Overview and Integration of Cellular Metabolism

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Week 02

Lecture 09: Regulation of Glycolysis and Neoglucogenesis (II) Cori Cycle, Rapoport Leubering Cycle, Futile Cycle

Welcome back everyone. So, in the session of overview and integration of cellular metabolism, today we will cover few topics like Cori cycle, Rapoport-Luberin cycle, Futile cycle and different associated other conditions of Neo glucosinases and glycolysis.

So, in this class the concepts which will be covered are one is feeder pathways of glycolysis, then few cycles like Cori cycle, glucose-alanine cycle, Rapoport-Luberin cycle and finally, few clinical conditions which are associated with glycolysis and Neo glucosinases. Now coming to the feeder pathways of glycolysis, in glycolysis what we have read that glucose is basically converted to pyruvate which is giving rise to acetyl coenzyme A. This acetyl coenzyme A is actually entering the TCA cycle to finally, produce ATP and the reducing equivalents like NADH and FADH2 and they are actually required for production of ATP. So, this is an energy supplying metabolic pathway.

Now what happens apart from glucose directly apart from glucose there are multiple other carbohydrate molecules which contributes to glycolysis definitely by forming glucose. What are those? The storage form of glucose like glycogen starch in our body mostly glycogen. Now this glycogen actually forms glucose via glycogenolysis which we will discuss in further classes. Now glycogen forms glucose 1 phosphate via glycogenolysis where the main enzyme is phosphorylase. Then with the help of a mutase this glucose 1 phosphate is finally, converted to glucose 6 phosphate and these glucose 6 phosphate it enters glycolysis.

Similarly different other monosaccharides like galactose, fructose, then also mannose they also can enter glycolysis. Galactose as you will learn in galactose metabolism class that galactose by forming UDP galactose which can form UDP glucose can enter the glycolysis pathway via forming glucose 1 phosphate. And similarly this glucose 1 phosphate just like glycogenolysis can enter glycolysis via formation of glucose 6 phosphate. Similarly mannose also can enter via mannose 6 phosphate formation and it

forms fructose 6 phosphate by phosphomanose isomerase. So, mannose also can contribute in some intermediate of glycolysis the intermediate is fructose 6 phosphate.

Similarly fructose directly with the help of hexokinase can form fructose 6 phosphate and enter glycolysis. Now, fructose it is it can be metabolite by some other pathway which you will once again learn in further class that fructose via formation of fructose 1 phosphate which is finally, degraded finally, split to form dihydroxy acetone phosphate and glyceraldehyde finally, enters glycolysis via forming glyceraldehyde 3 phosphate. Again lactose disaccharides lactose split of to via lactase enzyme that you have learned in the digestion and absorption class of carbohydrate where lactose via lactase enzyme can form glucose and galactose and they can enter the glycolysis also sucrose, trehalose all this can contribute in glycolysis by directly forming glucose or forming different intermediates of glycolysis they contribute in glycolysis pathway and finally, contribute to form energy. So, these are the feeder pathways of glycolysis. Next we will discuss about Corey cycle and glucose alanine cycle.

Now, regarding these two cycle the important enzyme is basically lactate dehydrogenase. Now, what happens these in erythrocytes you know there is anaerobic glycolysis where pyruvate is converted to lactate similarly in different anaerobic conditions which is very prevalent in skeletal muscle well when there is vigorous exercise there is anaerobic glycolysis in skeletal muscle there is formation of lactic acid. So, there is lactic acid accumulation of this lactic acid formation anaerobic glycolysis if you remember that lactate this formation of lactate is important not for metabolic purpose, but for formation of rather regeneration of NAD. This regeneration of NAD is required to continue the glycolysis by providing the NAD in glycolytic pathway, but then this lactic acid is accumulated inside the skeletal muscle and you know excess accumulation of lactic acid can cause lactic acidosis. So, what we need is clearing of this lactate in such a way that it can contribute in a good purpose how by transferring or transporting this lactate to liver where liver can utilize lactate in neo glucogenesis.

Now, you can see that in muscle via glycolysis there is formation of glucose 6 phosphate which finally, forms pyruvate via anaerobic glycolysis it forms lactate. Now, what happens these lactate via circulation enters liver in liver by neo glucogenesis it forms pyruvate which is finally, used up to form glucose. So, basically there is clearance of lactate from skeletal muscle which relieves from lactic acidosis and also this lactate is utilized to regenerate glucose. So, this is basically an indirect way of providing energy to skeletal muscle. So, skeletal muscle utilizes its own metabolite by transferring it to liver where from glucose once again comes to skeletal muscle.

So, this is an indirect supply of energy to skeletal muscle that is Cory's cycle. Now

what is glucose alanine cycle? Now glucose alanine cycle is important for two purposes one is clearance of the toxic ammonia from skeletal muscle as well as it helps in neo glucogenesis. How? Basically what happens alanine can form can be formed from pyruvate by transamination reaction. Now in fasting starvation there is depletion of the stored glycogen. So, what happens skeletal muscle proteins start to break down to provide energy and that carbon skeleton which has been generated from different amino acids amino acids which are generated by breaking down muscle proteins those carbon skeletons are to be transferred to liver where neo glucogenesis occurs.

Now how this happens? Via degradation of protein there is production of amino acids and there is also production of ammonia for from this at the amination of those amino acids. So, there is accumulation of ammonia which should be clear as well as amino acids like alanine should be utilized in such a way that it can contribute to production of glucose. Now what happens once again these alanine can be transported via circulation to liver. In liver alanine once again is transaminated to form pyruvate and it also releases the toxic ammonia and this toxic ammonia then is excreted from body via urea cycle. Urea cycle will be discussed in future classes.

So, basically there is two things happen once again that is the toxic product ammonia is transferred for excretion as well as alanine is reutilized alanine is utilized for neo glucogenesis. So, what happens in fasting the muscle proteins can contribute in neo glucogenesis via glucose alanine cycle. So, this is Corey cycle and glucose alanine cycle where there is transfer of different products from skeletal muscle to liver for formation of glucose in neo glucogenesis as well as as well as sorry excretion of ammonia through urea cycle. Next we will discuss another cycle which is known as Rapoport-Luberin cycle. Now, Rapoport-Luberin cycle is basically a supplementary pathway of glycolysis which actually occurs in erythrocytes or RBCs.

Now what happens if you remember in glycolysis there is formation of 1, 3 bisphosphoglycerate in the payoff phase and this 1, 3 bisphosphoglycerate forms 3 phosphoglycerate. Now these reaction is frequently bypassed in RBC via 2, 3 BPG cycle or Rapoport-Luberin cycle where 1, 3 bisphosphoglycerate instead of directly forming 3 phosphoglycerate it forms another intermediate that is 2, 3 BPG or 2, 3 bisphosphoglycerate. With the help of the enzyme mutase, it forms 1, 3 bisphosphoglycerate mutase and then this 2, 3 bisphosphoglycerate is converted to 3 phosphoglycerate with the help of the enzyme phosphatase. Now again to remind to basically this is basically a discussion all related to glycolysis neoglucogenesis and TCA cycle. So, if you remember that for while forming 3 phosphoglycerate from the 1, 3 BPG there was formation of ATP, but here you can see in this bypass pathway there is no ATP produced.

Then what is the utilization of this pathway? Basically there is an important role of 2, 3 BPG in RBC . Before discussing that once again to discuss that again these 2 enzyme 1, 3 bisphosphoglycerate mutase and 1, 2, 3 bisphosphoglycerate phosphatase these 2 activities are present in one single enzyme that is why this is a bifunctional enzyme. Now as we are discussing about the role of 2, 3 BPG in RBC. Now 2, 3 BPG is one allosteric regulator of hemoglobin and oxygen binding. What happens that 2, 3 BPG actually reduces the oxygen affinity towards RBC towards hemoglobin actually.

How it is helpful? With the effect or with the induction of 2, 3 BPG oxygen can be easily detached from hemoglobin which means it can be easily delivered to the tissue. Now it has immense role in those conditions where there is hypoxia. In hypoxia there is very low supply of oxygen. So, there is low low concentration low partial pressure of oxygen in tissue. So, the difference between the giver and the I mean the donor and the acceptors are low.

So, in these in these condition delivery of oxygen based on the concentration gradient will not be more helpful. What we need is some molecule which can detach the carried hemog the carried oxygen from hemoglobin to be delivered to the tissue that molecule is 2, 3 BPG. In hypoxic condition 2, 3 BPG condition 2, 3 BPG concentration is increased inside RBC and these helps detachment and delivery of oxygen to the tissues. Now it is helpful in those persons who are living in high altitude there is low partial pressure of oxygen. It is helpful in fetal circulation where there is more requirement of oxygen to the fetal tissue, but again to remember that there is no ATP generation.

Next we will discuss about few conditions clinical conditions related to glycolysis like lactic acidosis. When there is excess accumulation of lactic acid there is acidosis low pH and those can be this lactic acidosis can be seen in hypoxia, shock, pulmonary failure can be seen in alcohol abuse, in diabetes mellitus and in some mitochondrial cytopathies. Then there are few glycolytic enzymes which can be deficient, but that those conditions are very rare actually. Now one of the important enzyme to mention is pyruvate kinase and also hexokinase. Now as we have discussed in the class of glycolysis that enzyme deficiencies enzymes related to glycolysis if they are deficient they can give rise to hemolytic anemia.

Why again RBC is dependent totally on glycolysis for the supply of ATP or energy because why there is no TCA cycle or citric acid cycle in RBC. Why there is no mitochondria. And TCA cycle occurs inside mitochondria. So, basically for provision of energy RBC is totally dependent on glycolysis. Now if there is hampered glycolysis or defective glycolysis there is defective or low production of ATP and ATP deficiency

leads to RBC burst.

Swelling and burst of RBC why there was one transporter I have already discussed if you remember that is sodium potassium ATPase. The sodium potassium ATPase is dependent on ATP the function of sodium potassium ATPase is dependent on ATP and in absence or low ATP the transporter gets inactive or defective which causes RBC swelling and burst. Then pyruvate dehydrogenase is another enzyme which carries remains importance. Now if you remember once again pyruvate dehydrogenase there thiamine is used as a cofactor thiamine or vitamin B 1. Now in vitamin B 1 deficiency there is beriberi the disease called beriberi.

It is frequently seen that TPP deficiency in alcoholism causes pyruvate accumulation in tissues and resultant lactic acidosis. Then again inherited pyruvate dehydrogenase deficiency is also called lactic acidosis. So, these are all due to the either absence of pyruvate dehydrogenase enzyme or absence of the cofactor for which there is defective enzyme activity. So, that is the reason why in beriberi there is lactic acidosis in alcoholism also there is pyruvate accumulation which causes excess production of lactic acid causing lactic acidosis. Next we will move on to few clinical conditions which are associated with which is associated with neoglucogenesis that is deficiency of pyruvate carboxylase enzyme present in neoglucogenesis.

Now this is a type of autosomal recessive condition is a genetic disorder and a rare inbound error of metabolism which is mostly manifested as neurological symptoms mental retardation. Why again as we have discussed that brain is one such organ which is mostly dependent on glucose as the energy source. Now whenever there is deficiency of glucose or fasting conditions in those conditions what we need when the stores of glucose are depleted we need neoglucogenesis for supply of glucose to brain. Now when there is defective neoglucogenesis there is defective energy supply in brain and in nervous system. So, the remember in any type of defect in neoglucogenesis brain is one such organ which is highly affected.

Then again there is accumulation of lactic acid and keto acids which finally, leads to metabolic acidosis also there is hyper ammonia. So, these are the condition these are the situations or features of pyruvate carboxylase deficiency. Then another condition is malignant hypo hyperthermia which is related to one anesthetic halothane. Halothane causes inappropriate release of calcium from sarcoplasmic reticulum which finally, causes uncontrolled heat generation and these causes damage to the muscle cells or myocytes. After that we will come to the role of alcohol sometimes we call it alcohol poisoning also.

Now what happen in alcohol poisoning or with excess ingestion of alcohol there is inhibition of gluconeogenesis. Now what happens this what why there is defective neoglucogenesis? What happens in while there is excess amount of circulating alcohol or ethanol? These ethanol's are metabolized by utilizing NAD. Why ethanol is converted to acetaldehyde and this acetaldehyde is converted to acetic acid and in both of the cases there is utilization of NAD and this NAD is converted to NADH. So, basically there is raised amount of NADH in circulation site in cytoplasmic NADH is raised. Now what happens in neoglucogenesis there is formation of pyruvate to malate to oxaloacetate because there is excess amount of NADH present these neoglucogenetic reactions cannot be done.

So, there is accumulation of NADH which causes defect in neoglucogenesis. So, basically pyruvate cannot be converted to malate and oxaloacetate rather it is converted to lactate and this lactate cannot be utilized once again in neoglucogenesis because there is high level of NADH present in circulation and for conversion of lactate to pyruvate we need NAD. So, in alcohol poisoning what will we see there is lactic acidosis because there is hampered neoglucogenesis there is also high level of NADH. So, these are the things we have discussed in this class like feeder pathway of glycolysis where in addition to glucose there are many other carbohydrate which finally, contributes in glycolytic pathway for energy production. Then Corey cycle and glucose alanine cycle they these cycles are used for cycling of nutrients between skeletal muscle and liver Rapoport-Luberin cycle which is a supplementary pathway to glycolysis and that is concerned with synthesis of 2, 3 BPG in RBC and this 2, 3 BPG has immense role in hemoglobin oxygen binding and delivering oxygen to the tissues and finally, we have discussed few clinical conditions related to glycolysis and neoglucogenesis.

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