Overview and Integration of Cellular Metabolism

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Lecture 12: Glycogen Metabolism (I)

Hello everyone. Welcome back to the lecture series of Overview and Integration of Cellular Metabolism. For the next few classes we will discuss Glycogen Metabolism. So, in glycogen metabolism the concepts will be covered are the reactions how glycogen is synthesized and also the reactions how glycogen is broken down to provide glucose. Then we will learn about regulation of these two mechanisms as well as how they are reciprocally regulated. In this class we will discuss the pathways of glycogen synthesis and glycogen breakdown.

So, glycogen synthesis this reactions this pathway is known as glycogenesis and glycogen breakdown this pathway is known as glycogenolysis. Now before going into this major metabolic pathway let us learn something about glycogen the chemical structure that will help to understand the metabolic pathways. So, glycogen this is a glycogen molecule. Now glycogen as you all know that this is a storage form of carbohydrate and basically this is stored in liver and muscle and as a storage form of glucose.

So, multiple molecules of glucose actually helps to form glycogen molecule. Now in liver about 5 percent of the liver weight is actually made up of glycogen. In the structure of glycogen you will see that there is alpha 1 4 glycosidic bond alpha 1 4 glycosidic bond and also there are few branch points and those branch points are formed by alpha 1 6 glycosidic bond. So, there are 2 types of glycosidic bond present in glycogen molecule. Now glycogen molecule one interesting thing is glycogen molecule has one single reducing end this is that one single reducing end all these other ends the ends of branches are actually non reducing ends.

Now in inside the cells glycogen remains as alpha rosettes form and how this alpha rosette form is formed actually. So, basically the core structure the elementary structure of a glycogen alpha rosette is known as beta particle. Inside this beta particle about 50000 glucose units are present and these beta particles around 20 to 40 of these beta

particles are actually forming the granules of glycogen those granules which are present in cytoplasm of the cells and that 20 to 40 beta particles finally, forms the alpha rosette of glycogen molecule. Now as you can see there is extensive branching you can see there is extensive branching and these branch points are actually alpha 1 6 glycosidic bond. Now these extensive branching actually creates multiple non reducing ends which helps to solubilize this glycogen molecule in cell not only that basically those enzymes which help in glycogen synthesis and glycogen breakdown they are actually they can act over the non reducing end.

By this extensive branching this molecule actually provides the enzyme action site of those enzymes of glycogenesis as well as glycogenolysis. Now remember in the glycogen granule the granules of glycogen there is beta particle glycogen itself as well as the those enzymes which help in breakdown or synthesis of glycogen they are also present inside those glycogen granule as well as the I mean those molecules which induces or molecules which induce inhibit the breakdown or synthesis they are also incorporate incorporated inside the glycogen granule. So, basically this is a conglomerate structure where along with glycogen they are respective synthesizing enzymes and degrading enzymes are present. So, as we have discussed that glycogen is basically stored in liver and muscle now the storage of glycogen in liver and muscle they act differently how the stored glycogen in liver they basically provide glucose when there is requirement of glucose in circulation whereas, the stored glycogen in skeletal muscle they actually provide energy to for action of skeletal muscle. Now the glycogen content of liver is basically much more than skeletal muscle, but again ultimately the total amount of glycogen is more in skeletal muscle why because itself skeletal muscle tissue is more in our body.

So, even if the concentration of glycogen per 100 gram of hepatocytes are more is more than skeletal muscle, but then again the total content of glycogen if we see along the whole skeletal muscle present in our body that will be more than liver because liver is one single organ and you can see everywhere skeletal muscles are present in our body. To point out that all the glycogen enzymes of glycogenesis all the enzymes of glycogenolysis they are all cytoplasmic enzyme. Let us move on to the metabolic pathway of glycogen synthesis which is known as glycogenesis. Now for glycogen synthesis these are the enzymes as well as few other biomolecules which are required. The main enzyme which is required for glycogen synthesis is evident by the name glycogen synthase enzyme.

Now what it does this enzyme basically forms alpha 1, 4 glycosidic bond and by form between whom between 2 glucose residues and where are those glucose residues one is present over a pre pre existing glycogen primer then glucose is added from UDP glucose.

So, we will discuss this mechanism just after this. Then we need a protein that is glycogenin we need a protein remember this is a protein remember glycogen is synthesized even if glycogenin glycogen is a carbohydrate it is synthesized over a protein molecule that is known as glycogenin. This is a 37 kilo Dalton molecular weight protein it has the ability to be glycosylated means glucose can be added over this glycogenin in its specific tyrosine residues and those glucose are added by forming alpha 1, 4 glycosidic bond finally, they form a glycogen primer. So, over a protein molecule which is known as glycogenin the basic glycogen primer is formed.

Next important enzyme is branching enzyme they form remember we were we have discussed about alpha 1, 4 glycosidic bond as well as alpha 1, 6 glycosidic bond alpha 1, 4 glycosidic is glycosidic bond is formed by glycogen synthase whereas, alpha 1, 6 glycosidic bond is formed by branching enzyme. Next another important molecule that is UDP glucose remember carbohydrate all the monosaccharides all the carbohydrate molecules when they cannot directly be they directly take part in phosphoryl I mean for glucose transfer or other chemical reaction. So, they they should be activated activated by adding some nucleotides or nucleosides actually. So, here glucose is activated by forming UDP glucose by addition of UDP. Now, let us see what happens in this metabolic steps one metabolic mechanism one by one.

So, basically the first thing is activation of glucose where glucose has to be activated with addition of UDP and it starts from the very formation of glucose 6 phosphate where from this glucose 6 phosphates come if you remember it is the first step in glycolysis when there is excess glucose which enters inside the cell it forms with the help of hexokinase enzyme it forms glucose 6 phosphate. Now, this glucose 6 phosphate is converted to glucose 1 phosphate with the help of the enzyme phospho glucomutase this glucose 1 phosphate once again is the ultimate substrate which forms the activated glucose with the help of the enzyme UDP glucose pyrophosphorylase where glucose 1 phosphate reacts with UTP to form UDP glucose and pyrophosphate is released. Now, to make this reaction in a for to continue the reaction in a forward direction what happens actually this pyrophosphate is hydrolyzed by pyrophosphatase with release of energy. So, this is a this is an example of exorganic reaction and it keeps the metabolic flow towards formation of active glucose at this means towards formation of glycogen synthesis. So, finally, at the end of this discussion we are getting the activated glucose UDP glucose which can donate glucose molecule.

So, basically UDP glucose is adding glucose molecule over a glucose chain. Now glycogen synthase as we have discussed it forms alpha 1 4 glycosidic bond, but once again it needs a primer glycogen synthesis cannot synthesize the glycogen chain de novo cannot initiate the reaction. So, what it needs it needs a primer a primer which is made of

a preformed poly glucose chain which are which those poly glucose molecules are attached by alpha 1 4 glycosidic bond a preformed poly glucose chain or branch having at least 8 glucose residues. So, this is a primer where at least 8 glucose residues are present over that glycogen synthesis glycogen synthesis can act. Now, how this primer is synthesized with the help of glycogenin.

Now as we have discussed glycogenin is a protein it has tyrosine residues and those tyrosine residues can be glycosylated. Glycosylated by which enzyme? Glucosyltransferase, but remember this glucosyltransferase is the intrinsic activity of this glycogenin only. Basically this protein is having another function as a function of glucosyltransferase. So, it can activate the glucosylation of its own. So, basically there is transfer of glucose residues from UDP glucose over this glycogenin.

So, consecutively 8 glucose residues are consecutively 8 glucose residues are attached over glycogenin at least 8 glucose residues to form the glycogen primer and these glycogen primer can be dealt with glycogen synthase enzyme. So, here you can see there is formation of glycogen primer. Now that primer can be extended by addition of glucose further addition of glucose over this primer that is further formation of alpha 1 4 glycosidic bond can be done by glycogen synthase. So, basically what happens this glycogenin protein is actually buried inside beta particle covalently attached to the chain of glucose and there is that one single reducing end of glycogen present buried inside the beta particle. So, here you can see that from UDP glucose these glucose molecule this is the UDP glucose this is the whole UDP glucose from here the glucose the glucose molecule is transferred to the non reducing end this is the non reducing end of glycogen primer that is existing poly glucose chain and that chain is extended by formation of alpha 1 4 glycosidic bond with the help of the enzyme glycogen synthase.

Now another type of bond if you remember is present inside the glycogen that is alpha 1 6 glycosidic bond that is formed by branching enzyme. Beringenzyme is also known as amylo 1 4 2 1 6 trans glycosylase or sometimes in a simplified form we say glycosyl 4 6 transferase. Now what it does? It transfers a block of 6 to 8 glucose residues. So, it transfer a block of 6 to 8 glucose residues to the non reducing end of the branch and we are talking about the chain where at least 11 residues are present. So, basically you can see there are 1 2 3 4 5 6 7 8 9 10 11 glucose residues are present at least 11 residues should be present before action of branching enzyme from there from that branch 8 6 to 8 molecules of glucose as a chain is transferred to the previous branch you can see this was the previous branch here these 8 residues are transferred forming alpha 1 6 glycosidic bond.

So, this is how branching occurs. Once again these chains can be extended with the

help of glycogen synthase and again branching can be done with the help of a branching enzyme. So, basically this is a constant formation of alpha 1 4 and alpha 1 6 bond forming an extensive branching inside glycogen molecule. Now one important thing is you can see as we have discussed at least 4 residue away there should be also 4 residues before formation of alpha 1 6 bond. So, this is how glycogen is synthesized inside our body.

So, you can see this is the glycogen core with the help of the glycogen synthase the here is addition of glycogen forming alpha 1 4 glycosidic bond then these chain is extended you can see chains are extended with addition of glucose then there is formation of branching with the branching enzyme finally, there is an extensive branched molecule which is formed. So, this is all about glycogen synthesis. Next we will learn about glycogenolysis with the help of the enzymes glycogen phosphorylase, glucan transferase, debrancing enzyme, phospho glucomutase and glucose 6 phosphatase. So, glycogenolysis that is breakdown of glycogen is done with the help of all this enzyme. So, this is the glycogen molecule we have synthesized in glycogenesis here is alpha 1 4 linkage as well as alpha 1 6 linkage.

Now we were talking about the enzyme the first enzyme as we have discussed that glycogen phosphorylase remember this is the most important enzyme in glycogen breakdown. Now glycogen phosphorylase is actually causing phosphorolysis means there is phosphorylation as well as lysis or splitting off of what? Splitting off of alpha 1 4 glycosidic bond and also addition of phosphate how you can see these are the glucose molecules present in glycogen chain. Now these glucose molecules one by one is released by breaking down alpha 1 4 glycosidic bond and released as not glucose released as glucose 1 phosphate. So, there is phosphorylation of glucose. So, the glucose is released as glucose 1 phosphate and lysis of alpha 1 4 glycosidic bond.

So, these glucose molecules they are released one by one from this glycogen chain with the help of glycogen phosphorylase enzyme. So, up to when till there are about 4 glucose residues remains in either side of the branch. So, basically one by one release of glucose is there in the form of glucose 1 phosphate then till till up to when this lysis occurs or this splitting occurs till there are 4 glucose residues present in both side of the chain. Now the action of glucon transferase occurs. So, glucon transferase what it does you can see transfer of these 3 glucose residues to the nearby branch and what it does? It exposes this alpha 1 6 branch point and this branch point is acted upon by debranching enzyme.

So, basically debranching enzyme actually splits alpha 1 4 glycosidic bond and release the glucose as free glucose not glucose 1 phosphate. So, basically free glucose is

released by debranching enzyme and remember these glucon transferase and debranching enzyme they are actually present in a single enzyme molecule and that single enzyme is is a bifunctional enzyme protein. So, one single enzyme they it is having 2 types of enzymatic function glucon transferase as well as debranching function. Now these chain once again is treated by glycogen phosphorylase and further actions are done till there is extensive release of glucose from by breaking down glycogen molecule. So, this is how glycogen breakdown or glycogenolysis occurs.

Now those glucose 1 phosphates which were released by glycogen phosphorylase they are converted to glucose 6 phosphate with the help of phospho glucomutase and these 6 phosphate has different fate in liver and skeletal muscle. Now in liver as well as in kidney there is an enzyme present which is known as glucose 6 phosphatase. So, it is just the same one which is present in neo glucogenesis. So, from glucose 6 phosphate there is formation of glucose whereas, importantly you need to remember that this glucose 6 phosphatase is absent in skeletal muscle as well as in adipose tissue. So, even if there is glycogen breakdown in muscle and adipose tissue there is no glucose present apart from that free glucose which is formed by the debranching enzyme.

So, those glucose 6 phosphates actually accumulate inside skeletal muscle and adipose tissue and in skeletal muscle importantly those glucose 6 phosphate are reutilized they are reutilized for production of ATP via entering TCA cycle glycolysis and TCA cycle. So, basically once again to remind skeletal muscle in skeletal muscle glyco genolysis is required for production for provision of energy inside the skeletal muscles to continue its contraction which needs huge amount of ATP. Whereas, in liver liver is the organ which senses that there is fall of glucose in circulation and glucose function in such a way that circulation it can in circulation it can provide glucose by breaking down glycogen. So, this is about glycogenesis and glycogenolysis how the chemical reactions occur. Now, to remind that once again whenever there is fall of blood glucose level glycogen is broken down to maintain the blood glucose level and that function is done by liver.

Now what happens after a meal after 5 hours this blood glucose level tends to fall glycogen breakdown starts, but after 18 hours of fasting actually this liver glycogen content is depleted and then starts fatty acid oxidation where from energy comes and muscle glycogen it acts as a reserve fuel for the muscles own function. So, these are the key points which we have learned from this session that glycogen is stored in muscle and liver as large particle glycogen granules. Then sugar nucleotides UDP glucose it donates glucose residues to the non reducing end of glycogenin. Glycogenin is a protein on which glycogen is formed actually that chain is extended by with the help of glycogen synthase which forms alpha 1 4 glycosidic bond. Then branching is done by branching enzyme branching forms alpha 1 6 glycosidic bond.

Then this glycogen particles begin with an autocatalytic formation of glycosidic bond between glucoses of UDP glucose and glycogenin constant addition followed by addition of several residues to form the primer that can be acted upon by glycogen synthase. So, this is glycogen synthesis. On the contrary in case of glycogen breakdown the main enzyme is glycogen phosphorylase it catalyzes the phosphorylatic cleavage of in the non reducing end of glycogen produces like glucose 1 phosphate. And also in glycogen breakdown there is de branching enzyme phospho glucomutase as well as glucose 6 phosphatase once again to remind the key point that glucose 6 phosphatase it is present in liver for which liver can provide glucose from glucose 6 phosphate whereas, glucose 6 phosphatase is absent in skeletal muscle. So, skeletal muscle cannot provide glucose to circulation rather the glucose 6 phosphate which is formed in skeletal muscle it is utilized for its own contraction.

So, this is all about glycogen synthesis and breakdown. In the next class we will start discussion about how glycogen synthesis and breakdown is regulated ok. Thank you for now these are my references and see you in the next class.