Regulation of cellular respiration

How cellular respiration can be sped up or slowed down. Key enzymes and feedback inhibition.

Introduction

You can sometimes have too much of a good thing. For instance, consider ice cream sandwiches. Maybe you really like ice cream sandwiches and buy a bunch of them at the store. If you're very hungry, that might be a good choice: you can eat them all quickly, before they melt. If you're only a little hungry, though, that might be a bad choice: most of the sandwiches will melt uneaten, at which point you will have wasted some money.

Cells face a related problem when they break down fuels, such as glucose, to produce ATP. If the cell's supply of ATP is low, it would do well to break down glucose as quickly as possible, replenishing the ATP it needs to "keep the lights on." If the supply of ATP is high, on the other hand, it might not be such a good idea to oxidize glucose at top speed. ATP is an unstable molecule, and if it sits around in the cell too long, it's likely to spontaneously hydrolyse back to ADP. This is like the case of the melted ice cream sandwich: the cell has spent glucose to make ATP, and that ATP ends up going to waste.

It's important for a cell to carefully match the activity of its fuel breakdown (pathways to its energy needs at a given moment. Here, we'll see how cells turn cellular respiration pathways "up" or "down" in response to ATP levels and other metabolic signals.

Allosteric enzymes and pathway control

How is the activity of a pathway controlled? In many cases, pathways are regulated through enzymes that catalyse individual steps of the pathway. If the enzyme for a particular step is active, that step can take place quickly, but if the enzyme is inactive, the step will happen slowly or not at all. Thus, if a cell wants to control the activity of a metabolic pathway, it needs to regulate the activity of one or more of the enzymes in that pathway.

The primary target for regulation a biochemical pathway is often the enzyme that catalyses the pathway's first **committed step** (that is, the first step that is not readily reversible). The concept of a committed step can get a little complicated when there are many intersecting metabolic pathways, as in cellular respiration, but this is still a useful idea to keep in mind.

How are the enzymes that control metabolic pathways regulated? A number cellular respiration enzymes are controlled by the binding of regulatory molecules at one or more allosteric sites. (An **allosteric site** is just a regulatory site other than the active site.) Binding of a regulator to the allosteric site of an enzyme changes its structure, making it more or less active.

The molecules that bind cellular respiration enzymes act as signals, giving the enzyme information about the cell's energy state. ATP, ADP, and NADH are examples of molecules that regulate cellular respiration enzymes. ATP, for instance, is a "stop" signal: high levels mean that the cell has enough ATP and does not need to make more through cellular respiration. This is a case of **feedback inhibition**, in which a product "feeds back" to shut down its pathway.

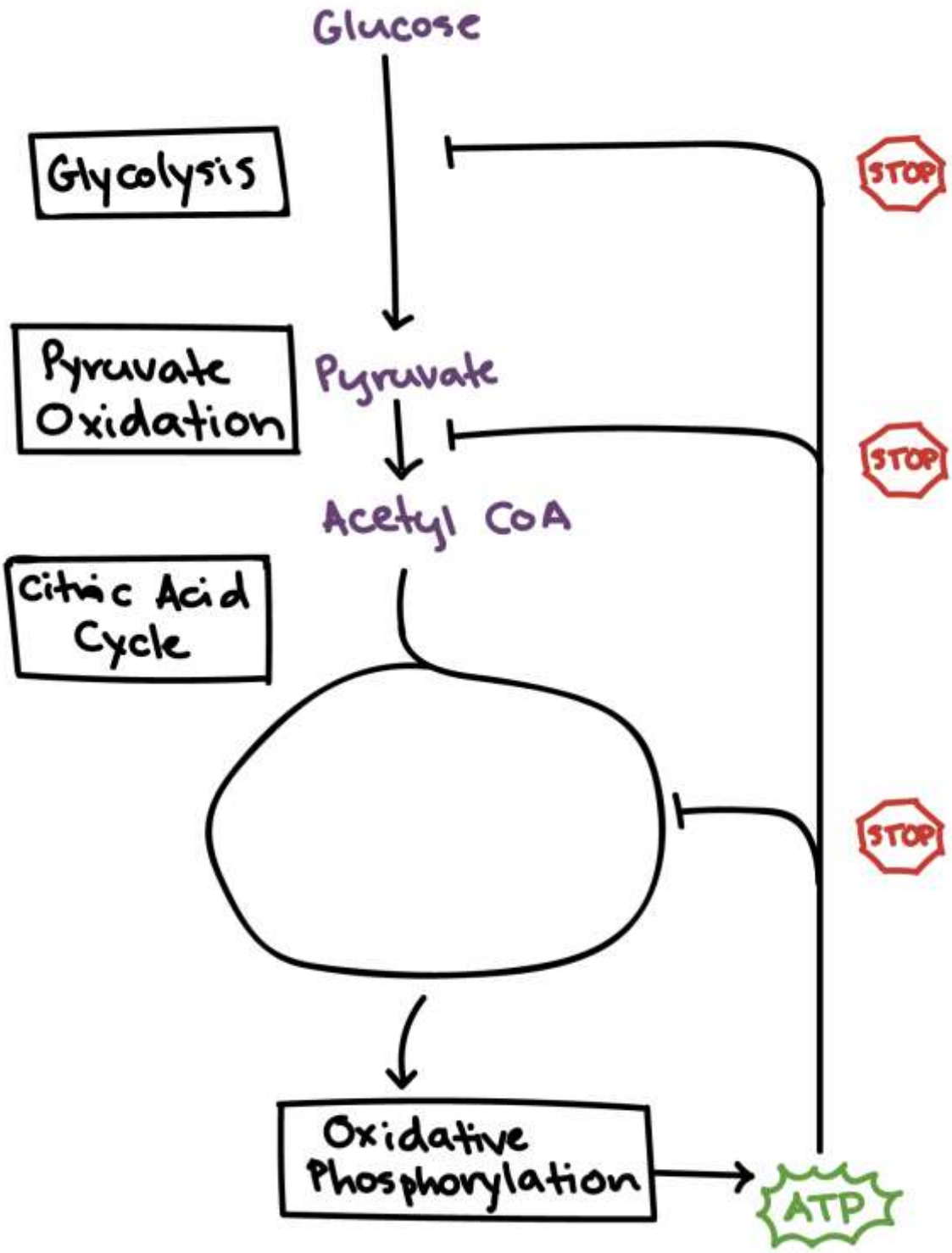

Diagram showing feedback inhibition of glycolysis, pyruvate oxidation, and the TCA cycle by the end product of cellular respiration, ATP.

Regulation of glycolysis

Several steps in glycolysis are regulated, but the most important control point is the third step of the pathway, which is catalysed by an enzyme called **phosphofructokinase** (**PFK**). This

reaction is the first committed step, making PFK a central target for regulation of the glycolysis pathway as a whole.

PFK is regulated by ATP, an ADP derivative called AMP, and citrate, as well as some other molecules we won't discuss here.

- **ATP.** ATP is a negative regulator of PFK, which makes sense: if there is already plenty of ATP in the cell, glycolysis does not need to make more.
- **AMP.** Adenosine monophosphate (AMP) is a positive regulator of PFK. When a cell is very low on ATP, it will start squeezing more ATP out of ADP molecules by converting them to ATP and AMP (ADP + AMP). High levels of AMP mean that the cell is starved for energy, and that glycolysis must run quickly to replenish ATP[2].
- **Citrate.** Citrate, the first product of the citric acid cycle, can also inhibit PFK. If citrate builds up, this is a sign that glycolysis can slow down, because the citric acid cycle is backed up and doesn’t need more fuel.

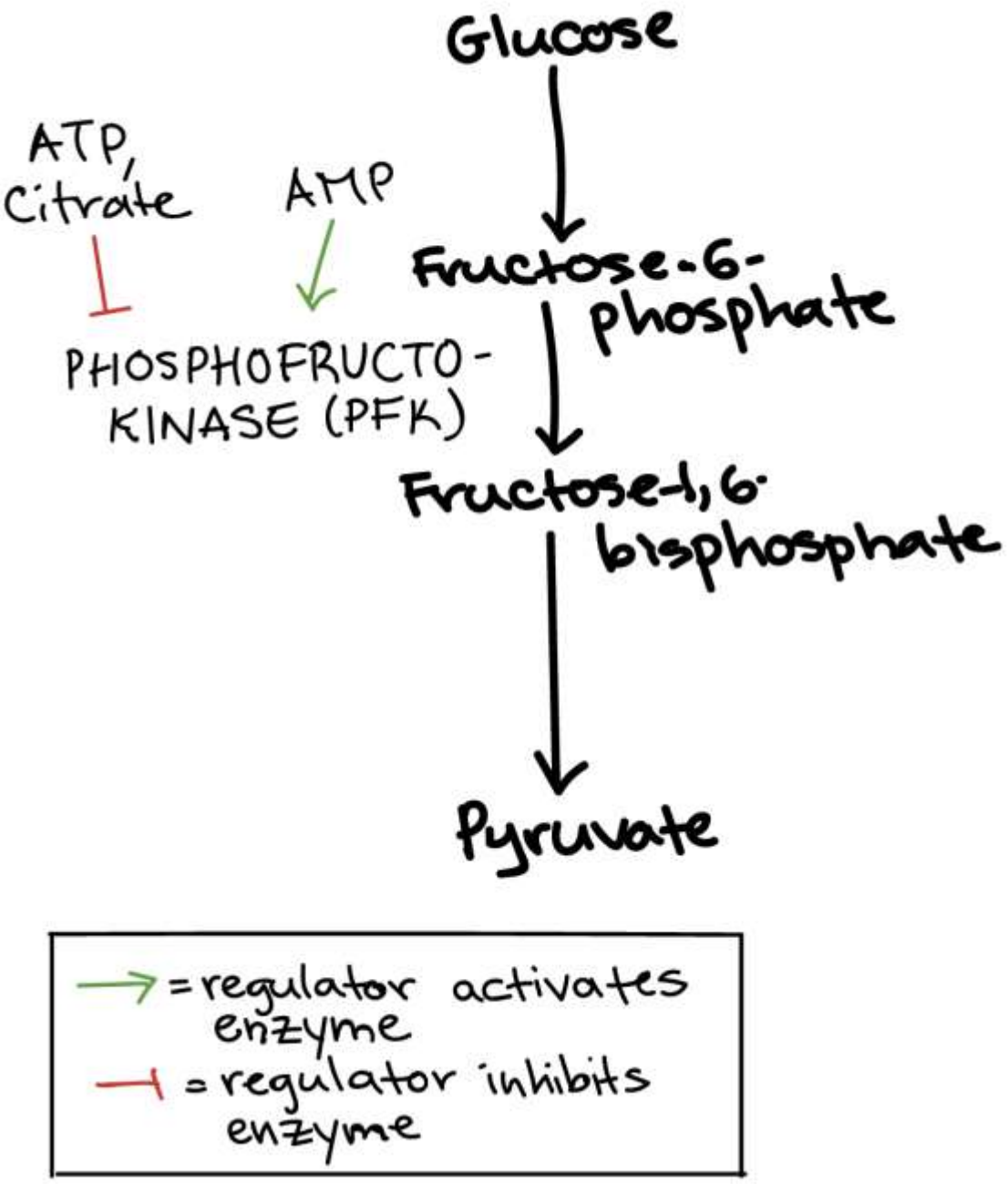

Diagram showing regulation of glycolysis via the enzyme phosphofructokinase (PFK). PFK catalyses the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate in glycolysis. PFK is inhibited by ATP and citrate and positively regulated by AMP.

Pyruvate oxidation

The next key control point comes after glycolysis, when pyruvate is converted to acetyl CoA. This conversion step is irreversible in many organisms and controls how much acetyl CoA "fuel" enters the citric acid cycle. The enzyme that catalyses the conversion reaction is called pyruvate dehydrogenase.

- ATP and NADH make this enzyme less active, while ADP makes it more active. So, more acetyl CoA is made when energy stores are low.

- Pyruvate dehydrogenase is also activated by its substrate, pyruvate, and inhibited by its product, acetyl CoA. This ensures that acetyl CoA is made only when it's needed (and when there's plenty of pyruvate available)[4].

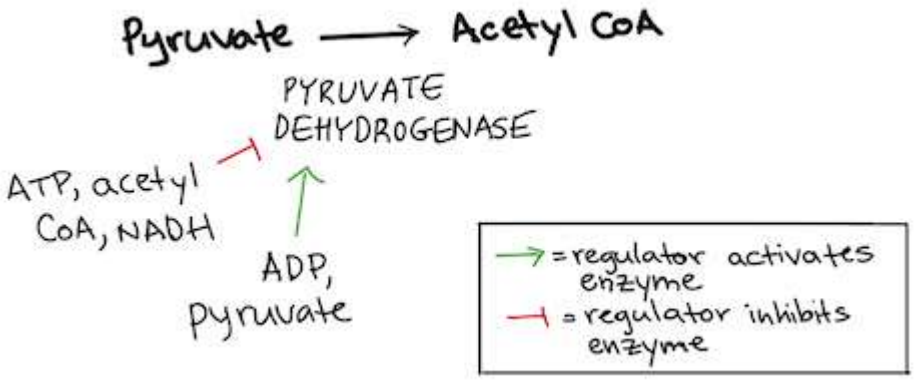

Diagram of the regulation of pyruvate oxidation. The enzyme pyruvate dehydrogenase catalyses the conversion of pyruvate to acetyl CoA. ATP, acetyl CoA, and NADH negatively regulate (inhibit) pyruvate dehydrogenase, while ADP and pyruvate

Citric acid cycle

Entry into the citric acid cycle is largely controlled through pyruvate dehydrogenase (above), the enzyme that produces acetyl CoA. However, there are two additional steps in the cycle that are subject to regulation. These are the two steps in which carbon dioxide molecules are released, and also the steps at which the first two NADH molecules of the cycle are produced.

- **Isocitrate dehydrogenase** controls the first of these two steps, turning a six-carbon molecule into a five-carbon molecule. This enzyme is inhibited by ATP and NADH, but activated by ADP.
- **α-Ketoglutarate dehydrogenase** controls the second of these two steps, turning the five-carbon compound from the previous step into a four-carbon compound bound to CoA (succinyl CoA). This enzyme is inhibited by ATP, NADH, and several other molecules, including succinyl CoA itself.

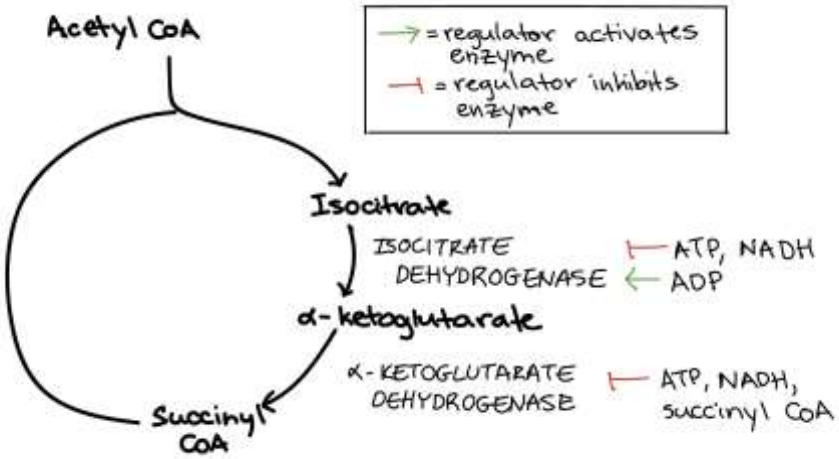

Diagram showing regulation of the citric acid cycle. The conversion of isocitrate to α-ketoglutarate is catalysed by the enzyme isocitrate dehydrogenase, while the conversion of α-ketoglutarate to succinyl CoA is catalysed by the enzyme α-ketoglutarate dehydrogenase.

Isocitrate dehydrogenase is inhibited by ATP and NADH and positively regulated by ADP.
α-Ketoglutarate dehydrogenase is inhibited by ATP, NADH, and succinyl CoA.

Putting it all together

There are lots of other regulatory mechanisms for cellular respiration besides the ones we've discussed here. For instance, the speed of the electron transport chain is regulated by levels of ADP and ATP, and many other enzymes are subject to regulation. However, these examples give you a feel for the kind of logic and strategies cells use to regulate metabolic processes. At each stage, we can see similar elements. For instance, we see feedback inhibition at many stages, at the level of pathways and of individual reactions. Monitoring of the cell's energy state through levels of molecules like ATP, ADP, AMP, and NADH is another common feature.
The diagram below summarizes the key enzymes we've discussed, along with some of their most important regulators.