BP203T BIOCHEMISTRY-THEORY

UNIT-TWO

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REGULATION OF THE BREAKDOWN OF GLYCOGEN (GLYCOGENOLYSIS) :

- Two distinct isoforms of glycogen phosphorylase exist; one is expressed in the liver and the other in the skeletal muscle. Because the process of glycogen metabolism is different in these two parts of the body, the **muscles and liver are regulated separately**.
- **Regulation of glycogen breakdown in skeletal muscle and all non-liver cells**

- Two forms of glycogen phosphorylase exist in the skeletal muscle: **phosphorylase a** (the active form) and **phosphorylase b** (the inactive form). The conversion of the inactive to the active form is catalyzed by phosphorylase **kinase**. This enzyme is activated by hormones. The enzyme **protein kinase A** (PKA) regulates the phosphorylase kinase by phosphorylation.
- **Calcium ions** also have an activating effect on the skeletal muscle. In a working muscle, the **sarcoplasmic reticulum** releases calcium ions, thus increasing the intracellular calcium concentration. The actual activation of glycogen phosphorylase is mediated by a **calcium-calmodulin complex**.
- **Phosphorylase b** is also subject to allosteric effects. The inactive enzyme can become partially active, and elevated levels of adenosine monophosphate (AMP) can activate phosphorylase b. Even before phosphorylase kinase becomes active in order to meet specific demands of the cell (hormonally controlled), ATP and glucose-6-phosphate inhibit the activation of phosphorylase b, which means that the inactive state is favored. This mechanism prevents unnecessary depletion of muscle glycogen stores when the metabolic demands have already been met.

Regulation of the breakdown of glycogen in the liver

In the liver, the enzyme phosphorylase kinase catalyzes the conversion of phosphorylase b to phosphorylase a. ATP and AMP are present in the liver; however, they are not relevant, because the liver does not degrade glycogen for its own use. Instead, **the liver meets its own energy requirements using fatty acids**.

Regulation of the synthesis of glycogen (glycogenesis)

Regulatory mechanisms of glycogen synthesis in the liver and skeletal muscles are the same. Glycogen synthase exists in an active dephosphorylated form, called **glycogen synthase a**. The inactive phosphorylated form is called **glycogen synthase b**. The conversion into the respective forms is mediated by protein kinase A, without further involvement of a kinase.

Also subject to allosteric regulation is the glycogen synthase b, which is activated by high concentrations of glucose-6-phosphate.

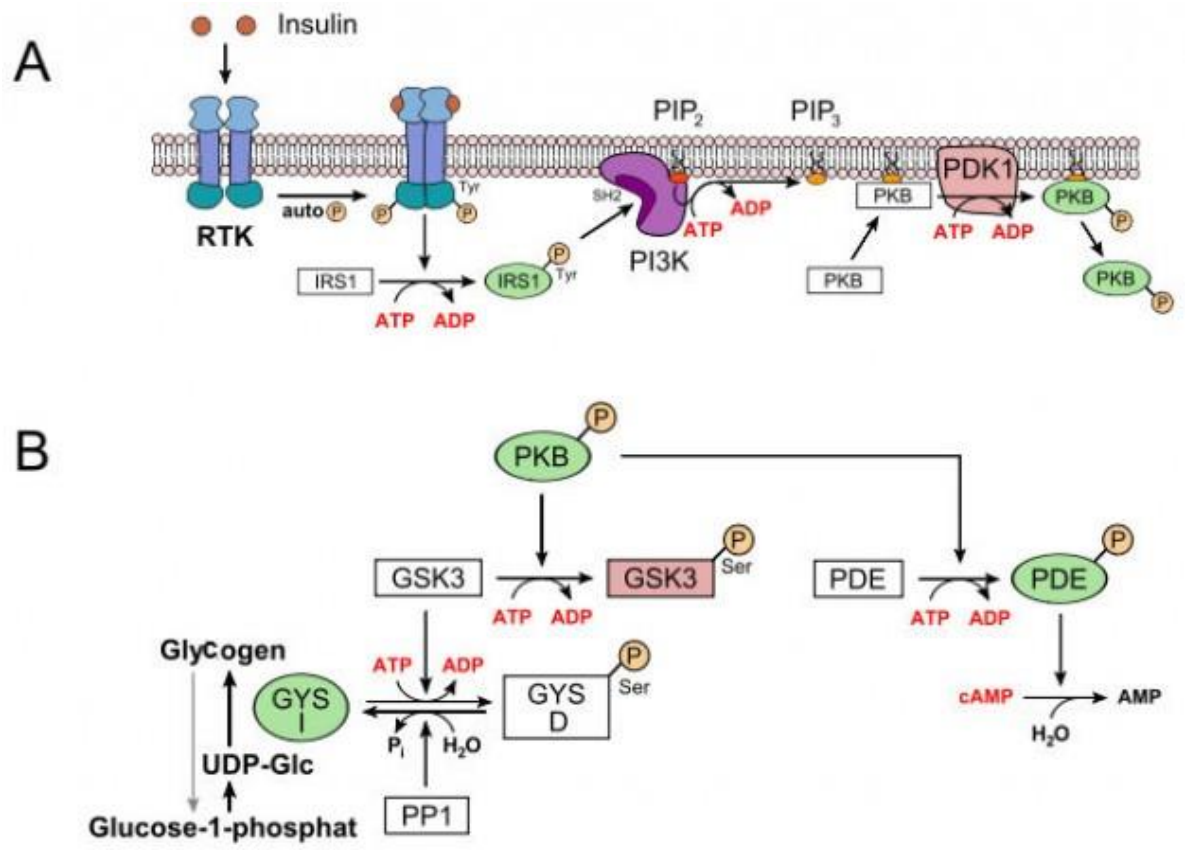
Note: Glycogen phosphorylase is activated by phosphorylation; glycogen synthase is activated by dephosphorylation.

HORMONAL CONTROL OF GLYCOGEN METABOLISM

- This important control mechanism prevents glycogen from being synthesized at the same time that it is being broken down. Three hormones play an important role here: **glucagon**, **adrenaline**, and **insulin**. Glucagon and adrenaline stimulate glycogen degradation, while insulin stimulates the synthesis of glycogen.
- Upon activation of the insulin receptor, the **phosphodiesterase** is activated, decreasing adenosine 3′,5′-cyclic monophosphate (**cAMP**) **levels** and inactivating **protein kinase** (PKA). An inactive PKA decreases the level of phosphorylation of the phosphorylase kinase, which has an inhibitory effect on this enzyme. This, in turn, decreases the rate of glycogen degradation.
- In addition, protein kinase B is activated, which reinforces the phosphorylation of **glycogen synthase kinase 3** (GSK3) and thereby inactivates it. As a result, GSK3 phosphorylates the glycogen synthase to a lesser extent, causing the latter to become more active, which amplifies glycogen synthesis.
- The phosphoprotein phosphatase 1 (PP1) catalyzes the key step, the **dephosphorylation of glycogen synthase**, which is responsible for glycogen synthesis. The latter can be inactivated by the **downstream metabolic effects** of adrenaline and glucagon (cAMP–PKA). Thus, adrenaline and glucagon contribute to the inactivation of glycogen synthesis.

Note: Adrenaline and glucagon have antagonistic effects on the mentioned signaling cascades, which are activated and inactivated by insulin.

The following illustrations show the different mechanisms at a glance:



Clinical Relevance: Glycogen Storage Diseases

Glycogenoses are a group of hereditary diseases affecting the metabolism of glycogen, resulting in the extensive accumulation of glycogen deposits in organs and in muscle tissue. Deficient enzymes involved in glycogen metabolism are responsible for glycogenoses. The most common disease is the autosomal recessive defect of glucose-6-phosphorylase wherein glycogen is synthesized, but cannot leave the cell.

The liver stores more and more glycogen, resulting in an enlarged liver (**hepatomegaly**) (up to 10 kg (22 lb)). Furthermore, glucose levels in the blood can no longer be maintained. This leads to severe **hypoglycemia** between meals.

So far, 11 distinct glycogen storage diseases and subforms have been identified. The typical symptoms and complications in addition to hepatomegaly include: hypoglycemia, nephromegaly, cirrhosis of the liver, and myasthenia.

These are the **most common types of glycogenoses**:

- Gierke’s disease (glycogen storage disease type 1)

- Pompe’s disease (glycogen storage disease type 2)
- Cori’s disease (glycogen storage disease type 3)

The treatment is aimed at maintaining a consistent blood glucose level in order to avoid severe hypoglycemia (especially at night).

Gluconeogenesis is the metabolic process by which organisms produce sugars (namely glucose) for catabolic reactions from non-carbohydrate precursors. Glucose is the only energy source used by the brain (with the exception of ketone bodies during times of fasting), testes, erythrocytes, and kidney medulla. In mammals this process occurs in the liver and kidneys.

Introduction

The need for energy is important to sustain life. Organisms have evolved ways of producing substrates required for the catabolic reactions necessary to sustain life when desired substrates are unavailable. The main source of energy for eukaryotes is glucose. When glucose is unavailable, organisms are capable of metabolizing glucose from other non-carbohydrate precursors. The process that coverts pyruvate into glucose is called gluconeogenesis. Another way organisms derive glucose is from energy stores like glycogen and starch.

Overview

Gluconeogenesis is much like glycolysis only the process occurs in reverse. However, there are exceptions. In glycolysis there are three highly exergonic steps (steps 1,3,10). These are also regulatory steps which include the enzymes hexokinase, phosphofructokinase, and pyruvate kinase. Biological reactions can occur in both the forward and reverse direction. If the reaction occurs in the reverse direction the energy normally released in that reaction is now required. If gluconeogenesis were to simply occur in reverse the reaction would require too much energy to be profitable to that particular organism. In order to overcome this problem, nature has evolved three other enzymes to replace the glycolysis enzymes hexokinase, phosphofructokinase, and pyruvate kinase when going through the process of gluconeogenesis:

1. The first step in gluconeogenesis is the conversion of pyruvate to phosphoenolpyruvic acid (PEP). In order to convert pyruvate to PEP

there are several steps and several enzymes required. Pyruvate carboxylase, PEP carboxykinase and malate dehydrogenase are the three enzymes responsible for this conversion. Pyruvate carboxylase is found on the mitochondria and converts pyruvate into oxaloacetate. Because oxaloacetate cannot pass through the mitochondria membranes it must be first converted into malate by malate dehydrogenase. Malate can then cross the mitochondria membrane into the cytoplasm where it is then converted back into oxaloacetate with another malate dehydrogenase. Lastly, oxaloacetate is converted into PEP via PEP carboxykinase. The next several steps are exactly the same as glycolysis only the process is in reverse.

2. The second step that differs from glycolysis is the conversion of fructose-1,6-bP to fructose-6-P with the use of the enzyme fructose-1,6-phosphatase. The conversion of fructose-6-P to glucose-6-P uses the same enzyme as glycolysis, phosphoglucoisomerase.
3. The last step that differs from glycolysis is the conversion of glucose-6-P to glucose with the enzyme glucose-6-phosphatase. This enzyme is located in the endoplasmic reticulum.

Glycolysis

Regulation

Because it is important for organisms to conserve energy, they have derived ways to regulate those metabolic pathways that require and release the most energy. In glycolysis and gluconeogenesis seven of the ten steps occur at or near equilibrium. In gluconeogenesis the conversion of pyruvate to PEP, the conversion of fructose-1,6-bP, and the conversion of glucose-6-P to glucose all occur very spontaneously which is why these processes are highly regulated. It is important for the organism to conserve as much energy as possible. When there is an excess of energy available, gluconeogenesis is inhibited. When energy is required, gluconeogenesis is activated.

1. The conversion of pyruvate to PEP is regulated by acetyl-CoA. More specifically pyruvate carboxylase is activated by acetyl-CoA. Because acetyl-CoA is an important metabolite in the TCA cycle which produces

a lot of energy, when concentrations of acetyl-CoA are high organisms use pyruvate carboxylase to channel pyruvate away from the TCA cycle. If the organism does not need more energy, then it is best to divert those metabolites towards storage or other necessary processes.

2. The conversion of fructose-1,6-bP to fructose-6-P with the use of fructose-1,6-phosphatase is negatively regulated and inhibited by the molecules AMP and fructose-2,6-bP. These are reciprocal regulators to glycolysis' phosphofructokinase. Phosphofructosekinase is positively regulated by AMP and fructose-2,6-bP. Once again, when the energy levels produced are higher than needed, i.e. a large ATP to AMP ratio, the organism increases gluconeogenesis and decreases glycolysis. The opposite also applies when energy levels are lower than needed, i.e. a low ATP to AMP ratio, the organism increases glycolysis and decreases gluconeogenesis.
3. The conversion of glucose-6-P to glucose with use of glucose-6-phosphatase is controlled by substrate level regulation. The metabolite responsible for this type of regulation is glucose-6-P. As levels of glucose-6-P increase, glucose-6-phosphatase increases activity and more glucose is produced. Thus glycolysis is unable to proceed.

Regulation of blood glucose is largely done through the endocrine hormones of the pancreas, a beautiful balance of hormones achieved through a negative feedback loop. The main hormones of the pancreas that affect blood glucose include insulin, glucagon, somatostatin, and amylin.

Insulin (formed in pancreatic beta cells) lowers BG levels, whereas glucagon (from pancreatic alpha cells) elevates BG levels.

Somatostatin is formed in the delta cells of the pancreas and acts as the “pancreatic policeman,” balancing insulin and glucagon. It helps the pancreas alternate in turning on or turning off each opposing hormone.

Amylin is a hormone, made in a 1:100 ratio with insulin, that helps increase **satiety**, or satisfaction and state of fullness from a meal, to prevent overeating. It also helps slow the stomach contents from emptying too quickly, to avoid a quick spike in BG levels.

As a meal containing carbohydrates is eaten and digested, BG levels rise, and the pancreas turns on insulin production and turns off glucagon production. Glucose from the bloodstream enters liver cells, stimulating the action of several enzymes that convert the glucose to chains of glycogen—so long as both insulin and glucose remain plentiful. In this postprandial or "fed" state, the liver takes in more glucose from the blood than it releases. After a meal has been digested and BG levels begin to fall, insulin secretion drops and glycogen synthesis stops. When it is needed for energy, the liver breaks down glycogen and converts it to glucose for easy transport through the bloodstream to the cells of the body (Wikipedia, 2012a).

In a healthy liver, up to 10% of its total volume is used for glycogen stores. Skeletal muscle cells store about 1% of glycogen. The liver converts glycogen back to glucose when it is needed for energy and regulates the amount of glucose circulating between meals. Your liver is amazing in that it knows how much to store and keep, or break down and release, to maintain ideal plasma glucose levels. Imitation of this process is the goal of insulin therapy when glucose levels are managed externally. Basal–bolus dosing is used as clinicians attempt to replicate this normal cycle.

While a healthy body requires a minimum concentration of circulating glucose (60–100 mg/dl), high chronic concentrations cause health problems and are toxic:

- **Acutely**: Hyperglycemia of >300 mg/dl causes polyuria, resulting in dehydration. Profound hyperglycemia (>500 mg/dl) leads to confusion, cerebral edema, coma, and, eventually, death (Ferrante, 2007).
- **Chronically**: Hyperglycemia that averages more than 120 to 130 mg/dl gradually damages tissues throughout the body and makes a person more susceptible to infections. The glucose becomes syrupy in the bloodstream, intoxicating cells and competing with life-giving oxygen.

The concentration of glucose in the blood is determined by the balance between the rate of glucose entering and the rate of glucose leaving the circulation. These signals are delivered throughout the body by two pancreatic hormones, insulin and glucagon (Maitra, 2009). Optimal health requires that:

- When blood glucose concentrations are low, the liver is signaled to add glucose to the circulation.

- When blood glucose concentrations are high, the liver and the skeletal muscles are signaled to remove glucose from the circulation.

The final stage of aerobic respiration is the **electron transport chain**, which is located on the inner mitochondrial membrane

- The inner membrane is arranged into folds (cristae), which increases the surface area available for the transport chain

The electron transport chain releases the energy stored within the reduced hydrogen carriers in order to synthesise ATP

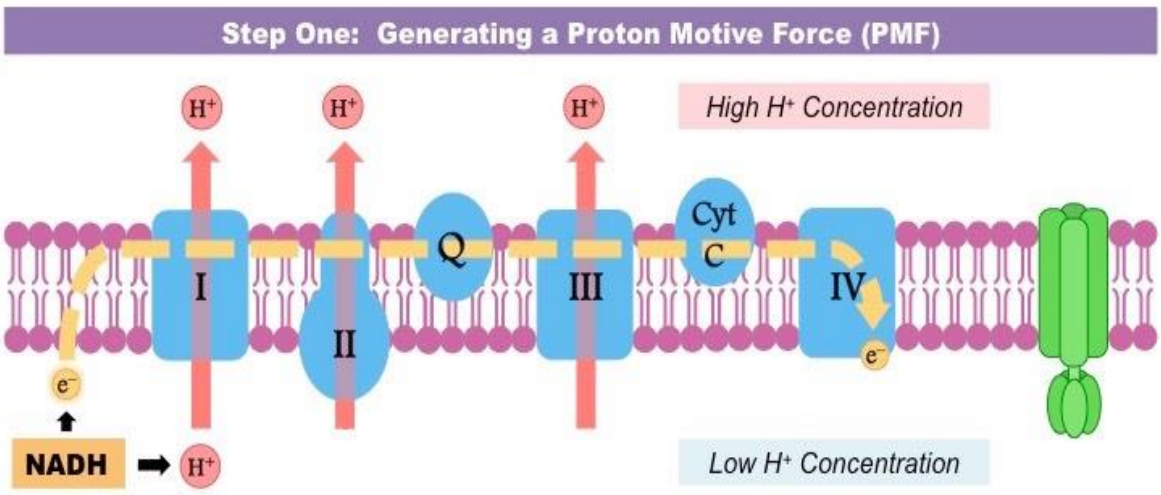
- This is called oxidative phosphorylation, as the energy to synthesise ATP is derived from the oxidation of hydrogen carriers

Oxidative phosphorylation occurs over a number of distinct steps:

- Proton pumps create an electrochemical gradient (proton motive force)
- ATP synthase uses the subsequent diffusion of protons (chemiosmosis) to synthesise ATP
- Oxygen accepts electrons and protons to form water

Step 1: Generating a Proton Motive Force

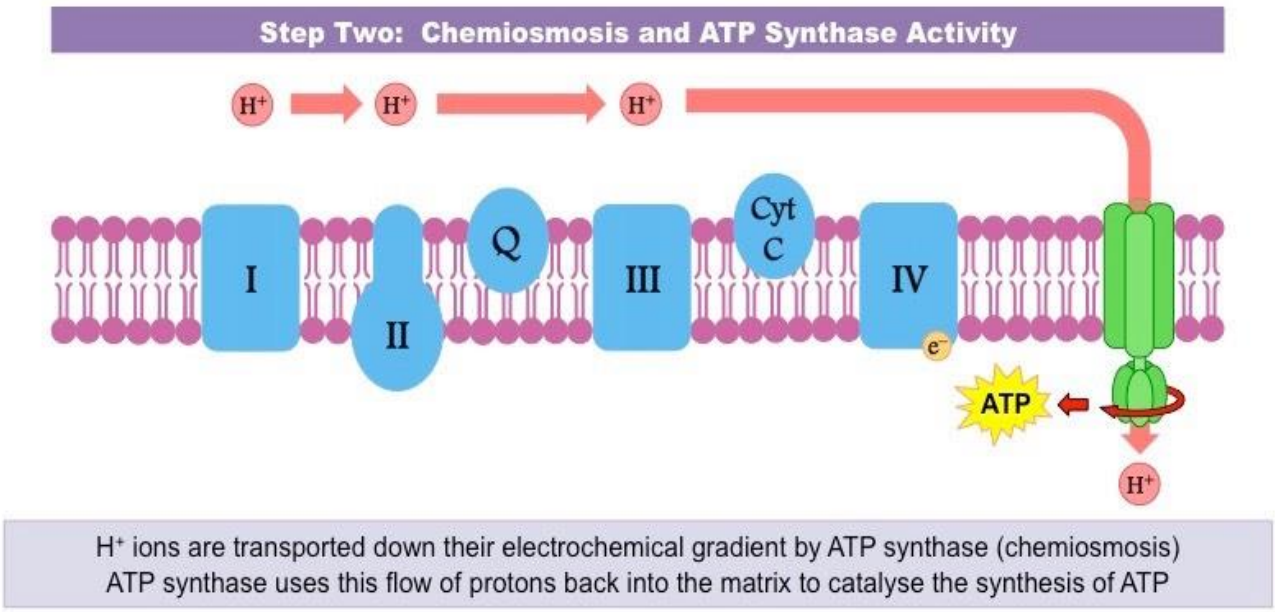
- The hydrogen carriers (NADH and $FADH_2$) are oxidised and release high energy electrons and protons
- The electrons are transferred to the electron transport chain, which consists of several transmembrane carrier proteins
- As electrons pass through the chain, they lose energy – which is used by the chain to pump protons (H^+ ions) from the matrix
- The accumulation of H^+ ions within the intermembrane space creates an electrochemical gradient (or a proton motive force)



High energy electrons released by hydrogen carriers are shuttled through the electron transport chain
The released energy is used to translocate H^+ ions from the matrix, creating an electrochemical gradient

Step Two: ATP Synthesis via Chemiosmosis

- The proton motive force will cause H^+ ions to move down their electrochemical gradient and diffuse back into matrix
- This diffusion of protons is called chemiosmosis and is facilitated by the transmembrane enzyme ATP synthase
- As the H^+ ions move through ATP synthase they trigger the molecular rotation of the enzyme, synthesising ATP

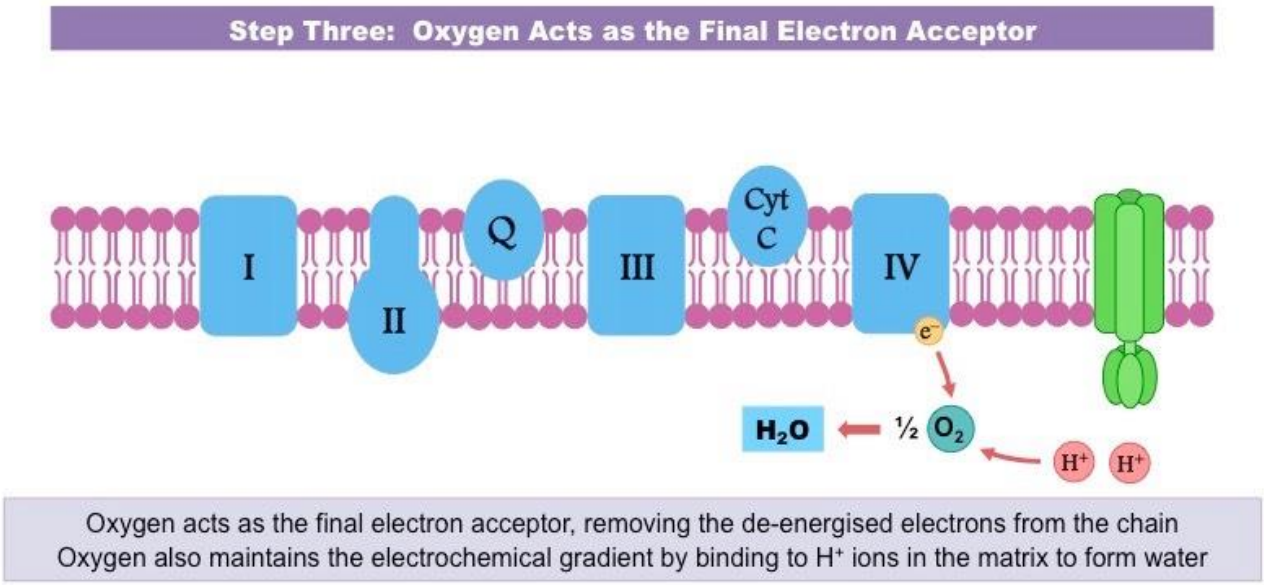


H⁺ ions are transported down their electrochemical gradient by ATP synthase (chemiosmosis)
ATP synthase uses this flow of protons back into the matrix to catalyse the synthesis of ATP

• Oxygen is needed to bind with the free protons to maintain the hydrogen gradient, resulting in the formation of water

Step Three: Reduction of Oxygen

- In order for the electron transport chain to continue functioning, the de-energised electrons must be removed
- Oxygen acts as the final electron acceptor, removing the de-energised electrons to prevent the chain from becoming blocked
- Oxygen also binds with free protons in the matrix to form water – removing matrix protons maintains the hydrogen gradient
- In the absence of oxygen, hydrogen carriers cannot transfer energised electrons to the chain and ATP production is halted



Oxidative Phosphorylation

- Hydrogen carriers donate high energy electrons to the electron transport chain (located on the cristae)
- As the electrons move through the chain they lose energy, which is transferred to the electron carriers within the chain
- The electron carriers use this energy to pump hydrogen ions from the matrix and into the intermembrane space
- The accumulation of H^+ ions in the intermembrane space creates an electrochemical gradient (or a proton motive force)
- H^+ ions return to the matrix via the transmembrane enzyme ATP synthase (this diffusion of ions is called chemiosmosis)
- As the ions pass through ATP synthase they trigger a phosphorylation reaction which produces ATP (from ADP + Pi)
- The de-energised electrons are removed from the chain by oxygen, allowing new high energy electrons to enter the chain
- Oxygen also binds matrix protons to form water – this maintains the hydrogen gradient by removing H^+ ions from the matrix

What is Oxidative Phosphorylation?

Oxidative phosphorylation, also known as electron transport-linked phosphorylation, refers to the metabolic pathway in which the energy released by nutrients during oxidation is utilized to generate ATP through electrical transport chain. And it is an important cellular energy conversion process and the final process of cell respiration in eukaryotes.

Oxidative phosphorylation occurs in the mitochondrial inner membrane of eukaryotic cells or the cytoplasm of prokaryotes.

Oxidative Phosphorylation & Substrate-Level Phosphorylation

When it comes to oxidative phosphorylation, we have to talk about its "good partner"--substrate-level phosphorylation.

Substrate-level phosphorylation is a metabolic reaction in which the energy-rich phosphorylated compound resulting from the coupled reaction transfers its phosphate group to ADP for ATP synthesis. Or GDP is recharged a phosphate group to generate GTP.

● The Similarities between Oxidative Phosphorylation and Substrate-level Phosphorylation

The main similarity between oxidative phosphorylation and substrate-level phosphorylation is that both their ultimate production is ATP.

● The Differences between Oxidative Phosphorylation and Substrate-Level Phosphorylation

The biggest difference between oxidative phosphorylation and substrate-level phosphorylation is the source of the energy needed to convert ADP to ATP. Substrate level phosphorylation directly phosphorylates ADP to ATP by using the energy from a coupled reaction. While oxidative phosphorylation involves two coupled reactions that are considered to simultaneously occur. In the period

of oxidative phosphorylation, the energy produced during the oxidative reaction is transferred to ADP to form ATP.

The Function of Oxidative Phosphorylation

Oxidative phosphorylation provides bulk ATP for living organisms, and the ATP is the main energy source for maintaining life activity. Oxidative phosphorylation also involves the formation of reactive oxygen species (ROS) and the regulation of apoptosis.

The Process of Oxidative Phosphorylation

When a hydroelectric dam works, it converts potential energy released from the falling water into kinetic energy, which turns into electrical energy. Similar to the steps of generating electricity from a hydroelectric dam, ADP makes ATP by a process called chemiosmosis during oxidative phosphorylation.

In eukaryotes, when catabolism such as glycolysis or citric acid cycle occurs, NADH is produced, which is a coenzyme containing a very high transfer electrical potential. When NADH is oxidized in the mitochondrial matrix, its electrons pass through the electron transport chain (ETC) to the electron receptor-oxygen, and simultaneously releases energy that pumps the resulting hydrogen ions through the inner mitochondrial membrane. It spontaneously forms an electrochemical concentration gradient across the inner mitochondrial membrane due to a higher concentration of hydrogen ions in the intermembrane space and a lower concentration in the matrix. When hydrogen ions pass through the inner mitochondrial membrane across electrochemical gradient, ATP synthase captures the proton-motive force for the production of ATP. This process is called chemiosmosis.

The electron transport chain is a series of proteins located on the inner membrane of the mitochondria.

● **NADH-Coenzyme Q Oxidoreductase**

The first enzyme in the electron transport chain is the NADH-CoQ oxidoreductase, also known as NADH dehydrogenase or complex I, which is the first entry of protons through the electron transport chain. It catalyzes the oxidation of NADH through coenzyme Q10. As two electrons pass through complex I, four protons are pumped from the mitochondrial matrix into the intermembrane space.

● Succinic-Coenzyme Q Oxidoreductase

The second enzyme that allows protons to passes through the electron transport chain is succinic-coenzyme Q oxidoreductase, also known as succinate dehydrogenase or complex II. It catalyzes the oxidation of succinic acid to form fumarate and the reduction of coenzyme Q10 to ubiquinone (QH2). This reaction does not involve the transfer of electrons, nor does it pump out protons, providing less energy to compare with the oxidation process of NADH. The third entry to the proton on the electron transport chain is electron transfer flavin-coenzyme Q oxidoreductase, also known as electron transfer flavin dehydrogenase, which reduces Q10 by using electrons from electron transfer flavin in the mitochondrial matrix.

● Coenzyme Q-cytochrome C Reductase

Coenzyme Q-cytochrome C reductase, also known as complex III, catalyzes the oxidation of QH2, and the reduction of cytochrome c and ferritin. In this reaction, cytochrome C carries an electron. Coenzyme Q is reduced to QH2 on one side of the mitochondrial membrane, while QH2 is oxidized to coenzyme Q10 on the other side, resulting in the transfer of protons on the membrane, which also contributes to the formation of proton gradients.

● Cytochrome c Oxidase

The last protein complex in the electron transport chain is cytochrome c oxidase, also called complex IV. It mediates the final reaction on the electron transport chain - transferring electrons to the final electron receptor oxygen -

oxygen reduces to water - pumping protons through the membrane. At the end of this reaction, protons that directly pumped out and that consumed by the reduction of oxygen to water increase the proton gradient.

Finally, the proton-motive force generated by the proton concentration gradient drives the ATP synthase to phosphorylate ADP to form ATP.

There is another electron-donating molecule - FADH2 in eukaryotes. FADH2 is also the intermediate metabolite during the earlier stage of cellular respiration such as glycolysis or citric acid cycle. In the FADH2 electrical transport chain, FADH2 bypasses the complex I and enters the electrical transport chain by the complex II because it contains less electrical potential than NADH. FADH2 is oxidized to FAD and coenzyme Q is reduced to QH2 in the reaction. And this reaction does not pump out protons either. The subsequent reactions are nearly the same as those in the NADH2 electron transport chain.

Prokaryotes such as bacteria and archaea have many electron transfer enzymes that can use a very wide range of chemicals as substrates. As the same with eukaryotes, electron transport in prokaryotic cells also uses the energy released by oxidation from the substrate to pump protons across the membrane to create an electrochemical gradient, which drives ATP synthase to generate ATP. The difference is that bacteria and archaea use many different substrates as electron donors or electron receptors. This also helps prokaryotes to survive and grow in different environments.

Factors Affecting Oxidative Phosphorylation

- **Inhibitors**

Under normal conditions, electron transfer and phosphorylation are tightly coupled. Some compounds can affect electron transport or interfere with phosphorylation reactions, all of which cause oxidative phosphorylation abnormalities. Here introduce four factors affecting oxidative phosphorylation.

Respiratory chain inhibitor: A substance that blocks electron transport at a certain part of the respiratory chain and inhibits the oxidation process. Some respiratory chain inhibitors bind to iron-sulfur proteins in NADH-Q reductase and block the transmission of electrons from NADH to CoQ, such as rotenone, phenoxymycin A, and barbital, ampicillin. Some substances inhibit the electron transfer between Cytb and Cytc1, such as antimycin A and dimercaptopropanol. Cyanide, azide, H2S, and C0 inhibit cytochrome oxidase, making electrons unable to pass to oxygen.

Oxidative phosphorylation inhibitors: These reagents directly interfere with the formation of ATP and also prevent electron transfer. The combination of oligomycin and dicyclohexylcarbonyldiimide with the F0 unit of ATP synthase prevents the hydrogen ions from flowing back from the proton channel, rendering the phosphorylation process incomplete, thus blocking the oxidative phosphorylation of intact mitochondria.

Uncoupling agent: The uncoupling agent separates the two coupling processes of electron transfer and ATP synthesis. Such compounds only inhibit the formation of ATP, but do not affect the electron transfer process. So the free energy generated by electron transfer is converted into heat energy, which excessively uses oxygen and fuel substrates. Such agents cause the electron transfer to lose normal control, resulting in excessive utilization of oxygen and fuel substrates, and energy is not stored. A typical uncoupler is 2,4-dinitrophenol (DNP). Because DNP is a fat-soluble substance, it can move freely in the mitochondrial membrane. When it enters the matrix, it can release H+. Return to the cytosol side. The H+ can be combined to eliminate the transmembrane gradient of H+, so that the energy released by the oxidation process cannot be used for the synthesis reaction of ATP, but referred to as a proton carrier.

● The Regulation of ADP

The rate of oxidative phosphorylation in normal organisms is mainly regulated by ADP. When the body uses ATP increase, the ADP concentration increases and the oxidative phosphorylation rate is increased after transporting into the mitochondria; otherwise, the ADP deficiency causes the oxidative phosphorylation rate to slow down. This regulation allows the rate of ATP production to adapt to physiological needs.

- **Thyroid Hormone**

Thyroid hormone can activate Na+-K+ATPase on the cell membrane of many tissues, accelerate the decomposition of ATP into ADP and Pi, and increase the number of ADP into mitochondria, thus decreasing the ATP/ADP ratio and accelerating the oxidative phosphorylation rate. As the synthesis and decomposition rate of ATP increases, the body's oxygen consumption and heat production increase, the basal metabolic rate increases, and the basal metabolic rate are one of the most important clinical indications for patients with hyperthyroidism.

- **Mitochondrial DNA Mutation**

Due to its naked circular double helix structure and the absence of protein protection and damage repair system of mitochondrial DNA (mtDNA), it is susceptible to mutate by oxidative phosphorylation. mtDNA encodes 13 proteins involved in oxidative phosphorylation. Therefore, mtDNA mutations can affect the oxidative phosphorylation process, resulting in a decrease in ATP yield and thus leading to many related diseases.

Diseases and Abnormal Oxidative Phosphorylation

Oxidative phosphorylation exerts a multiply role in the body. So once it is abnormal, it will cause diseases.

Many mitochondrial diseases are linked to defective oxidative phosphorylation. And tissues with high energy requirements are particularly susceptible to undergo oxidative phosphorylation defects, like brain, nerves, retina, bone and heart muscle. When there is impairment in oxidative phosphorylation in these

tissues, it could clinically manifest as seizures, hypotonia, ophthalmoplegia, convulsions, muscle weakness, and cardiomyopathy, etc.

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