Overview and Integration of Cellular Metabolism

Prof. Aritri Bir

Dr. B.C. Roy Multi-Speciality Medical Research Centre

Indian Institute of Technology Kharagpur

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Lecture 14: Glycogen Metabolism (III)

Hello, we are back with the lecture series overview and integration of cellular metabolism. So, in the previous two classes we have discussed how glycogen is synthesized, how glycogen is broken down glycogenesis and glycogenolysis. Then in the next previous class we have discussed how glycogenolysis or glycogen breakdown is regulated. In this class we will discuss regulation of glycogenesis or formation of glycogen and also the reciprocal regulation of glycogenesis and glycogenolysis. So, to remind once again what is the important enzyme most important enzyme of glycogen synthesis is ye it is glycogen synthase. So, regulation of glycogen synthesis is basically the regulation of glycogen synthase enzyme.

Now, in the previous class we have discussed how an enzyme can be activated following a series of phosphorylation a cascade of enzyme action and that is done through phosphorylation and dephosphorylation. So, this that is an example of covalent modification of enzyme activity and this covalent modification is mostly triggered by some hormones, hormones like glucagon epinephrine. Then again enzymes of glycogen metabolism both for glycogenesis and glycogenolysis can be regulated by some allosteric molecules allosteric regulators. So, let us see how glycogen synthase is regulated.

This is the same type of regulation which we have read already in glycogen phosphorylase regulation. So, once again there are two form of glycogen synthase present inside cell one is glycogen synthase A that is the active form another is glycogen synthase B that is the inactive form. But unlike the glycogen phosphorylase where if you remember glycogen in for glycogen phosphorylase the active form is the phosphorylated form here it is just the opposite. The active form of glycogen synthase is the unphosphorylated or dephosphorylated form and the inactive form is the phosphorylated one. So, basically whenever there is phosphorylation of glycogen synthase so, that is causing inactivation of glycogen synthase.

And if there is activation of glycogen synthase we mean dephosphorylation of glycogen synthase. So, definitely the phosphorylation of glycogen synthase is done by protein kinase the enzyme is kinase here. Now, glycogen synthase is one very important enzyme which can be phosphorylated in different residues. So, basically there are different serine or triene in residue present in glycogen synthase those can be phosphorylated or dephosphorylated on requirement not only that there are at least 11 types of protein kinases which can deliver this activation or I mean phosphorylation of glycogen synthase. Amongst them the important ones are cyclic AMP dependent protein kinase, calmodulin dependent protein kinase and GSK3 glycogen synthase kinase 3.

So, these are the very important 3 protein kinases which regulates glycogen synthase activity and definitely it causes these kinases causes actually deactivation. Now, once again to remind that cyclic AMP dependent protein kinase is activated by epinephrine via cyclic AMP formation cyclic AMP once again to remind you cyclic AMP which has been formed by adenyl cyclase and that cyclic AMP causes activation of cyclic AMP dependent protein kinase. Similarly, calmodulin dependent protein kinase is activated by calcium. Here we will discuss about glycogen synthase kinase induced regulation of glycogen synthase. So, these are all the examples of protein kinase.

So, this protein kinases actually causes deactivation of glycogen synthase whereas, activation is done by the phosphatase causing dephosphorylation. Again there is that inhibitor 1 substrate inhibitor 1 which is activated the activated form is definitely the phosphorylated one. So, this inhibitor 1 is activated with the help of the cyclic AMP dependent protein kinase on activation this inhibitor inhibit phosphatase. So, basically all cyclic AMP dependent protein kinase does is actually inactivation of glycogen synthase. Inactivation means synthesis of glycogen is inhibited not only by forming not only by inactivating the active form even it inactivate the process by which it is activated.

So, basically it inactivates the phosphatase. So, phosphatase when inactivated it cannot form the active glycogen synthase. So, this is how cyclic AMP dependent protein kinase regulates glycogen synthesis rather inhibits glycogen synthesis. Again glucose 6 phosphate is there as an allosteric regulator glucose 6 phosphate it actually inactivates the phosphorylation causing activation of glycogen synthase helping glycogen synthesis and these glucose 6 phosphate is actually formation of this glucose 6 phosphate is actually induced by insulin. Now this is how glycogen synthase is regulated.

So, basically the active one is the dephosphorylated one whereas, the phosphorylated one is the inactive form. Activation is done by protein phosphatase by dephosphorylation and these protein phosphatase is activated with the help of insulin with the help of formation of glucose 6 phosphate glucose 6 phosphate here acts as allosteric activator of

protein phosphatase also glucose can also activate this protein phosphatase and dephosphorylation whereas, hormones like glucagon epinephrine they deactivate this protein phosphatase. Whereas, protein kinases like glycogen synthase kinase 3 they causes phosphorylation of glycogen synthase and actually inactivates it. Now, remember there is another important enzyme mentioned here which is casein kinase 2. Now glycogen synthase kinase requires some priming for its phosphorylation and that priming is done by casein kinase 2.

Now how this priming is happening? So, this is the glycogen synthase kinase molecule this one is the glycogen synthase kinase molecule and this is the glycogen synthase molecule enzyme. Now these are the residues where phosphorylations can be done. Now when glycogen synthase kinase needs to fit over glycogen synthase that is basically that fitting is done over a phosphate residue. So, there is requirement of requirement of a phosphate residue in glycogen synthase molecule which can acts as which can act as anchor for the glycogen synthase. So, here this is this 0 is the serine D 0 then these are the serine residues where actual phosphorylation occurs for inactivation of glycogen synthase.

But before that there is another serine residue which is phosphorylated by casein kinase 2 and over that phosphate residue this glycogen synthase molecule is anchored. And this anchoring is done in such a way that the active side of the enzyme fits over the target serine residue. So, it can phosphorylate the target serine residue. Now you can see on phosphorylation it moves towards the other residues. So, on the next step over these phosphorylated residue see the glycogen synthase kinase will fit will anchor in such a way that the catalytic site will be over the next serine residue and it can phosphorylated.

So, basically what casein kinase 2 is doing is actually phosphorylating a serine residue of glycogen synthase definitely that phosphorylation is not causing deactivation. But what it is causing it is helping in anchoring the GSK 3 over the glycogen synthase. Now in absence of casein kinase 3 what happens glycogen synthase kinase has its own serine residue it when phosphorylated it when phosphorylated it acts as a pseudo substrate which occupies this anchoring part. So, that the GSK 3 is folded upon itself and basically is not able to not able to attach over the target glycogen synthase target not only glycogen synthase it is also phosphorylating other protein other enzymes also. So, it cannot bind with the target enzyme.

So, casein kinase 2 is basically the priming enzyme required for the action of GSK 3. Next we have discussed about phosphoprotein phosphatase. Now phosphoprotein phosphatase everywhere we have seen that it is causing dephosphorylation removing phosphoryl group from all the 3 enzymes which has been phosphorylated by glucagon

and epinephrine as well. So, all the 3 enzymes like phosphorylase kinase, glycogen phosphorylase, glycogen synthase all these 3 enzymes which were phosphorylated by glucagon or epinephrine they are dephosphorylated by one single enzyme that is phosphoprotein phosphatase. And this phosphoprotein phosphatase is regulated by insulin.

Insulin stimulate or rather activate this phosphoprotein phosphatase and causes dephosphorylation of all these 3 enzymes. So, phosphoprotein phosphatase is basically attached to all these 3 enzymes phosphorylase kinase, glycogen phosphorylase and glycogen synthase. These are the 3 enzymes to which phosphoprotein phosphatase is attached via another molecule glycogen targeted protein or GM it is represented as GM. GM basically anchors this phosphoprotein phosphatase with all these 3 enzymes and they are present in the glycogen granule. Remember in the glycogen granule in the very first class of glycogen metabolism .

I told you that in the glycogen granule there is glycogen as well as all the enzymes which are required for glycogen synthesis required for glycogen breakdown as well as those molecules which modulates or influences their function. So, basically this glycogen targeted protein is one such molecule which actually influences the function of these 3 enzyme. This glycogen targeted protein it anchors phosphoprotein phosphatase to all these 3 enzymes. Now, this GM can be phosphorylated in 2 residues. Insulin activates the insulin sensitive kinase it phosphorylates in a single site in the single site of this GM and that causes activation of phosphoprotein phosphatase.

So, insulin basically activates phosphoprotein phosphatase, but when this GM is phosphorylated in both the 2 sites there is such a conformational change that it needs to be dissociated from the glycogen granule. So, basically it is detached from the this dual phosphorylated GM is detached from these 3 enzyme. So, there is the loss there is loss of the anchoring molecule which was actually anchoring phosphoprotein phosphatase. So, phosphoprotein phosphatase is also dissociated from these 3 enzymes. So, epinephrine is actually causing dissociation of phosphoprotein phosphatase.

So, basically it is inactivating phosphoprotein phosphatase. Not only that epinephrine if you remember that epinephrine was activating this inhibitor 1 molecule inhibitor 1 which I told you it is actually inhibitor 1 when activated it causes deactivation of phosphoprotein phosphatase. How it actually binds this released phosphoprotein phosphatase and stops it from reassembly. So, this is how phosphoprotein phosphatase is regulated it is phosphoprotein phosphatase activity is activated by insulin whereas, it is inactivated by epinephrine. Apart from that glucose 6 phosphate is 1 allosteric regulator of this phosphoprotein phosphatase it basically activates glucose 6 phosphatase is an

allosteric activator of phosphoprotein phosphatase.

So, this is how phosphoprotein phosphatase is regulated both in case of glycogen synthesis and glycogen breakdown. Now, we will move on to the coordinated regulation or reciprocal regulation of glycogenesis and glycogenolysis. Now, remember induction of a pathway or repression of a pathway are solely dependent on the body on bodies requirement of energy. When body requires more energy it induces those pathway which causes production of ATP which causes supply of those intermediate which finally, can generate ATP. And when there is requirement of energy when there is requirement of ATP simultaneously those pathway which actually are storing energy those are inhibited.

So, this is a simultaneous phenomena in case of bodies requirement. So, remember that once again that glycogen synthesis occurs when there is excess energy excess supply of glucose and that glucose can be stored. Whereas, glycogen breakdown happens when there is requirement of energy when there is utilization of glucose has already been done then we need to utilize the stored glucose we need to break down glycogen. So, this is this glycogenolysis or glycogen breakdown happens when there is requirement of energy. Now, this is very evident that these 2 pathway cannot be activated in same condition.

So, when body needs energy once again we need to break down glucose. So, there is low glucose in circulation that is sensed by either epinephrine or glucagon. Now, they these hormones activate cyclic AMP forms cyclic AMP that activate cyclic AMP dependent protein kinase. Now, this protein kinase activate phosphorylase kinase by phosphorylation also it inactivates glycogen synthesis by phosphorylation. So, when protein kinase is activated is causes phosphorylation of both the enzyme on phosphorylation phosphorylase is activated and glycogen synthesis deactivated which actually the net result is actually glycogen breakdown.

Similarly, when there is adequate amount of energy adequate amount of glucose in circulation that is sensed by insulin. Insulin acts as different a way to prevent glycogen breakdown also to stimulate glycogen synthesis. How? Insulin activate phosphoprotein phosphatase this phosphoprotein phosphatase this phosphoprotein phosphatase causes dephosphorylation of both the enzymes. Now, on dephosphorylation glycogen synthesis is activated, but glycogen phosphorylase is inactivated. So, the net result is glycogen synthesis and also it stops glycogen the breakdown.

Not only that insulin it activates the enzymes phosphodiesterase. Phosphodiesterase what it does? It converts cyclic AMP to 5 prime AMP. Now, cyclic AMP when it is converted to 5 prime AMP there is deactivation of this protein kinase there is deactivation of this protein kinase cyclic AMP dependent protein kinase. Now, when

cyclic AMP dependent protein kinase is deactivated the activation of phosphorylase is inhibited deactivation of glycogen synthesis is inhibited. So, basically signals like epinephrine glucagon it simultaneously inhibits glycogen synthesis and induces glycogen breakdown.

Whereas, signals hormones like insulin it induces glycogen synthesis, but prevents glycogen breakdown. So, this is how reciprocal regulation of glycogen metabolism occurs with respect to bodies requirement of energy. So, what we have learnt from this session that glycogen synthesis is inactivated by phosphorylation and that phosphorylation is catalyzed by different protein kinases 11 different protein kinases amongst them glycogen synthesis kinase 3 is important one. Now, this glycogen synthesis kinase 3 is blocked by insulin, but insulin activates phosphoprotein phosphatase that phosphoprotein phosphatase reverses the inhibition by dephosphorylating glycogen synthesis. And then regulation of glycogen metabolism is affected by the balance between synthesis and breakdown which is actually dependent on bodies requirement of energy.

So, this is about glycogen synthesis glycogen breakdown regulation of both of this pathway and how they are coordinated with each other. These are my references. Thank you. See you in next session.