Review Article

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Cellular bioenergetics: Glycolysis, oxidative phosphorylation, and lipid metabolism pathways

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ABSTRACT

Cellular bioenergetics is the foundation for understanding how cells acquire, store, and use energy to maintain vital functions. This process primarily involves the metabolic pathways of lipid metabolism, oxidative phosphorylation, and glycolysis. Glycolysis functions to break down glucose in the cytoplasm, producing pyruvate and NADH as the initial energy source. The Krebs cycle in the mitochondria subsequently breaks down pyruvate further, generating reductants that aid in oxidative phosphorylation. At this point, the proton gradient is effectively used by the electron transport chain to transform chemical energy into ATP. The Krebs cycle and oxidative phosphorylation are triggered by the massive amounts of acetyl-CoA, NADH, and $FADH_2$ that are produced by lipid metabolism through lipolysis and β-oxidation. Energy sensors like AMPK and mTOR are involved in this extremely tight cross-pathway control, which synchronizes the balance between anabolism and catabolism based on the energy condition of the cell. Cells can adapt to a variety of physiological situations, including rest, exercise, and fasting, thanks to the integration of glucose and lipid metabolism. Many metabolic and degenerative diseases, including diabetes, obesity, cancer, and mitochondrial disorders, are caused by bioenergetic dysfunctions, such as abnormalities in glycolysis, lipid oxidation, or oxidative phosphorylation. Thus, in addition to being crucial for physiological aspects, a thorough understanding of bioenergetic mechanisms and controls also creates prospects for the development of therapeutic approaches based on metabolism.

Introduction

Cellular bioenergetics is a field of study that examines how cells obtain, store, and utilize energy to support their vital functions (Swerdlow, 2016). The majority of biological energy is stored as adenosine triphosphate (ATP), which serves as a universal energy source for a number of metabolic reactions (Casanova *et al*., 2023). ATP is the main driver of various cellular activities, including muscle contraction, transport of molecules across the plasma membrane, signal transduction, and DNA replication and repair (Zong *et al*., 2024). Thus, preserving cellular homeostasis requires a fundamental balance between energy generation and consumption (Vergara *et al*., 2019). The bioenergetic system can be disturbed, leading to a number of metabolic dysfunctions that can cause long-term conditions such diabetes mellitus, obesity, cancer, and neurodegenerative illnesses (Bhatti *et al*., 2022).

Cells generate energy through a variety of interrelated metabolic pathways in order to sustain their survival (Corsetti *et al*., 2024). The three main pathways that are central to cellular bioenergetics are glycolysis, oxidative phosphorylation, and lipid metabolism (Rigoulet *et al*., 2020). These three pathways each have a function, but they are also a part of a complex regulatory network that enables cells to adapt their energy supply to the availability of substrates and physiological demands (Li *et al*., 2023a).

The initial and primary process of glucose catabolism is glycolysis, which occurs in the cytoplasm (Kierans and Taylor, 2024). This process yields NADH, pyruvate, and a trace quantity of ATP (Mookerjee *et al*., 2017). Glycolysis has the advantage of being quick and oxygen-free, even though its energy-producing efficiency is not as high as that of oxidative phosphorylation (Yetkin-Arik *et al*., 2019). Glycolysis is therefore a crucial mechanism in anaerobic environments, such as during vigorous muscle contractions or in cancer cells that depend on anaerobic metabolism (Zhou *et al*., 2022).

On the other hand, the most effective method for producing ATP is oxidative phosphorylation, which takes place in the inner membrane of the mitochondria (Bhullar and Dhalla, 2023). This process depends on the electron transport chain, in which electrons from $FADH_2$ and NADH are moved through protein complexes before being absorbed by oxygen as the last acceptor (He *et al*., 2023). ATP synthase uses the proton gradient created by the energy of the electron flow to create a significant amount of ATP (Davis and Kramer, 2020). Maintaining equilibrium between energy generation and oxidative stress regulation is crucial because oxidative phosphorylation also generates potentially harmful reactive oxygen species (ROS) (Wang *et al*., 2024a).

Lipids are another important energy substrate that cells use in addition to carbs, particularly during extended exercise or fasting (Muscella *et al*., 2020). Fatty acid β-oxidation in mitochondria results in acetyl-CoA, NADH, and $FADH_2$, which subsequently proceed to the Krebs cycle and oxidative phosphorylation (Lei *et al*., 2025). Lipids are an extremely effective long-term energy reserve since they can store a lot of energy (Olsen *et al*., 2021). Hormones including insulin, glucagon, and epinephrine tightly regulate lipid metabolism, enabling metabolic adaptations to shifting physiological situations (Zhang *et al*., 2022a).

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The integration of oxidative phosphorylation, glycolysis, and lipid metabolism is therefore essential for understanding the fundamental physiology of cells as well as for identifying the pathogenic pathways behind a number of disorders. This review article aimed to provide a comprehensive overview of these three pathways, highlighting their mechanisms, regulation, and implications for health and disease.

Glycolysis pathway

The most basic metabolic pathway in cellular bioenergetics is glycolysis, which involves a sequence of enzyme processes in the cytoplasm that gradually convert glucose molecules into pyruvate (Chen *et al*., 2023). This mechanism is a crucial first step in linking the metabolism of carbohydrates with other energy pathways including fermentation and the Krebs cycle, in addition to offering a rapid source of energy in the form of ATP and the reductant NADH (Kierans and Taylor, 2024).

Overview of the process and main stages

A key metabolic process called glycolysis takes place in the cytoplasm of nearly all cell types. Its purpose is to use 10 successive enzyme processes to change one glucose molecule ($C_6H_{12}O_6$) into two pyruvate molecules ($C_3H_4O_3$) (Chandel, 2021a). This route is a vital component of a universal energy source since it can function in both aerobic and anaerobic environments (Liu *et al*., 2025). The primary byproducts of glycolysis are NADH molecules, which can be used in oxidative phosphorylation when oxygen is present, and trace amounts of ATP generated directly by substrate-level phosphorylation (Tseng and Wei, 2022).

Broadly speaking, glycolysis can be divided into two main phases. Energy investment is the initial phase, during which glucose is phosphorylated and converted to fructose-1,6-bisphosphate by using two ATP molecules (Judge and Dodd, 2020). This reaction is catalyzed by key enzymes such as hexokinase and phosphofructokinase-1 (PFK-1) (Xie *et al*., 2016). This phase is critical because it guarantees that glucose is confined within the cell and directed toward more metabolic breakdown.

In the second phase, known as the energy-producing phase, fructose-1,6-bisphosphate is broken down into two triose phosphate molecules, glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). These molecules are then converted to one another to create two G3P molecules (Pirovich *et al*., 2021). After then, each G3P goes through a sequence of phosphorylation and oxidation processes that result in the production of ATP and NADH (Fessel and Oldham, 2018). This process involves important enzymes such as glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, and pyruvate kinase (Chandel, 2021a). Each glucose molecule produces four ATP in total at the end of the process, with a net gain of two ATP after deducting the ATP needed in the first phase (Kukurugya *et al*., 2024).

Key enzymes

In the glycolysis pathway, hexokinase, phosphofructokinase-1 (PFK-1), and pyruvate kinase are the three primary regulatory points, even though all phases of the enzymatic activities contribute to the conversion of glucose to pyruvate (Tanner *et al*., 2018). These three enzymes function as "gatekeepers" in controlling the movement of metabolites along the glycolysis route because they catalyze irreversible reactions and have high free energy changes (ΔG) values (Kalapos *et al*., 2022).

The first enzyme to start glycolysis is hexokinase, which uses ATP to phosphorylate glucose to glucose-6-phosphate (Tian *et al*., 2024). This reaction is not only the initial step in glucose degradation but also serves to maintain glucose within the cell because the phosphorylated form cannot penetrate the plasma membrane (Wasserman, 2022). As a type of negative feedback regulation, hexokinase activity is allosterically regulated by glucose-6-phosphate, its reaction product, to avoid an excessive build-up of the metabolite (Pan *et al*., 2025).

The subsequent step, which is primarily responsible for determining the glycolysis pathway's pace, is the PFK-1-catalyzed reaction that converts fructose-6-phosphate to fructose-1,6-bisphosphate (Li *et al*., 2018). This enzyme is sensitive to variations in the cell's energy status, which makes it a key regulator of glycolysis (Lynch *et al*., 2024). PFK-1 activity is inhibited by high ATP concentrations and activated by increasing AMP, ADP, or fructose-2,6-bisphosphate (Wang *et al*., 2024b). This system makes sure that glycolysis only speeds up when the cell needs more energy and slows down when its energy stores are enough (Chandel, 2021a).

The last regulatory enzyme is pyruvate kinase, which catalyzes the substrate-level phosphorylation that produces ATP and converts phosphoenolpyruvate (PEP) to pyruvate (Schormann *et al*., 2019). Pyruvate kinase activity is also strictly regulated by covalent modification and allosteric regulation (Taguchi *et al*., 2024). For instance, the upstream step's fructose-1,6-bisphosphate functions as an allosteric activator (feed-forward activation), facilitating the metabolites' seamless passage to the last stage (Yang *et al*., 2023). On the other hand, ATP and alanine function as inhibitors to keep the metabolism in balance and stop excessive energy production (Mori *et al*., 2023).

Regulation of glycolysis

Glycolysis as the main metabolic pathway in cellular energy production is tightly regulated to ensure a match between energy supply and physiological needs (Jeon, 2024). This regulation takes place on multiple levels, such as hormone modulation, adaptation to cellular circumstances, and allosteric control of important enzymes (Rojas-Pirela *et al*., 2025).

Control mostly takes place at the allosteric level in three irreversible reaction-carrying enzymes: pyruvate kinase, phosphofructokinase-1 (PFK-1), and hexokinase (Campos and Albrecht, 2024). Negative feedback regulates hexokinase by causing glucose-6-phosphate to build up, preventing excessive glucose intake when energy stores are enough (Geidl-Flueck and Gerber, 2017). The most crucial regulatory point, PFK-1, is extremely sensitive to the cell's energy state (Kanai *et al*., 2019). High levels of ATP signal energy sufficiency and prevent this enzyme from functioning, whereas when energy is scarce, elevated levels of AMP, ADP, and fructose-2,6-bisphosphate activate PFK-1 to speed up glycolysis (Fernandes *et al*., 2020). ATP and alanine inhibit pyruvate kinase to prevent excessive energy production, whereas fructose-1,6-bisphosphate (feed-forward mechanism) activates the enzyme to ensure steady metabolite flow to the final step (Jeon, 2024).

Hormones also affect glycolysis in addition to allosteric modulation (Ayyildiz *et al*., 2020). Hormone insulin increases the flow of glucose into this route under hyperglycemic situations by promoting the production and activity of glycolytic enzymes such pyruvate kinase, PFK-1, and glucokinase (Petersen and Shulman, 2018). On the other hand, under hypoglycemia circumstances, glucagon and adrenaline inhibit the liver's glycolysis by phosphorylating enzymes, such as pyruvate kinase (Zhang *et al*., 2019). A metabolite produced by the bifunctional enzyme phosphofructokinase-2/fructose-2,6-bisphosphatase (PFK-2/FBPase-2) called fructose-2,6-bisphosphate also plays a significant role (Bartrons *et al*., 2018). This compound plays a key role in regulating glycolysis and gluconeogenesis in response to hormonal cues since it is a strong PFK-1 activator and fructose-1,6-bisphosphatase inhibitor (Yu *et al*., 2021).

Cellular factors can have a significant impact on the regulation of glycolysis (Zhan *et al*., 2025). The destiny of pyruvate is primarily determined by the availability of oxygen (Fan *et al*., 2025). In anaerobic situations, pyruvate is converted to lactate to regenerate NAD^+, allowing glycolysis to proceed, whereas in aerobic settings, it is delivered to the mitochondria to undergo oxidative decarboxylation to acetyl-CoA and enter the Krebs cycle (Schurr, 2024). Enzyme activity can also be impacted by variations in pH, intracellular ions, and nutrition availability (Alghalayini *et al*., 2023). This phenomenon, known as the Warburg effect, is seen in cancer cells, where enhanced glycolysis occurs even when oxygen is present (Liberti and Locasale, 2016). The cell's response to the requirement for quick

growth is reflected in this metabolic reprogramming, which promotes glycolysis by controlling the expression of genes and enzymes (Navarro *et al*., 2022).

Product and its relationship with other pathways

Glycolysis yields two pyruvate molecules, two net ATP molecules, and two NADH molecules for every glucose molecule (Bonora *et al*., 2012). This pathway's endpoint, pyruvate, is a crucial metabolic junction because it can be diverted into a number of different following pathways based on cellular conditions, most notably the availability of oxygen (Prochownik and Wang, 2021).

The pyruvate dehydrogenase enzyme complex transports pyruvate into the mitochondrial matrix and transforms it into acetyl-CoA under aerobic circumstances (Lee *et al*., 2016). The Krebs cycle is then entered by this acetyl-CoA, generating NADH, $FADH_2$, and GTP/ATP, which are subsequently utilized in oxidative phosphorylation to generate significant amounts of energy (Martínez-Reyes and Chandel, 2020). Therefore, the glycolysis pathway is the first source of substrate that connects aerobic cellular respiration and glucose metabolism (Kierans and Taylor, 2024).

Pyruvate, on the other hand, is unable to reach the oxidative route in anaerobic environments when oxygen is insufficient as the last electron acceptor in the electron transport chain (Saari *et al*., 2019). Glycolysis can proceed in this situation because the cell redirects pyruvate to the fermentation route in order to replenish NAD^+ from NADH (Wang *et al*., 2022). Pyruvate can be transformed into ethanol or other fermentation products in some bacteria, but in vertebrate cells, the enzyme lactate dehydrogenase reduces it to lactate (Fang *et al*., 2023). This process enables cells to continue producing ATP even in hypoxic environments, despite the fact that fermentation produces a lot less energy than aerobic respiration (Arias *et al*., 2025).

Furthermore, several metabolic pathways are closely related to the intermediate metabolites of glycolysis. For instance, 3-phosphoglycerate can be utilized for the production of the amino acid serine, whereas glyceraldehyde-3-phosphate and dihydroxyacetone phosphate can serve as precursors in lipid synthesis by forming glycerol-3-phosphate (Jin *et al*., 2023). This highlights glycolysis's dual function as a source of anabolic raw materials and as a process that produces energy (Kierans and Taylor, 2024). Figure 1 illustrates the glycolysis pathway, highlighting the energy-investment and payoff phases, the key regulatory enzymes (hexokinase/glucokinase, PFK-1, pyruvate kinase), and the aerobic versus anaerobic fates of pyruvate.

Oxidative phosphorylation

Oxidative phosphorylation is the last stage of cellular respiration, which occurs in the inner membrane of the mitochondria. Here, ATP synthase and the electron transport chain transform the chemical energy from the oxidation of NADH and $FADH_2$ into ATP (Nolfi-Donegan *et al*., 2020). This mechanism is crucial for preserving redox equilibrium and controlling cellular metabolism in addition to being the primary source of energy production in eukaryotic cells (Wilson, 2017).

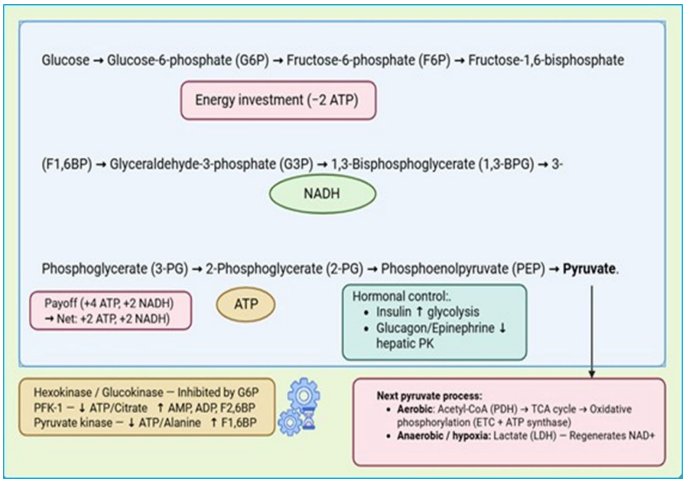

Figure 1. Glycolysis pathway with energy phases, key regulators, and pyruvate fates.

Location in mitochondria

The last phase of cellular respiration, known as oxidative phosphorylation, occurs in the inner membrane of the mitochondria, a structure created especially to aid in the energy conversion process (Kowalczyk *et al*., 2021). The inner membrane is highly impermeable to ions and charged molecules, which is one of its many distinct properties from the outer membrane (Látrová *et al*., 2021). This characteristic is crucial for preserving the proton gradient that forms as the foundation of the mechanism for ATP synthesis (Pham *et al*., 2024). Furthermore, the inner membrane contains a unique lipoprotein known as cardiolipin, which supports the electron transport protein complex's function while offering structural stability (Yoo *et al*., 2025).

Folds known as cristae are formed by the inner membrane structure, greatly increasing the surface area (Leveille *et al*., 2017). The electron transport chain's enzymatic complexes, such as Complexes I–IV, coenzyme Q, cytochrome c, and ATP synthase, can be accommodated by the increased surface area (Zhao *et al*., 2019). This is the location of the pumping of protons from the mitochondrial matrix to the intermembrane space and a sequence of electron transfers from NADH and $FADH_2$ to oxygen (Nolfi-Donegan *et al*., 2020).

Table 1. Electron Transport Chain (ETC) components and their main functions.

ETC components	Electron entry point / Source	Cofactor / Structure	Main role	Proton pumping
Complex I (NADH dehydrogenase / ubiquinone oxidoreductase)	NADH	FMN and Fe-S cluster	Transferring electrons from NADH to coenzyme Q and initiating a proton gradient	4 protons per electron pair
Complex II (Succinate dehydrogenase / ubiquinone reductase)	$FADH_2$ (succinate oxidation → fumarate)	FAD and Fe-S cluster	Transferring electrons from $FADH_2$ to coenzyme Q	0 proton
Coenzyme Q (Ubiquinone)	From Complex I and II	Membrane-soluble lipid molecules	The electron carriers move to Complex III and engage the Q-cycle for additional proton pumping.	Indirect contribution through Q-cycle
Complex III (Cytochrome bc_1 / ubiquinol-cytochrome c oxidoreductase)	Ubiquinol (QH_2)	Cytochrome b, cytochrome c_1, and Fe-S Rieske protein	Transferring electrons to cytochrome c and strengthening the proton gradient through the Q-cycle	4 protons per electron pair
Cytochrome c	From Complex III	Intermembrane space soluble proteins	Carries electrons one by one to Complex IV and plays a role in apoptosis	Does not pump protons
Complex IV (Cytochrome c oxidase)	Cytochrome c	Cytochrome a, cytochrome a_3, and Cu_A and Cu_B	Reduce oxygen to water and ETC terminals	2 protons per electron pair

The matrix and the intermembrane space have different proton distributions, which results in an electrochemical gradient (proton motive force) (Berry *et al*., 2018). A big enzyme called ATP synthase, which is also found in the inner membrane, uses this gradient to transform the potential energy of protons into chemical energy in the form of ATP (Neupane *et al*., 2019). Therefore, the inner mitochondrial membrane serves as both the physical site of the electron transport chain and a bioenergetic hub from which the majority of the cell's metabolic energy is derived (Bao *et al*., 2025).

Electron transport chain (ETC) components: complexes I–IV, coenzyme Q, and cytochrome c

Several integral membrane protein complexes and electron carrier molecules found on the inner membrane of the mitochondria make up the electron transport chain (ETC) (Kühlbrandt, 2015). All of these elements cooperate to pump protons into the intermembrane gap, creating an electrochemical gradient, and transport electrons from NADH and $FADH_2$ to oxygen (DeBalsi *et al*., 2017). Table 1 summarizes the function of each component of the electron transport chain (ETC) in the inner mitochondrial membrane.

Complex I (NADH dehydrogenase/ubiquinone oxidoreductase) is the main entry point for electrons from NADH (Gutiérrez-Fernández *et al*., 2020). The redox cofactors in this big complex are an iron-sulfur (Fe-S) cluster and flavin mononucleotide (FMN) (Grivennikova *et al*., 2024). After initially moving to FMN and then via the Fe-S group, electrons from NADH are ultimately reduced to coenzyme Q (ubiquinone) (Read *et al*., 2021). Four protons are pumped from the matrix into the intermembrane gap during this phase (Guerra and Pagliarini, 2023).

Complex II (succinate dehydrogenase/ubiquinone reductase) serves as an alternative entry point for electrons through the oxidation of succinate to fumarate in the Krebs cycle (Bandara *et al*., 2021). This complex includes multiple Fe-S groups and FAD (Huang *et al*., 2021). Complex II contributes less to the proton gradient than Complex I because it routes electrons directly to coenzyme Q rather than pumping protons (Okoye *et al*., 2023).

The lipid molecule known as coenzyme Q (ubiquinone) is soluble in membranes and functions as a mobile electron carrier (Pallotti *et al*., 2021). Electrons are transferred to Complex III by ubiquinone after being accepted from Complex I and II (Mantle *et al*., 2024). Furthermore, coenzyme Q plays a role in the Q-cycle process, which adds to the proton pumping (Wang *et al*., 2024c).

Complex III (cytochrome bc_1/ubiquinol-cytochrome c oxidoreductase) accepts electrons from ubiquinol (the reduced form of coenzyme Q) and transfers them to cytochrome c via the Q cycle (Havens *et al*., 2023). This process is accompanied by the pumping of four protons into the intermembrane space for each pair of electrons transferred (Mantle *et al*., 2024). Cofactors for Complex III include the Fe-S Rieske protein, cytochrome b, and cytochrome c_1 (Fernandez-Vizarra and Zeviani, 2018).

The tiny protein cytochrome c is a mobile electron transporter between complexes and dissolves in the intermembrane gap (Pérez-Mejías *et al*., 2020). This molecule moves electrons from Complex III to Complex IV one at a time (Gomila *et al*., 2022). The release of cytochrome c into the cytoplasm contributes to the mechanism of apoptosis in addition to its function in the ETC (Mustafa *et al*., 2024).

Complex IV (cytochrome c oxidase) is the terminal enzyme in the ETC that accepts electrons from cytochrome c and transfers them to molecular oxygen, producing water (Watson and McStay, 2020). This complex contains important cofactors in the form of cytochrome a, cytochrome a_3, and copper ions (Cu_A and Cu_B) (Swaminathan and Gohil, 2022). Two protons are pumped into the intermembrane gap in conjunction with this process, which strengthens the proton gradient even more (Blomberg, 2021).

The mechanism of proton gradient formation and the role of ATP synthase

The foundation of oxidative phosphorylation is chemiosmotic theory, which was initially put forth by Peter Mitchell. This theory states that protons (H^+) are pumped from the matrix to the intermembrane space via the inner mitochondrial membrane using the free energy from electron transfer along the electron transport chain (ETC) (Mitchell, 2011). Complexes I, III, and IV are where this proton pumping mostly takes place; Complex II does not directly contribute to the proton gradient (Wikström and Springett, 2020). Proton buildup in the intermembrane space results in a membrane potential ($\Delta\psi$) and a differential in proton concentration (ΔpH), which together make up the proton motive force (PMF) (Lee, 2019).

The inner membrane stores the electrochemical potential energy produced by this PMF (Selim and Wojtovich, 2025). The inner membrane is impervious to H^+ ions, yet the naturally accumulated protons have a tendency to return to the matrix to reach equilibrium (Naima and Ohta, 2024). The only method to re-enter the body is through ATP synthase (Complex V), a big multiprotein enzyme with two primary functional domains: F_1, which extends into the matrix and works as the catalytic site for ATP synthesis, and F_0, which is found in the membrane and functions as a proton channel (Vlasov *et al*., 2022).

The F_0 subunit rotates as a result of protons flowing down its gradient, which is how ATP synthase functions (Zharova *et al*., 2023). The F_1 subunit subsequently receives the mechanical energy from this rotation and uses inorganic phosphate (P_i) to catalyze the conversion of ADP to ATP (Sobti *et al*., 2021). Three ATP molecules are produced for every full rotation (Ueno *et al*., 2025). Since ATP synthase transforms electrochemical potential energy into chemical energy in the form of ATP, it functions as a nano-biological energy converter (Macdonald and Ashby, 2025).

This process is incredibly effective, enabling oxidative phosphorylation to generate roughly 30–32 ATP for every fully oxidized glucose molecule (Mookerjee *et al*., 2017). Furthermore, other physiological functions as the active transport of metabolites across the mitochondrial membrane and the control of apoptosis are also influenced by the existence of a proton gradient (Chlubek and Baranowska-Bosiacka, 2024).

ATP production efficiency and its regulation

Oxidative phosphorylation is the most efficient pathway for producing energy in eukaryotic cells (Wilson, 2017). It takes about 30 to 32 ATP molecules to completely oxidize one glucose molecule through the Krebs cycle, glycolysis, decarboxylation of pyruvate, and the electron transport chain (Chandel, 2021a). This estimate depends on the amount of NADH and $FADH_2$ produced, as well as the contribution of each molecule to the proton gradient (Manoj, 2018). One NADH oxidation typically yields around 2.5 ATP, but one $FADH_2$ oxidation yields about 1.5 ATP. This is because the electrons from $FADH_2$ enter the ETC more slowly (Complex II), pumping fewer protons (Ivanishchev, 2025).

This efficiency is influenced by physiological variables in addition to the reaction's stoichiometry. Other processes than ATP generation, like matrix volume modulation, thermogenesis through uncoupling proteins (UCPs), and metabolite transport across the mitochondrial membrane, can consume some of the energy from the proton gradient (Nicholls, 2021). As a result, the true effectiveness of oxidative phosphorylation differs among cells and tissues and may be reduced under pathological circumstances (Hajam *et al*., 2022).

The availability of the substrate and the cell's energy state are the main factors governing the regulation of oxidative phosphorylation (Zhang *et al*., 2022b). This process, referred to as respiratory control, causes the rate of ATP synthesis and oxygen consumption to rise in states of high ADP concentration (state 3 respiration) and fall in states of sufficient ATP (state 4 respiration) (Divakaruni and Jastroch, 2022). Therefore, the main signals influencing this pathway's activity are the ATP/ADP and $NADH/NAD^+$ ratios (Amjad *et al*., 2021).

Other physiological elements also affect regulation in addition to energy control. The ETC depends on oxygen levels, the last electron acceptor; low oxygen will reduce efficiency and cause metabolism to change to anaerobic glycolysis (De Leon-Oliva *et al*., 2025). The activity of NADH/$FADH_2$-supplying dehydrogenases, the production of ETC complexes, and mitochondrial biogenesis can all be enhanced by hormonal regulation, such as that induced by the thyroid, insulin, and catecholamines (Lindsay and Rhodes, 2025). On the other hand, oxidative stress can reduce ATP generation by inhibiting certain complexes through oxidative protein modification (Chen *et al*., 2024).

Oxidative stress and the role of ROS as byproducts

Oxidative phosphorylation serves as the primary pathway for energy production and is also the primary cause of the development of reactive oxygen species (ROS) in cells (Akhigbe and Ajayi, 2021). The electron transport chain (ETC) produces ROS as a consequence of electron transfer, particularly when electrons leak and react directly with molecular oxygen to produce superoxide radicals ($O_2•^-$) (Zhao *et al*., 2019). Complex I (NADH dehydrogenase) and Complex III (cytochrome bc_1) are the most common sites for this electron leakage, particularly when there is an excess of reductive substrate (high NADH/$FADH_2$) or when the proton gradient is too great, which slows down electron transport (Chavda and Lu, 2023).

The enzyme superoxide dismutase (SOD) can then transform superoxide radicals into hydrogen peroxide (H_2O_2) and, via the extremely reactive Fenton reaction, hydroxyl radicals (•OH) (Fujii *et al*., 2022). Oxidative stress, a state of imbalance between ROS production and the antioxidant system's capacity in cells, can be brought on by excessive ROS (Pizzino *et al*., 2017). Oxidative stress can damage important biomolecules such as DNA, proteins, and membrane lipids, which ultimately contribute to the aging process, apoptosis, and various degenerative diseases, including neurodegeneration, diabetes, and cancer (Pooja *et al*., 2025).

However, ROS is not only destructive. ROS act as signaling molecules at the physiological level, controlling immunological responses, proliferation, differentiation, and signal transduction pathways (Sinenko *et al*., 2021). For instance, H_2O_2 contributes to the activation of transcription factors that are crucial for stress and hypoxia adaptation, including NF-κB and HIF-1α (Luo *et al*., 2022). As a result, oxidative phosphorylation-induced ROS generation is a bipolar phenomena that is advantageous when under control but detrimental when out of control (Głombik *et al*., 2021).

The glutathione and thioredoxin systems, glutathione peroxidase, and catalase are examples of endogenous antioxidant mechanisms that cells have in order to preserve this equilibrium (Ighodaro and Akinloye, 2018). Redox equilibrium requires strict control over the production of ROS and detoxification (Chen *et al*., 2025). As shown in Figure 2, electrons from NADH and $FADH_2$ flow through Complexes I–IV to drive proton pumping across the inner mitochondrial membrane, and the resulting gradient powers ATP synthase to generate ATP.

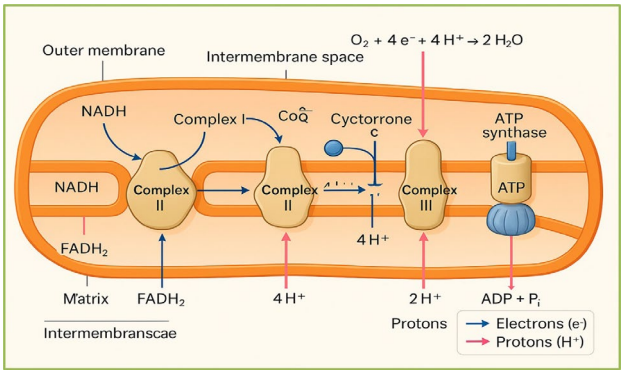

Figure 2. Oxidative phosphorylation in the mitochondrion: electron transport chain and ATP synthase

Lipid metabolism

Lipid metabolism is a significant bioenergetic route that contributes significantly to energy supply, particularly when glucose availability is restricted (Peeters and Jellusova, 2024). Triglycerides are broken down by the process of lipolysis, which releases free fatty acids, which the mitochondria use as oxidative substrates for β-oxidation (Chandel, 2021b). This pathway is closely controlled by enzymatic systems and hormonal signals to maintain cellular energy balance under a variety of physiological conditions, including fasting, exercise, and ketosis, in addition to contributing to the production of large amounts of ATP through its linkage with the Krebs cycle and oxidative phosphorylation (Liu *et al*., 2025).

Lipolysis and β-oxidation of fatty acids

The first step of lipid metabolism, known as lipolysis, attempts to liberate free fatty acids from adipose tissue's triglyceride reserves (Li *et al*., 2022). This process is catalyzed by a series of key enzymes, including adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL) (Brejchova *et al*., 2021). Hormonal signals tightly regulate lipolysis activity; insulin inhibits the cAMP–protein kinase A (PKA) pathway, which phosphorylates and activates HSL, while catecholamines and glucagon activate the process (Althaher, 2022). Free fatty acids and glycerol are the end products of lipolysis; free fatty acids serve as the primary substrate for β-oxidation, while glycerol might enter the gluconeogenesis or glycolysis pathway (Panov *et al*., 2024).

β-oxidation is a fatty acid catabolism pathway that takes place in the mitochondrial matrix (Tamas *et al*., 2024). The acyl-CoA synthetase enzyme uses ATP to first convert fatty acids into acyl-CoA before they can proceed with this action (Wang *et al*., 2024d). Transport necessitates the carnitine system, which includes carnitine acyltransferase I (CAT I) on the outer membrane, carnitine translocase on the inner membrane, and carnitine acyltransferase II (CAT II) on the matrix side, since the inner mitochondrial membrane stops acyl-CoA from passing through (Xiang *et al*., 2025). Following its entry into the matrix, acyl-CoA goes through four cyclic reactions: acyl-CoA dehydrogenase oxidizes it dehydrogenatively (producing $FADH_2$), enoyl-CoA is hydrated to hydroxyacyl-CoA, hydroxyacyl-CoA dehydrogenase oxidizes it again (producing NADH), and β-ketothiolase thiolyzes it, cleaving two carbon atoms to produce acetyl-CoA (Sharma and McKenzie, 2025).

The fatty acid chain is shortened by two carbon atoms per cycle of β-oxidation, yielding one molecule of acetyl-CoA, one $FADH_2$, and one NADH (Sharpe and McKenzie, 2018). After that, acetyl-CoA goes into the Krebs cycle to generate more energy, and NADH and $FADH_2$ contribute electrons to the electron transport chain to help oxidative phosphorylation (Arneth, 2023). Lipid metabolism is the most energy-rich process since a single molecule of a long saturated fatty acid, like palmitic acid (C16:0), can completely oxidize to yield up to 106 ATP (Morales *et al*., 2021).

The role of carnitine in fatty acid transport into mitochondria

The primary substrates for β-oxidation in the mitochondrial matrix are long-chain fatty acids; however, the acyl-CoA molecules that result from fatty acid activation are unable to directly cross the inner mitochondrial membrane (Adeva-Andany *et al*., 2019). Fatty acids must thus be able to enter the areas of energy breakdown, which is made possible by a unique transport mechanism called the carnitine shuttle (Longo *et al*., 2016).

This process starts on the cytosolic side of the outer mitochondrial membrane, where an acyl group is transferred from acyl-CoA to a carnitine molecule, creating acyl-carnitine, by the enzyme carnitine palmitoyltransferase I (CPT-I or CAT-I) (Qu *et al*., 2016). Carnitine–acylcarnitine translocase (CACT) can move this more soluble substance across the in-

ner membrane (Tonazzi *et al*., 2021). The enzyme carnitine palmitoyltransferase II (CPT-II or CAT-II) releases the carnitine molecule back into the intermembrane space for reuse after returning the acyl group to coenzyme A in the mitochondrial matrix. This regenerates acyl-CoA, which is then prepared to join the β-oxidation cycle (Joshi and Zierz, 2020).

The carnitine system serves as a regulatory mechanism for energy metabolism in addition to facilitating the transfer of long-chain fatty acids (Volpicella *et al*., 2025). Malonyl-CoA, a crucial product of fatty acid biosynthesis, functions as a strong inhibitor to regulate CPT-I activity (Liang, 2023). Thus, cells can preserve metabolic efficiency by avoiding the simultaneous oxidation and synthesis of fatty acids (Rodríguez-Rodríguez *et al*., 2025).

Fatty acid buildup in the cytoplasm and a reduction in the capacity of cells to generate energy from lipids might result from carnitine shortage or enzyme abnormalities in the carnitine shuttle (Qu *et al*., 2016). This condition is associated with serious metabolic disorders, including hypoketotic hypoglycemia, muscle weakness, and cardiomyopathy (Alhasaniah, 2023). As a result, carnitine is crucial for maintaining cellular energy homeostasis in addition to its function as a transport molecule (Farahzadi *et al*., 2023).

Relationship with the Krebs cycle and oxidative phosphorylation

The Krebs cycle and oxidative phosphorylation are tightly related to lipid metabolism, especially through the β-oxidation of fatty acids, as part of the bioenergetic integration of cells (Szrok-Jurga *et al*., 2023a). Acetyl-CoA is the primary result of β-oxidation and provides a direct pathway into the Krebs cycle (Arneth, 2023). Each incoming acetyl-CoA will completely oxidize to CO_2 while also generating high-energy reductants like NADH and $FADH_2$ (Manoj, 2018). Therefore, in addition to providing carbon substrates, β-oxidation also produces reduced coenzymes, which serve as the main source of energy for mitochondrial respiration (Dikalov *et al*., 2024).

At every two-carbon shortening cycle, β-oxidation directly generates NADH and $FADH_2$ in addition to acetyl-CoA (Borkum, 2023). Following that, these reductant molecules are directed toward the mitochondria's inner membrane's electron transport chain (ETC) (Wan *et al*., 2019). Complex I is where NADH gives its electrons, and Complex II is where $FADH_2$ enters the ETC (Gnaiger, 2024). Proton pumping, which occurs in tandem with this electron flow, creates an electrochemical gradient that ATP synthase uses to transform this potential energy into significant amounts of ATP (Berry *et al*., 2018).

Additionally dynamic and interdependent is the relationship between oxidative phosphorylation, the Krebs cycle, and lipid metabolism (Arnold and Finley, 2023). Only when there is a enough supply of oxaloacetate in the Krebs cycle can acetyl-CoA from β-oxidation be effectively oxidized (Zhelev *et al*., 2022). Oxaloacetate deficiency conditions, such as diabetes or extended fasting, will prevent the Krebs cycle from using acetyl-CoA and cause metabolism to change toward ketogenesis (Emanuele *et al*., 2025). This demonstrates that a balance between the Krebs cycle and carbohydrate metabolism is necessary for smooth lipid oxidation (González *et al*., 2023).

Regulation of lipid metabolism

The intricate process of regulating lipid metabolism maintains equilibrium between the mobilization of fatty acids for energy requirements and the storage of energy in the form of triglycerides (Yoon *et al*., 2021). This process is controlled by integrated enzymatic interactions and hormonal signals.

The hormone-sensitive lipase (HSL) enzyme is crucial in hydrolyzing triglycerides into free fatty acids and glycerol during the triglyceride mobilization stage in adipose tissue (Althaher, 2022). Hormonal status has a significant impact on HSL activity. The cAMP–protein kinase A (PKA) pathway is activated by the hormones glucagon and catecholamines (epinephrine, norepinephrine) to promote lipolysis (Guilherme *et al*., 2023). PKA facilitates enzyme access to triglycerides by phosphorylating the perilipin and HSL proteins on the surface of lipid droplets (Sztalryd and Brasaemle, 2017). On the other hand, insulin inhibits lipolysis by triggering phosphodiesterase, which lowers cAMP levels, and prompting phosphoprotein phosphatase to dephosphorylate and inactivate HSL (Zhao *et al*., 2020). As a result, HSL takes the lead in regulating the release of triglyceride reserves (Cho *et al*., 2023).

Following lipolysis, the free fatty acids that are liberated are carried into the mitochondria where they undergo β-oxidation (Bezawork-Geleta *et al*., 2025). The mitochondrial outer membrane contains the enzyme carnitine palmitoyltransferase I (CPT1), which regulates the crucial step in this transport (Wang *et al*., 2021). Acyl-CoA is changed by CPT1 into acyl-carnitine, which is able to pass through the inner mitochondrial membrane (Virmani and Cirulli, 2022). The main allosteric inhibitor that controls CPT1 is malonyl-CoA, a crucial molecule of fatty acid production (Bowman and Wolfgang, 2019). An ineffective metabolic cycle is avoided by this inhibition, which stops fatty acid oxidation from taking place concurrently with lipid synthesis (Li *et al*., 2023b).

The primary hormonal factor governing lipid metabolism is the equilibrium between insulin and glucagon (Zhang *et al*., 2023). Insulin, which predominates in postprandial settings, inhibits lipolysis by deactivating HSL and promotes triglyceride production by activating lipoprotein lipase (Petersen and Shulman, 2018). On the other hand, glucagon and catecholamines are more prevalent during fasting or hunger, which activates CPT1 by promoting lipolysis through HSL activation and speeding up fatty acid oxidation by decreasing malonyl-CoA production (Hayashi, 2021).

Special conditions

The ability of lipid metabolism to adjust to shifts in energy levels and physiological demands is quite flexible. Under normal circumstances, when glucose is scarce, fatty acid oxidation provides the primary support for energy production (Kemp *et al*., 2024). However, lipid metabolic pathways change significantly in response to unique conditions like ketosis, fasting, and vigorous exercise (Huang *et al*., 2020).

In ketosis, which usually happens when there is a prolonged lack of carbohydrates, either during a lengthy fast or uncontrolled diabetes, there is not enough oxaloacetate for the acetyl-CoA generated from β-oxidation to enter the Krebs cycle (Kadir *et al*., 2020). Acetyl-CoA is subsequently diverted by the liver to the ketogenesis pathway, where it produces ketone bodies such as acetoacetate, β-hydroxybutyrate, and acetone (Puchalska and Crawford, 2017). After being released into the bloodstream, these ketone bodies are used as a substitute energy source by the kidneys, skeletal muscles, and most importantly, the brain, which typically uses glucose (Mechchate, 2025). This process is a crucial adaptation tactic to preserve energy homeostasis in situations where glucose stores are low (Ashtary-Larky *et al*., 2022).

During fasting, lipid metabolism undergoes progressive changes according to the duration of the lack of energy intake (Vasim *et al*., 2022). The primary substrate for β-oxidation is free fatty acids, which are produced when lipolysis in adipose tissue rises during the first phase (Kersten, 2023). Tissue reliance on glucose is lessened as a result of the gradual transition towards using ketones as the primary energy source shown by the rise in plasma ketone body content (Mechchate, 2025). The goal of this adaptation is to preserve glucose for tissues that require it most, like some types of nerve tissue and erythrocytes (Remesar and Alemany, 2020).

In physical activity or sport, lipid metabolism is an important source of energy, especially in moderate to high intensity and long duration exercise (Alghannam *et al*., 2021). Muscle contraction activity speeds up intramuscular lipid oxidation and enhances the absorption of fatty acids from plasma (Muscella *et al*., 2020). This process is mediated by lower-

ing insulin levels, which typically prevent lipid mobilization, and raising catecholamine concentrations, which stimulate lipolysis (Jönsson *et al.*, 2019). Exercise thereby promotes long-term metabolic changes, such as improved muscle oxidative efficiency and mitochondrial density, in addition to initiating the use of lipids as energy source (Smith *et al.*, 2023). As summarized in Figure 3, lipid metabolism channels free fatty acids released by adipocyte lipolysis through the carnitine shuttle for mitochondrial β-oxidation, fueling the TCA cycle and oxidative phosphorylation to produce ATP.

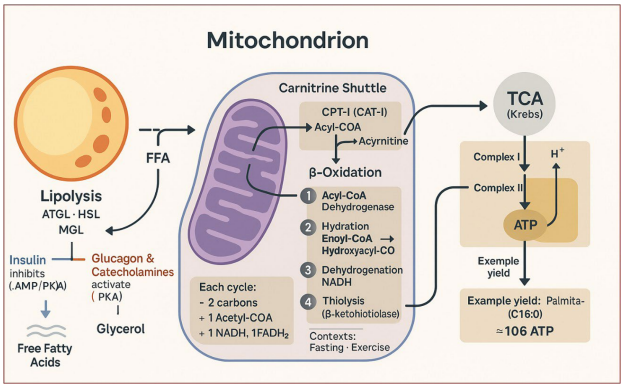

Figure 3. Lipid metabolism: from lipolysis to mitochondrial ATP production.

Metabolic pathway integration

Maintaining cellular energy balance requires the integration of metabolic pathways, where fatty acid oxidation, glycolysis, and oxidative phosphorylation interact dynamically to fulfill energy demands under different physiological situations (Panov *et al.*, 2024). This mechanism is controlled by molecular regulatory systems, such as AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR), which act as energy sensors and determinants of the direction of metabolic substrate allocation (Purnomo *et al.*, 2025). Energy homeostasis is preserved because of these cross-pathway interactions, which enable cells to flexibly adjust to changes in the environment, such as periods of rest, vigorous exercise, and fasting (Liu *et al.*, 2025).

The relationship between glycolysis, fatty acid oxidation, and oxidative phosphorylation

Cellular bioenergetics is based on the interplay of fatty acid oxidation, glycolysis, and oxidative phosphorylation (Simon and Molina, 2022). These three routes work together to provide energy in the form of ATP to support essential cell operations rather than operating independently. Table 2 describes the interrelationships of the three main cellular bioenergetic pathways.

The primary mechanism for the cytoplasmic breakdown of glucose is glycolysis, which yields pyruvate and reductants in the form of NADH (Kierans and Taylor, 2024). The mitochondria's pyruvate dehydrogenase complex can subsequently transform pyruvate into acetyl-CoA, which subsequently enters the Krebs cycle (Zeng *et al.*, 2021). The electron transport chain (ETC) uses the end products of the Krebs cycle, NADH and $FADH_2$, as fuel for oxidative phosphorylation (Arneth, 2023).

In the meantime, fatty acid oxidation by β-oxidation yields significant amounts of $FADH_2$, NADH, and acetyl-CoA (Panov *et al.*, 2024). Lipid-derived acetyl-CoA enters the Krebs cycle, whereas NADH and $FADH_2$ are sent straight to the ETC (Williams and O'Neill, 2018). Thus, the supply of high-energy reductants that propel oxidative phosphorylation is facilitated by both glycolysis and lipid oxidation (Liu *et al.*, 2025).

The last step of metabolic integration is oxidative phosphorylation, where a proton gradient is created across the inner mitochondrial membrane using energy from electron transport (Nolfi-Donegan *et al.*, 2020). ATP synthase is driven by this gradient to produce ATP (Kulish *et al.*, 2016). The efficiency of oxidative phosphorylation is highly dependent on the availability of substrates from both glycolysis and lipid oxidation, as well as the metabolic balance between the two (Wilson, 2017).

These three routes have a fluid connection that varies according to physiological circumstances. Glycolysis is more prevalent in postprandial situations with high glucose availability, while lipid oxidation takes over as the primary energy source during fasting or extended physical activity (Smith *et al.*, 2018). Fatty acid synthesis and oxidation are prevented from happening at the same time via cross-regulation, such as the inhibition of carnitine palmitoyltransferase I by malonyl-CoA (Liang, 2023).

Metabolic control through energy regulation

Molecular regulatory systems that can recognize changes in energy status and modify metabolic activity are essential for maintaining cellular energy homeostasis (Lennicke and Cochemé, 2021). The two primary regulators in this process are mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), which function as energy sensors and modulators of anabolic and catabolic metabolic pathways (Garza-Lombó *et al.*, 2018).

An energy deficiency condition is indicated by an increase in the AMP/ATP ratio, which activates AMPK, a main energy sensor (Wu and Zou, 2020). A sequence of adaptive reactions is triggered by AMPK activation in order to restore energy balance. AMPK generally inhibits anabolic processes that use energy, such as the production of proteins, fatty acids, and cholesterol, while stimulating catabolic pathways that generate ATP, such as fatty acid oxidation and glycolysis (Garcia and Shaw, 2017). For instance, AMPK increases fatty acid oxidation in mitochondria by deactivating the enzyme acetyl-CoA carboxylase (ACC), which lowers malonyl-CoA levels and increases the activity of carnitine palmitoyltransferase 1 (CPT1) (Szrok-Jurga *et al.*, 2023b). In this sense, AMPK is crucial for maintaining energy availability during metabolically stressful situations like fasting or exercise (Juszczak *et al.*, 2020).

On the other hand, mTOR functions as a master regulator of anabolic processes that are triggered in the presence of an abundance of nutrients and energy (Rabanal-Ruiz and Korolchuk, 2018). mTOR activation promotes lipid biosynthesis, cell division, and protein synthesis, especially via the mTORC1 complex (Chouhan *et al.*, 2024). Growth signals via the

Table 2. Integration of cellular bioenergetic pathways.

Metabolic pathways	Main products	Role in oxidative phosphorylation	Dominant condition	Cross-lane regulations
Glycolysis	Pyruvate and NADH	Pyruvate is converted into acetyl-CoA → enters the Krebs cycle and NADH is distributed to the ETC	Postprandial / high glucose availability	Acetyl-CoA production supports oxidative phosphorylation and malonyl-CoA inhibits lipid oxidation when glucose is abundant
Fatty acid oxidation (β-oxidation)	Acetyl-CoA, NADH, and $FADH_2$	Acetyl-CoA enters the Krebs cycle and NADH/$FADH_2$ directly into the ETC	Fasting / prolonged physical activity	CPT1 is controlled by malonyl-CoA and ensures that lipid oxidation does not coincide with lipid synthesis
Oxidative phosphorylation	ATP	Using electrons from NADH/$FADH_2$ to form a proton gradient → ATP synthase produces ATP	All conditions, depending on the substrate available	Efficiency depends on the supply of substrates from glycolysis and β-oxidation and flexible integration according to energy needs

PI3K–Akt pathway, energy status, and amino acid availability all have a significant impact on mTOR regulation (Roy *et al.*, 2023). mTOR facilitates cell division and proliferation by directing metabolic resources toward anabolism when there is enough energy available (Linke *et al.*, 2017).

Although these two paths are adversarial, they are complementary. AMPK can stop mTORC1 activation under low energy conditions by directly phosphorylating upstream components like Raptor or TSC2 (tuberous sclerosis complex 2) (Sukumaran *et al.*, 2020). Together, these interactions create an effective system for regulating energy, with mTOR directing energy toward growth and biosynthesis when substrates are adequate and AMPK ensuring cell viability through energy recovery (Szwed *et al.*, 2021).

Differences in energy use under physiological conditions

The amount of energy that cells and tissues use varies depending on the physiological circumstances they are in (Flood *et al.*, 2023). This difference reflects the body's bioenergetic flexibility in optimizing the availability of metabolic substrates to maintain energy homeostasis.

Fatty acid oxidation serves as the primary energy source for metabolism when at rest, particularly in cardiac and skeletal muscle tissue (Muscella *et al.*, 2020). Particularly, the central nervous system and erythrocytes, which are entirely reliant on glycolysis metabolism, continue to consume glucose (Patil *et al.*, 2022). Overall, though, lipids account for 60–70% of basal energy, with glucose and a trace quantity of amino acids providing the remaining portion (Amaro-Gahete *et al.*, 2020).

Energy consumption during periods of high physical activity is influenced by the length and intensity of exercise. Anaerobic glycolysis is predominant during the early phase or high intensity activity, producing ATP quickly by breaking down glucose to lactate (Hargreaves and Spriet, 2020). The use of muscle glycogen as a rapid energy source and lipid oxidation through β-oxidation, however, play a major role in the transition towards aerobic oxidation that occurs in longer-duration and moderately intense exercises (Alghannam *et al.*, 2021). This adaptation makes it possible to maintain the energy supply despite a sharp increase in ATP demand.

The body changes its metabolism to release stored energy when fasting (Wang and Wu, 2022). Adipose tissue experiences an increase in lipolysis, which releases free fatty acids for oxidation in different tissues (Li *et al.*, 2022). The brain and extrahepatic tissues use the ketone bodies (acetoacetate and β-hydroxybutyrate) that the liver produces from acetyl-CoA from β-oxidation as an alternate energy source (Suresh *et al.*, 2025). This process lessens the reliance of tissues on glucose, allowing erythrocytes and tissues that are unable to directly use lipids or ketones to preserve glucose reserves (Liu *et al.*, 2025). Figure 4 illustrates the integrated control of cellular energy metabolism, linking glycolysis, β-oxidation, and oxidative phosphorylation under AMPK–mTOR regulation.

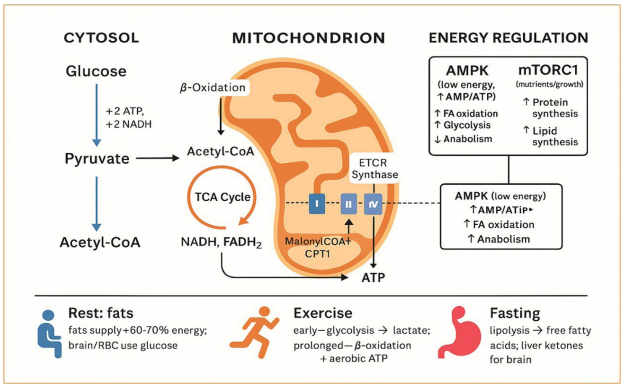

Figure 4. Integrated Cellular Energy Metabolism under AMPK–mTOR Control

Physiological and pathological implications

Energy balance is impacted by disturbances in cellular bioenergetic pathways, which also directly contribute to the emergence of a number of metabolic and degenerative disorders (Rajan and Fame, 2024). Pathological illnesses like diabetes mellitus, obesity, cancer, and mitochondrial abnormalities have been related to dysfunction in glycolysis, lipid oxidation, and oxidative phosphorylation (Wang *et al.*, 2025a). This suggests that cellular bioenergetics has wide-ranging health implications. Understanding these mechanisms in detail is not only essential for comprehending the pathophysiology of disease, but it also creates opportunities for the development of therapeutic approaches to restore energy homeostasis at the cellular level, such as AMPK modulators, glycolysis inhibitors, and agents that target the electron transport chain. Table 3 summarizes the relationship between cellular bioenergetic disorders and major pathological conditions, while highlighting therapeutic strategies that target energy pathways.

Energy metabolism disorders in disease

Cellular bioenergetic dysfunction plays a central role in the pathogenesis of various chronic diseases (San-Millán, 2023). In addition to showing how cells adapt to metabolic stress, changes in glycolysis, lipid oxidation, and oxidative phosphorylation also aid in the advancement of disease (Liu *et al.*, 2024).

In diabetes mellitus, there is an imbalance between glucose and lipid utilization due to insulin resistance (Dilworth *et al.*, 2021). Insulin is not well absorbed by cells, which leads to increased oxidation of fatty acids and decreased uptake of glucose (Clemen *et al.*, 2024). As a result of this imbalance, harmful lipid molecules like ceramide and diacylglycerol build up and worsen insulin resistance by interfering with PI3K–Akt signaling (Elkanawati *et al.*, 2024). Furthermore, diabetes-related mitochondrial dysfunction increases oxidative stress and tissue damage (Caturano *et al.*, 2023).

Table 3. Physiological–pathological implications of cellular bioenergetics disorders and potential therapeutic targets

Disease / Condition	Bioenergetic disorders	Pathological consequences	Potential therapeutic targets
Diabetes mellitus	Insulin resistance, imbalance in glucose and lipid utilization, and impaired mitochondrial function	Decreased glucose uptake, increased fatty acid oxidation, accumulation of toxic metabolites (DAG and ceramide), and oxidative stress	AMPK activators (e.g., metformin and AICAR), enhance mitochondrial function
Obesity	Excess energy intake, lipotoxicity, and abnormal activation of mTOR	Triglyceride accumulation, altered adipokine secretion, chronic low-grade inflammation, and insulin resistance	AMPK activators, mTOR inhibitors (e.g. rapamycin), and lipid metabolism regulators
Cancer	Warburg effect (dominant aerobic glycolysis despite sufficient oxygen) and metabolic reprogramming	Rapid growth, provision of biosynthetic precursors, AMPK suppression, and oncogene activation (c-Myc)	Glycolysis inhibitors (e.g., 2-DG and hexokinase inhibitors), mTOR inhibitors, and combined metabolic therapy–chemotherapy
Mitochondrial disease	Mitochondrial/nuclear DNA mutations and ETC or Krebs cycle disorders	Decreased ATP production, increased ROS, and multisystem symptoms (neurological, muscle, and vital organs)	ETC regulators (e.g. coenzyme Q10 and MitoQ) and mitochondrial antioxidant therapy

In obesity, excess energy intake promotes the accumulation of triglycerides in adipose tissue and non-adipose organs (lipotoxicity) (Nakamura, 2024). This disorder disturbs energy balance, raises chronic low-grade inflammation, and modifies the pattern of adipokine release (Cavaliere *et al*., 2023). Obesity-related aberrant mTOR pathway activation promotes lipogenesis and suppresses lipid oxidation, resulting in a feedback loop that worsens excess energy storage and raises the risk of insulin resistance and metabolic syndrome (Wen *et al*., 2022).

In cancer, cells undergo metabolic reprogramming known as the Warburg effect, which is a tendency to use aerobic glycolysis even when sufficient oxygen is available (Liberti and Locasale, 2016). Cancer cells can produce energy quickly because to this adaptability, which also gives them the biosynthetic building blocks they need to grow and spread (Lin *et al*., 2019). The glycolysis pathway's dominance in tumor cells is further supported by modifications in mitochondrial function, oncogene activation (such as c-Myc), and regulation of energy regulators like AMPK (Zhao *et al*., 2024). Because of this phenomena, energy metabolism could be a target for cancer treatment.

In mitochondrial diseases, genetic mutations in mitochondrial or nuclear DNA disrupt components of the electron transport chain or enzymes of the Krebs cycle (Hossain *et al*., 2025). This leads to a significant decrease in ATP synthesis and an increase in the creation of free radicals (Mei *et al*., 2025). Symptoms of this illness include neurological abnormalities, muscle weakness, and even malfunctioning key organs (Heath *et al*., 2025). Damage to mitochondria has intricate and cumulative systemic repercussions since they are the hub of metabolic integration (Zong *et al*., 2024).

Potential therapeutic targets

Since many metabolic and degenerative disorders are caused by changes in cellular bioenergetics, the pathways of glycolysis, lipid oxidation, and oxidative phosphorylation are prime candidates for therapeutic intervention (Liu *et al*., 2025). These initiatives aim to modulate important enzymes and energy sensors in order to restore energy balance, lower oxidative stress, and stop the course of disease.

Glycolysis inhibitors are one method; these have been thoroughly investigated in malignancies that exhibit the Warburg effect (Bhattacharya *et al*., 2016). Hexokinase inhibitors and 2-deoxy-D-glucose (2-DG) are two examples of agents that can decrease the pace of glycolysis, which lowers the amount of quick energy and biosynthetic precursors that cancer cells receive (Pajak *et al*., 2019). It is anticipated that this approach will delay the growth of tumors, particularly when paired with radiation or chemotherapy (Singh *et al*., 2023).

Furthermore, AMPK activators show promise as treatment options for metabolic disorders like diabetes and obesity (Li *et al*., 2025). As AMPK activation suppresses lipid synthesis and excess energy production through mTOR inhibition, it also promotes catabolic pathways that boost lipid oxidation and glycolysis (Bashah *et al*., 2025). It is well established that medications like AICAR and metformin activate AMPK, which enhances systemic energy homeostasis, lowers hepatic gluconeogenesis, and improves insulin sensitivity (Rena *et al*., 2017).

Therapeutic approaches also focus on controlling the electron transport chain (ETC) at the mitochondrial level (Yamada *et al*., 2020). The efficiency of oxidative phosphorylation can be increased and the electron leakage that causes ROS formation can be decreased by agents that stabilize complex I–IV function or enhance the integrity of the inner membrane of the mitochondria (Okoye *et al*., 2023). Interventions include, for example, using coenzyme Q10 as an ETC cofactor and antioxidant compounds that target mitochondria, such MitoQ, to lessen oxidative damage (Gutierrez-Mariscal *et al*., 2020).

Additionally, mTOR inhibitors like rapamycin are being explored to treat anabolic pathway hyperactivation in cancer, diabetes, and obesity (Marafie *et al*., 2024). This medication lowers excessive cell proliferation, promotes autophagy, and aids in the restoration of energy homeostasis by inhibiting mTORC1 activity (Kumar *et al*., 2025).

Challenges and future research directions

The field of cellular bioenergetics research keeps evolving in tandem with developments in systems technology and molecular biology. Although the fundamentals of oxidative phosphorylation, glycolysis, and lipid metabolism are widely known, their use in clinical and translational settings is still constrained by a number of conceptual and methodological issues.

The advancement of bioenergetics and metabolomics technologies presents fresh chances to investigate metabolic dynamics in greater detail (Pang and Hu, 2023). Understanding tissue metabolic patterns in real-time is made possible by the ability to identify thousands of metabolites in a single assay using mass spectrometry and nuclear magnetic resonance (NMR)-based metabolomics (Gowda and Raftery, 2021). However, single-cell metabolomics and fluxomics methods offer a comprehensive view of cell-to-cell metabolic variability, which is crucial when discussing metabolic, neurodegenerative, and cancerous disorders (Wang *et al*., 2025b).

Future research is also heavily focused on the possibility for metabolism-based medicines. These tactics include the invention of certain inhibitors of metabolic enzymes, the use of pharmacological manipulation of energy sensors like AMPK or mTOR, and nutritional therapy that focus on particular bioenergetic pathways (Smiles *et al*., 2024). The ability of metabolic therapies to affect basic mechanisms that promote cell growth, differentiation, and survival makes them seem promising (Hu *et al*., 2024). The primary obstacle, though, is ensuring target specificity without interfering with normal tissues' energy homeostasis (Ren *et al*., 2024).

Furthermore, little is currently understood about how organ metabolism is integrated. The systemic interconnections between organs, such as those involving the liver, muscle, adipose tissue, and brain, have not yet been thoroughly mapped, and the majority of current bioenergetics research concentrates on the cellular or tissue-specific level (Tseng *et al*., 2010). In fact, energy homeostasis in multicellular organisms depends on the coordination of metabolism across organs through hormonal, neural, and circulating metabolite signals (Castillo-Armengol *et al*., 2019). An integrated cross-organ approach to research is anticipated to yield a more thorough understanding of the pathophysiology of systemic metabolic illnesses such metabolic syndrome, diabetes, and obesity.

Conclusion

Cellular bioenergetics is an integrated system involving glycolysis, oxidative phosphorylation, and lipid metabolism in maintaining energy availability. These three pathways work dynamically to adapt cell needs to physiological conditions and metabolic stress. Cellular function depends on the balance of pathways, whereas bioenergetic imbalance leads to a number of metabolic and degenerative disorders. Strategic potential for the development of future metabolism-based medicines arise from a better understanding of the regulation and interactions across these pathways.

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Conflict of interest

The authors declare that there is no conflict of interest.

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