JOHN ESSIGMANN: Let's go now to storyboard 36, starting with panel A, Regulation of Metabolism. So far in 5.07, we have looked at metabolic pathways from the perspective of the cell in organelles within the cell. Using physiological scenarios, I've tried to show you how pathways within the cell respond to a change in the environment, for example, by running away from a stressor, such as a dog or dealing with the problems of starvation or diabetes.

We have looked a little bit at the ways that individual steps and pathways are regulated. We have not, however, looked at the ways that individual pathways and individual organs coordinate their respective activities in order to accommodate the needs of the entire organism. Coordinated pathway networking is the focus of this lecture.

Let's turn to panel B. I'm going to start out by talking a little bit about the seven pathways that we have studied in detail in 5.07 and look at how they're regulated. As I've said before, typically pathways are regulated at their rate-determining steps, that is, the step at which you'll find an enzyme that has a large free-energy change associated with the conversion of substrates to products.

In the first pathway we studied, glycolysis, there are three irreversible steps, specifically the glucokinase/hexokinase step; secondly, the phosphofructokinase-1 step; and thirdly, the last step, pyruvate kinase. These are all sites of pathway regulation.

Our second pathway, the tricarboxylic acid cycle, or Krebs cycle, was regulated at every step at which NADH is produced, that is, citrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase. While pyruvate dehydrogenase is not formally part of the TCA cycle, I'll point out here that it is also regulated by NADH.

In all four cases, NADH feedback inhibits the enzymes that produce it. Under conditions of excessive TCA cycle activity, you'll find that NADH levels will drop, and accordingly NAD+ levels will increase. The reduction in NADH will result in activation of the pathway. In other words, the disappearance of NADH results in the uninhibition of the pathway.

Our third pathway, gluconeogenesis, is regulated at the pyruvate carboxylase step at the fructose 1,6-bisphosphatase step and at the glycogen synthase/glycogen phosphorylase steps. We're going to be looking at this pathway in some detail in a little while.

Our fourth pathway, fatty acid catabolism, is regulated at the CAT, or Carnitine Acyltransferase step, which is inhibited by malonyl coenzyme A. Malonyl CoA is one of the key precursors for fatty acid biosynthesis. It makes sense that the concentration of malonyl coenzyme A, if high, would inhibit the uptake of fatty acids into the mitochondrial matrix.

Keep in mind that uptake into the matrix is the job of CAT1. Shutting down CAT1 by the high concentration of malonyl CoA prevents entry of fatty acids into the mitochondrial matrix, where they otherwise would be subjected to beta-oxidation. By turning off CAT1, malonyl coenzyme A prevents the futile cycle of simultaneous fatty acid degradation and biosynthesis.

The fifth pathway is fatty acid biosynthesis. Acetyl-CoA Carboxylase, or ACC, is the enzyme that makes malonyl coenzyme A out of its precursor, acetyl coenzyme A. This enzyme, ACC, is activated by insulin. As we've seen before, insulin detects the fed state in the organism. Hence, following a meal, insulin levels rise, and that's the signal that tells the cells of the body to take up nutrients.

That's just one example. After a meal, glucose levels will rise in the blood. Insulin will be released and drive the glucose into the cell. The cell will then activate pathways by which the glucose is converted to acetyl-CoA. Then the acetyl-CoA will be converted into fatty acids, and then ultimately, into triacylglycerides for energy storage.

Our sixth regulated pathway is the pentose phosphate pathway. Glucose 6-phosphate dehydrogenase is the first step in the pathway. And as we often see, an early or committed step is where regulation happens. One of the products of the pentose phosphate pathway is NADPH. If the cell has used a lot of NADPH, for example for biosynthesis, its levels will drop. Coordinately, there will be an increase in NADP+.

In the case of glucose 6-phosphate dehydrogenase, we find that NADP+, which is the product of excessive reductive biosynthesis, as well as other activities, such as combating oxidative stress, activates the dehydrogenase in order to enable the synthesis of additional NADPH in order to sustain biosynthesis.

The last pathway, the seventh, is electron transport and oxidative phosphorylation. This is our

most robust pathway for the production of ATP. When there's a lot of demand for ATP, ADP levels will rise in the cell. And it's ultimately the level of ADP that regulates electron transport in oxidative phosphorylation. More about that in a few minutes.

Let's now look at panel C. Organs communicate with one another by the nervous system, of course, but also by hormones, small molecules that are secreted by one organ that will have an effect at one or more organs distal to the first organ. Changes in our environment are detected by the brain with input from our sensory organs.

Our internal organs, such as the liver, pancreas, kidneys, adrenal glands, and muscles will detect signals, either independently of the brain or after an instruction set is received from the brain. The resulting signal network will allow the entire organism to be able to adapt to the new environment, be it one of stress, for example, being chased by a dog, or one of, for example, hunger.

We'll talk later about the adrenal glands, which are going to respond to signals that come in from sensory organs that tell our muscles to start running and to tell the liver to start to provide the muscles with the glucose they need in order to sustain running.

Later we'll be looking in some detail at the adrenal-produced hormone epinephrine, also called adrenaline. Adrenaline will have a profound impact, both in the muscles and in the liver, to allow these organs to do their respective jobs.

The pancreas is a very important organ in that it provides exocrine functions that help with digestion and endocrine functions that enable us to regulate or balance fuel metabolism. The alpha cells of the pancreas produce glucagon.

The alpha cells sense hunger. They secrete glucagon into the blood, which travels to organs that represent our fuel depots. And fuel from those depots, for example, fatty acids and glucose, will then be supplied to other tissues of the body that are in need of nutrition. The beta cells of the pancreas sense what we call the fed state, and they produce insulin. Insulin instructs the various organs of the body to take up fuel in the wake of us having eaten a meal.

Now let's look at panel D. There are three general paradigms by which pathways are regulated. The three hormones that I've just mentioned typically will cause the activation of a kinase that will phosphorylate a target protein, resulting in either increased or decreased activity of that protein. We call this hormonal or, more properly, covalent control, because

there will be a covalent modification of a protein that will be responsible for pathway regulation.

The second major paradigm by which pathways are controlled is allosteric regulation. Earlier in 5.07, JoAnne Stubbe showed us how hemoglobin, the molecule that carries oxygen in the blood, is controlled by bisphosphoglycerate and protons, which act as allosteric effectors. Similarly, other small molecule effectors will control the major pathways of metabolism. We're going to be looking at phosphofructokinase-1 as our prime example.

The third strategy of regulation is what I call "acceptor control." This is the way that electron transport and oxidative phosphorylation are regulated. To the right side of panel D is an abbreviated metabolic pathway that I'm going to use to describe each of these three paradigms.

At the upper left is a box that contains glycogen synthase and glycogen phosphorylase. Earlier in 5.07, I told you how phosphorylation of a specific C-ring residue on glycogen phosphorylase results in a dramatic increase in the activity of that enzyme.

A little later, we'll see that covalent modification, again, by serine phosphorylation of glycogen synthase, results in a decrease in activity of that enzyme. Hence, covalent modification of these two proteins enables, in one case, activation of the enzyme and, in the other case, inhibition of the enzyme. This reciprocal control prevents futile cycling.

Now let's look at the box in the center of this abbreviated metabolic pathway. The glycolytic enzyme, PFK-1, Phosphofructokinase-1, converts fructose 6-phosphate to fructose 1,6-bisphosphate. We're going to see that a small molecule derivative of fructose 6-phosphate, specifically fructose 2,6-bisphosphate, will act as a powerful allosteric stimulator of PFK-1.

I'll also point out that AMP, Adenosine Monophosphate, will also stimulate this enzyme. I'll also point out here that PFK-1 is a tetramer. Oftentimes, as JoAnne taught us, proteins that are multimers are the ones that are subject to allosteric regulation.

Our third paradigm of regulation is accepter control, shown in the box at the bottom of panel D. During periods of intense physical activity, ATP is consumed and converted to ADP, and NADH is converted to NAD+. Rising levels of ADP in the mitochondrial matrix activate the proton-translocating ATP synathase. As more protons flow through the synthase, more ATP is made.

They call this accepter control, because the regulatory molecule is ADP, which is the, quote

unquote, "acceptor of phosphate" in the synthesis of ATP. Because we covered accepter control in some detail in the lecture on electron transport and oxidative phosphorylation, I'm going to leave that topic for now and focus on covalent control and allosteric control.

Let's turn now to storyboard 37, starting with panel A. With regard to the paradigm of covalent control, I'm going to focus on the pair of enzymes, glycogen synthase and glycogen phosphorylase, which reciprocally regulate glycogen synthesis and glycogenolysis.

Let's consider a scenario in which there's some kind of stressor. The muscles have to be activated in order to be able to deal with the stress, and the liver has to be able to provide the resources to the muscles that will allow the muscles to continue intense physical activity.

Now let's look at panel B. In our scenario, you've just seen something frightening. Your brain then sends an electrical signal to the adrenal glands, which then send a chemical signal, specifically adrenaline, to the liver and to the muscles.

At the top part of this response scenario, both the liver and muscles are going to be responding in a very similar way. However, at the bottom part of the response scenario, the liver and muscles are going to be activating very different pathways. Specifically, we're going to see that muscles will strongly activate glycolytic pathways in order to enable the production of ATP to keep the muscles running.

The liver, by contrast, is going to be activating pathways that are more like those of gluconeogenesis, that is, spilling out fuel from the liver to provide the muscles with the energy-rich resources that it needs to keep us running away from our stressor. Adrenaline, or epinephrine, travels from the adrenal glands through the blood. It takes only a second or two for this to happen. It's received by the liver and the muscles at the beta-adrenergic receptor.

The blood concentration of epinephrine is very low, something of the order of 10 to the minus 10 molar at this point. There's going to be a very substantial signal amplification as we move ahead. Keep in mind for later that the initial triggering signal is in the 10 to the minus 10 molar range.

The arrival of epinephrine at the receptor results in structural changes in the transmembrane domain of the beta-adrenergic receptor. The signal is received by a heterotrimeric G protein, shown as the circle with alpha, beta, and gamma subunits. This G protein, in its inactive state, has a bound molecule of GDP, that is, guanosine diphosphate.

Upon receipt of the signal from the beta-adrenergic receptor, the heterotrimeric G protein ejects the beta and gamma subunits, and the GDP molecule, which is non-covalently bound, is released. The GDP is replaced by a GTP, guanosine triphosphate. This replacement results in the formation of the alpha subunit with a non-covalently bound GTP. This is the active form of the enzyme.

It translocates along the inner surface of the membrane until it encounters AC, or adenyl cyclase. The GTP-bound G protein activates adenyl cyclase. The activated AC dynamically starts converting ATP, which is very abundant in the cell, into cyclic AMP. We call cyclic AMP the second messenger.

In our scenario, the first messenger is epinephrine, which interacted with the beta-adrenergic receptor. The second messenger is cyclic AMP, which is produced by the activation of adenyl cyclase, which is asymmetrically associated with the inner surface of the cell's membrane.

Let's turn now to panel C. In the upper left of panel C, you'll see a box. This box depicts the chemical mechanism leading to the production of cyclic AMP. Let's now look at the main part of the panel. In a very short period of time, a matter of seconds, the concentration of cyclic AMP within the cell goes from about 1 micromolar up to about 5 micromolar.

So the presence of epinephrine at the 10 to the minus 10 molar concentration outside the cell results in a perturbation of cyclic AMP concentrations inside the cell, bringing cyclic AMP concentration to about 10 to the minus 6 molar. This is a very substantial increase in signal, which an engineer would call gain.

The increasing cyclic AMP concentration is going to activate a kinase cascade. And the initial kinase that's going to be activated is called Protein Kinase A, or PKA, which is represented symbolically as a C with a circle around it in my drawing.

In its inactive state, protein kinase A is in a complex involving two molecules of itself and two molecules of a regulatory protein, which I've indicated as an R in the middle of a circle. Cyclic AMP forms a tight complex with R.

This basically causes R to dissociate from the active subunit C, that is, the catalytic portion of protein kinase A. The catalytic portion of protein kinase A is now free to act as a kinase to phosphorylate the next kinase in the cascade, which is called SPK, or Synthase Phosphorylase

Kinase.

A serine residue on SPK is phosphorylated, and that event converts this kinase into its active form. I'll also point out that one of the subunits, the delta subunit of SPK, is the calcium-binding protein calmodulin, which gives a second level of regulation to this enzyme. Specifically, this enzyme is regulated not only by the concentration of cyclic AMP, but also by the levels of calcium within the cell.

The activated SPK, or synthase phosphorylase kinase, is now going to phosphorylate two other proteins, glycogen phosphorylase and glycogen synthase. As I mentioned earlier, phosphorylation of glycogen phosphorylase results in the enzyme becoming more active. That is, it starts breaking down glycogen by phosphorolysis to produce glucose 1-phosphate, which will then be available for further metabolic processing.

In the muscle, glucose 1-phosphate will be converted by phosphoglucomutase into glucose 6-phosphate, which will then be a substrate to initiate glycolysis, with the ultimate generation of lots of ATP for the muscle.

In the liver, phosphoglucomutase will convert glucose 1-phosphate into glucose 6-phosphate, but in this case, gluconeogenesis will be activated. Glucose 6-phosphatase will remove the phosphate from glucose 6-phosphate, converting it to glucose. The glucose will then be secreted from the liver, go out into the blood, and then go to the muscle to help the muscle carry out glycolysis.

Now let's look at the other target of SPK, synthase phosphorylase kinase, specifically, glycogen synthase. In this case, glycogen synthase phosphorylation results in a less active protein, and hence, glycogen synthesis will cease. This makes sense, because a cell under stress would not want to be making glycogen. It wants to be using energy and not storing fuel.

Let's step back and look at the big picture at this point. The interaction of a hormone resulted in the covalent modification of proteins. One of those phosphorylated proteins, glycogen phosphorylase, triggered glycogen breakdown. Phosphorylation of a second protein, glycogen synthase, turned it off. Turning off glycogen synthase helped us avoid the otherwise futile simultaneous synthesis and breakdown of glycogen.

So overall, this is an example of a hormone causing covalent modification of proteins in such a way that it altered the activity of those proteins in a manner that made sense given the

physiological challenges to the organism.

Next, let's turn to storyboard 38, panel A. Our next regulatory paradigm will be the use of allosteric effectors to regulate a pathway. As before, I'm going to use the physiological scenario of stress. But in this case, I'm going to show how stress will cause the production of small-molecule allosteric effectors that will activate glycolysis in the muscle and activate gluconeogenesis in the liver.

Our focal point is going to be PFK-1, phosphofructokinase-1, of glycolysis. Of central importance is going to be a small molecule, fructose 2,6-bisphosphate, which we'll see is going to be a very powerful allosteric stimulant of PFK-1.

Fructose 2,6-bisphosphate is made by the enzyme PFK-2, phosphofructokinase-2. Let's start out by looking at the very short biochemical pathway shown in panel A. We see glucose converted by hexokinase or glucokinase to glucose 6-phosphate and then some equilibrium steps up until we get fructose 6-phosphate.

Ordinarily, we think of fructose 6-phosphate as continuing in the glycolytic pathway, but let's not think of it that way right now. The chemical structure of fructose 6-phosphate is shown slightly to the right. Note that fructose 6-phosphate has a phosphate on the 6-hydroxyl group, and that the 1-hydroxyl functionality has only a hydrogen.

This is the alpha anomer of fructose, as evidenced by the fact that the hydroxyl group on carbon-2, the anomeric position, is down, or under the furanose ring. With a little bit of electron pushing, you can change the stereochemistry at the 2-carbon such that the hydroxyl group would be up, or in the beta configuration.

In the beta configuration, the hydroxymethyl group of fructose 6-phosphate, which includes its 1-carbon, would be down. The beta and alpha-anomers of fructose 6-phosphate are in equilibrium. That is, they both exist at the same time.

The kinase, phosphofructokinase-2, catches the beta anomer of fructose 6-phosphate and phosphorylates it, producing the molecule at the lower right of this panel. That's the actual structure of fructose 2,6-bisphosphate. This is the molecule that's going to serve as the allosteric effector of the glycolysis pathway.

The PFK-2, or phosphofructokinase-2 enzyme, is shown to the left. It's a complex enzyme having lots of different functionalities. The hatched circle within the larger circle at the top

represents the phosphofructokinase domain, which converts fructose 6-phosphate to fructose 2,6-bisphosphate. That is the structure at the lower right.

The hatched domain at the bottom is the fructose bisphosphatase domain. This is an unusual enzyme. In the top domain, it acts as a kinase, in the bottom domain, acts as a phosphatase.

PFK-2 has two hydroxylated amino acids, one at about 3 o'clock as drawn and the other at about 6 o'clock. When the hydroxyl group at the bottom is present as a pure, unmodified hydroxyl group, the protein acts as a kinase. When the 6 o'clock domain is phosphorylated, the enzyme acts as a phosphatase.

Protein kinase A, or PKA, from the previous storyboard, where we talked about hormonal regulation, is the kinase that phosphorylates the hydroxyl group at 6 o'clock on the protein. As we'll see later, the hydroxyl group at 3 o'clock is targeted by a kinase called AMP kinase in the muscle.

Before we go on, I want you to look carefully at the structure of fructose 2,6-bisphosphate at the bottom right of panel A. Compare that structure with the structure of fructose 1,6-bisphosphate at the right in panel B. If you squint and look at these two molecules, you'll see that they look remarkably alike.

In both cases, the phosphate group is above the plane of the furanose sugar. However, in the case of fructose 2,6-bisphosphate, the phosphate is on the 2-carbon, whereas with fructose 1,6-bisphosphate, the phosphate is on the 1-carbon. The way these molecules look will become important in a few minutes.

Now let's take a look at the pathway as shown in panel B. Panel B reflects the liver in its normal, that is, non-stress state. So this is just the liver doing everyday liver business. Glucokinase of the liver is converting glucose to glucose 6-phosphate. The alpha anomer of fructose 6-phosphate is produced.

Most of the fructose 6-phosphate is converted to fructose 1,6-bisphosphate. In the liver cell at this time, there's probably some low level of glycolytic activity going on. However, because of natural anomerization, some of the alpha-fructose 6-phosphate is converted to its beta-anomer.

Phosphofructokinase-2, or PFK-2, is shown to the lower left, and it's active. Note that neither

of its hydroxyl groups, at this point, are phosphorylated. And its kinase site will be converting the beta-fructose 6-phosphate anomer to its phosphorylated form, that is, beta-fructose 2,6-bisphosphate, which has the structure shown at the bottom right of the previous panel.

Fructose 2,6-bisphosphate is a positive allosteric effector of phosphofructokinase-1. So it facilitates the glycolytic pathway that is enabling net flux from left to right in the pathway as shown.

In addition to stimulating glycolysis, fructose 2,6-bisphosphate strongly inhibits gluconeogenesis. It does this by binding at the active site of fructose 1,6-bisphosphatase, the gluconeogenic enzyme, clogging up the active site, and thus disabling the gluconeogenic pathway.

The reason that it's such a good inhibitor of gluconeogenesis stems from an examination, once again, of the structures of fructose 2,6-bisphosphate in the bottom right of the previous panel and fructose 1,6-bisphosphate shown to the right on this panel.

Keep in mind that fructose 1,6-bisphosphate, while it's the product in glycolysis, is the substrate for the gluconeogenic reaction. If the active site of the fructose 1,6-bisphosphatase is clogged by fructose 2,6-bisphosphate, then it's not going to be able to process the fructose 1,6-bisphosphate in the gluconeogenic direction. Hence, gluconeogenesis is strongly inhibited.

All of the above shows us that fructose 2,6-bisphosphate is really important. It stimulates the forward direction in the liver that is causing glycolysis to have a net flux from left to right. And in addition, it strongly inhibits the back reaction, that is, the reaction in the gluconeogenic direction.

Turn at this point to panel C. Now let's ramp up the scenario and think about a situation in which you're being chased by a dog. You want to be able to generate glucose in the liver and then export that glucose to the muscles so that you can run away from your foe. This is a situation in which you would like to have your liver stop doing glycolysis. You want the liver to strongly turn to gluconeogenesis in order to manufacture glucose for the muscle.

At this point, refer back to the storyboard that dealt with covalent control, where protein kinase A was activated. Recall the part of the lecture when I talked about covalent control, and we were talking about the glycogen phosphorylase step in the liver.

In the liver, we generated first glucose 1-phosphate and then glucose 6-phosphate. And then

the phosphate was lopped off the glucose 6-phosphate to produce glucose that went out into the blood.

In the present case, we're looking at a step that's further down in the gluconeogenesis pathway. Specifically, we want to activate the fructose 1,6-bisphosphatase in order to push even more carbohydrate toward the production of glucose.

So in panel C, we see stress inducing the cyclic AMP cascade that results in activation of protein kinase A. And protein kinase A is going to phosphorylate the southernmost, that is, 6 o'clock domain, on the PFK-2, or phosphofructokinase-2 protein.

As I indicated earlier, phosphorylation of the 6 o'clock domain results in conversion of phosphofructokinase-2 from a kinase into a phosphatase. The phosphatase produced from PFK-2 will act upon the pool of fructose 2,6-bisphosphate and convert that pool to fructose 6-phosphate. That is, the 2-phosphate will be lopped off of the fructose 2,6-bisphosphate molecule.

By doing this biochemistry in the liver, we've done two things. First, we destroyed the fructose 2,6-bisphosphate pool. Hence, this molecule is no longer available to act as an allosteric stimulator of PFK-1.

Secondly, removing fructose 2,6-bisphosphate from the pool has resulted in removal of the active-site inhibitor of fructose 1,6-bisphosphatase. This enzyme, therefore, becomes active and is able to push the net flux of carbon from right to left in the direction of gluconeogenesis, producing glucose that will then spill out into the blood.

Please turn now to panel D. We just saw that the liver, post-stress, produces glucose. Now we're going to take a look at the muscle, which, of course, is going to be using that glucose. In response to the stress state, the muscle is going to activate an enzyme called the AMP-dependent protein kinase, or AMP kinase, also known as AMPK.

AMPK activates metabolic pathways that generate ATP. The 3 o'clock phosphorylated PFK-2 proves to be an exceptionally competent enzyme for converting fructose 6-phosphate into fructose 2,6-bisphosphate. This increases further the concentration of fructose 2,6-bisphosphate in the muscle cytoplasmic pool.

And keep in mind that fructose 2,6-bisphosphate itself is a powerful allosteric stimulator of

glycolysis by its effect on PFK-1. So in the muscle cell, we're able to achieve extraordinarily high concentrations of fructose 2,6-bisphosphate, thus favoring glycolysis.

Let's turn now to storyboard 39. Let's start with panel A. The way that AMP kinase stimulates glycolysis in the muscle post-stress is illustrated in this abbreviated metabolic pathway. Starting at the lower left, the stressor has created the cyclic AMP cascade that activates AMP kinase.

AMP kinase phosphorylates the 3 o'clock domain on PFK-2, converting it to its phosphorylated derivative that shows powerful kinase activity to convert fructose 6-phosphate into fructose 2,6-bisphosphate. This enhanced pool of fructose 2,6-bisphosphate will now act as a powerful allosteric stimulator of PFK-1 to favor glycolysis.

I want to point out that muscles do not do gluconeogenesis. Only the liver and renal cortex do this pathway. So muscles do not have fructose 1,6-bisphosphatase, the gluconeogenic enzyme. Accordingly, in muscles we don't have to worry about gluconeogenesis being turned on to some extent and thus dampening the glycolytic effect in the muscle that's needed in order for the muscle to generate the ATP needed to outrun your foe.

On this panel, we also see that there are several other effectors that influence the activity of PFK-1. One is citrate. Another is ATP. Another one is AMP, or Adenosine Monophosphate. I want to say a couple of words about AMP in this regard.

Let's look at panel B. AMP is not as powerful an allosteric effector on PFK-1 as is fructose 2,6-bisphosphate. But we know a lot about its activity as an allosteric effector because it's been studied quite thoroughly.

PFK-1 is a tetramer, and its activity is regulated by cooperativity. This graph shows the activity of PFK-1 as a function of the concentration of one of its substrates, fructose 6-phosphate. When there's no ATP present, which is not a realistic situation, you see the regulatory pattern following that of a rectangular hyperbola. That's scenario A.

Scenario B shows what would happen to the activity of the enzyme when ATP is present at a concentration of about 1 millimolar, which is quite realistic, and what you see is suppressed activity. When the heterotropic allosteric effector AMP is added, you see the curve shift to the left. That is, you get enhanced activity at a given substrate concentration. My guess is that fructose 2,6-bisphosphate would push the curve even further to the left.

Let's now look at panel C. I think it's useful to use AMP to help us construct a model for what fructose 2,6-bisphosphate might be doing as an allosteric stimulator of the PFK-1 enzyme. The equilibrium diagram that I've drawn shows the relationship between the relaxed, that is, more active state of the PFK-1 tetramer, and the tense, that is, more inactive state of the enzyme.

When ATP is abundant within a cell, it binds more strongly to the tense state, and hence, ATP inactivates PFK-1. This makes sense, because if ATP is abundant, you do not want to be doing glycolysis to make even more ATP.

However, when the ATP pool of a cell is challenged by doing heavy work or biosynthesis, the AMP is going to bind more tightly to the R state of PFK-1. And that's going to help convert the enzyme into its more active state.

That's a little snapshot of how a small molecule, in this case, AMP or perhaps fructose 2,6-bisphosphate can dramatically regulate the activity of an enzyme at a specific step in metabolism.