ATP: The Fuel of Life

Welcome. I'm Chris Schubert. I'm a teacher and researcher here at Harvard and MIT, where I'm back right now just enjoying a lovely burrito for my breakfast. Let's jump right into my Blossoms lesson. Have you ever asked yourself why we humans have to eat so regularly? I mean, beyond the pleasures of food tasting so good and it being a lot of fun to cook it, why do we actually have to eat? Why can't we just like other species, for example bears, eat one big meal at a time and then go into hibernation for a long time?
Keep these questions in mind, as we'll move through today's lesson. But before we move on, I'd like to challenge you to an in-class question, which you can discuss with your peers. How many molecules do you think are essential to converting the energy we gain from our food into a form our bodies can use readily? Is it 1? Is it 10? Is it 100? Is it 1,000? Is it 10,000? While you and your peers are discussing and answering this question, I'm going to move into a classroom for the next segment.

So how did you do? How did it go? Well, the correct answer is one. Think about that for a moment. One molecule drives all of our daily activities. That molecule's called ATP, or by its chemical name, Adenosine Triphosphate. And it's the central theme of my Blossoms lesson today. It's a molecule that's the end product of all of our metabolic pathways and it has fascinated physicians and scientists since its discovery in 1929 only secondary to the discovery DNA.
ATP was discovered in 1929 by the German biochemist Karl Lohmann. This is the structure of the molecule. Think about this for a while. Lohmann had to come up with the structure based on pure reasoning and the extent of knowledge he had of biomolecules at that time. He had none of the fancy machines available that we have as scientists today. Even though the structure of ATP was established in 1935, it took another 13 years for the molecule to be first synthesized. It was first synthesized by Lord Alexander Todd, a Scottish biochemist, who for his work got the Nobel Prize for chemistry in 1957.
If you come across a chemical structure of ATP today, be it in a lecture, textbook, scientific article, or some website, you will most likely see it in one of these popular representations, a skeletal formula, the ball-and-stick model, or space-filling model. The skeletal formula of ATP is a shortened representation of its molecular structure. This structure gives us a sense what atoms are in the molecule and how they're connected to each other. The ball-and-stick model of ATP isa molecular model displaying both the three dimensional position of the atoms and the bonds between them, spheres, connected by rods which represent the bonds, typically represent atoms.
The space-filling filling model of ATP uses full-size balls to represent the effective shape and relative dimensions of the molecule, in particular the region of space occupied by it. Now that you've been introduced to the molecule and its chemical structure, let's think about what might make this molecule so centrally important to us humans. Where is it produced and how might it function? To give you a clue for the next in-class challenge question, think about that the molecule is called the fuel of life for a particular reason.
For your next in class activity, I challenge you to think about the following two questions. What is it in the food we eat that makes eating such a necessary habit? The second question might give you a bit of a clue as to what we're looking for in the first question. What's the purpose of the various biomacromolecules in our body?

We all need energy to live and be active. But how do we do it? In answering this last challenge question, you've come up with the four major classes of biomacromolecules, which are carbohydrates, proteins, lipids, and nucleic acids. These four groups allow life to exist. Let's discuss now how three of these four major groups we ingest daily in our food are broken down into the molecular pieces that allow us to maintain the correct level of energy we need to stay alive and be active every day.
But before we do that, let's take a quick detour to remind ourselves of the first law of thermodynamics, which is central to how our body manages its energy demand, supply, and reserves. So why are we interested in the first law of thermodynamics? The law states that energy can be converted from one form to another, but it cannot be created nor destroyed. It was formulated in 1850 by Rudolf Clausius, a German physicist and mathematician, and the central founder of the field of thermodynamics. Thermodynamics is critical to understanding how our body handles its energy demands and supply.

The key is to understand that energy can neither be created nor destroyed. But it can be converted from one form to another. This is exactly what happens when we ingest our food and it gets digested and transformed into ATP. This is happening in a process called cellular metabolism. So let's take an initial look at how this happens. Cellular metabolism, where energy is extracted from food and converted into energy storage molecules is a very complex affair. However, the details are of no concern to us here. Rather, I'd like to briefly walk you through the breakdown pathways of three major food groups: proteins, sugars, and fats, to show you that they all end in two common pathways.
First, the citric acid cycle illustrated here in the middle of the figure shown on the left and named after one of its main molecules, citric acid. And second, a process called oxidative phosphorylation marked by the green arrow below the citric acid cycle. As you can see, all three food groups feed into these pathways where the vast majority of ATP is made in our cells. We can generalize the process into three steps.
First, the breakdown of large macromolecules into simple subunits such as amino acids, simple sugars, and fatty acids. Second, the conversion of the energy stored in these simple subunits into energy carrier molecules such as Acetyl-CoA, NAHD, and FADH2. Lastly, the conversion of the energy stored in these carrier molecules into large amounts of ATP. As you've just discovered, ATP is the major output from cellular metabolism. Each of our cells contains about one billion ATP molecules. It's a molecule that's used to power a vast variety of processes within ourselves.
It's used to build DNA or it can make muscles contract. ATP is called the fuel of life. It's an energy currency molecule and as such the most important source of mechanical and chemical energy within ourselves. But what makes it such a special molecule? Let's think about that in the next in-class activity. The goal of this exercise is to get you thinking about the components that make up the ATP molecule, how they are connected, and what could make this molecule such a preferred choice of metabolic output. In addition, can you think of which class of organic macromolecules is composed of monomers similar to ATP? The answer will follow in a brief animation before the next segment.
ATP molecules store and supply energy for cellular processes. An ATP molecule contains three building blocks. The flat purine ring system containing multiple nitrogen atoms shown in blue, the ribose sugar in the middle, and the three phosphate groups with the phosphorus atoms shown in yellow.

Welcome back. I hope you've had a lively discussion about the components of ATP that might make it such a central and special molecule. Let me briefly summarize why ATP is so central to us as an energy currency. As you've just discovered in the brief animation, the components of ATP are three organic phosphate groups, one ribose, and one adenine base, all chemically connected in the way indicated in this figure. So what is it that makes this molecule the fuel of life?
The key to understanding what makes ATP such a special energy molecule lies in the two outermost phosphate groups which are held to the rest of the molecule by so-called phosphoanhydride bonds which are high in energy and are readily transferred. As indicated, water can be added to ATP to form ADP and inorganic phosphate. This hydrolysis of the terminal phosphate of ATP yields between 11 and 13 kilocalories per mole of usable energy. And depending on intracellular conditions, it is enough to power the vast majority of cellular processes that keep us alive.
So what do we need ATP for? Well, the simple answer is, it keeps us alive and well. In more specific detail, let's look at some metabolic uses of ATP. It's, for example, used to make macromolecules like protein, fats, sugars, and lipids. It is also used to generate the electricity we need to power the cells of our nervous system, as well as to expand and contract the muscles that keep us moving. Lastly, much like cars and trucks on our streets and highways, cells need to move stuff around and ATP is the critical fuel for that purpose.
So how much fuel do you think a typical human needs per day? In the next in-class activity, I challenge you to think about, based on what you know about ATP so far, how much ATP an average human might use per day? To give you a clue, keep in mind the metabolic processes that use ATP as an energy source -such as running, walking, thinking - convert it back into its precursors ADP and inorganic phosphate, utilizing one water molecule through a process known as hydrolysis. Let's assume an average human has a body weight of 70 kilograms. How much ATP do you think he or she hydrolyzes every day of his or her life? Please give a brief justification with why you chose your number as you discuss this with your peers.

Welcome back. I hope you had a lively discussion in the last-in class activity. To answer the question, let's rephrase and make a couple of assumptions. Assume an average human of 70 kilograms body weight consumes 125 moles of ATP each day. The disodium salt of ATP has a molecular weight of 551 grams per

mole. The question now becomes to figure out how much ATP does this average human hydrolyze per day? To figure this out, we have to multiply the amount of ATP hydrolyzed per day, which is 125 moles, with the molecular weight of ATP, 551 grams per mole. The answer is quite amazing.
The average adult human with a typical weight of 70 kilograms thus consumes approximately 69 kilograms of ATP per day, which equals nearly the amount of his or her own body weight. That's really cool. So what does this mean? It means that the amount of ATP in our body isn't nearly enough to power the calorific demand of the average human. After a brief challenge question, let's think about how ATP can be remade from its components ADP and inorganic phosphate. If you had to put a price tag on our daily ATP production, how much do you think each of us would be worth if we could make the ATP we produce and sell it off on a commercial market? You might be surprised.
To put a price tag on this ATP turnover at current commercial prices of about $20 per gram of ATP, it would cost approximately $1.4 million per day. More than $1 million! In this context, the ability of our body to biochemically sustain its amazing activity is even more fascinating and deserves our deepest respect. So let's see how all this value is actually produced. Now that you've gotten the first glimpse at the astounding ability of our body to make ATP, let's take a brief look at the three major pathways where this ATP is actually produced in our body.
This happens in a process called cellular respiration, a set of metabolic reactions and processes that take place in the mitochondria of cells,which you can imagine as many little power plants inside the cell that convert biochemical energy from nutrients into ATP and then release waste products. This respiration is one of the key ways the cell gains useful energy to fuel its activities. Inside the cell, metabolism is very complicated. And this figure only shows a very small part of it. However, whether we start from proteins, sugars, or fats, we always end up at the same place, the production of ATP in a reaction called oxidative phosphorylation.
Let me briefly walk you through the middle axis of this figure, which shows the breakdown of sugars to ATP in three major steps. First, we go through glycolysis, which breaks down glucose into simpler compounds. Second, these compounds are fed into the citric acid cycle, which converts these simpler compounds into so-called electron carrier molecules reduction equivalents, NADH and FADH2. And lastly, we enter oxidative phosphorylation, which uses the energy stored in these electron carriers in presence of oxygen to make large amounts of ATP. In fact, almost 90% of the ATP generated by cellular respiration comes from oxidative phosphorylation.
So let's take a closer look at this last step in the production of ATP. Following glycolysis and the citric acid cycle, NADH and FADH2 account for most of the energy extracted from food. These two electron carriers transport electrons through a series of chain reactions, the so-called electron transport chain, to a tiny machine that makes ATP, the ATP synthase. But more on that later. Can you take a guess how much ATP this tiny machine can produce from one glucose molecule? Is it 2, 4, 20, 40, or 100 molecules? Let's discuss this with your peers in the next in-class activity.

Welcome back. I hope you came up with the right answer, which is about 40 molecules of ATP that can be made from one glucose molecule. Think about that for a moment. That's an amplification factor of 40-fold. So where does all this energy come from? How is it made? To answer that, let's finish our 30,000-foot view of oxidative phosphorylation. In the previous segment, we learned that glucose is broken down in a series of steps and that the energy stored in one glucose molecule is largely transferred to NADH and FADH2, which carry electrons. But where do they carry them?
Turns out, each of our cells operates many thousand small power plants the so-called mitochondria, which fuel our cells. Inside the cell membrane of these mitochondria, the electron transport chain operates much like a molecular conveyor belt where electrons are shuffled from NADH and FADH2 to power ATP synthesis and generate water as a byproduct. Let's take a brief look at the details. Making ATP requires energy. But where does this energy come from? Turns out, that electron transfer in the electron transport chain causes large protein complexes to pump protons across the mitochondria membrane as shown by the arrows indicating the flow of protons in this figure.
The details are very complex, but the end result is critically important as it creates a separation of charge across the membrane. Think about this like a capacitor or like a little battery. Positive charge is now stored on one side of the membrane and this electrochemical energy can now be used to make ATP. This process is also called the proton motive force, indicating its capacity to do work. So how does it work? The way large amounts of ATP are generated in our body happens through an amazing molecular machine, the ATP

synthase. And rather than me explaining it to you, let's take the next in-class activity to watch a beautiful animation that showcases how this amazing molecular machine works.

ATP synthase is a molecular machine that works like a turbine to convert the energy stored in a proton gradient into chemical energy stored in the bond energy of ATP. The flow of protons down their electrochemical gradient drives a rotor that lies in the membrane. It is thought that protons flow through an entry open to one side of the membrane and bind to rotor subunits. Only protonated subunits can then rotate into the membrane away from the static channel assembly.

Once the protonated subunits have completed an almost full circle and have returned to the static subunits, an exit channel allows them to leave to the other side of the membrane. In this way, the energy stored in the proton gradient is converted into mechanical rotational energy. The rotational energy is transmitted via a shaft attached to the rotor that penetrates deep into the center of the characteristic lollipop head, the F1-ATPase, which catalyzes the formation of ATP.

The F1-ATPase portion of ATP synthase has been crystallized. Its molecular structure shows that the position of the central shaft influences the confirmation and arrangement of the surrounding subunits. It is these changes that drive the synthesis of ATP from ADP. In this animated model, different conformational states are lined up as the temporal sequence as they would occur during rotation of the central shaft.

Like any enzyme, ATP synthase can work in either direction. If the concentration of ATP is high and the proton gradient low, ATP synthase will run in reverse, hydrolyzing ATP as it pumps protons across the membrane. To show the rotation of the central shaft, a short, fluorescent actin filament was experimentally attached to it. Single filaments attached to single F1-ATPases can be visualized in the microscope. When ATP is added, the filament starts spinning directly demonstrating the mechanical properties of this remarkable molecular machine.

Wow, what a cool machine. Isn't it amazing what nature can do with interplay of mechanics and chemistry? While you're discussing what you've just watched in this video with your peers, I'll go inside and get myself a healthy snack. See you soon!

Welcome back. I hope you've had a good discussion. Before we close, let's summarize briefly what you've learned today conceptually about ATP and energy metabolism. During cellular respiration, most energy flows in this sequence. Glucose and other foods are broken down and fed into the citric acid cycle where they're transformed into NADH and FADH2, which carry electrons to the electron transport chain where they help generate the proton motive force that drives the synthesis of ATP by the ATP synthase during oxidative phosphorylation.

Overall, about 40% of the energy in one glucose molecule is transferred to ATP during cellular respiration, making about 36 to 40 ATP molecules in the process. This is an amplification of about 40-fold, which is amazing. But although our brain tries to, we humans as a whole can't live on sugar alone. So let's take a brief last look at some alternative pathways that can yield us energy in the form of ATP especially if little or no oxygen is around. A much less efficient way to generate ATP from glucose is a process called fermentation, which occurs in the absence of oxygen.

Fermentation bypasses the electron transport chain completely and ATP is solely produced through substrate-level phosphorylation. Ultimately, the goal is to regenerate NAD+ from NADH produced during glycolysis. Two common types are alcoholic fermentation with the end product being ethanol, and lactic acid fermentation with the end product being lactic acid. It's worth pointing out that both of these processes are incredibly inefficient in producing ATP from one molecule of glucose compared to oxidative phosphorylation. It's two ATPs verses around 40 ATPs.

So what else can we do to get more ATP? While glycolysis occurs in nearly all organisms, it's inefficient in the absence of oxygen. Ultimately, not all the foods we eat consist of carbohydrates. But you've learned that the major intersection of glycolysis, the citric acid cycle, is a critical pathway to produce large amounts of ATP through subsequent oxidative phosphorylation. Remember, that the end products of the citric acid cycle are NADH and FADH2. So technically, all we need to do to increase ATP production is to have the citric acid cycle increase its output of these two products.

Following electrons from many catabolic pathways, for example from the breakdown of proteins or fats, directly into glycolysis of the citric acid cycle can do this, thus ultimately increasing our final production of ATP through oxidative phosphorylation. Obviously, not all the foods we eat consist of sugars. Our bodies are really versatile at adapting to the variety of food sources we find in our environment. For example, one gram of oxidized fat can produce twice the amount of ATP compared to 1 gram of glucose. That's where the hibernating bears get their energy from. So ask yourself, would you rather be awake and active or asleep and lazy? With that, until next time happy eating!

Hello, I'm Chris. Thank you for your interest in using this session. This session is really intended to spark interest in students, I think, who have a little bit of background knowledge in what makes up a cell, what are the chemical components in a cell, what are some of the metabolic pathways within the cell that supply us with a lot of energy that we need to power our bodies. So rather than taking you through the general pathways of metabolism and energy production within a cell, as they're often displayed in standard biochemistry or biology textbooks, this session really is focused on ATP, which is the true energy currency of the cell. And as such has been dubbed the fuel of life, as it really powers all of the activities and provides all of the energy that we use every day.
In this session, I'll take you through the discovery of ATP, the structural components of ATP, as well a 30,000-foot view of the production pathways of ATP, to end up, which is, I think, a very, very cool example of an amazing interplay between chemistry and mechanics, which is the actual molecule that makes ATP within the mitochondria of the cell - the ATP synthase. From there, the session will end at particular pathways, fermentation through ethanol production as well as lactic acid production, that provide alternative pathways to ATP production in the absence of oxygen when the ATP synthase is not available.
The first segment is designed to get students thinking about why we humans have to eat. Why can't we just be like other animals who hibernate? Like bears, for example, who eat once a very large amount and then just stay asleep for six months. The segment will end with a challenge question in which the student should think about how many molecules are really central to providing us as humans with energy. And the goal, of course, is that it's one molecule, and that molecule is ATP. For the first in-class activity, I would give the students one to two minutes to think about the answers of the questions that are embedded in the video lesson. And then, maybe take a poll by a show of hands or some other means to collect the answers.
I think it's important to emphasize that there are certain orders of magnitude within these numbers to at the end arrive at the conclusion that it's an amazing fact that only one molecule really is responsible for the vast majority of all of the energy metabolism within ourselves. The answer will actually be provided at the beginning of segment two. Segment two will start with answering the challenge question for segment one. Followed by that, after ATP has been identified as being the sole molecule that provides most of our energy, we'll go through and discuss the discovery and history of ATP, different chemical structures, different representations, and we will end by discussing the physical principles that are behind ATP that actually make it so central to the molecule.
We will then end the segment with a challenge question that should lead the students to think about the four major molecules that are involved in energy that we get from our food which, of course, are proteins, lipids, sugars, and nucleic acids. For activity two, I think it's important to set the context and tell the students not to think about very specific molecules. First, in other words, don't think about the general names of food groups like bread, or meat, or fruit, but get them to think about actual biochemical meanings like carbohydrates, or proteins, or lipids, or nucleic acids.
I think a good way to illustrate that would be if one could bring some food into the classroom. For example, a piece of bread would illustrate carbohydrates, milk or a piece of meat would illustrate proteins or cheese could illustrate proteins and fats and, of course, fruit and vegetables would illustrate vitamins and nucleic acids. I think alternatively, if a school lunch is provided at your lunch, you could ask the students to simply think about what's typically on their lunch plate and how that might relate to energy production in their daily life.
In segment three, we'll start out by answering the challenge question posed in activity number 2. Followed by that, we'll go through an introduction of the broad metabolic pathways from protein digestion to carbohydrate digestion to lipid digestion that ultimately all lead in the production of one central molecule, which is ATP. I think it's really the key point to emphasize that independently of where the food comes from, the energy that is being made is always ATP. In the next in-class activity, we will then challenge the students to think about what it might be structurally that makes ATP such a special molecule.
In the third activity, the goal really is to get the students thinking about what the different components of ATP are. In other words, thinking about that there are inorganic phosphates, that there's a sugar molecule in there which is the ribose, as well as a nucleic acid base which is the adenine component. As part of that, once the students have identified the three major components of ATP, an additional question one could ask is: Is ATP actually involved in other processes than the energy metabolism in the cell? Which, of course, it

is since it's a major building block of our DNA and RNA. Depending on the prior level of understanding of the students, they might actually arrive at this conclusion.

In segment four, we will go through, in detail, the structural components and the energetic pieces of ATP that make it such a special molecule to really provide the fuel for life. Of course, the energy is stored in the phosphoanhydride bond in the terminal phosphate group, which is the key molecule part to understand for the students since it's this part of the molecule that gets cleaved off under the involvement of one molecule to make ATP into ADP and inorganic phosphate. Optionally, if the time allows, one could compare ATP with other energy carrying molecules like NADH or acetyl-CoA or FADH2 and see that they are structurally very, very different. And thus provide a different means of providing energy.

In activity four, it's important to set the stage and let students know that ATP does not constantly stick around as ATP in its pure form. When we use energy, ATP is converted into ADP and inorganic phosphate in processes such as thinking, sitting around, running, or simply walking. And the question is now to get the students thinking about how much ATP is actually being used up in an average human per day. And the answer is quite amazing. If you take a 70 kilogram body weight for an average human, we turn over about that equal body weight, 70 kilograms of ATP every day.

In segment five, we'll answer the question posed in activity number four in detail. I will go through the calculation that shows how the hydrolysis of about 70 kilograms of ATP every day can actually happen.

Activity five is a simple in class poll to ask students to get a sense of what they think the commercial value of the ATP would be that is stored in their bodies every day. I would suggest, after a brief in-class discussion, to come back to the lesson video where I will walk the students in detail through the calculation of the commercial value of ATP stored in our bodies.

At the beginning of segment six, I will introduce the commercial value of ATP in an average human of 70 kilograms to be about $1.4 million every day. Which is quite amazing and should be a point that is emphasized with the students. Following that calculation, the segment will introduce the flow of metabolic substrates from glucose breakdown, as an example, through glycolysis, into the citric acid cycle, through oxidative phosphorylation to make ATP in the ATP synthase molecule. It's important to point out that the focus of this session really is on oxidative phosphorylation and ATP production through ATP synthase, which will be explained in detail in the next segment.

In activity six, I challenged the students to think about what they've just learned in the last segment about the flow of energy from glucose breakdown all the way down to the production of ATP by the ATP synthase. And have them think about what they think the number is of ATP molecules that can actually be produced from one single molecule of glucose. I provide you with a set of answers, and I again would suggest simply taking a class poll and having a brief discussion to have the students justify why they came up with a particular choice.

In segment seven, we will answer the challenge question to segment six and show that it is about 38 to 40 molecules of ATP that are being produced from one molecule of glucose. We will then go through the details of oxidative phosphorylation, and most importantly introduce the concept of a proton gradient or also called the proton motive force, which allows the ATP synthase to work as a mechanical machine to produce large amounts of ATP. At the beginning of this segment, rather than doing an in-class activity, the students will simply watch a very short video animation that illustrates how the ATP synthase phase works.

In the last segment, I will recap the major principles of metabolism we talked through in the lesson, all focused on the major production of ATP as the final common product. ATP really is the fuel of life, and the segment will end to challenge the students to think about the next time they eat, what actually happens to the food and where the energy comes from that allows them to live a healthy and active life. So thanks for your interest in using the sessions, and I really hope you and your students will enjoy the lesson. If you have any questions, please don't hesitate to get in touch. You can contact me by email at blossoms.crs@gmail.com.