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The Central Role of ATP in Cellular Energy Metabolism: Structure, Function, and Regulatory Mechanisms

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Abstract This study focuses on the role of ATP (adenosine triphosphate) in providing energy to cells, and also talks about its structure, mode of action, and how it is controlled. ATP is synthesized in the mitochondria of cells, specifically by something called F-ATP synthase, which is produced in an aerobic environment. This process requires the proton driving force provided by the respiratory chain. The ratio of ATP to ADP in cells is critical, and it affects many cellular activities, such as the activation of certain enzymes and the use of energy. The activity of ATP synthase is affected by ADP, ATP itself, and calcium ions. These factors are important for cells to maintain energy balance and can also regulate mitochondrial function. Another key player is AMP kinase (AMPK). It can "sense" the energy situation of the cell and regulate the production and use of ATP. If these regulatory processes go wrong, some diseases may occur, indicating that ATP is important for cell health. ATP is a core part of cellular energy metabolism. Understanding its synthesis, use, and regulation process can not only help us better understand the operation of cells, but also may provide new methods for treating diseases related to energy metabolism.
Keywords ATP; Cellular energy metabolism; Oxidative phosphorylation; F-ATP synthase; AMPK; Mitochondrial function; Energy homeostasis

1 Introduction

Energy metabolism in cells is the process of converting food into energy that the body can use. This process is very important for life activities. Most of this energy exists in the form of adenosine triphosphate (ATP), which is like the "energy currency" in cells (Erecínska and Silver, 1989; Erecínska and Wilson, 2005; Wilson and Matschinsky, 2022).

There are two main ways to generate ATP: one is glycolysis, which takes place in the cytoplasm; the other is oxidative phosphorylation, which occurs in mitochondria (Erecínska and Silver, 1989; Erecínska and Wilson, 2005; Wilson and Matschinsky, 2022). The efficient synthesis of ATP has a great impact on maintaining cell stability, growth and various functions (Erecínska and Wilson, 2005; Boon et al., 2020). Cells adjust the production and use of ATP to meet energy needs according to different physiological states (Erecínska and Wilson, 2005; Yu and Pekkurnaz, 2018).

To understand how ATP works, we must first understand its structure, function, and regulation. ATP plays a key role in energy transfer and is involved in many cellular activities, such as muscle contraction, neurotransmission, and various synthetic reactions (Erecínska and Silver, 1989; Erecínska and Wilson, 2005).

If there is a problem with the production or use of ATP, it may cause problems in cells and lead to some diseases, such as metabolic disorders, neurodegenerative diseases, and even cancer (Herzig and Shaw, 2017; Yu and Pekkurnaz, 2018; Vercellino and Sazanov, 2021). Cells maintain ATP balance in many ways, such as the regulation of AMPK (an energy-sensing protein kinase) or the dynamic changes of mitochondria, which help cells cope with energy stress (Dzeja and Terzic, 2003; Herzig and Shaw, 2017).

This study will focus on the synthesis and utilization pathways of ATP, especially the processes of glycolysis and oxidative phosphorylation. It will also explore the interaction between ATP and other molecules and its regulatory

mechanisms, including the role of key enzymes such as AMPK. It will analyze the relationship between ATP metabolism and health and disease, and see the problems caused by ATP imbalance.

2 Structure of ATP

2.1 Molecular composition of ATP

ATP (adenosine triphosphate) is composed of three parts: adenine, ribose, and three phosphate groups. Adenine is a nitrogenous base, and ribose is a five-carbon sugar. The three phosphate groups are arranged in a row, and the high-energy phosphoanhydride bond in the middle connects them (Angeli et al., 2016; Ley-Ngardigal and Bertolin, 2021; Fontecilla-Camps, 2022). It is this structure that allows ATP to store and transfer energy well.

2.2 Structural dynamics: phosphate groups, adenine, and ribose

The function of ATP is closely related to its structure. ATP has three phosphate groups called α, β, and γ, which are connected together through high-energy bonds. When these bonds are hydrolyzed, energy is released. These energies can be used to support many activities within cells (Angeli et al., 2016; Fontecilla Camps, 2022). Adenosine and ribose combine to form "adenosine". This part helps ATP to be recognized and bound by enzymes or other proteins in the cell (Walsh et al., 2017; Deng and Walther, 2020) (Figure 1). The function of ribose is to connect adenine and phosphate groups, and it also plays a role in energy and signal transmission (Ramdani and Langsley, 2014).

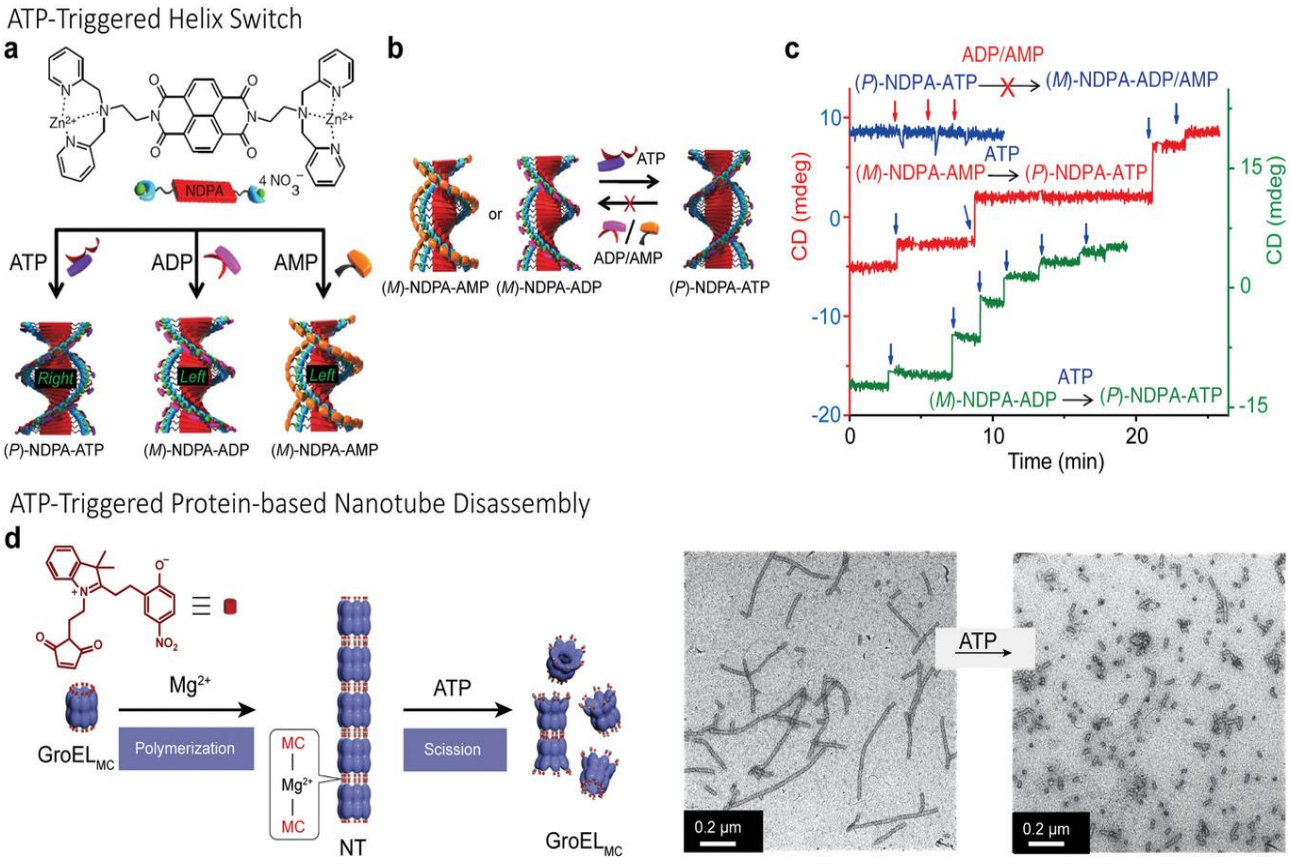

Figure 1 ATP-responsive co-assembled supramolecular polymers and breakage of protein supracolloidal polymers (Adopted from Deng and Walther, 2020)

Image caption: a) Helical supramolecular polymers with different chirality/helicity formed by co-assembly of adenosine phosphates (AXP; ATP, ADP, and AMP) with NDPAs bearing terminal ZnDPA groups. b) The addition of ATP to NDPA-ADP and NDPA-AMP supramolecular polymers inverts the helical structure of the supramolecular polymers from M-configuration to P-configuration. c) CD values during adding of ATP to NDPA-ADP (green) or NDPA-AMP (red) demonstrate inversion of the helicity, while addition of ADP or AMP to NDPA-ATP does not lead to a change in the CD signal. d) Protein-based nanotubes showing ATP-responsive disassembly, as seen by TEM. A-c) Reproduced with permission (Kumar et al., 2014); d) Reproduced with permission (Biswas et al., 2013) (Adopted from Deng and Walther, 2020)

2.3 Conformational changes in ATP hydrolysis and energy release

When ATP is hydrolyzed, its terminal γ-phosphate group is cut off and becomes ADP (adenosine diphosphate) and an inorganic phosphate (Pi). This process releases a lot of energy, which cells can use to complete some tasks that require energy (Angeli et al., 2016; Hardie, 2018; Fontecilla-Camps, 2022).

In some proteins, such as motor proteins or transport proteins, ATP binds to these proteins and hydrolyzes them, causing their structures to change, thereby driving the proteins to move or transport things outside the cell membrane (Glancy and Balaban, 2012; Fontecilla-Camps, 2022).

When ADP and Pi leave the protein complex, the protein will undergo new structural changes so that it can return to its original state and prepare for the next round of work (Zhang et al., 2021; Fontecilla-Camps, 2022).

3 ATP Synthesis Mechanism

3.1 Glycolysis: ATP generation under anaerobic conditions

Glycolysis is carried out in the cytoplasm of cells and is a very basic metabolic method. In the absence of oxygen, cells obtain energy through glycolysis. Simply put, it is to break down one molecule of glucose into two molecules of pyruvate and produce two molecules of ATP at the same time. Although the efficiency is not high, it is the main source of ATP when there is little oxygen or the cells grow very fast (Jourdain et al., 2021; White and Yang, 2022).

The glycolysis process requires the participation of many enzymes, which is closely related to the energy status of the cell. Generally, we use the indicator [ATP]/[ADP][Pi] to judge the energy situation (Wilson and Matschinsky, 2022). When cells are in an oxygen-deficient environment, they can only rely on glycolysis to maintain energy, although each molecule of glucose only produces 2 ATP, which is much less than aerobic metabolism (Erecínska and Silver, 1989; Erecínska and Wilson, 2005).

3.2 Krebs cycle and oxidative phosphorylation in mitochondria

When oxygen is sufficient, cells mainly rely on the Krebs cycle and oxidative phosphorylation in mitochondria to produce ATP. The Krebs cycle oxidizes acetyl-CoA produced by the decomposition of carbohydrates, fats and proteins to produce NADH and FADH2. These substances then enter the respiratory chain of the mitochondria and finally synthesize a large amount of ATP (Erecínska and Wilson, 2005; Vercellino and Sazanov, 2021).

One molecule of glucose can produce approximately 36 ATP, while glycolysis only produces 2 (Erec í nska and Silver, 1989). The H^+- ATP synthase in mitochondria plays a crucial role by utilizing the proton gradient on the membrane to synthesize ATP.

The regulation of this process is complex, for example, the phosphorylation status of IF1 protein can affect the activity of H^+- ATP synthase (Garcia Bermudez et al., 2015). Cells adjust the rate of ATP production according to their own needs (Erec í nska and Wilson, 2005).

3.3 Photosynthetic ATP synthesis in chloroplasts (plant cells)

In plant cells, ATP can also be produced through photosynthesis. Photosynthesis converts light energy into chemical energy, producing ATP and NADPH at the same time. The "light reaction" of this process occurs on the thylakoid membrane, forming a proton gradient, which then drives the chloroplast ATP synthase to synthesize ATP.

These ATP will be used in the "dark reaction" or Calvin cycle to fix carbon dioxide into organic matter such as sugars. Chloroplasts and mitochondria work together to maintain energy balance in cells. Mitochondria adjust metabolism according to the state of chloroplasts to help replenish ATP (Igamberdiev and Bykova, 2022).

Intermediates such as malic acid and citric acid are transported back and forth between the two organelles, which can maintain the redox state of the cell and the reasonable distribution of energy, so that photosynthesis and respiration can proceed smoothly.

4 The Role of ATP in Cellular Processes

4.1 The role of ATP in cellular respiration and energy transfer

ATP plays a crucial role in cellular respiration and energy transfer, particularly in the oxidative phosphorylation process of mitochondria within cells. In mitochondria, there are five enzyme complexes and two electron donating molecules that combine the energy generated from oxidation reactions to synthesize ATP. During this process, a proton gradient is formed, which is the main pathway for cells to obtain energy. In order to prevent respiratory chain problems from causing diseases, the entire process has strict regulatory mechanisms (Kadenbach, 2020; Vercellino and Sazanov, 2021). A protein called adenine nucleotide transporter (ANT) allows ADP and ATP to cross mitochondrial membranes (Atlante and Valenti, 2021).

4.2 ATP as a substrate for phosphorylation reaction

Phosphorylation reactions are crucial for many intracellular activities. F-type ATP synthase can convert ADP into ATP, and this process provides energy through the electrochemical gradient on the membrane. The concentration of ADP and ATP regulates this reaction, maintaining the energy balance within the cell (Turina, 2022). ATP can also reversibly phosphorylate cytochrome c oxidase (COX), regulate the rate of oxidative phosphorylation, and reduce the production of reactive oxygen species (Kadenbach, 2020).

4.3 The role of ATP in active transport and ion channels

ATP also participates in the active transport of ions on the cell membrane, which is important for maintaining ion balance inside and outside the cell. By hydrolyzing ATP, ATPase can provide energy and help Na+, K+, and Ca2+ions cross the cell membrane, which is crucial for neural signal transduction and muscle activity (Ji et al., 2021). There is also a type of structure called ABC transporters, which utilize the energy generated by ATP breakdown to transport toxins and nutrients into or out of cells (Rigoulet al., 2020).

4.4 The role of ATP in muscle contraction and cytoskeletal dynamics

ATP is also very important in muscle contraction and cytoskeletal activity. During muscle contraction, ATP binds to the myosin head, helping it separate from actin filaments and prepare for the next contraction cycle (Figure 2). This process occurs repeatedly in the cross-linking cycle and is the basis for muscle contraction and movement (Alghannam et al., 2021). ATP is also crucial for the polymerization and depolymerization of actin filaments, which are the main part of the cytoskeleton, maintaining cell morphology and movement, and participating in processes such as cell division (White and Yang, 2022).

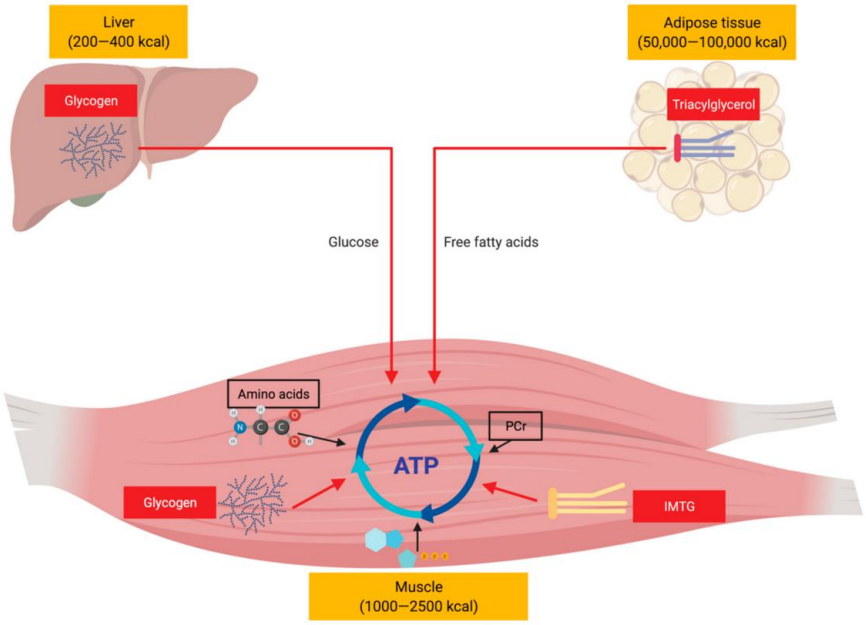

Figure 2 Simplified overview illustrating the major fuel sources supporting endurance-type exercise. ATP, adenosine triphosphate; PCr, phosphocreatine; IMTG, intramyocellular triacylglycerol (Adopted from Alghannam et al., 2021)

5 Mechanisms Regulating ATP Production and Utilization

5.1 Allosteric regulation of key enzymes (such as ATP synthase)

When cells make ATP, some key enzymes are "allosterically regulated", which is a way to regulate enzyme activity. ATP synthase is one of the most important enzymes. IF1 (an inhibitor) can inhibit its activity in certain cases, thereby preventing unnecessary ATP from being wasted (Domínguez-Zorita et al., 2022) (Figure 3). In F-type ATP synthase, ADP and ATP also regulate the efficiency of the enzyme, keeping the ratio of H+ and ATP generation reasonable, which helps maintain the energy balance of the cell (Turina, 2022).

In the glycolysis process, pyruvate kinase is an important enzyme. Its activity will change due to different small molecules, thus helping cells adjust the metabolic rate according to actual needs (Schormann et al., 2019). There is also AMPK (AMP-activated protein kinase), which is activated by AMP or ADP when the cell is short of energy, allowing the cell to start producing more ATP (Matos et al., 2019).

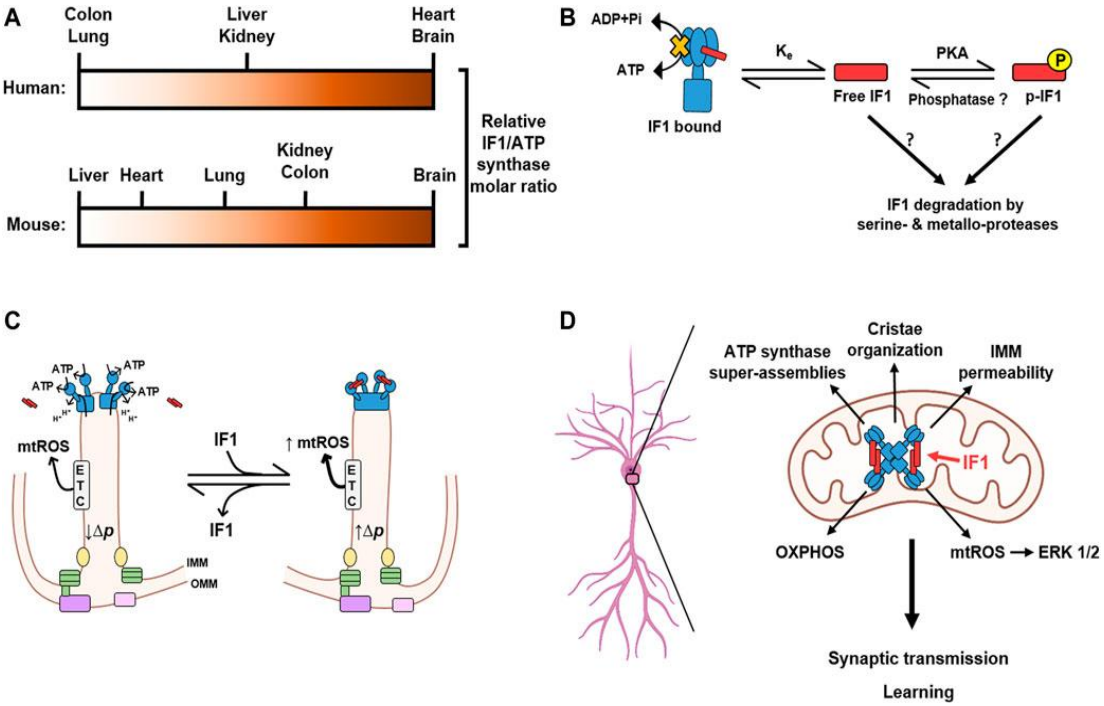

Figure 3 IF1 is tissue-specifically expressed and plays a central role in neuronal function and learning (Adopted from Domínguez-Zorita et al., 2022)

Image caption: (A) The ratio of IF1 to ATP synthase varies across tissues and between humans and mice, with the highest expression observed in specific organs. (B) IF1 binding to ATP synthase is reversible and regulated by phosphorylation, which limits its availability for binding, and potentially by rapid degradation through proteases. (C) IF1 binding promotes ATP synthase tetramer formation, increasing proton-motive force and mitochondrial ROS production. (D) In hippocampal neurons, IF1 helps organize mitochondrial cristae and modulate oxidative phosphorylation, contributing to synaptic transmission and learning through mtROS-activated signaling pathways like ERK 1/2 (Adapted from Domínguez-Zorita et al., 2022)

5.2 Feedback mechanisms in metabolic pathways (such as ADP/ATP ratio)

Cells use a method called "feedback regulation" to control ATP production. This method adjusts enzyme activity according to the ratio of ADP to ATP to keep energy balanced. In mitochondria, there is an enzyme called cytochrome c oxidase (COX). It will be inhibited when there is a lot of ATP, so that the mitochondrial membrane potential will not be too high, while reducing the generation of harmful reactive oxygen species (ROS) and protecting cells from damage (Kadenbach, 2020).

When the ADP concentration is high, it will relieve the inhibition of ATP synthase and help cells replenish ATP quickly (Turina, 2022). In glycolysis, ADP and ATP can also regulate the activity of pyruvate kinase, allowing the entire process to operate flexibly according to energy needs (Schormann et al., 2019).

5.3 Cellular response to fluctuations in ATP demand

Cells will make corresponding adjustments according to changes in ATP demand. The respiratory chain and oxidative phosphorylation systems of mitochondria play a central role, and the structure and activity of these systems can be regulated to adapt to different needs (Vercellino and Sazanov, 2021). For example, the heart can quickly switch between different energy sources to adapt to various situations (Karwi et al., 2019).

PGC1 family proteins are important in regulating mitochondrial number and function, and they can also regulate metabolic processes, which is very helpful for cells (Coppi et al., 2021). The mitochondrial permeability transition pore (mPTP) also plays a role in regulating certain parts of the ATP synthase, especially in developmental or degeneration-related states (Mnatsakanyan and Jonas, 2020).

6 ATP and Cellular Stress Response

6.1 The role of ATP in apoptosis and survival pathways

ATP is very important to cells. It not only provides energy, but also affects whether cells continue to live or enter the process of death. Mitochondria are the main source of ATP and play a key role in this process. When the permeability of the mitochondrial membrane increases, cell death may occur, which is an important step in the cell "suicide" process (intrinsic apoptosis). Mitochondria can also coordinate some cellular stress responses, such as autophagy (cells "eat" part of themselves) and necrosis, which help cells survive under stress (Galluzzi et al., 2012). In addition, protein kinase A (PKA) phosphorylates some subunits of cytochrome oxidase (COX), such as COXIV-1, which can regulate the energy flow of mitochondria, avoid ATP inhibition of COX, and help cells maintain normal function (Acín-Pérez et al., 2011).

6.2 Adaptation of ATP synthesis under hypoxic or nutrient-deficient conditions

When cells are deprived of oxygen or nutrients, they will try to adjust their energy production methods so that ATP can continue to be synthesized. At this time, HIF-1α (a hypoxia-inducible factor) comes into play. It allows cells to increase glycolysis-related enzymes so that cells can use more glycolysis to replenish energy and make up for the lack of mitochondrial respiration (Kierans and Taylor, 2020). There is also a protein kinase called AMPK, which is also activated when energy is insufficient. AMPK can increase ATP production and reduce energy waste by phosphorylating some enzymes or growth control points (Herzig and Shaw, 2017). Hypoxia signals and the AMPK/mTOR signaling pathway also interact with each other, which allows cells to better adapt to hypoxia and try to ensure that ATP can continue to be produced (Chun and Kim, 2021).

6.3 Mitochondrial adaptation to maintain ATP homeostasis

In order to cope with changes in energy demand, mitochondria will also make some adjustments to try to maintain a stable supply of ATP. Mitochondria change shape, sometimes merge together, sometimes separate, and move inside the cell to where energy is more needed, so that energy can be distributed more rationally (Yu and Pekkurnaz, 2018). The respiratory chain of mitochondria needs to be properly assembled and regulated so that electron transfer is efficient and ATP can be synthesized efficiently. The formation of respiratory supercomplexes can improve this efficiency (Vercellino and Sazanov, 2021). When mitochondria are stressed, they also initiate some protective mechanisms, such as mitophagy (removal of damaged mitochondria) and UPR^MT (a mechanism for processing unfolded proteins), which help maintain the quality and function of mitochondria and ensure that ATP continues to be produced steadily (Hill and Remmen, 2014).

7 Pathologies Associated with ATP Dysregulation

7.1 Disorders of ATP production (e.g., mitochondrial diseases)

Mitochondrial diseases are usually caused by problems with ATP production. Most of these diseases are caused by defects in the mitochondrial respiratory chain, which is important for the production of ATP through oxidative phosphorylation. The mitochondrial oxidative phosphorylation system consists of five enzyme complexes and two electron carriers that work together to produce ATP. If this system goes wrong, different types of mitochondrial diseases may result, which also shows that we need to understand how these complexes are assembled and regulated (Vercellino and Sazanov, 2021). If the mitochondrial ATP synthase is damaged under pathological

conditions, the problem of energy production becomes more serious (Rizza et al., 2009; Lippe et al., 2019). The regulation of the mitochondrial ATP synthase is also very important, and it can be adjusted according to the energy needs of the cell. If its function is not good, it may cause some pathological conditions (Das, 2003).

7.2 Role of ATP deficiency in aging and neurodegenerative diseases

ATP deficiency is a key factor in aging and neurodegenerative diseases. Mitochondria play an important role in the process of ATP production. Their defects or disorders are considered to be one of the causes of aging and some neurodegenerative diseases (Annesley and Fisher, 2019). The regulation of mitochondrial ATP synthase is essential for maintaining the energy level of the cell. If it goes wrong, it will lead to energy deficiency in neurodegenerative diseases (Das, 2003). The dynamic processes of mitochondria, including their fusion, fission and quality control, are particularly important. They have a great impact on maintaining energy balance, especially in neurological diseases (Yu and Pekkurnaz, 2018).

7.3 Cancer metabolism and ATP dynamic changes

Cancer cells often have abnormal ATP dynamics, a phenomenon called the Warburg effect. Even in an aerobic environment, they still rely on glycolysis to generate ATP. This metabolic change is related to mitochondrial function and ATP generation disorder. Mitochondria are not only the main place for ATP generation, but they also play an important role in cell signaling and metabolic regulation, which is very important for the proliferation and survival of cancer cells (Annesley and Fisher, 2019). Under certain circumstances, mitochondrial F-ATP synthase may become an energy-consuming state, affecting the metabolic efficiency of the cell and potentially promoting cancer (Lippe et al., 2019). Regulating mitochondrial dynamics is critical for cancer metabolism because changes in mitochondrial shape and function directly affect energy generation and cellular metabolic processes (Yu and Pekkurnaz, 2018).

8 Treatment Methods for ATP Metabolism

8.1 Pharmacological preparations affecting ATP synthesis and utilization

The potential of drug intervention in ATP metabolism has been demonstrated in the treatment of some diseases. F1Fo ATP synthase is a key enzyme for ATP production. Research has found that regulating this enzyme can help treat heart disease, cancer, diabetes and other diseases, and regulating the activity of this enzyme can improve energy balance and mitochondrial health (Johnson and Ogbi, 2011). When studying the glucose metabolism of cancer cells, especially the Warburg effect, it is recommended to intervene in this process to inhibit tumor growth. The use of anti glycolytic drugs, especially in combination with other treatment methods, may be effective (Abdel Wahab et al., 2019). AMPK (AMP activated protein kinase) plays an important role in the generation and utilization of ATP, and it is a potential target for the treatment of type 2 diabetes, obesity and cancer (Carling et al., 2012; Herzig and Shaw, 2017).

8.2 Gene therapy and enzyme replacement strategies in ATP related diseases

Through high-throughput gene screening, scientists have discovered key genes that maintain ATP levels, such as mitochondrial ribosomal protein and CoQ10 synthesis genes. Supplementing with CoQ10 can restore ATP deficiency caused by genetic defects, demonstrating the potential of gene therapy in repairing metabolic defects (Mendelsohn et al., 2018). The ATP synthase/IF1 pathway is associated with cancer progression, and regulating this pathway may help inhibit tumor growth and spread. Studying the regulatory mechanisms of ATP synthase and its inhibitor IF1 may provide new targets for treatment (Dom í nguez Zorita and Cuezma, 2023). MicroRNAs regulate mitochondrial energy metabolism genes and control ATP levels (Siengdee et al., 2015).

8.3 Future research directions for ATP targeted therapy

The study of the effects of physiological agonists and drugs on ATP synthase function, as well as the search for new regulatory mechanisms, are the focus of future research (Johnson and Ogbi, 2011). Developing more effective anti glycolytic agents and combining them with other therapies may improve the efficacy of cancer treatment (Abdel Wahab et al., 2019). Studying the role of AMPK in maintaining mitochondrial health and exploring its potential as a therapeutic target may provide new therapeutic approaches for metabolic diseases

(Carling et al., 2012; Herzig and Shaw, 2017). Gene therapy and enzyme replacement strategies, including the use of CoQ10 and miRNA based therapy, may provide new ideas for correcting ATP related metabolic defects (Siengdee et al., 2015; Mendelsohn et al., 2018).

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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