Introduction to Biomolecules
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Lecture-31
Cholesterol Biosynthesis and Lipid Transport (Part-1/2)

So, in the last class we saw fatty acid biosynthesis primarily looking at how palmitic acid is biosynthesized. So, there again the precursor is acetate in the form of acetyl-CoA. So, acetyl-CoA activated by carboxylation to form malonyl CoA and then we saw how the decarboxylation of that helps in the condensation of acetyl-CoA and malonyl CoA and how repetitive a condensation of those 2 molecules finally form the 16 carbon palmitoyl CoA. So, for cholesterol biosynthesis again the starting material is the same acetate.

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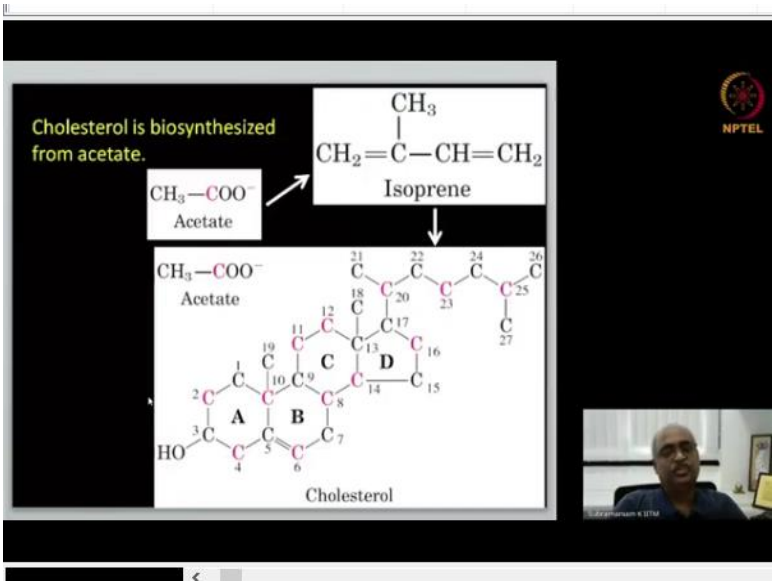

But it follows a very different route because the end product we are going to have is a cyclical molecule cholesterol; as you see here it has 4 ringed structure and this is one of the complex biosynthetic processes that exist and took lot of effort for those who figured this out. So, essentially it has 3 major steps and we will see them first and then we will see step by step, but we will not see all the steps, we actually are going to see only the first 2 parts in some detail but we are not getting into any enzyme mechanisms.

So, here the colour indicates the carbons. For example this black one comes from this acetyl group and then this red one comes from this carboxyl group. So, that is the colour code shown here and finally in this structure where these 2 carbons are. So, the first step is

formation of this iso, well this is only showing 2 steps there is an intermediate important first step.

So, acetate to isoprene to cholesterol and this biosynthesis primarily happens in the cytoplasm of hepatocytes meaning liver cells. So, liver is the primary place where cholesterol is produced as well as degraded and it is not probably are familiar with cholesterol whether you are a student of biology or not in general people are familiar with cholesterol in a bad way, people think that high cholesterol means higher probability of heart disease.

So, that is how cholesterol is in the public imagination, but in reality cholesterol is an essential molecule and that is why it exists. But you do not need it in the food; our cells have the ability to produce cholesterol from acetyl-CoA. So, we do not need it in the food, but it is an essential molecule. So, it is an essential component of plasma membrane of all cells and this is the precursor for the bile salts and bile acids which are important for emulsifying lipid for digestion in small intestine.

And cholesterol is the precursor for steroid hormones corticosterones, aldosterones and testosterone and estradiol. And it is also precursor for vitamin D the 725 cholecalciferol is what its name is dihydroxy 725 cholecalciferol. So, it is an essential molecule and these are the things that a biochemistry textbook lists, but cholesterol has another important role as a signaling molecule.

So, there is a peptide signaling molecule that is important in cell-cell signaling during development of our embryos and there that peptide needs to be covalently attached to cholesterol and that cholesterol modified signaling molecule is what is critical in that particular signaling called hedgehog signaling. So, it is an important molecule and therefore let us look at how it is biosynthesized. And the chemistry of this biosynthesis itself is fascinatingly complex. So, let us look at that.

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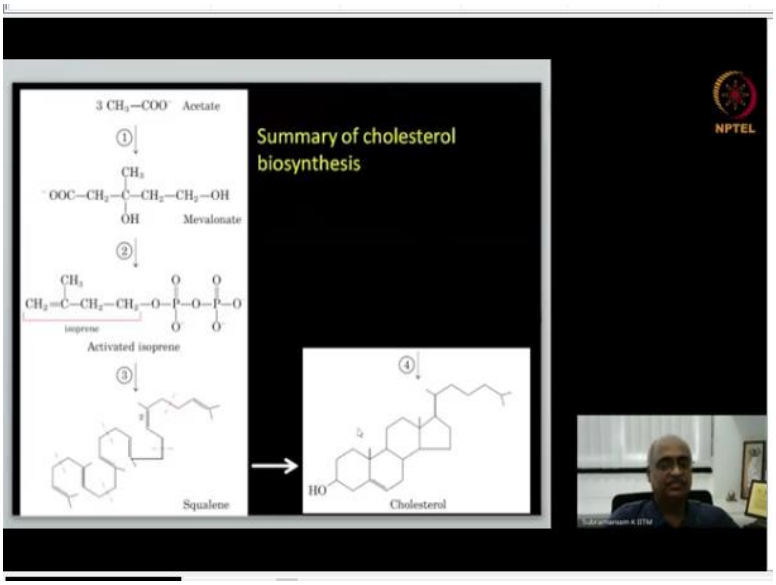

So, here are the steps here, so first is formation of the mevalonic acid. So, this is a different route than the route by which free fatty acids are produced and from mevalonic acid we make activated isoprenes and that is the second step. Then the isoprenes join together to form a long 30 carbon chain like 5 of them. So, these are 5 isopentenyl group. So, we got 1, 2, 3, 4, 5. So, this **5,** 6 of them, so 6 times 5 30 form a linear 30 carbon linear chain.

And that converts as shown here in this cartoon, it is linear molecule but it is drawn to indicate how it cyclizes to form cholesterol. So, this squalene into cholesterol is the fourth one. So, the activated isoprene the activation is by this pyrophosphate group and an intermediate as another phosphate also in the third carbon. So, this phosphorylation is the activated isoprene and the activated isoprenes condense to form this squalene. So, that is the third step. So, let us look at one by one.

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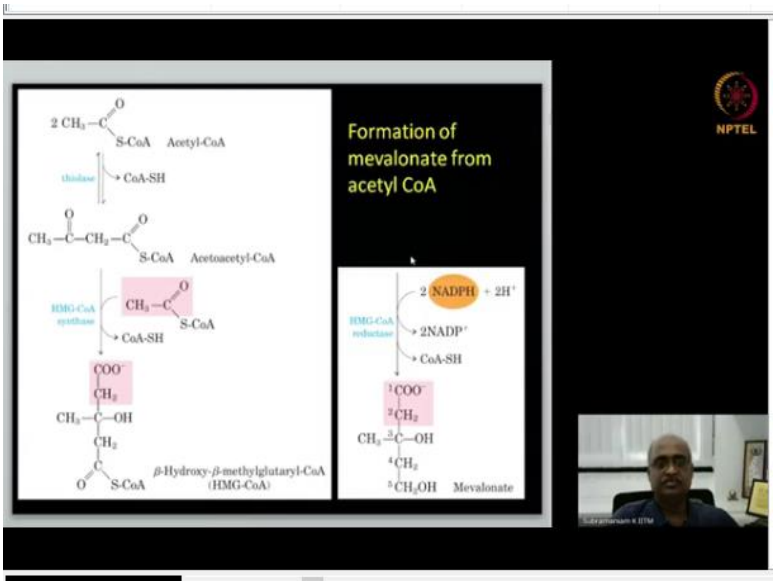

So, the first reaction is familiar to you thiolase. So, this is the similar enzyme but that happens in mitochondrial matrix in beta oxidation the last step where that acetyl group after the beta ketone is formed that acetyl group removal is by thiolase, like this opposite reaction from this structure going this. So, beta oxidation would have created this ketone group and then this acetyl group is removed by the thiolase.

That is how we saw in the mitochondrial matrix in beta oxidation. Here the reverse of this combines 2 acetyl-CoA releasing 1 coenzyme A and the free energy available from the thioester hydrolysis itself is enough for this condensation forming acetoacetyl CoA and this acetoacetyl CoA combines with another acetyl CoA, so we have consumed 3 molecules producing 1-6 carbon molecule HMG CoA beta hydroxy.

So, this alpha and beta, so if you take from this carboxyl group also it is the same but because this is attached this cell we will count, either way this is beta. So, beta hydroxy beta methylglutaryl you have CH 2 CH 2 and then see glutamic acid would have had an amino group here and this would have been an amino acid. So, that is where this glutaral comes from. So, shortly this is very familiar to any biochemistry student as HMG CoA.

So, that is HMG CoA synthase, then HMG CoA reductase reduces this carboxylic acid group into an alcohol group and that is mevalonate and that reduction consumes NADPH and this thioester is also released and then you have mevalonic acid. So, this is the production of mevalonic acid, the step one in this acetate to mevalonate, step 1. So, in this process this

HMG can go into many other reactions, but reducing it to mevalonate is a committed step to cholesterol biosynthesis and by extension to other steroid biosynthesis as well.

So, this enzyme commits acetyl-CoA to the formation of cholesterol. So, when you want to reduce cholesterol level in blood this is the enzyme that is targeted. So, the statins that are the famous drugs used to regulate blood cholesterol level targets this enzyme. Similarly if you want to inhibit steroid biosynthesis, for example immunosuppression drugs etcetera they target this enzyme.

So, this enzyme is a key target of drugs as well as this is highly regulated in this metabolic pathway, because this commits the acetyl-CoA as I just said to cholesterol biosynthesis, mevalonic acid does not go to do anything else, it just goes to form cholesterol. So, we have seen similar committed steps in the earlier pathways as well.

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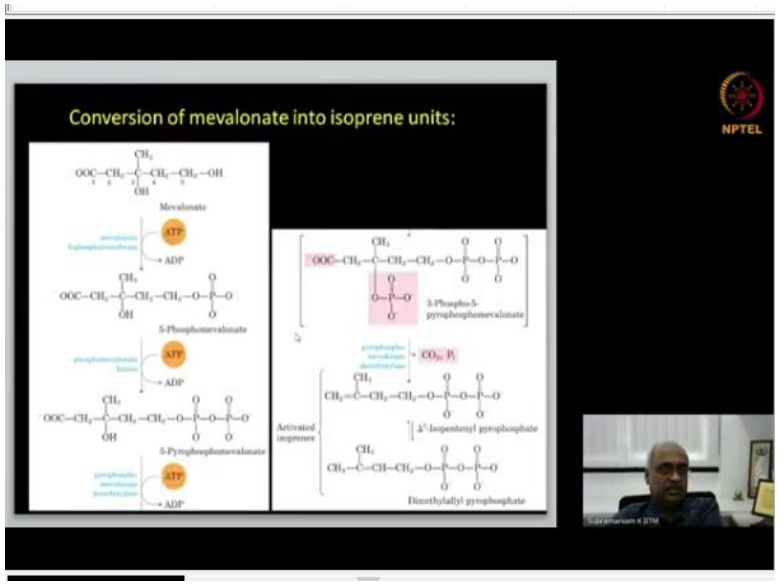

So, the next is the activation of mevalonic acid to form these active isoprene units, this isopentenyl group. So, that is the second step. So, that is shown in this cartoon. So, here you have this mevalonic acid then you have a phosphorylation by mevalonate 5 pyro phosphotransferase, so it is a standard phosphorylation reaction, this alcohol group is phosphorylated.

And then another kinase phosphorylates that once more making a 5 pyrophosphomevalonate. So, this is the fifth carbons are numbering from here 1, 2, 3, 4, 5. So, we start from this main functional group and that is why this is fifth one. Forming this pyrophosphate group then a

decarboxylase converts this into the isopentenyl version of it, it does 2 things one transiently it further activates by phosphorylating this hydroxyl group.

So, it becomes 3 phospho and then 5 prime pyrophosphomevalonate and this decarboxylase enzyme then removes this carboxyl group here as well as it cleaves this phosphate as well generating isopentenyl. So, the pentynl is because of this double bond, iso because this methyl group is not part of the linear chain, pentynl because it is a 5 carbon. So, if this is fully saturated you would have called it as isopentane.

And if this was part of the linear chain that would have been simply the aliphatic group or hydrocarbon pentane. So, isopentenyl pyrophosphate then this can I summarize to form switching this double bond dimethylallyl pyrophosphate and this IPP and DPP these are the activated isoprenes. So, again going back, first step mevalonate and the second step we just finished seeing is the formation of this IPP and DPP the active isoprene units and they will again condense 2 rounds of condensation to form squalene.

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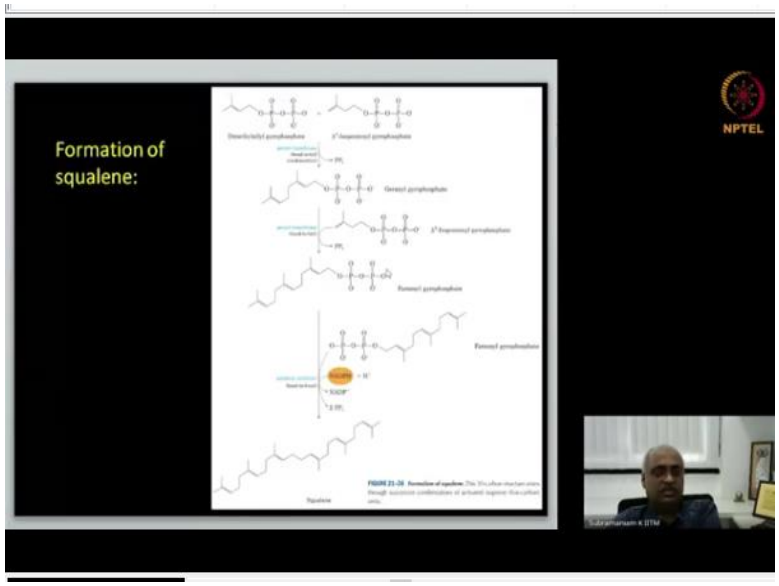

So, this I will blow up because it is small, so I hope this is readable. So, we just saw isoprene and pyrophosphate formation that can isomerize into DPP. So, this phosphorylated end of this chain is called the head and the other end is the tail. So, here you have a head to tail condensation of these 2 molecules forming geranyl pyrophosphate. So, these names like geranyl and the next one farnesyl comes from the original source from which these molecules are identified.

For example the flower geranium has this in abundance and that is where from it was originally isolated and that is why it is called geranium. Similarly this was from another flower furnace, so I forgot the second name of this botanical name that is why this is called farnesyl group. So, 2 of these 5 carbon structures joining together condensation forms geranyl pyrophosphate. To that one more IPP joining head to tail again, this is tail and that is a head joining gives you the farnesyl pyrophosphate.

So, this is 15 carbon, so 5, 5 and one more 5, so we started with 3 acetyl, so means 6, one disappeared as carbon dioxide in the decarboxylation reaction, here so this carbon disappeared, so that is why you have 5 and three 5's 1, 2, 3, joined together forms the farnesyl pyrophosphate and so 2 molecules of farnesyl pyrophosphates head to head condensation scrolling synthase.

So, 15, 15 you form the 30 carbon squalene. So, this is the third step and this involves NADPH oxidation and then this pyrophosphate is released. So, you have this squalene molecule, it is a linear 30 carbon chain. So, up to this we have seen step by step all steps, next we are not going to look at all the steps because it is a quite complex series, there are 20 steps from squalene to cholesterol and we are not going to go through this. So, conceptually the main important ones we have just seen**.**

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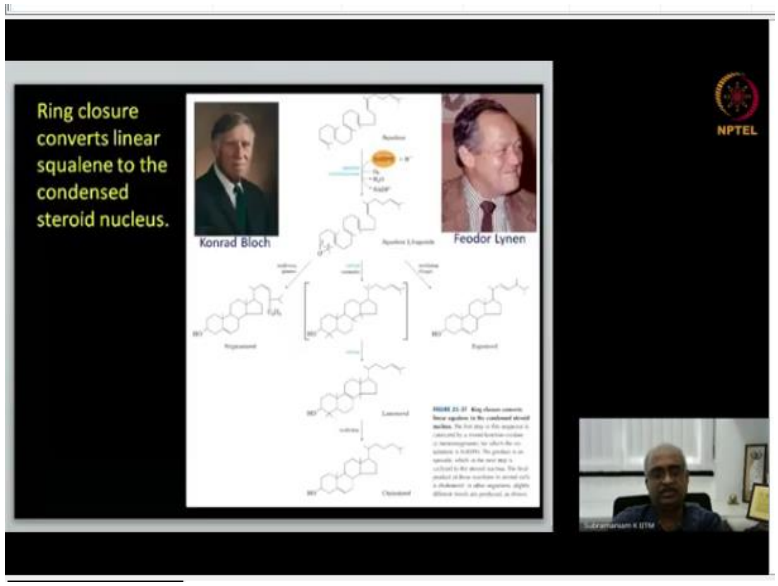

And these are the guys then 2 more whose picture and name I do not have, but the book has them. But these are the main guys who worked out this cholesterol biosynthetic pathway. So, here you go, so this is the squalene as written here the same linear molecule you saw in the

previous one as written here helps you to understand how it cyclizes. So, the double bond arrangement that is produced by the way the condensations happened head to tail twice and then head to head condensation generates a molecule that readily cyclizes, all you need is an epoxide formation, an oxygen from oxygen molecules.

So, the other oxygen takes up electrons from NADPH and becomes H2O and the other oxygen is added to this double bond like peroxidation reaction forming squalene epoxide. So, now a cyclase enzyme that reduces this to the hydroxide makes connection here that shifts the double bond here that shifts here and so on leads to a remarkable joining of these double bonds to generate this cyclical molecule. So, that is an intermediate and then this carbocation is stabilized and then finally you have a lanosterol, the stable sterol version. So, you have the characteristic steroid nucleus.

So, these 4 carbon rings are called the steroid nucleus and because of the presence of this alcohol group in all the sterols that exist in the biological system they are called this all sterol cholesterol, lanosterol, stigmasterol in plants and ergosterol in fungi and cholesterol in animals. So, essentially the steps that we are skipping by simply labeling multi-step involves a series of double bond reduction and shifting or removing of these methyl groups jutting out here.

See here you have 2 methyl groups and then additional methyl groups here and so this methyl group is shifted to this, these 2 methyl groups are removed and then you have a double bond here and those rearrangements in lanosterol results in cholesterol. So, this is what happens in animals, this does not happen in plants and in plants a slightly different party makes stigmasterol.

Plants do not produce cholesterol, so any vegetable oil advertisement that you see which says 0 cholesterol, it does not mean that company has done anything special favour for you to remove cholesterol here, plants do not synthesize cholesterol, any make of vegetable oil that you buy from any source is cholesterol free, any plant food is cholesterol free because plants do not make cholesterol.

So, cholesterol is produced only in animals and fungi produce ergosterol and another point I wanted to highlight probably some of you interested in industrial applications may get

excited is this is the pathway to produce some of the plant-derived fragrant molecules the sense, you have jasmine likes artificial smelling, fragrance that you buy rose scent artificial that you buy.

Those are all produced by this kind of a pathway. So, understanding cholesterol biosynthetic pathway is essential to produce those molecules. Many of the fragrance molecules are intermediates of this pathway, like for example geranium contains this geranyl phosphate, farnesyl group is present in that plant I told you whose name I forgot, you can check the book has this name.

So, this cholesterol biosynthetic pathway therefore is important for all the secondary metabolites which are sweet smelling h, fragrant molecules of flowers. So, this is all we are going to learn about cholesterol biosynthesis, the main thing you need to remember is all these carbon molecules of this ring structure all come from the simple precursor acetate, starting in the form of acetyl-CoA.

And second you need to know is that this does not follow the free fatty acid biosynthetic pathway instead it produces maybellinate via HMG reductase and then by that decarboxylation HMG only we form the mevalonate, but from mevalonate then we produce this isopentenyl activated isoprene 5 carbon molecules IPP and DPP.

And this IPP DPP condensation generates squalene and squalene cyclization, the main step in that is this epoxide formation and the reduction of that automatically leads to the cyclical structure. So, these 4 essential points you should remember with respect to cholesterol biosynthesis and as I told you another important point to remember is this HMG CoA reductase.

This is a committed step catalyzing enzyme and this is subjective regulation in normal metabolism as well as many drugs target this enzyme HMG CoA reductase. So, again I just told this wrongly the decarboxylation is what activates mevalonate to form IPP. So, the reduction of HMG makes the mevalonate. So, the next what we are going to do is now that we know how cholesterol is made.

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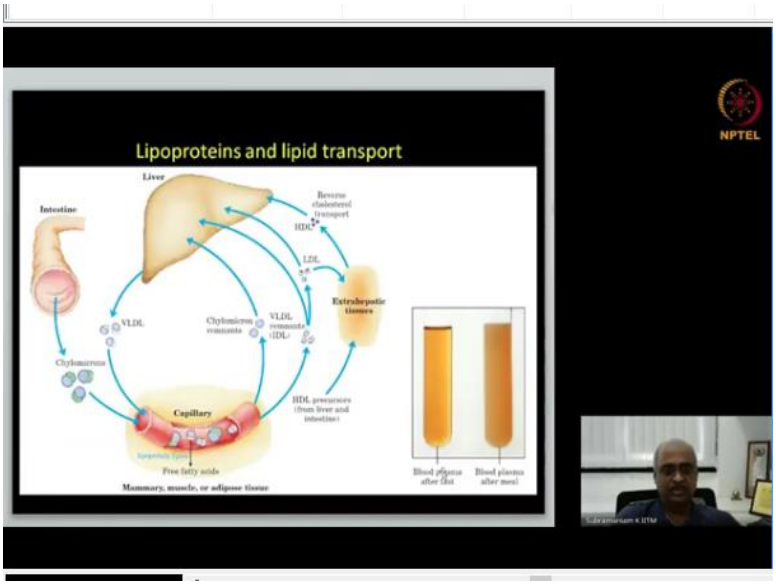

Next we are going to look at cholesterol transport in different forms not just cholesterol as well as little bit about triacylglycerol which we already know. So, we will see this in couple of slides because this is actually an important general knowledge education. Because a lot of people talk about bad cholesterol, good cholesterol and what is cholesterol level, what is HDL level, what is LDL level?

These are common terms regularly used when people have problems with heart disease or metabolic syndrome the collective term that describes high blood glucose level combined with high triacylglycerol level, cholesterol level being high, LDL level being high, HDL level being low and deposition of lipids on blood vessels leading to their constriction and causing cardiovascular disease.

What normally they call the deposition as atherosclerosis. So, these are all directly non-infectious lifestyle related diseases and this is highly prevalent in India more than 40% of men aged above 50% suffer from metabolic disorders. So, visiting doctors at that age is quite common nowadays in India and in that context they talk about these terms. So, here is an opportunity for you to learn the basic science behind that.

So, some of this we are already familiar, for example the triacylglycerols coming through the diet we learnt get emulsified in the intestine and then it gets hydrolyzed into free fatty acids and glycerol, taken into intestinal mucosa, there it is converted again into triacylglycerol and associated with the lipoproteins forming chylomicrons. So, we have learnt this.

And the upper protein, this green structure shown on this circles here chylomicrons apoC 2 that activates this lipoprotein lipase in the blood while it is circulating in the capillary that hydrolyzes it into free fatty acids triacylglycerol becomes free of fatty acids which are taken up by the tissues that are going to use or store these free fatty acids. So, we have seen up to that. So, we are already familiar with the term lipoproteins.

The one lipoprotein that we are learnt is chylomicron. So, these are large and lowest density of other all the lipoprotein groups, simply because these have lot of lipid molecules and less proteins and I have shown you at that time the structure is shown here once more here.

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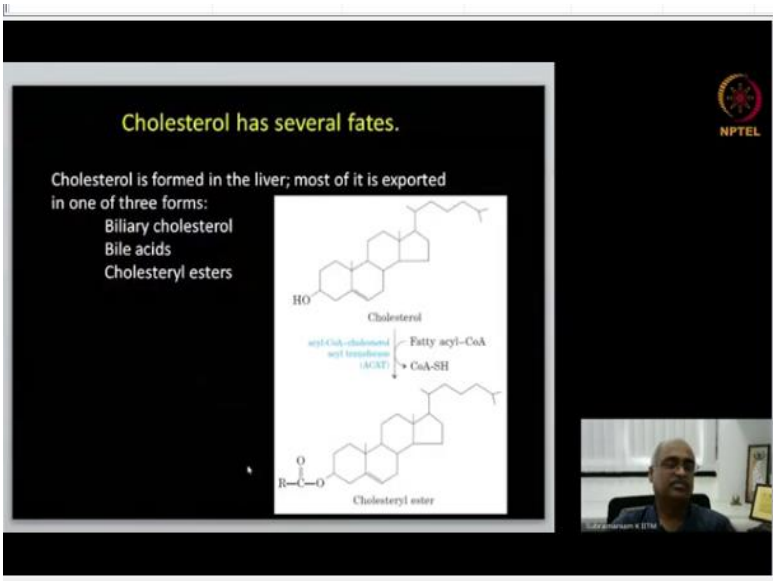

I missed a few other steps, let us cover that and then come back to this. Otherwise, continuity will be lost. So, I will be back a little bit and go from cholesterol. So, we saw squalene becoming cholesterol and now what we are going to look at is what are the fates of cholesterol; like what happens to cholesterol? Remember I use this word fate for pyruvate also when we finished glycolysis.

So, similarly here what are the pathways in which cholesterol is going to enter? One biliary cholesterol where it is going to form bile acids and these bile acids are stored in gall bladder and that is what is used to emulsify the diet triacylglycerol that I just showed you showing that a small intestine in that carton, which is going to appear again. So, that is one role of cholesterol.

And second it forms a cholesterol ester, this hydroxyl group, this alcohol group can be esterified with the carboxyl group of free fatty acids as shown here. So, this is highly hydrophobic molecule because this sterol ring is hydrophobic, then this R group is a long aliphatic chain. So, it is highly hydrophobic and this is one of the storage versions of lipids. So, that is another role of cholesterol and the one more which is not shown here is incorporation into membranes.

So, cholesterol is an important component of membranes, then steroid hormone producing glands like adrenal glands as well as testes, ovary etcetera, they take up cholesterol and they use them to make those steroid hormones. So, these are the fates of cholesterol. So, this is an important enzyme ACAT acyl-CoA that would be the fatty acyl group, this R group, cholesterol acyl transferase. So, between these 2 molecules like fatty acyl-CoA and cholesterol, it transfers the acyl group and that is why it is acyl transferase.

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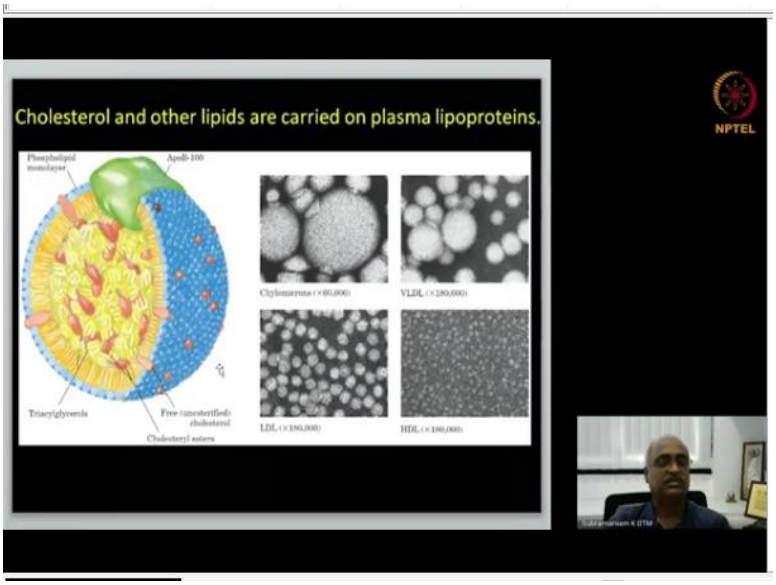

So, now let us return to the lipoprotein discussion. So, this is the structure of chylomicron we have already seen, one good detail that we now cover which we did not think about in the last time we encountered this is this free cholesterol, remember the chylomicron has one layer of phospholipid and that is how it can be in accuse blood and then inside you have the triacylglycerol.

So, this is the phospholipids, this orange group is the phospholipids tail and that is hydrophobic. So, that can readily have hydrophobic interaction with the triacylglycerols. So, the pink stuff that you have here is the esterified cholesterol. So, cholesterol ester is inside

while the free cholesterol is on the membrane, because it is alcohol group is hydrophilic and that could jut out and you have the lipoproteins and this apoB 100 is shown.

This is critical for one variety of a lipoprotein uptake by cells that we will see in the next slide. So, among the lipoproteins, so lipoproteins are carrying lipid transport in plasma in blood. So, the reason for the lipoproteins existence is because our bulk of the body fluids and the blood are aqueous while the lipids are hydrophobic. But they need to be transported in this aqueous solvent and that is why you need these lipoproteins.

They make a structure that is hydrophilic on the surface and therefore it can be transported and these protein components alone are called apoproteins that again we have discussed earlier and these apoproteins help in transport primarily recognition and uptake by cells. Because cells have receptors for specific apoproteins and that helps them in these lipoprotein particles to bind to them.

And then the receptor ligand rather receptor this apoproteins interaction helps in internalizing these lipid carriers. So, among these lipoproteins chylomicron is the biggest, because it has a lot of saturated hydrophobic lipids and they are less of protein. For example here you see the electron micrograph size at 60000 magnifications. So, they are this big, while the next biggest one at 180000 they are this size, very low density lipoproteins.

So, these also have lot of lipids but less than chylomicron, we will see where they function in the next slide? Then from VLDL when you take out triacylglycerol primarily in liver, liver cells are called hepatocytes. So, when hepatocytes take up some of the triacylglycerols they become LDL, the density increases, as you remove the lipids then the lipid protein ratio decreases.

And when you have more protein less lipid then the density increases. So, you have LDL and another one which has really no triacylglycerols and primarily only cholesterol but that too not a lot of cholesterol and more of protein, they are HDLs. So, they are the smallest and they are the densest. So, these are the 4 major types of lipoproteins. So, their roles are explained in this slide. So, this is the slide I first showed you by skipping others accidentally.

So, now we look at this in good detail. So, we have seen up to this chylomicron from the intestine, circulating in the blood and that activates this lipoprotein lipase and then the free fatty acids produced, enter into the cells that use the molecule either for storage, if it is adipose tissue, muscle beta oxidation producing energy and glands like mammary gland to make lipids that need to go into milk.

And these are like the consumers where it is getting delivered and the remnants of that chylomicron after it unloads the lipid cargo goes back to liver and another route is the excess carbohydrate or other ways by which acetyl groups are produced and that is not required by other cells, they would be used to make triacylglycerols as well as cholesterol in liver. And they are combined with the lipoproteins and such production of lipoproteins are VLDN.

The one that comes from diet is chylomicron, but similar lipid cargo produced by liver and being sent to other tissues is VLDN and the VLDL again is going to be taken up by these tissues that use them or store them and during the process when they take up the triacylglycerol the density reduces and that is what becomes LDL low density lipoproteins. These are very little or no triacylglycerol but they have a lot of cholesterol that is one of the reasons people say LDL is bad cholesterol.

So, LDL should be low and HDL should be high to be healthy. So, oftentimes when the labs measure your cholesterol level as well as LDL and HDL cholesterol level they talk about LDL cholesterol ratio, HDL cholesterol ratio. So, if the HDL cholesterol ratio is high then even if you have high cholesterol it is not so bad, because you have the machinery to handle it because the HDL will take up and take it to liver.

So, I will come to that in a minute; first let us finish this part. So, VLDL is carrying the lipid cargo produced from liver, this happens usually when you have high calorie diet like carbohydrate rich diet where the glucose available from it is more than necessary for all the organs to get their carbon skeleton and energy. And that excess carbohydrate is what is converted into triacylglycerol and cholesterol and loaded into VLDL particles.

So, this is internal production of lipids in contrast to this chylomicron that they take from digestive system, this is coming from the diet. So, these are produced from non-lipid source excess and this happens in liver, so that is why liver is very, very important organ in

biochemistry. So, this is where all the biochemistry of our body happens particularly processing dietary components.

So, this VLDL when it loses triacylglycerol in these target tissues it becomes LDL and that LDL might deliver, this is an important route. Like for example if you are very vigorously exercising LDL will be taken up by other tissues, that is why this is called extra hepatic, this all the other tissues that use up fat are called extra hepatic because hepatic, this liver is a main site where many things are happening.

So, this LDL taken up by extra hepatic tissue is a healthy thing because they are taking up and burning it away you do not want it to go to adipose tissue and get stored because from there it will be mobilized and be circulating you will have high amount of LDL and VLDL. So, once that is removed then remnants will go to liver to get broken down into amino acids and to be recycled.

So, that is the role of LDL. So, LDL forms from VLDL after triacylglycerol is used up and that LDL delivers cholesterol we will see how we deliver that itself is a big thing that we will see in a separate slide and it delivers and the remnants go to liver and in addition to these 3 versions of lipoproteins liver and intestine produces a particle called a high density lipoproteins.

So, these are slightly different apoproteins and these take up cholesterol excess cholesterol from different sources and transport it to multiple places but the main thing shown here is the reverse transfer that is taking the cholesterol from other tissues into liver, where it is going to be used up. So, that is the HDL role. So, high HDL means a good way of clearing excess cholesterol by taking into liver and also indicating that you do not have lipid loaded apoproteins in your .

So, that is when you will have high density lipoprotein higher. So, when you have LDL what it means is you have a lot more lipids than the apoproteins that are there and that is why apoproteins are all loaded with lipids and they are low density. So, that is why people call this as bad cholesterol. So, LDL is not cholesterol, LDL is low density lipoprotein where the apoproteins are associated with cholesterol and cholesteryl esters.

So, it is a complex looking like this. It is not a version of cholesterol; it is the proteins with which cholesterol is associated. So, similarly for example HDL could take cholesterol to adrenal gland or test is to be used to make the hormones or it could take some of them into liver for metabolizing. So, this is the route of lipid transport and the central role of lipoproteins in this.

So, here it shows this is after fasting your plasma, plasma is blood minus the blood cells like RBCs and white blood cells and so on. So, the liquid part of blood looks this clear and when you after having good meal where it is loaded with the chylomicron and primarily chylomicrons then it looks milky and it becomes clear again by the action of these, this portion primarily.

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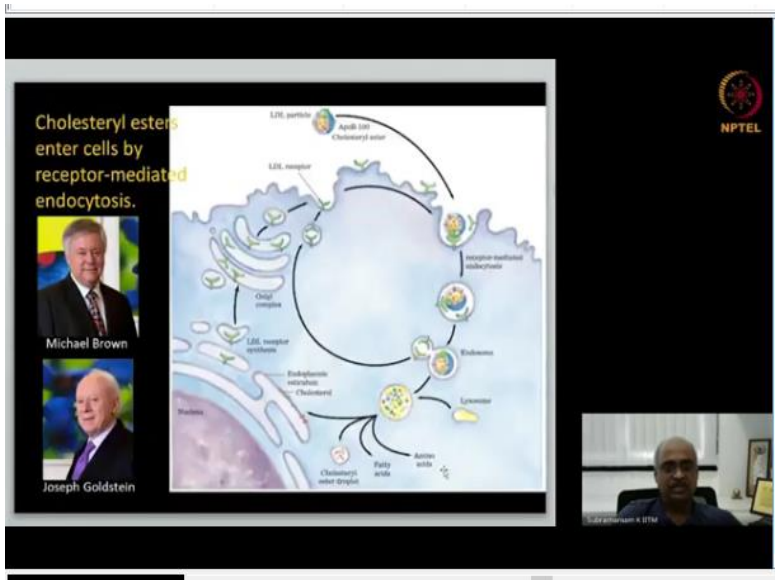

And this LDL route was discovered and worked out how it works and how the regulation happens by Michael Brown and Joseph Goldstein and these 2 people own Nobel prize for that because this was like a long tedious work and it is a central pathway in cholesterol regulation and due to that it attracted a lot of attention and these 2 people got Nobel prize quite a long time ago.

So, let us briefly look at how this pathway happens? It is quite simple we are not getting into serious mechanistic details today; we will primarily look at this cartoon alone. So, LDL particle remember that I talked about apoproteins being important in signaling this transport and uptake of lipids. So, here we see that. So, here you have LDL receptor on surface of cells, the cells that use of cholesterol.

Like for example adrenal gland cells or adipose tissue or muscle cells which are actively requiring energy in a vigorously exercising muscle cells. So, they have this receptor that is specific for this apoB 100 ligand which is the main apoprotein of LDL. So, the LDL via this apoB 100 binds to this LDL receptor and this receptor ligand binding leads to pinching of the membrane in a process called endocytosis which you probably will learn in cell biology course, if you have a cell biology course.

So, essentially what happens is when it binds that induces this process called endocytosis. Endocytosis in simple terms is internal imagination of the plasma membrane like this forming a pit and then finally this ends will join and it get pinched off. So, that is a very complex process and a lot of cell biology labs actively work on how that happens and how that is regulated? And these lipid vesicles called endosomes.

Because they have lipid vesicles and inside the cytoplasm that is why they are called endosomes, they fuse to lysosomes which contain hydrolytic enzymes and they cleave the proteins like the apoprotein itself into amino acids and that goes into the central amino acid pool. However, this receptor does not get hydrolyzed and that goes back and fuses to the membrane and that is how it gets recycled for continuous operation of this endocytosis uptake and the delivery of these carbo to lysosomes.

And then the lipase in lysosome convert into fatty acids and then cholesterol may be used or converted into cholesteryl ester and that is stored as lipid droplet in the cell if it is adipose tissue and it is also incorporated into the membrane, remember I told you cholesterol is an important component of membrane. So, membrane biosynthesis happens by incorporating phospholipids and cholesterol into endoplasmic reticulum and that is how membrane expands.

So, that is how membrane biosynthesis happens, membranes are not made DNO from phospholipids aggregating to form a sheet of membrane. So, membrane is formed by incorporating phospholipids and cholesterol into an existing membrane and that membrane expands and that expanding membrane in a process like endocytosis pinches and forms vesicles and those vesicles go and fuse whichever organelle needs membrane or if the plasma membrane requires it goes and chooses to the plasma membrane.

So, that is how the membrane biosynthesis happens, since we would not be learning about membrane biosynthesis I briefly told you in this context. So, this is the main role of LDL in delivering the cholesterol and other lipid cargo to the cells that we use of these lipid molecules. So, with this we will stop cholesterol biosynthesis and how cholesterol is taken up by the tissues that you consume them.

So, in the next class we will look at cholesterol regulation which is slightly complex and little longer one and then I will initiate our discussion on hormonal control of metabolism and on Wednesday we will complete that. So, I will stop here and if you have questions I will be happy to answer.