL and those were important for if you remember those were important for reverse cholesterol transport those were important for different lipid exchange in between. So, those will not happen.

Similarly, fish eye disease is another alpha lipoprotein deficiency where there is partial remember there is partial LCAT deficiency. So, lecithin cholesterol acyl transferase enzyme partially deficient in fish eye disease. So, this LCAT is once again that is a lesson from the previous classes that LCAT is responsible for converting cholesterol to cholesterol ester in HDL. So, that is forming once again the whatever cholesterol is actually up taken from the extra hepatic tissues those are converted to cholesterol ester and forming the hydrophobic core. So, those are the spherical.

So, LCAT is responsible for forming the spherical HDL matured HDL that is HDL 3 HDL 2 those were formed by LCAT. So, once again the matured HDL will be absent in circulation. Similarly, APO A 1 deficiency is another important thing if APO A 1 is deficient there will be defect in pre beta HDL formation even. So, finally, what will happen there will be low or near absence of HDL in circulation. Now if there is absence of HDL remember HDL was acting as the store of different APO proteins one very important APO protein is APO C 2.

So, if you remember once again that the nascent chylomicron and the nascent VLDL they have been matured with transfer of APO C 2 and that transfer occurs from HDL to the nascent chylomicron or nascent VLDL and that APO C 2 was important why for activation of lipoprotein lipase. So, lipoprotein lipase was that important enzyme which is finally, degrading triacyl glycerol and providing the free fatty acid or free fatty acid to the peripheral tissues. So, that will not happen. So, lipoprotein lipase will not be activated because there will be no HDL. So, there will be no APO C 2 delivery and there will be no lipoprotein lipase activation.

So, what will happen? The circulatory triacyl glycerol will be increased because the matured ah chylomicron or matured VLDL they will be having triacyl glycerol inside them, but they cannot be able to deliver the ah lipids to the peripheral tissue. So, what will happen? There will be predisposition of atherosclerosis because of increased circulatory triacyl glycerol due to absence of HDL. So, these are the 2 hypolipoprotein amias. Next we are coming to hyperlipoproteinemia. So, primary or familial hyperlipoproteinemia are of different type amongst them.

Type 1 is due to lipoprotein lipase deficiency. So, type 1 is known as familial lipoprotein lipase deficiency where the function of lipoprotein lipase is defective. Now, this defective lipoprotein lipase can be due to deficiency of lipoprotein lipase or the factor which is activating lipoprotein lipase that is APO C 2 deficiency that is also causing inefficient lipoprotein lipase function. So, finally, the effect will be there is no delivery of triacyl glycerol or ah no no breakdown of circulatory triacyl glycerol in chylomicron and VLDL. So, the clearance of those chylomicron and VLDL circulating VLDL and ah chylomicron will be low, but it happens.

So, coronary disease risk is comparatively low in this condition. Now coming to the type 2a which is known as hypercholesterolemia and this is due to the defect in LDL receptor. Now, remember LDL once again where we have discussed the structure of LDL receptor like all receptor there is a ligand binding domain. Now, in type 2a dislipoproteinemia that ligand binding domain of LDL receptor is basically defective. So, even if there is LDL receptor they cannot bind the APO B 100.

So, what will happen? LDL will not be catabolized or up taken inside the liver or inside the peripheral tissues. So, there will be elevated LDL in circulation causing hypercholesterolemia circulating cholesterol is very high and that will finally, be deposited those cholesterol will be deposited in ah coronary vessels hard vessels causing atherosclerosis. Next condition is type 3. So, type 3 hyperlipoproteinemia is also known in different other names like broad beta disease, remnant removal disease, familial dysbeta lipoproteinemia. Now, this remnant removal disease if you remember you can

remember what happens in this type 3 condition.

What happens is basically there is a defective remnant removal remnant means chylomicron remnant or VLDL remnant as well. So, what will actually where is the defect? The defect is in APOE. Now, remember the remnants VLDL remnant IDL or chylomicron remnant they were up taken by the receptors and those receptors were actually sensing APOE in those remnants. So, if APOE is defective in that case chylomicron remnant or VLDL remnant they will not be up taken inside the liver. So, there will be definitely more circulating chylomicron and VLDL remnant that will be causing hypercholesterolemia, deposition of those cholesterol in skins causing ah xanthoma as well as atherosclerosis.

Next is type 4 familial hypertriglycerolemia. Here is overproduction of VLDL. VLDL is produced in huge amount and this condition is associated with glucose intolerance as well as hyperinsulinemia. So, basically ah this type 4 condition is associated with different other ah metabolic condition like coronary artery disease, coronary heart disease, type 2 diabetismolytosis, obesity, alcoholism and it is also induced by progesterone based hormones administration of progesterone based hormones. So, this is about type 4 hypertriacylglycerolemia, then familial hyper alpha lipoproteinemia.

HDL concentration is increased. So, this is a sort of beneficial condition. Then there is deficiency of hepatic lipase. So, that hepatic lipase was important for clearing the residual triacylglycerol present in the remnants of HDL or chylomicron those will not be cleared. Then familial LCAT deficiency, lecithin cholesterol, acyltransferase enzyme deficiency which is important for reverse cholesterol transport. So, if there is LCAT deficiency the reverse cholesterol transport will be hampered.

Then another important one is familial lipoprotein A-XS. Now, lipoprotein A is a specialized form of apoprotein which has the lipoprotein has apo A. So, this apo A is in small letter. Now this apo A has the structural resemblance with the plasminogen. Now this plasminogen is basically inhibits the clot removal.

So, this is a pro-atherogenic form causes atherosclerosis because it inhibits the clot removal, it inhibits the clot resolution. So, with this type of this familial lipoprotein A-XS condition of this lipoproteinemia definitely there is predisposition of coronary heart disease, premature coronary heart disease due to atherosclerosis and as well as different other vessels are more predisposed to thrombotic blockage because there is inhibition of fibrinolysis because of this apo A. Plasminogen is important for fibrinolysis remember sorry plasminogen is important for this clot removal or fibrinolysis. So, that clot removal is inhibited because of apo A. So, causing thrombosis in different other

vessels.

Now coming to the important role of LDL in causing atherosclerosis. Atherosclerosis is basically narrowing of vessels, narrowing of circulatory vessels due to deposition of different forms of lipid as well as different inflammatory cells. So finally, there is low circulation, low blood circulation through the vessels due to narrowing of the vessels. Now LDL plays one very important role in this atherosclerosis pathogenesis. Now atherosclerosis is a brought the pathogenesis of atherosclerosis are having different hypothesis different phenomena we are highlighting how LDL is contributing to atherosclerosis.

Now remember LDL while going through the circulation if it remains in circulation for more time it is predisposed to different cellular environment. Now where oxidative stress or free radical generation is high in those conditions LDL or low density lipoprotein can be modified to different forms one very important form is ox LDL that is oxidized LDL. Now this oxidized LDL is important with regard to pathogenesis of atherosclerosis. Now what happens when there is more oxidized LDL formation the receptors which uptakes this oxidized LDL are synthesized in more quantity or more amount.

One such receptor is LOX 1. Now LOX 1 is known as lectin like oxidized LDL receptor 1. Now this LOX 1 receptor is highly expressed in endothelial surface. Endothelial means blood vessels endothelium this end then this in this blood vessels endothelium LOX 1 receptor is expressed in high amount when there is high circulation of oxidized LDL. Now LOX 1 binds to the ox LDL that is a receptor ligand binding and it delivers the oxidized LDL inside the intima media of blood vessel. Now in this intima media there is a pro oxidant environment there is already oxidative stress in the cellular environment which is which has already triggered the inflammation.

Inflammation has cause inflammation has caused intrusion of macrophages inside the intima media. Now these macrophages are very much predisposed to uptake oxidized LDL. Now the oxidized LDL which is bound to the LOX 1 receptor is uptaken by macrophage by various type of scavenger receptors like scavenger receptor A 1 remember this is A 1 not B 1. Then CD 36 LOX 1 these are the scavenger receptors which takes oxidized LDL from the endothelium.

Inside the macrophage this oxidized LDL is processed. How processed? Definitely it is uptaken by receptor mediated endocytosis that endosome formed is fused with the lysosome forming endolysosome. In the lysosome there is lysosomal acid lipase lysosomal acid lipase degrades the cholesterol esters of oxidized LDL to free cholesterol

and fatty acids. Now free these free cholesterol once again can be esterified by another enzyme known as one enzyme known as ACAT 1. ACAT 1 stands for acyl coenzyme A acyltransferase. Now this ACAT 1 basically re esterifies the free cholesterol inside endoplasmic reticulum.

Now these stored cholesterol in cholesterol ester in endoplasmic reticulum can be degraded with the help of the enzyme neutral cholesterol ester hydrolase to release cholesterol free cholesterol and that free cholesterol can be uptaken by HDL if you remember by the reverse cholesterol transport. Now problem is when there is a prooxidant environment in cell which is predisposing to different which is causing release of different cytokines different pro inflammatory cytokines accumulating different pro inflammatory cells pro inflammatory macrophages in those conditions what happens? These receptors these receptors related to reverse cholesterol transport like ABC A 1 receptor ABC G 1 receptor SRB 1 receptor these receptors are down regulated. So, the reverse cholesterol transport is hampered. Remember when there is a balanced condition when there is a homeostasis in lipoprotein metabolism even if this oxidized LDL is entering the in macrophages they can be delivered to liver by a reverse cholesterol transport, but the problem happens when there is this the the prooxidant condition or inflammatory condition is exaggerated so much so that the homeostasis cannot be maintained. So, in those cases these receptors related to reverse cholesterol transport are very much down regulated.

So, the reverse cholesterol transport is hampered as well as this ACAT activity is very high the macrophage receptor which are causing uptake of oxidized LDL they are expressed in very high concentration. So, what happens there is high there is increased uptake of oxidized LDL in macrophages those LDL are basically delivering cholesterol and thus cholesterol esters are accumulated inside the macrophages which cannot be cleared by reverse cholesterol transport. So, the macrophages are now highly full with the cholesterol ester forming foam cell. Now those foam cells are actually accumulated in intima media of the vessels causing formation of fatty streaks you can see there is formation of fatty streaks which is you can see causing narrowing of the lumen. So, the lumen diameter is narrowed down and finally, they are forming atherosclerotic plaque.

Now, this atherosclerotic plaque is important for narrowing of blood vessels finally, predisposing to myocardial infarction. So, this is how LDL contributes to formation of atherosclerotic plaque finally, causing atherosclerosis and myocardial infarction. So, another important role here I want to discuss is that the role of CETP. Remember CETP was important for exchange of triacylglycerol and different cholesterol esters in between HDL and other lipoproteins like VLDL or IDL or LDL. Now, the problem is when there is inhibition of CETP the HDL 3 cannot be converted to HDL 2.

Remember that there is a cycle of HDL if you remember that HDL 3 was actually forming HDL 2 by donating triacyl sorry by up taking triacylglycerol from VLDL or IDL with the help of the protein CETP. Now, this circulation this cycle will be hampered and remember HDL 2 was actually used to be up taken by liver. So, what will happen there will be increased concentration of HDL 3 in absence of CETP this conversion to HDL 2 will not happen. Similarly, HDL 2 will not be up taken by liver because there that is not HDL 2 that is HDL 3 hepatic lipase is acting less also the scavenging function of HDL will be low.

So, finally, CETP inhibition is associated with atherosclerosis. Now, there are different drugs which causes inhibition of CETP those are actually predisposing to atherosclerosis. So, what we have seen that LDL is related to positively related to the risk of cardiovascular disease, but the role of HDL is not absolute. Remember even if HDL 3 is very high in circulation that is causing atherosclerosis. So, what is required is LDL HDL ratio which can be used as a diagnostic tool for cardiovascular disease.

So, the good one LDL HDL ratio is taken as 3.5. So, in this session what we have learnt is a detailed reverse cholesterol transport how HDL is actually transferring back the peripheral or extra hepatic cholesterol to liver. Then the role of HDL in atherosclerosis via formation of foam cells through different modified LDL like oxidized LDL and also we have discussed different primary dislipoponemia or primary lipoprotein metabolism disorder. So, these are my references. Thank you all. See you in the next session. Thank you.