Overview and Integration of Cellular Metabolism

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Lecture 60: Metabolism in Cancer Cells

Hello everyone, welcome back our lecture sessions, overview and integration of the integration of cellular metabolism. We are at the very end of our class, this is the 60th lecture of this NPTEL lecture session and it is about a very important topic that is metabolism of cancer cells. These are the concepts we are going to discuss in this class, what is the unique metabolic characteristics in cancer cells, one very important phenomena Warburg effect, then what are the different metabolic pathways or rather the metabolic pathways which are occurring differently from normal cells in cancer cells we are going to discuss, what are the drivers of these type of metabolic changes or rather metabolic reprogramming. Then finally, how this metabolic reprogramming can be exploited as a therapeutic target. So, we are going to cover these in our this lecture session. So, let us start brief about cancer cells actually what happens in cancer cells you all know the normal growth control mechanism is lost in cancer cells.

There is uncontrolled cell revision, uncontrolled cell proliferation which is finally, leading to formation of tumor mass. Now, metabolism of tumor is not a full tumor cell metabolism rather it has in it is influenced by the surrounding cells surrounding blood vessels, the metabolic environment surrounding the cancer cells, metabolic environment inside the cancer cells. So, that is a holistic metabolic milieu and that is called tumor micro environment or TME. So, basically TME is the effect which is imparted over the surroundings, stromal and immune cells, extracellular matrix, blood vessels the effects imparted over these non cancerous tissues by the cancer cell as well as how these tissues and their metabolic environment can affect cancers metabolism.

So, that is the tumor micro environment and that can be delivered via different metabolites, different signaling molecule and also proteins in the intracellular space. So, as a whole this forms the basis of the metabolic reprogramming in cancer cell. Now, what is the metabolic reprogramming? This is the changes of these are the changes of metabolism inside cancer cells which is different from the normal cells and those have been adapted for the survival of the cancer cells, for the therapeutic evasion of the cancer

cells, metastasis or spread of the cancers throughout the body and also how they exploit the surroundings for their own nutrients. So, that is the metabolic reprogramming in cancer cells. Now, remember all the cells in a cancer are not actually showing same type of metabolism not even two different cancer cells are showing different types of metabolism.

Suppose cancer in kidney, Reynolds and carcinoma, cancer in lung they might not be similar in the from the metabolic perspectives. So, it is metabolic heterogeneity we call. So, this can be intratumoral diversity in different sub population as well as tumor to tumor variation definitely exist. Now, why this metabolism in cancer cells should be studied? Because definitely this is the important thing which is finally, helping tumors to develop to progress. So, those valuable insights are needed for understanding how tumor is processed.

Identifying the key mechanisms, who is the driving factor for the growth of the cancers we can understand from it. Then finally, we can develop different therapeutic targets the metabolism which are specific for tumor or different to the tumor cancer cells we can target those pathways to develop effective treatment module. So, these are the purpose of studying metabolism in cancer cells. Now, in 1924 Otto Henrik Warburg, he is a very famous Nobel Laureate for his groundbreaking work in the field of cancer metabolism which started very early in 1924. Can you imagine it is 1924 after around 50 to 100 years actually after centuries rather when the cancer metabolism is presently is gaining the attention in recent days.

But in very early time he actually observed the very peculiar phenomena when his colleagues when is when the similar researchers are actually on the speculation that tumor cells are gaining energy from uncontrolled replication of proteolysis or lipolysis protein from protein and lipid actually. Warburg observed that cancer cells it uptakes glucose very rapidly and convert them into lactate even in presence of oxygen. Remember this is very important even in presence of oxygen if you remember in glucose metabolism we have talked about glycolysis as well as TCA cycle. Now, if you remember once again glycolysis occurs in aerobic condition as well as anaerobic condition the anaerobic fate of glycolysis is formation of lactate from pyruvate whereas, in case of aerobic glycolysis pyruvate enters the TCA cycle and in absence of oxygen anaerobic glycolysis is preferred. But in cancer cell even if there is oxygen supply cancer cell prefers glycolysis.

So, it converts pyruvate to lactate and shows a varied rapid consumption of glucose and these phenomena is coined as Warburg effect. It was long ignored rather long not studied when it has been postulated by Warburg, but later it gained the attention and the term

was and the phenomena was coined Warburg effect and this is the ground breaking discovery which gained the attention towards cancer metabolism. Now, what is the difference between the normal cellular proliferation versus tumor cellular proliferation? Remember tumor cells are actually they have lost the controlled cellular proliferation. What is controlled cellular proliferation which occurs in mammalian cellular mammalian cells non cancerous cells basically cellular proliferations are based on some extracellular stimuli like growth factor one very important stimulus is growth factor. Now, these growth factors interact with the receptors activate some intracellular signaling cascades and it delivers a very finely controlled mechanism for the cell division and that also depends on it is not just the cells property it is also depending on the neighboring cells different chemical signals its micro environment and also the cell itself.

But in case of cancer cells what happens these growth receptors there is some mutation which causes increase in growth factor receptors. So, the there are increased receptors also the intracellular signalings which promote the cellular proliferation they are constantly switched on or amplified. So, there are increased receptor those receptors are giving some amplified signal and tumor cells are dividing rapidly. Now, for rapid cell division as well as this enormous tumor mass they need more nutrient they need more biomolecules for that biosynthetic capability of the tumor cell should be increased like fatty acid supply nucleotide supply those should be increased in amount. And majority of the tumors metabolism is basically targeted or fulfill this target that the tumor needs more biosynthetic molecules for its uninterrupted proliferation and finally, metabolic and autonomy.

As I told that the in the normal non cancerous cells the cell division is based on the surroundings here it is not the cancer cell gains autonomy for its proliferation. So, it so, actually through metabolism what it needs more energy more molecules for its proliferation and that is the ultimate target of cancer cell metabolic reprogramming. Now, this Warburg effect which is also known as aerobic glycolysis what are the advantages of this why this aerobic glycolysis is there? Number one is instead of going through glycolysis and TCA cycle which actually supply in a from a one molecule of glucose it actually supplies more ATP in comparison to glycolysis or formation of lactate formation of lactate from pyruvate via glycolysis from one molecule of glucose there is rather less number of ATP, but remember only glycolysis is of short duration. So, what is done in cancer cell there is multiple cycles of glycolysis in a short duration which actually generate more ATP per unit time. So, there is rapid glycolysis rapid ATP production and this glycolytic intermediates are actually the source of carbons required for different biosynthetic pathways.

What are those glucose 6 phosphate if you remember it enters the pentose phosphate

pathway to generate two important molecule one is NADPH another is molecules for nucleotide synthesis ribose 5 phosphate is actually provided from pentose phosphate pathway. And another one very important biosynthetic pathway is shunting the 3 phosphoglycerate into serine and glycine biosynthetic pathway. How you can see in this cell 3 phosphoglycerate can form 3 PHP which is 3 phosphohydroxy pyruvate with the help of the enzyme 3 phosphoglycerate dehydrogenase where NAD is utilized and PHP is converted to 3 PS phosphoserine with the help of the enzyme PSAT which is phosphoserine amino transferase and finally, the phosphoserine is converted to serine with phosphoserine phosphatase. So, finally, you can see serine can be synthesized from 3 phosphoglycerate and from serine there are multiple biosynthetic pathways can be followed like formation of phosphatidylserine which helps in membrane lipid formation, sphingolipid formation. Then serine can be converted to glycine by a serine hydroxy methyl transferase and then glycine is helpful for formation of glutathione and then here you can see methionine also is taking part in this pathway.

So, basically these amino acids are important as well as biosynthetic pathway can be followed from the glycolytic intermediates. Then NADPH you know NADPH is the is important for reductive biosynthesis of different types of lipid membrane lipid then fatty acid synthesis phospholipid biosynthesis is enabled by conversion of dihydroxy acid on phosphate to glycerol 3 phosphate also fructose 6 phosphate one intermediate of glycolysis can enter the hexosamine pathway and this pathway is important for different post translational modifications of proteins which are important in the survival of cancer cells. And ultimately you we have discussed about glutathione how it can be how glutathione formation can be helped via glycolysis. Now, glutathione is very important for cancer cell survival because remember when there is TCA cycle TCA cycle the products while go while going through the electron transport chain in site mitochondria those are the sites where free radicals are formed and much flux through the TCA cycle and electron transport chain there is much formation of ROS or reactive oxygen species. Now, just assume that when there is high rates of proliferation in cancer cells if it would have been the condition that that much high metabolism is going through metabolic flux is going through glycolysis TCA cycle and electron transport chain there would have been high production of ROS which would have been harmful to the survival of cancer cells.

And then whatever ROS is produced in the cancer cells can be dealt via increased glutathione production. So, these are the helpful effect of Warburg effect or aerobic glycolysis over cancer cell survival. Now, in aerobic glycolysis what are the enzymes or what are the proteins which are altered in their expression starting from the very glucose transporters which are over expressed GLUT 1, GLUT 3 these are the glucose transporters very much expressed over the cancer cells and that those actually cause

rapid uptake of glucose inside cancer cells. Different glycolytic enzymes are over expressed like hexokinases these are the isoforms I have mentioned triose phosphate isomerase, phosphoglycerate kinase, enolase, pyruvate kinase M 2, aldolase A, phosphoglucomutase, pyruvate dehydrogenase these are the a lot of enzymes rather in the glycolytic pathway is actually over expressed. Moreover the very important regulatory bifunctional enzyme phosphofructokinase and fructose 2, 6 bisphosphatase remember from the class of glycolysis and neo glucogenesis we have discussed how they are regulated we have discussed this enzyme which is a bifunctional enzyme phosphofructokinase, fructose 2, 6 bisphosphatase this is also activated or rather differentially differently expressed in comparison to the normal cells in cancer cells.

Now, you can see that this is the GLUT 1 transporter which is over expressed in cancer cells. So, there is increased glucose uptake which is converted to glucose 6 phosphate via increased expression of hexokinase. Now, hexokinase forms fructose 6 phosphate and here the enzyme phosphofructokinase which is a bifunctional enzyme is important. Now, you can see there are different isoforms of phosphofructokinase 2 such isoforms are phosphofructokinase, fructose bisphosphatase, isoform 3 and phosphofructokinase, fructose bisphosphatase, isoform 4. Now, these two are actually acting differently phosphofructokinase, fructose bisphosphatase 3, isoenzyme is actually helping in formation of fructose 2, 6 bisphosphate.

So, basically what it is causing it is increasing the flux through glycolysis remember if there is more formation of fructose 2, 6 bisphosphate which is one allosteric activator for the glycolysis. So, if there is more formation of fructose 2, 6 bisphosphate what it causes it it increases the flux through glycolysis. But to its contrary phosphofructokinase, fructose bisphosphatase 4 isoform it basically converts the fructose 2, 6 bisphosphate to fructose 6 phosphate. So, basically these fructose phosphofructokinase, fructose bisphosphate, isoform 4 it inhibits the flux through glycolysis causes accumulation of fructose 6 phosphate which in back flow causes accumulation of glucose 6 phosphate. So, glucose 6 phosphate can be diverted towards pentose phosphate pathway.

Now, there is another enzyme which is also known as TIGER. TIGER stands for T P 53 induced glycolysis regulatory phosphatase. Now, these enzyme along with fructose phosphofructokinase, fructose 2, 6 bisphosphatase, isoform 4 they together inhibits the flux of glycolysis rather favors the flux of pentose phosphate pathway. Now, it has been seen that both of these isoform are actually expressed in different tumor cells based on their requirement. So, even pentose phosphate pathway is increased which is helping the cancer cell via formation of nucleotide and NADPH which are actually delivering multiple roles in the tumor cell metabolism as well as glycolysis.

If glycolysis is favored there will be formation of pyruvate which will finally, form lactate. Now, very important lactate formation is also required for the cancer cell survival. Why we are going to discuss? You can see that in cancer cell or rather in cells actually lactate is secreted out from the cell via one transporter, monocarboxylate transporter monocarboxylate isoform 4. And their expression is also increased in tumor cells causing more release of lactate from cell in to the cellular surrounding environment. So, what are the drivers for this Warburg effect? One very important pathway or rather one very important kinase enzyme activation play a important role plays an important role in delivering the aerobic glycolysis that is one serine threonine kinase which is also known as protein kinase BAKT.

Their activation causes as a whole increase of ATP level through the regulation of both glycolysis as well as oxidative metabolism which finally, what is the effect? There is increased oxygen consumption. Similarly, glucose transporters are more expressed over the cell surface. So, basically they are translocated more towards the cell surface hexo kinase expression is increased and also in glycogen metabolism glycogen synthase kinase is also inhibited here. Then this pathway activation of phosphatidyl ionocetal 3 kinase PI 3 K AKT pathway activation of these pathway makes the cell more glucose dependent so, that the energy mostly comes from the glucose because in cancer cell what happens beta oxidation of fatty acid is actually inhibited. So, Warburg effect is not only helping the to supply the biosynthetic molecules to the cells it also helps in tumor cell survivals via evading apoptosis as well as it is spread via inducing metastasis how? Now, there is one very special type of apoptosis which is known as anoikis where if the cells are detached from the extracellular matrix the accumulation of reactive oxygen species they triggered this anoikis.

Now anoikis can be can be exempted in case of cancer cells how? Because in cancer cells as I told you mitochondrial ROS formation reactive oxygen species formation is reduced not only via synthesis of increased glutathione from increased NADPH production, but also there is low flux through oxidative phosphorylation which is a soft target for ROS production. So, basically ROS production is decreased which actually triggers the anoikis. So, this extra extracellular matrix detachment in cancer cells it this phenomena can be uninhibited causing not only evasion from metastasis, but also helpful not only evasion from apoptosis, but also helpful in metastatic dissemination of tumor cells that is spread to distance size within the body. Apart from that there are few therapeutic and diagnostic role of Warburg effect what is that? In diagnosis PET, PET is positron emission tomography. Positron emission tomography is one imaging technique where radio labeled glucose analog which is fluorodeoxy glucose is utilized to detect those areas where high glucose consumption is there and these enables the detection of cancerous tissue.

So, here this is how increased glycolysis or increased consumption of glucose is exploited in diagnosis of the tumor cells or rather specifically locating where the tumor cells are. And finally, outcome prediction can also be helped because this glycolytic patterns or rather increased glycolysis is actually a poor outcome and that can be studied via different gene expression profiling. Then metabolism in cancer cells and their micro environment can be different as I told you there is heterogenicity in this micro environment. Now, cancer cells can be hypoxic can be normoxic as well as there is acidosis which is present in cancer cell because I told you there is huge amount of lactic acid production which causes lactic acidosis or a generalized acidosis surrounding the tumor cell because lactate is actually secreted. And it is also seen that partial pressure of oxygen in tumor cell is frequently lower than the surrounding normal tissue.

Now, this infratumoral hypoxia by prognosis it has larger risk of local spread, distant spread in terms of metastasis and also poor therapeutic outcome and mortality. Also hypoxia renders resistance of the tumor cells towards mitochondria dependent apoptosis and also the metabolic reprogramming of tumor cells which changes the metabolic flux through the mitochondria Krebs cycle etcetera. They are actually the effect or rather adaptation of the tumor cells toward this hypoxic conditions. And for that one very important molecule is should be name that is hypoxia inducible factor HIF 1. Now these hypoxia inducible factor it is activation are related is related to different gene expression.

Enzymes or rather proteins or enzymes of glycolysis, enzymes or enzymes of lactate production, different transporters of lactate or proton transporters not only that tumors own phenomena like angiogenesis or formation of new blood vessels. Then metastasis also iron metabolism those are influenced by hypoxia inducible factor. Now hypoxia inducible factor enhances different glycolytic enzymes expression of different glycolytic enzyme glucose transporters like GLUT 1, 3. What are the lactate production related enzymes? Lactate dehydrogenase told you the transporter, monocarboxylate transporter their expressions are enhanced by HIF. Also in pyruvate dehydrogenase kinase expression is induced then pyruvate dehydrogenase activity is inactivated.

So, basically entry to the TCA cycle is inactivated. And finally, fate of cancer severity of cancer can be predicted by the expression of HIF 1. Hypoxia inducible factor as you can see it is basically one heterodimeric complex there are two subunit HIF 1 alpha and HIF 1 beta. Now the beta form is constitutively expressed constantly expressed not influenced by others that is constitutive expression of a gene. So, HIF 1 beta its expression is not changed it is constitutively expressed.

Whereas, HIF 1 alpha is basically dependent on the oxygen availability. So, what how it

is influenced by the presence of oxygen? Oxygen causes the presence of oxygen causes its degradation that is why it is known as hypoxia inducible factor fine. Now what happens in presence of oxygen as you can see in presence of oxygen HIF 1 is hydroxylated with the enzyme prolyl hydroxylase prolyl hydroxylase domain protein is also known it is also known by that. So, the enzyme is prolyl hydroxylase and this prolyl hydroxylation is recognized by another protein which is known as VHL Von Hippel Lindau protein and this Von Hippel Lindau bound HIF 1 alpha is targeted by proteosomal degradation. So, these are the phenomena which happens in presence of oxygen and this prolyl hydroxylase enzyme is actually activated via the metabolism which is occurring in TCA cycle.

But remember when alpha ketoglutarate is converted to succinate or there is formation of fumarate as well in TCA cycle their excess accumulation actually inhibits this proteosomal degradation. Now what happens in tumor cell? Even in normoxic condition VHL can be inactive. So, basically proteosomal degradation targeting can be inactive PhD can be inactivated by accumulation of succinate or fumarate because remember the enzymes of TCA cycles are actually their expression is reduced. So, finally, what happens as I told you there is accumulation of succinate and fumarate which is finally, causing inhibition of PhD. So, it actually generating a situation of pseudo hypoxia finally, inhibiting the proteosomal degradation of HIF 1 alpha.

Moreover the AKT pathway it also increases the HIF s function via its m r increased HIF 1 alpha mRNA translation. So, all these phenomena actually causes increased functional efficiency or synthesis of hypoxia inducible factor which causes increased expression of different types of glycolitic enzymes or transporters. Now as I told you these metabolic reprogramming can be exploited therapeutically. How there are different therapeutic molecules which are targeted towards this aerobic glycolysis like glucose transporter, GLUT 1 transporter, silybenin. Silybenin is one GLUT 1 transporter inhibitor there these drugs causes decreased uptake of glucose in tumor cell.

Lonidamine causes inhibition of the enzyme hexokinase. Similarly glucose analogs like 2 ox 2 deoxyglucose is utilized which inhibits the enzyme glucose 6 phosphate isomerase. There are different in molecules in this glycolytic pathway which are inhibits in cancer targeted therapy. Also enzyme like lactate dehydrogenase A can be inhibited by gossypol, galloflavin, then glycogen synthase kinase 3 beta can be can also be inhibited. So, these are the different therapeutic target which is targeted towards this aerobic glycolysis.

As I told you there are different TCA cycle enzymes which their expressions are altered namely succinate dehydrogenase, fumarate hydrate isocitrate dehydrogenase their effect

are mostly over ROS expression. Then cellular metabolism dysregulation via accumulation it causes accumulation of succinate succinate dehydrogenase which stabilizes HIF. Similarly fumarate hydrate is also causing fumarate accumulation stabilizing HIF. Moreover fumarate accumulation inhibits enzymes involved in DNA and histone methylation causing epigenetic changes which favors cancer pathogenesis. Then isocitrate dehydrogenase mutation it renders neomorphic activity.

Now, neomorphic activities are the newer activity which is rendered in a cancer cell. So, basically what happens alpha ketoglutarate instead of proceeding to the normal TCA cycle forms a new metabolite which is a oncometabolite. Oncometabolites are those whose accumulation is reflected by the toxic effect of cancer cells. So, the new oncometabolite 2-hydroxyglutarate is accumulated from alpha ketoglutarate and this 2-hydroxyglutarate it inhibits alpha ketoglutarate dependent dioxygenases like histone dimethylase DNA dimethylases. So, basically they are also causing defective DNA and histone dimethylation causing epigenetic expression ultra epigenetic expression.

So, these are the effect of TCA cycle enzyme mutation in cancer cell. Now, there is a metabolic symbiosis between aerobic and cancer cell. As I told there is metabolic heterogenicity in cancer cells in a tumor few cells are living in normoxic condition few cells are living in hypoxic condition. Those cells which are actually located far far away from the blood vessels they are actually towards them oxygen supply is low. So, they are in hypoxic condition, but those cells those cancer cells which are beside those blood vessels they are in normoxic condition.

Now, they are these normoxic and hypoxic cells they are in a metabolic symbiosis state how? So, you can see there is real formation of lactate in hypoxic cancer cells. Now, accumulation of this excess lactate can be harmful for the hypoxic cancer cells. So, what happens these hypoxic cancer cells they secrete lactate via MCT 4, monocarboxylate transporter 4 and these lactate is taken up by the normoxic cancer cells by MCT 1 monocarboxylate transporter 1. And what is the fate of this lactate? Lactate enters the oxphos system via pyruvate formation through lactate dehydrogenase and it is getting utilized via formation of ATP. So, you can see there is a metabolic symbiosis in hypoxic and normoxic cancer cells.

Then also acidosis apart from hypoxia acidosis is also favoring the tumor cells metabolism. How? Now, why there is acidosis definitely there is increased amount of lactate formation also carbon dioxide is a significant source of acidic extracellular pH. So, in the tumor micro environment extracellular pH is also acidic. Now, these acidosis promotes extracellular matrix degradation which is helpful for the invasiveness or metastasis of cancer, local spread of cancer. Also in normoxic acidosis here tumor cell

inhibits the proteasomal degradation of HIF 1 because this nucleolar sequestration of von hippel lindau and HIF 1 complex these complexes sequestration is inhibited by acidosis.

Moreover in the intracellular compartment there are changes in different other proteins like sodium hydrogen exchange exchanger their expression change monocarboxylate transporter different protein proton pumps also carbonic anhydrase. These their expressions are altered in tumor cells which renders acidosis not only inside the cell, but also in the extracellular environment. Now coming to one very important metabolism of cancer that is glutamine metabolism. Glutamine remember it is if you remember that glutamine is the non-essential amino acid and this is the most abundant amino acid circulating in the blood stream and it can be utilized as a source of different biomaterials in tumors. Now what happens glutamine the circulating glutamine it is up taken inside the cell via different transporters.

Transporters like ASCT 2 alanine serine cysteine transporter 2 amino acid transporter also system N transporter SN 2. So, these are the transporter which up takes up take glutamine inside cell. Once inside the cell glutamine is converted to glutamate via the enzyme glutaminase. Now remember this is the this glutaminase is the cytosolic glutaminase whereas, in mitochondria there is another glutaminase which is very much activated by the high inorganic phosphate concentration. So, finally, even in inside the mitochondria glutamine can be glutamine can be converted to glutamate.

So, there is increased uptake of glutamine and it is hydrolysis to glutamate and ammonia and this process is known as glutaminolysis. Now glutaminolysis is important in cancer cell why because remember glutamate here in cancer cell is important for anaplerosis. If you remember anaplerosis is basically replenishment of the intermediate of TCA cycle and here glutamine via formation of glutamate actually replenishing the depleted oxaloacetate in TCA cycle why? So, once again you can see glutamate formed glutamate can form alpha ketoglutarate via amino transferase and this alpha ketoglutarate can be utilized for replenishment of the intermediates in TCA cycle which causes restoration of the reduced glutathione pool as well which is helpful for fighting ROS. Also this glutamine help is helpful in nitrogen donation for synthesis of purine and pyrimidine nucleotides different amino acids can be formed from this the amino group of the glutamine. So, glutamine is basically helpful for biosynthetic capability of the tumor cell.

Now you can see glutamate can be catalyzed by 3 different amino transferase you remember if you remember SgOT and SgPT here you can see GPT is the Glutamic Pyruvate Transaminase. So, Pyruvate can be formed Pyruvate can be converted to alanine while glutamate is forming alpha ketoglutarate. Similarly formation of alpha ketoglutarate can be helped by glutamic oxaloacetate oxaloacetate transaminase where

oxaloacetate is converted to aspartate and another amino transferase which is known as phosphocerine amino transferase. So, here you can see 3 phosphohydroxy pyruvate is converted to phosphocerine by phosphocerine amino transferases where we are getting alpha ketoglutarate which is utilized in anaplerosis in TCA cycle also the other metabolites like serine as I told it enters formation of glycine and glutathione are there. So, these are for cellular proliferation and they are target these enzymes are basically targeted to treat cancer.

Similarly tryptophan tryptophan in tryptophan metabolism enzymes like indolamine 2, 3 dioxygenase or tryptophan 2, 3 dioxygenase they are over expression actually helpful for the immune targeting of the cancer cells. Basically these cancer cells are targeted by different immune cells and these enzymes provides immunity from this immunological destruction of the cancer cells. So, basically glutamine is glutaminolysis rather is helping in biosynthetic properties anaplerosis of the TCA cycle and also immunological immunity for the cancer cells. Glutamine metabolism is also helpful for NADPH formation. So, here you can see that the flux of glutamate to alpha ketoglutarate forms malate and this malate can form pyruvate via formation of NADPH and this NADPH can be utilized for the reductive biosynthesis as well as ROS scavenger and ROS scavenging action.

How this glutaminolysis is regulated? One very important mechanism is via the oncogene MYC and this MYC oncogenes product is one very one important transcription factor which is known as CMIC and what is the function of this CMIC? CMIC actually regulate the expression of different genes and micro RNA related to cell cycle, glucose metabolism, glutamine metabolism as well as biogenesis of mitochondria, biogenesis of ribosome. So, basically these are exaggerated in a cancer cell through the CMIC. Now, CMIC increases the glutamine flux inside the cell via the expression of micro RNA, micro RNA 23 A B basically their transcriptional expression is decreased which causes increased mitochondrial glutaminase expression which finally leads to glutamine metabolism also the transporter of glutamine uptake. They are also their expression is also enhanced. Moreover CMIC also induces the expression of lactate dehydrogenase enzyme which is helping in cancer cells metabolism and these are the current therapeutic strategies targeting towards glutaminolysis.

So, you can see glutamine depletion can be enhanced, its metabolism can be inhibited via the enzyme inhibition, transporters can be inhibited different glutaminomimetic can be glutaminomimetics here when it is actually targeted towards the transporter enters the cell basically inactivates the glutamine dehydrogenase enzyme, amino transferases can be inhibited. So, these are the different targets towards glutaminolysis. Then we are coming to the lipid metabolism which is also altered the de novo fatty acid synthesis is

altered. Now, there are three important enzymes in de novo fatty acid synthesis if you remember there is citrate lyase which is ATP dependent causes acetyl coenzyme and oxaloacetate formation from citrate, acetyl coenzyme a carboxydase which helps in formation of malonyl coenzyme A and finally, fatty acid synthesis which is the main enzyme for fatty acid synthesis and which is NADPH dependent as well. Now, fatty acid synthesis over expressed also ATP dependent citrate lyase is over expressed acetyl coenzyme A also is over expressed.

Moreover citrate lyase reinforces the Warburg effect by preventing the accumulation of citrate cytosolic citrate accumulation is actually by rather diverted towards fatty acid synthesis and this citrate acts as a glycolysis inhibitor. So, basically aerobic glycolysis can go uninterruptedly. So, it has been thoroughly discussed that glycolysis or aerobic glycolysis is the is one very important pathway which is enhanced in cancer cell rather cancer cells are depending on this aerobic glycolysis not only for the ATP, but also for different intermediate which is targeted towards biosynthesis. But remember what happens to the electron transport chain definitely it is there in the normoxyl cells as I told you there is electron transport chain and ATP production via this pathway, but cells are metabolically flexible tumor cells. When there is oxygen available there is electron transport chain, but when there is depleted oxygen cancer cells undergo adaptation.

You can see electron transport chain in nutrient and oxygen poor environment they can survive in as low as 0.5 percent oxygen availability. And their micro environment are adapted via decreasing the ATP demand like if you remember sodium potassium ATPase one very important transporter which is dependent on the supply of ATP their requirement is very much reduced their expression is very much reduced. Moreover one enzyme kinase AMPK kinase which we have discussed thoroughly in obesity how this AMPK is activated while there is ATP depletion and AMP accumulation rather AMP is formed from ADP AMP kinase is activated and that causes adaptation towards the nutrient poor or oxygen poor environment. But otherwise pyruvate can be derived from glycolysis also this fatty acids and amino acids they can serve the intermediates of TCA cycle via anapredosis also glutaminolysis is causing anapredosis different branch and amino acids like isoleucine valine leucine they can also form acetyl coenzyme and other intermediates of TCA cycle.

So, basically the flux towards TCA cycle is increased causing increased ATP formation even if there is mutation of the TCA cycle enzyme if the substrate flux are increased it might increase the form formation of products and finally, ATP formation through ETC. So, these are all the metabolic alteration in cancer cell. So, you can see in a normal cell which is very much dependent on the oxygen availability causing aerobic glycolysis as well as oxphos in cancer cell there is basically anaerobic glycolysis which is termed as

aerobic glycolysis which occurs in even in presence of oxygen and forms lactate. Also glutaminolysis which is very important in cancer cell fatty acid biosynthesis which is enhanced in cancer cell and ROS formed in electron transport chain normal cells are vulnerable, but cancer cells are resistant towards formation of reactive oxygen species. So, these are the key points from these cancer cell metabolism that cancer cell exhibits aerobic glycolysis which is also known as Warburg effect from where they preferent where they preferentially utilizes glucose even if there is oxygen available then cancer cell rewire their metabolic pathways and utilize nutrients differently compared to normal cells they adapt their metabolism to produce more energy or synthesize more bio molecules for their rapid growth and survival.

Pentose phosphate pathway is enhanced glutaminolysis is one very important pathway which helps in anaplerosis fatty acid synthesis lipogenesis they are up regulated then redox balance. The ROS formation is is modulated to cope up the cell survival it also manipulate the tumor micro environment its own environment as well as the surrounding environment for its proper growth and evade apoptosis and immune response and who are responsible for that different oncogenes different tumor suppressor genes hypoxia inducible factor they help in metabolic reprogramming of cancer cell and finally, how this cancer cell can be cancer metabolism can be utilized via designing different therapeutic target. So, here we have discussed all this thing. So, we have reached the very last session of this NPTEL lecture series and it was wonderful taking the totally integrated metabolism as well as highlighting different clinical condition or metabolic diversions from the normal scenario. We have vividly discussed obesity, diabetes mellitus, protein energy malnutrition as well as cancer metabolism and as a whole one holistic integration of all the metabolism which is occurring in mammalian cell as well as human body. So, thank you all see you in the live session. Thank you.