Script - The Energy of Life

Introduction

Hello and welcome to the n-lorem podcast series. I am Stan Crooke, the chairman and CEO of n-Lorem, and your host for the podcast series. Today, we will be chatting about the energy of life.

Let's say you own an acre of land in a nice residential area and you decide to build a house, and let's say you are a real do-it-yourselfer (not the klutz I am) and you decide to build it yourself. Let's also say that you are worried about the supply chain and inflation, so you go to Home Depot and buy all the material you will need, and have it delivered to the site. The wood is delivered by the wood supplier, and all the different kinds of wood and different lengths are stacked at the site along with all the stone, electrical wire, fixtures, nails, and screws of all sizes and shapes that you will use.

Now let's say your neighbor drives by and says "my god, what a mess." He says it is a mess because it is not in the shape of a house - it is less orderly than he expects for a residential neighborhood. He says "my god" because humans like order. However, the natural state of the universe is maximally disordered and extremely messy. All the order that you see around you and in the skies at night is due to an amazing amount of energy created at the Big Bang that is constantly being used to create structures or order out of chaos. The scientific measurement of disorder is entropy.

Now let's say that your neighbor drives by again in a few months and he says "oh, there's the foundation and frame." He is happier because he is beginning to see the orderliness he expects created out of what looked disordered to him. He is happier because you have invested enormous energy to create that orderliness. You have invested energy to overcome disorder, or entropy.

KEY POINT 1:
The natural state of the universe is maximal disorder. Energy is used to create and maintain order. The measure of disorder is called entropy.

Now let us say that you forgot something, so you get in your car, push the button, and the engine starts. You look down at the gauge and say, "oh my, I am out of gas, I need to gas up or the battery is low and I need to plug in the car." You have a choice about the type of energy you use to power your car.

Cells are a part of the universe, so they behave in accordance with the rules governing the universe. They need to invest energy to create and maintain the order that makes them cells of a certain type that do what those cells do. Like you, when you drive your car, cells have two choices about how they use the materials nature gives them to provide the energy they need to be the cells they are, do the tasks they do and maintain the order that makes them the cells they are. The two choices that cells can use are called aerobic or anaerobic metabolism, i.e., directly using oxygen to make energy or not. They are also called oxidative phosphorylation or glycolysis respectively. Oxidative phosphorylation is also called the Krebs cycle in honor of the great scientist who unraveled the cycle. I will use the Krebs cycle in this chat because it is easier to describe.

If you think about it for a minute, it is not surprising that you have two sources of energy because sometimes your cells have plenty of oxygen and other times they don't.

High Energy Chemicals

The cell uses chemicals that liberate a good bit of energy when they are broken down to create, then store energy. Most are phosphate-containing chemicals because phosphate bonds are readily formed and broken down in biological systems and when these bonds are broken, they liberate energy. The most prominent member of the high energy releasing chemicals is ATP - adenosine triphosphate. Yes, it is our old friend, one of the nucleotides used in DNA and RNA. Another is GTP - guanosine triphosphate, another nucleoside used in DNA and RNA. You can envision the chemical as an adenosine -p-p-p or guanosine-p-p-p.

When this chemical is broken down, the phosphate farthest from adenosine is lost, and that liberates a good bit of energy. In that reaction, water causes the loss of the first phosphate which results in adenosine with two phosphates - ADP. Removal of the next phosphate also liberates energy, but in biological systems the water mediated degradation of ATP is coupled to a system that uses that energy and the second phosphate is not cleaved.

KEY POINT 2:
Nutrients are broken down by cells to create energy in a form that is biologically useful. The high energy chemicals that are most commonly used in cells are ATP and GTP, but especially ATP.

ATP is a nucleotide, a building block for DNA and RNA. This is a perfect example of how parsimonious biological systems are. A solution to one problem - in one case information storage and management – is used for other purposes - in this case storage of energy in a form that can be used by cells.

Glycolysis

Though you have access to a more effective source of energy, you can use glucose as a source of energy. The term glycolysis simply suggests that a sugar, in this case glucose, is broken down – glycol, a general prefix for a sugar; lysis - a suffix saying the sugar is degraded. Most of the sugar you eat is sucrose. Sucrose is a di-saccharide which means two sugars linked together. The two sugars are very similar but differ in how they are used to make energy and the two sugars are glucose and fructose. Sucrose is a byproduct of plant metabolism and is present in almost all fruits and vegetables, but when you eat sucrose, it is rapidly broken down into glucose and fructose. Because glucose is an essential nutrient, all the cells in your body have proteins in the membrane that actively take up glucose.

Glucose uptake by cells is very carefully regulated and you have a meaningful fraction of an organ, the beta cells of the pancreas that make a key glucose regulatory hormone. The hormone is insulin. Of course, you know that having the right amount of insulin is of life and death importance and there are systems that regulate the amount of insulin in the blood. Type One diabetes is a disease in which beta cells are destroyed because of an immune reaction that has gone bad. The precursor to Type Two diabetes is called the metabolic syndrome. This usually results from overeating, particularly fatty foods and sugar. In response, insulin secretion increases, but eventually it cannot keep up with the amount of glucose in blood and therefore, glucose levels increase. This effort to remain healthy -remember that it is called homeostasis- makes things worse by causing fat to accumulate in the liver.

Another hormone, glucagon has essentially the opposite effect of insulin on glucose uptake by cells. This yin and yang approach, or an accelerator and a brake system, to regulating insulin is a frequent design in biological systems because it provides more precise regulation than a single approach can provide.

Remember that I mentioned that in biological systems, there are many pathways and cycles. Glycolysis - glycol, sugar – lysis – degradation. Degradation of glucose is a pathway but not a cycle. This means it goes in only one direction and that results in glucose, which has six carbons being broken down into three-carbon fragments, one of which is pyruvate and this degradative process generates two molecules of the high energy chemical ATP.

In normal cells with plenty of oxygen, the end product of glycolysis is pyruvate and that enters the Krebs or citric acid cycle that generates three molecules of ATP. So pyruvate is unique in that it couples glycolysis to the oxidative phosphorylation or Krebs cycle. When oxygen is in short supply, the Krebs cycle is not coupled to the glycolytic pathway, and lactic acid is produced. Lactic acid is painful and that is why after you exercise, you have aching muscles. Glycolysis also results in fatty acid production which makes diabetes worse.

KEY POINT 3:
Glycolysis is a pathway that splits glucose, a six-carbon sugar, into three-carbon fragments, one of which is pyruvate. In the process, two molecules of ATP are created from each glucose molecule broken down.

KEY POINT 4:
Glucose is a vital nutrient, so cells have active processes that bring glucose into cells. That process is regulated by the hormone insulin. To be sure that glucose levels are carefully managed, you have a second hormone that has essentially the opposite effect.

The Krebs Cycle

When there is sufficient oxygen, the products of glycolysis are converted to pyruvate in tiny organelles called mitochondria by the glycolytic pathway and are used immediately. The cycle can also be fed by other molecules like citric acid. The Krebs cycle generates three ATP molecules for every cycle. This is beneficial because your cell generates more energy and results in fewer byproducts that can be harmful. There are multiple sites at which different chemicals can enter the Krebs cycle. That too is beneficial because the amount of a specific nutrient like glucose can vary. So being more versatile is a survival advantage.

Humans are aerobic - oxygen dependent - organisms, so we are designed to use the Krebs cycle to produce most of the energy we need. Anaerobic organisms, like some bacteria, do not use oxygen so they depend solely on the glycolytic pathway for energy.

KEY POINT 5:
In the presence of sufficient oxygen, most of the final product of glycolysis, pyruvate, enters the Krebs cycle and generates three more ATP molecules.

The Anaerobic State

Since we breathe constantly, I am sure that you are asking when and why would a cell switch to glycolysis as its primary source of energy. Well the amount of oxygen delivered to a cell is proportional to the amount of blood it can access, and that is proportional to the distance of a cell from the nearest capillary. For example, if you were to look at liver cells near a capillary vs ones more distant, you would find that the cells differ in their levels of ATP and metabolic profiles. A more sinister way cells can become more glycolysis dependent is cancer. Why? A partial answer is that in cancer cells, the glycolytic pathway is more robust, and the Krebs cycle reduced. That is a nice true statement, but science always asks the next question. In this case, why do cancer cells prefer glycolysis? That is not fully understood - or at least I do not fully understand it. One reason is that cancer cells proliferate, grow, and invade other organs. That often means that the leading edge of a cancer is made of cells farther away from blood vessels and therefore short on oxygen.

Some cells use glycolysis more than the Krebs cycle. That is to protect cells from low oxygen levels.

Conclusions

Your cells have two systems that take nutrients, break them down, and use that process to generate energy. The glycolytic pathway is in the cytoplasm of your cells, not the nucleus, and it produces only two molecules of ATP for every glucose degraded and can result in the production of metabolic products that can be harmful.

The second system uses oxygen directly and is called the Krebs cycle. It is so important that the machinery for this cycle is housed in tiny organelles called mitochondria. Their main job is to generate the energy you need in a form that cells can use. When oxygen is plentiful, most of the final product of the glycolytic pathway is used by the Krebs cycle to make more energy. In low oxygen accessible cells, glycolysis is used to a greater degree and generally, cancer cells depend more on glycolysis than the Krebs cycle.