Review Article

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The AMPK–mTOR axis as a central regulator of cellular metabolism and physiology

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ABSTRACT

The AMPK–mTOR axis is a central regulator of cellular metabolism that balances catabolic and anabolic pathways according to energy, nutrient, and growth factor status. AMPK acts as an energy sensor, activated when the AMP/ATP ratio increases, which promotes fatty acid oxidation, glucose uptake, and autophagy while suppressing protein synthesis, lipogenesis, and cell proliferation. In contrast, mTORC1 integrates nutrient and growth factor signals to promote protein synthesis, organelle biogenesis, and cell growth when environmental conditions are favorable. The dynamic interplay between AMPK and mTOR enables cells to maintain energy balance, regulate growth and metabolism, and preserve the integrity of their organelles. AMPK–mTOR axis dysregulation has been associated with a number of clinical illnesses, such as cancer, obesity, type 2 diabetes, neurodegenerative diseases, and chronic inflammation. Over-activation of mTORC1 or insufficient AMPK activation can result in insulin resistance, lipid buildup, reduced autophagy, and aberrant cell survival and proliferation. On the other hand, medication or lifestyle changes like mTOR inhibitors, AMPK activators, intermittent fasting, or exercise can help rebalance these pathways, enhance organ function, and lower the chance of disease development. This review aimed to summarize the molecular mechanisms of the AMPK–mTOR axis, its role in cellular metabolism and physiology, and its implications for the therapy of metabolic diseases, cancer, and neurodegenerative disorders. An in-depth knowledge of AMPK–mTOR interactions can serve as the foundation for the creation of precision treatment plans that maintain energy homeostasis in both healthy and diseased states, balance catabolic and anabolic pathways, and improve cellular adaptability.

Introduction

Energy homeostasis and regulation of cellular metabolism are essential foundations for optimal physiological function (Vergara *et al*., 2019). The ability of living cells to adjust their growth, differentiation, proliferation, and survival in response to the availability of energy and nutrients is essential (Munteanu and Schwartz, 2022). Imbalances in this process can lead to a variety of metabolic disorders, including obesity, type 2 diabetes, liver dysfunction, and neurodegenerative disorders and cancer (Ruze *et al*., 2023). Therefore, understanding the molecular mechanisms that coordinate metabolic pathways and cellular growth is crucial in cell biology and the development of therapeutic strategies.

Mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) have been found to be key regulators in preserving cellular metabolism and energy balance (Garza-Lombó *et al*., 2018). AMPK functions as a cell energy sensor, activated when the Adenosine Monophosphate/Adenosine Triphosphate (AMP/ATP) ratio increases, or the cell's energy condition decreases (Bashah *et al*., 2025). AMPK activation suppresses energy-consuming anabolic processes like protein synthesis, lipogenesis, and cell proliferation while inducing catabolic pathways to provide energy, such as enhanced fatty acid oxidation, glycolysis, and autophagy (Garcia and Shaw, 2017). On the other hand, under supportive environmental conditions, mTOR, particularly in the form of the mechanistic Target of Rapamycin Complex 1 (mTORC1), promotes protein synthesis, lipogenesis, organelle biogenesis, and cell growth by integrating nutritional signals, growth factors, and energy status (Boutouja *et al*., 2019). The AMPK–mTOR axis, which is the dynamic balance and interaction between AMPK and mTOR, is a crucial mechanism that enables cells to maintain organelle quality and cellular viability while adjusting metabolic activity and growth to physiological demands (Chun and Kim, 2021).

A growing body of research indicates that a number of pathological disorders are influenced by dysregulation of the AMPK–mTOR axis (Jeon, 2016; Li *et al*., 2024a; Wang *et al*., 2025a). The accumulation of damaged organelles and proteins, insulin resistance, lipid buildup, aberrant cell proliferation, and reduced autophagy can all result from either excessive mTORC1 activation or insufficient AMPK activity (Stanciu *et al*., 2024). This condition is the basis for the pathogenesis of metabolic diseases, cancer, neurodegenerative disorders, and chronic inflammation (Yan *et al*., 2017; Ling *et al*., 2020; Huynh *et al*., 2023; Liu *et al*., 2024; Marafie *et al*., 2024). It has been demonstrated that pharmacological modulation or lifestyle treatments that target this axis, such as mTOR inhibitors, AMPK activators, intermittent fasting, or exercise, can enhance organ function, restore energy balance, and lower the risk of disease development (Matawali *et al*., 2025). This confirms the clinical and biological relevance of research on AMPK–mTOR.

Even though AMPK and mTOR have each been the subject of several investigations, little is known about how these two pathways interact and are cross-regulated (González *et al*., 2020; Li *et al*., 2024b; Zhang *et al*.,

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2024). The AMPK–mTOR axis not only influences energy metabolism but also regulates proliferation, differentiation, cell cycle, apoptosis, autophagy, and mitochondrial biogenesis in various tissues, including skeletal muscle, liver, pancreas, and the nervous system (Rey and Tamargo-Gómez, 2023). A comprehensive understanding of this axis is essential for developing therapeutic strategies that precisely balance catabolic and anabolic pathways, reduce side effects, and enhance cellular adaptation to metabolic stress.

Against this background, this review was designed to summarize recent developments regarding the roles of AMPK and mTOR in cellular metabolism and physiology, and to integrate our understanding of their interactions and cross-regulation. The aim of this review was to provide a comprehensive overview of the molecular mechanisms of the AMPK–mTOR axis, its impact on cellular homeostasis and organ physiology, and its therapeutic implications, so that it can serve as a reference for further research and the development of clinical interventions based on modulation of the AMPK–mTOR pathway.

Theoretical basis and molecular mechanisms

The AMPK–mTOR axis is a central signaling pathway that integrates cellular energy and nutrient information, thus playing a crucial role in the regulation of cell metabolism and physiological function.

AMPK

AMPK is a serine/threonine kinase enzyme that functions as a cellular energy sensor and the main regulator of metabolic homeostasis (Sharma *et al*., 2023). The three primary subunits of AMPK are the catalytic (α), regulatory (β), and nucleotide sensor (γ) subunits. The β subunit serves as a scaffold to stabilize the complex, the α subunit has the catalytic site needed to phosphorylate the target protein, and the γ subunit has Adenosine Monophosphate (AMP) and Adenosine Triphosphate (ATP) binding domains that allow for cellular energy sensing (Garcia and Shaw, 2017). The γ subunit undergoes conformational changes in response to an increase in the AMP/ATP or Adenosine Diphosphate/Adenosine Triphosphate (ADP/ATP) ratio, which suggests an energy deficit (Marín-Aguilar *et al*., 2017). This increases the affinity of AMPK for upstream kinases like Transforming Growth Factor-β-activated kinase 1 (TAK1), Calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ), and Liver Kinase B1 (LKB1), which perform activating phosphorylation on the α subunit's Threonine residue number 172 (Thr172) (Glosse and Föller, 2018). This activation allows AMPK to coordinate cellular responses to energy stress.

After activation, AMPK controls several metabolic processes that are essential for energy conservation. One of its primary functions is to suppress anabolic pathways that use ATP, such as lipid, glycogen, and protein synthesis, while inducing catabolic pathways that generate energy, such as glycolysis, fatty acid oxidation, and autophagy (Lin and Hardie, 2018). AMPK mediates these effects by directly phosphorylating important target proteins, such as mTORC1 through its upstream regulators, regulatory-associated protein of mTOR (Raptor) and Tuberous Sclerosis Complex 2 (TSC2), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and acetyl-CoA carboxylase (ACC) (Van Nostrand *et al*., 2020). Thus, AMPK ties metabolic status to the regulation of cell growth and proliferation in addition to balancing energy production and consumption (Wang *et al*., 2021).

Apart from its function in energy metabolism, AMPK also contributes to the adaptability of cells to oxidative stress, hypoxia, and damage to Deoxyribonucleic Acid (DNA) (Keerthana *et al*., 2023). AMPK activation improves the cell's capacity to maintain redox homeostasis by controlling the autophagy, glutathione, and Nicotinamide Adenine Dinucleotide (NAD^+/NADH) pathways (Han *et al*., 2016). Additionally, AMPK affects mitochondrial metabolism by promoting mitochondrial biogenesis by activating Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α), which raises cells' oxidative capability (Abu Shelbayeh *et al*., 2023). This function highlights how AMPK serves as a bridge connecting cell defense mechanisms, cellular stress, and energy sensors (Garcia and Shaw, 2017).

Physiologically, AMPK has a broad influence on various tissues and organs. AMPK promotes fatty acid oxidation and glucose absorption in skeletal muscle while suppressing gluconeogenesis and lipid synthesis in the liver (Steinberg and Carling, 2019). AMPK promotes lipolysis and inhibits lipogenesis in adipose tissue, and it also regulates appetite and energy homeostasis in the central nervous system (Wang and Cheng, 2018; Göransson *et al*., 2023). This function implies that AMPK plays a part in the systemic control of energy metabolism in addition to its cellular relevance (Trefts and Shaw, 2021).

AMPK imbalance or dysfunction has been linked to various metabolic diseases, including obesity, insulin resistance, type 2 diabetes, cardiovascular disease, and even cancer (Li *et al*., 2019; Entezari *et al*., 2022; Peng *et al*., 2024; Penugurti *et al*., 2024; Tesfa *et al*., 2025). AMPK is therefore a possible target for therapeutic intervention, either by pharmaceutical activators like berberine, 5-Aminoimidazole-4-Carboxamide Ribonucleotide (AICAR), and metformin, or by dietary and lifestyle strategies that boost this kinase's activity (Hall *et al*., 2018). A thorough understanding of the structure, activation mechanisms, and function of AMPK is essential for developing effective strategies to modulate this pathway for metabolic health and cellular physiology.

mTOR

mTOR is a serine/threonine kinase that acts as a key regulator of cell growth, metabolism, and energy homeostasis (Saxton and Sabatini, 2017). mTOR creates two protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which are physically and functionally different. mTORC1 is especially sensitive to the availability of nutrition, energy, and growth hormones. It is made up of mTOR, Raptor, mammalian Lethal with SEC13 Protein 8 (mLST8), Proline-Rich AKT Substrate of 40 kDa (PRAS40), and DEP Domain-Containing mTOR-Interacting Protein (DEPTOR) (Liu and Sabatini, 2020). Activation of mTORC1 triggers protein, lipid, and nucleotide synthesis, and inhibits autophagy, thereby promoting cell growth and proliferation when environmental conditions are favorable (Dai and Thomson, 2019; Wang *et al*., 2025b). mTORC2, which consists of mTOR, rapamycin-insensitive companion of mTOR (Rictor), mLST8, mammalian Stress-Activated MAP Kinase-Interacting Protein 1 (mSin1), Protein Observed with Rictor/Proline-Rich Protein 5 (Protor), and DEPTOR, regulates cytoskeleton reorganization, proliferation, and cell survival through the activation of kinases such as Protein Kinase B (AKT), Serum and Glucocorticoid-Regulated Kinase 1 (SGK1), and Protein Kinase C (PKC) (Zhang *et al*., 2021).

mTORC1 activation is triggered by upstream signals involving growth factors (e.g., Insulin-like Growth Factor 1 (IGF-1)), cellular energy, and amino acid availability (Luo *et al*., 2025). One of the key regulators is the tuberous sclerosis complex (TSC1/2), which functions as a GTPase-activating protein (GAP) for Ras homolog enriched in brain (Rheb), a small Guanosine Triphosphatase (GTPase) ase that activates mTORC1 (Luo *et al*., 2025). Cellular stress or low energy levels trigger AMPK activation, which phosphorylates Raptor and TSC2 to block mTORC1 (Ling *et al*., 2020). However, in the presence of growth hormones and nutrition, the Phosphoinositide 3-Kinase–Protein Kinase B (PI3K–AKT) pathway inhibits TSC1/2, allowing Rheb to remain active and mTORC1 to become active (Manning and Toker, 2017).

The main functions of mTORC1 include stimulation of protein translation through phosphorylation of Eukaryotic Translation Initiation Factor 4E-Binding Protein 1 (4E-BP1) and Ribosomal Protein S6 Kinase Beta-1 (S6K1), enhancement of lipogenesis through Sterol Regulatory Element-Binding Protein (SREBP), and regulation of mitochondrial biogenesis (Majeed *et al*., 2021). Furthermore, mTORC1 prevents the break-

down of proteins and organelles in the presence of enough nutrition by phosphorylating Unc-51-Like Kinase 1 (ULK1), which inhibits autophagy (Park *et al*., 2016). Cell differentiation and adaptive responses to environmental cues depend on mTORC2's involvement in AKT activation at the Serine 473 (Ser473) residue, glucose metabolism regulation, cytoskeleton remodeling, and cell survival (Ragupathi *et al*., 2024).

Physiologically, mTOR plays a role in various tissues and organs. mTORC1 controls the synthesis of proteins and lipids in the liver, stimulates the production of proteins in skeletal muscle to increase muscle size, stimulates the production of lipogenesis in adipose tissue, and affects glucose metabolism and systemic energy homeostasis (Han and Wang, 2018; Mao and Zhang, 2018; Bodine, 2022). mTOR dysregulation has been linked to obesity, type 2 diabetes, cancer, neurodegenerative diseases, and immune disorders (Ardestani *et al*., 2018; Tian *et al*., 2019; Maiese, 2020; Amin *et al*., 2024; Shinde and Shannahan, 2024). Owing to its numerous and vital functions, mTOR has emerged as a significant therapeutic target. Rapamycin and its analogs are examples of inhibitors that are used to regulate immunological responses and cellular proliferation (Jhanwar-Uniyal *et al*., 2024).

The relationship between mTOR and AMPK highlights how crucial it is to strike a balance between cell development and cellular energy status. The AMPK–mTOR axis is a dynamic regulatory mechanism that combines metabolic signals and cellular development (Garza-Lombó *et al*., 2018). AMPK functions as an energy sensor, inhibiting mTORC1 when energy is low and promoting anabolism when nutrients are abundant (Smiles *et al*., 2024).

AMPK–mTOR interaction

The AMPK–mTOR axis is a crucial cross-regulatory system in balancing cellular energy status with growth, metabolism, and physiological functions (González *et al*., 2020). The AMP/ATP ratio rising or the ADP/ATP ratio being high, which indicates an energy deficit, activates AMPK, a cellular energy sensor (Coccimiglio and Clarke, 2020). The phosphorylation of downstream targets brought on by AMPK activation inhibits anabolic pathways and enhances catabolic ones (Vazirian *et al*., 2018). One of the main mechanisms of interaction with mTOR occurs through phosphorylation of the upstream regulators TSC2 and Raptor (Melick and Jewell, 2020). The GAP activity of TSC2 toward Rheb, a tiny GTPase that activates mTORC1, is increased when TSC2 is phosphorylated by AMPK. This inhibits mTORC1 at low energy levels (Cormerais *et al*., 2025). Furthermore, Raptor can be directly phosphorylated by AMPK, which lowers mTORC1 activity and encourages autophagy, a crucial process for energy conservation and the breakdown of damaged organelles (Cabrera-Serrano *et al*., 2025).

However, under the right environmental conditions, mTORC1 promotes protein synthesis, lipogenesis, and organelle biogenesis by integrating signals from nutrients, growth factors, and energy (Lee *et al*., 2017). The PI3K–AKT pathway indirectly inhibits AMPK function by activating mTORC1, which raises energy status and anabolic metabolism (Zhong *et al*., 2025). Therefore, a dynamic feedback loop is established by the AMPK–mTOR connection, enabling cells to modify growth, proliferation, and metabolism in response to the availability of energy and nutrients (Sukumaran *et al*., 2020).

Furthermore, AMPK–mTOR interacts through other metabolic pathways in addition to direct control via Raptor and TSC2 (Panwar *et al*., 2023). For instance, AMPK can activate ULK1 to cause the production of genes linked to autophagy, while mTORC1 inhibits ULK1 to stop autophagy in the presence of abundant nutrition (Sadria and Layton, 2021). This interaction shows how the balance between biomolecule synthesis and degradation is coordinated by the AMPK–mTOR axis, which is crucial for maintaining energy homeostasis and adapting to metabolic stress (Garcia and Shaw, 2017).

Physiologically, the AMPK–mTOR balance affects various organs and tissues. In the liver, AMPK reduces lipogenesis and gluconeogenesis by suppressing mTORC1, whereas in skeletal muscle, AMPK activation during energy deficit lowers protein synthesis (Thomson, 2018; Reis-Barbosa *et al*., 2022). This axis affects hunger regulation and neuronal energy metabolism in the central nervous system, while AMPK–mTOR controls immune cell activation and proliferation in immunological tissues (Wang and Cheng, 2018; Clemente-Suárez *et al*., 2023). Dysfunction in this interaction is associated with a variety of pathological conditions, including obesity, insulin resistance, cancer, and neurodegenerative diseases (Liu and Chern, 2021; Liu *et al*., 2022; Marcondes-de-Castro *et al*., 2023; Al-Kuraishy *et al*., 2025).

Not only is knowledge of the AMPK–mTOR connection crucial for fundamental biology, but it also creates new treatment possibilities. mTOR inhibitors are used to regulate cellular proliferation in cancer and other hyperproliferative conditions, while AMPK activators, such as metformin and AICAR, can indirectly lower mTORC1 (De la Cruz-López *et al*., 2024). Therapies that target this axis can improve compromised physiological processes, increase autophagy, and restore metabolic balance (Liu *et al*., 2025).

The role of the AMPK–mTOR axis in cellular metabolism

The AMPK–mTOR axis plays a central role in regulating cellular metabolism by balancing energy production, biomolecule synthesis, and response to nutrient stress.

Regulation of glucose, lipid, and protein metabolism

The AMPK–mTOR axis coordinates the catabolic and anabolic pathways to function as a major regulator of the metabolism of cellular macromolecules, such as proteins, lipids, and glucose (Smiles *et al*., 2024). In the case of glucose, AMPK is triggered when cellular energy is low, which promotes glucose uptake by activating important glycolysis enzymes, including phosphofructokinase-2 (PFK-2) and increasing the expression and transport of Glucose Transporter Type 4 (GLUT4) in skeletal muscle (Troncoso *et al*., 2021). In addition to increasing the flow of glucose into pathways that produce energy, this activation inhibits gluconeogenesis in the liver by phosphorylating and deactivating enzymes like Glucose-6-Phosphatase (G6Pase) and Phosphoenolpyruvate Carboxykinase (PEPCK) (Yip *et al*., 2017). In contrast, mTORC1 supports anabolic glucose metabolism when resources are available, encouraging glucose storage in the form of glycogen through stimulation of glycogen synthesis and control of the insulin/AKT pathway (Uehara *et al*., 2024).

In lipid regulation, AMPK increases fatty acid oxidation by activating carnitine palmitoyltransferase 1 (CPT1) and inhibits lipogenesis by inhibiting the activity of acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, important enzymes in fatty acid and cholesterol synthesis (Cai *et al*., 2025). In turn, when energy and nutrients are plentiful, mTORC1 stimulates lipogenesis by activating the transcription factor Sterol Regulatory Element-Binding Protein 1c (SREBP1c), which leads to an increase in the production of lipogenic enzymes and fat formation (Jiang *et al*., 2020). Cells can regulate lipid production and oxidation in response to energy status through the AMPK–mTOR relationship, preventing excessive lipid buildup or severe energy deficiencies (Xu *et al*., 2024).

In protein metabolism, AMPK suppresses protein synthesis through mTORC1 inhibition, particularly by phosphorylation of Raptor and activation of TSC2, which reduces the phosphorylation of downstream mTORC1 targets such as S6K1 and 4E-BP1 (Nakashima and Ishida, 2022). As a result, less ATP is used for translation initiation and protein synthesis, freeing up ATP for essential cell functions. On the other hand, mTORC1 promotes protein synthesis in the presence of ideal energy and nutrition, boosting cell division and growth by triggering ribosome biogenesis and

the cap-dependent translation pathway (Rosario *et al*., 2020). This balance is important to coordinate protein production with energy availability, prevent metabolic stress, and ensure cellular homeostasis (Chouhan *et al*., 2024).

Response to energy and nutrient stress

Energy and nutritional stress occur in cells when the AMP/ATP ratio rises or when there is a shortage of growth hormones, glucose, or amino acids (González *et al*., 2020). As the major energy sensor in these circumstances, AMPK is triggered, starting adaptive reactions to preserve cellular homeostasis (Ovens *et al*., 2021). Cellular priorities change as a result of AMPK activation, moving from energy-intensive anabolic processes like protein, lipid, and glycogen synthesis to energy-producing catabolic processes like fatty acid oxidation, glycolysis, and autophagy (Rakoubian *et al*., 2025). Protein synthesis is reduced, and energy loss is avoided when nutrients are scarce because phosphorylation of downstream targets like TSC2 and Raptor inhibits mTORC1 activity (Yamada *et al*., 2019).

However, under ideal nutritional conditions, mTORC1 is an active growth regulator (Viola *et al*., 2024). In addition to suppressing anabolism, AMPK's inhibition of mTORC1 during energy stress also initiates autophagy, which breaks down damaged proteins and organelles and repurposes cellular components as energy sources (Kazyken *et al*., 2024). Autophagy must be activated in order to produce vital metabolites, sustain ATP synthesis, and restore organelles that have been harmed by oxidative stress or nutritional deficiencies (Gómez-Virgilio *et al*., 2022).

AMPK–mTOR also influences mitochondrial metabolism (Garza-Lombó *et al*., 2018). PGC-1α and associated transcription factors are activated by AMPK activation, which promotes mitochondrial biogenesis and raises cellular oxidative capacity and energy generation efficiency (Qian *et al*., 2024). Thus, the AMPK–mTOR axis protects cells from harm caused by metabolic stress and enables cells to flexibly change energy metabolism and growth processes, balancing energy needs with synthetic capabilities (Wang *et al*., 2024).

These are contextual and dynamic responses. For instance, AMPK enhances fatty acid oxidation and glucose uptake in skeletal muscle while suppressing gluconeogenesis and lipogenesis in liver cells when energy levels are low (Dang *et al*., 2022). In order to preserve systemic physiological function, AMPK–mTOR controls neuronal energy balance and glucose deprivation adaptation in neural tissue (Belo *et al*., 2022). All things considered, the AMPK–mTOR axis serves as a key regulator that combines signals from nutritional stress and energy stress to control cell growth, metabolism, and survival (Park *et al*., 2023).

Impact on autophagy and mitochondria

The AMPK–mTOR axis is essential for controlling autophagy, a process that breaks down and recycles damaged or unnecessary proteins and cellular organelles (García-Juan *et al*., 2025). The autophagy starting complex, ULK1, is phosphorylated by AMPK activation during energy deprivation or nutritional stress, which starts the creation of autophagosomes (Lin and Hurley, 2016). At the same time, AMPK phosphorylates Raptor and TSC2, inhibiting mTORC1 and reducing its activity, which in turn suppresses ULK1 (Pezze *et al*., 2016). This suppression of mTORC1 allows autophagy induction to occur optimally when energy is limited, so that cells can utilize internal components as a source of essential metabolites to maintain ATP production and survival (Rabanal-Ruiz and Korolchuk, 2018). This autophagy mechanism helps to preserve the integrity of proteins and organelles, avoiding the buildup of damaged molecules that could cause oxidative stress or apoptosis, in addition to providing reserve energy (Ornatowski *et al*., 2020).

The AMPK–mTOR axis is important for mitochondrial biosynthesis and function in addition to autophagy (Wang *et al*., 2022). AMPK activation raises PGC-1α expression, a crucial transcription factor that controls cell oxidative capability and mitochondrial biogenesis (Wu *et al*., 2022). Cells can better adapt to long-term energy deficiencies by increasing the number and efficiency of mitochondria through PGC-1α activation, which also improves fatty acid oxidation and ATP production (Cheng *et al*., 2018). On the other hand, too much mTORC1 activity can prevent mitochondrial autophagy, or mitophagy, which leads to the buildup of damaged mitochondria, elevated oxidative stress, and reduced metabolic effectiveness (Li *et al*., 2022). The dynamic interplay between AMPK and mTOR maintains energy homeostasis and organelle integrity by balancing the production, upkeep, and breakdown of mitochondria in accordance with cellular demands (Cork *et al*., 2018).

Physiologically, the regulation of autophagy and mitochondria by the AMPK–mTOR axis is crucial in various tissues. Energy sustainability during exercise or fasting is supported in skeletal muscle by AMPK-mediated autophagy activation and enhanced mitochondrial biogenesis (Spaulding and Yan, 2022). When the supply of nutrients is restricted, this process aids the liver in maintaining the metabolism of fats and carbohydrates (Jamioł-Milc *et al*., 2023). The balance between AMPK and mTOR is crucial for the health of neuronal mitochondria in the nervous system because it inhibits the buildup of Reactive Oxygen Species (ROS) and cell damage that can lead to degeneration (Garza-Lombó *et al*., 2018). As a result, the AMPK–mTOR axis serves as a key regulator that combines energy status with organelle maintenance via mitochondrial biogenesis and autophagy, eventually promoting cellular survival and physiological adaptation (De la Cruz López *et al*., 2019). Figure 1 shows a three-panel schematic of the AMPK–mTOR axis, depicting energy/nutrient state, key pathways for glucose, lipid, and protein metabolism, and tissue-level outcomes in muscle, liver, and neurons.

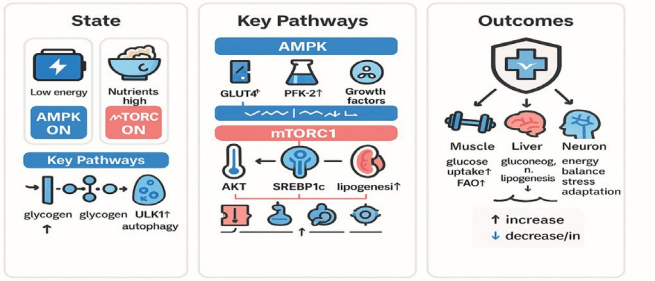

Figure 1. AMPK–mTOR axis: State, key pathways, and outcomes.

The role of the AMPK–mTOR axis in cellular physiology

The AMPK–mTOR axis not only regulates cellular metabolism but also plays a crucial role in coordinating cell growth, proliferation, differentiation, and survival in various tissues and organs.

Effect on cell growth, proliferation, and differentiation

A crucial regulator, the AMPK–mTOR axis combines signals from growth factors, nutrients, and energy to dictate the fate of cells in terms of growth, proliferation, and differentiation (Sadria and Layton, 2021). Cell growth and proliferation are directly supported by mTORC1 activation, which stimulates anabolic metabolism, organelle biogenesis, and protein synthesis (Ben-Sahra and Manning, 2017). The phosphorylation of mTORC1 downstream targets, including S6K1 and 4E-BP1, boosts the cell's ability to translate, allowing for the synthesis of structural and enzymatic proteins required for cell division and growth (Linke *et al*., 2017). Furthermore, mTORC1 controls the pathways for glucose metabolism and lipogenesis, which supply energy and biomolecular substrates to enable active proliferation (Mao and Zhang, 2018).

In contrast, when cell energy is low, AMPK acts as an energy sensor and prevents growth (Lin and Hardie, 2018). AMPK activation reduces

protein synthesis and other anabolic processes by suppressing mTORC1 through phosphorylation of TSC2 and Raptor (Thomson, 2018). Therefore, AMPK prevents metabolic stress and cell damage by ensuring that proliferation only happens when energy and nutritional conditions are adequate (Smiles *et al*., 2024). This process validates AMPK's function as an energy conservation regulator, which is critical for cell survival (Cui *et al*., 2023).

The AMPK–mTOR axis also influences the pathways leading to cell specialization during differentiation (Chun and Kim, 2021). mTORC1 activation promotes tissue-specific transcription factor expression and protein synthesis, which aids in the differentiation of neurons, myocytes, and adipocytes, among other cell types (Ye *et al*., 2019). In contrast, AMPK can modify cell differentiation through energy status adjustments and autophagy pathway regulation, which is crucial for preserving organelle quality throughout the differentiation process (Kim *et al*., 2024). The balance between AMPK and mTOR ensures that cell differentiation occurs optimally, in line with energy availability and metabolic needs (Steinberg and Carling, 2019).

Relationship with apoptosis and cell cycle

The AMPK–mTOR axis plays a critical role in the regulation of apoptosis and the cell cycle, two key processes that determine cellular survival, proliferation, and integrity (González *et al*., 2020). Growth factors, including cyclin D1 and cyclin E, which control the G1 to S phase transition, are expressed, and protein translation pathways are activated by mTORC1 to promote growth and cell cycle progression (Lamm *et al*., 2019). A key factor in cancer and aberrant proliferation is unchecked cell proliferation, which can be encouraged by excessive mTORC1 activity (Tufail *et al*., 2025). On the other hand, AMPK-induced mTORC1 inhibition during metabolic stress or low energy results in a brief cell cycle arrest at the G1/S or G2/M checkpoint (Zhou and Liu, 2022). This system shields cells against metabolic stress and incorrect DNA replication, which may harm organelles (Ling *et al*., 2020).

AMPK is an energy and DNA stress sensor that adaptively adjusts cell death pathways during apoptosis (Szewczuk *et al*., 2020). Pro-apoptotic proteins like Bcl-2–associated X protein (Bax) and caspase activation via the mitochondrial intrinsic route are upregulated when AMPK is activated, but mTORC1-mediated anti-apoptotic pathways like B-cell lymphoma 2 (Bcl-2) and survivin are suppressed (Sharma *et al*., 2019). Therefore, apoptosis can be used to stop the growth of damaged cells in the event of an energy shortage or DNA damage, whereas mTORC1 activity keeps cells in ideal nutritional conditions (Singh *et al*., 2019).

Furthermore, autophagy is influenced by AMPK–mTOR as a substitute mechanism for cell survival before apoptosis (Bloemberg and Quadrilatero, 2019). AMPK activation induces autophagy through ULK1 phosphorylation, while mTORC1 inhibits this process when nutrient conditions are sufficient (Wang *et al*., 2022). The AMPK–mTOR axis uses this cross-regulation to control whether cells will undergo apoptosis or autophagy in response to metabolic stress or irreparable damage (Lee *et al*., 2021).

Physiologically, the balance between AMPK and mTOR in the regulation of the cell cycle and apoptosis is important for tissue and organ homeostasis. This axis permits the elimination of damaged cells while guaranteeing controlled proliferation in proliferative organs like bone marrow or epithelium (Li *et al*. 2022). This control aids in shielding neurons in the nervous system from the buildup of oxidative damage (Anwar *et al*., 2025). The pathophysiology of cancer and degenerative illnesses can be influenced by AMPK–mTOR imbalance, which can result in aberrant cell proliferation, resistance to apoptosis, and excessive mTOR activation or failure of AMPK activation (Keerthana *et al*., 2023).

Relationship with organ systems

As a key regulator of energy balance, the AMPK–mTOR axis plays a wide range of roles in controlling metabolism and physiology in different organs (Liu *et al*., 2025). Table 1 summarizes the complementary roles of AMPK and mTORC1 in regulating cellular metabolism, function, and adaptation in various organs.

In skeletal muscle, AMPK is activated during energy deficits, such as exercise or starvation, and increases glucose uptake via the GLUT4 transporter and promotes fatty acid oxidation to generate ATP (Kjøbsted *et al*., 2018). Additionally, AMPK activation increases muscle cells' oxidative capability and energy endurance by inducing mitochondrial biogenesis through PGC-1α (Yamada *et al*., 2022). In contrast, mTORC1 drives muscle protein synthesis and hypertrophy through S6K1 activation and cap-dependent translation, allowing muscle growth and repair when nutrients and energy are abundant (Bodine, 2022). Muscle can adapt to shifting energy situations thanks to the dynamic balance between AMPK and mTORC1, which maximizes performance and promotes tissue healing (Liu *et al*., 2025).

In the liver, AMPK suppresses gluconeogenesis and lipogenesis during low-energy periods, reduces glucose and lipid synthesis, and increases fatty acid oxidation to maintain systemic energy homeostasis (Woods *et al*., 2017). In addition to triggering hepatocyte autophagy, AMPK activation aids in the breakdown of damaged proteins and organelles, preserving liver function (Raza *et al*., 2023). However, in the presence of abundant nutrition, mTORC1 promotes the synthesis of proteins and lipids, which is critical for hepatocyte development and metabolic function maintenance (Plata-Gómez *et al*., 2024). The liver's AMPK–mTOR interactions play a critical role in insulin resistance prevention, lipid buildup prevention, and response to dietary changes and metabolic stress (Marcondes-de-Castro *et al*., 2023).

In the pancreas, especially the β cells of the islets of Langerhans, AMPK modulates insulin secretion based on the energy status of the cells (Szkudelski and Szkudelska, 2019). AMPK activation during energy deficit suppresses insulin secretion to prevent excess glucose consumption,

Table 1. Role of the AMPK–mTOR axis in organ systems.

Organ systems	The role of AMPK	The role of mTORC1	Physiological functions / implications
Skeletal muscle	Activated during energy deficit; increases glucose uptake (GLUT4) and fatty acid oxidation; induces mitochondrial biogenesis via PGC-1α	Promotes muscle protein synthesis and hypertrophy through S6K1 and cap-dependent translation	Maximize muscle performance, energy adaptation, and tissue recovery
Liver	Suppresses gluconeogenesis and lipogenesis during low energy; increases fatty acid oxidation; triggers hepatocyte autophagy	Supports protein and lipid synthesis when nutrients are sufficient	Maintain systemic energy homeostasis, prevent excess lipid accumulation, and insulin resistance
Pancreas (β cells)	Modulates insulin secretion during energy deficits, suppresses secretion to conserve glucose	Increases proliferation and protein synthesis of β cells when energy and nutrients are sufficient	Maintain systemic metabolic balance and insulin secretory capacity; prevent β-cell stress
Nervous System	Enhances autophagy and mitochondrial maintenance during low energy; protects neurons from ROS and oxidative damage	Supports synaptic protein synthesis and dendritic growth when nutrients are sufficient.	Maintaining neuronal energy homeostasis, synaptic plasticity, cognitive function, and learning; dysregulation associated with neurodegenerative diseases

while mTORC1 increases β-cell proliferation and protein synthesis when energy and nutrients are sufficient, supporting their secretory capacity (Jaafar *et al*., 2019). In addition to preventing β-cell stress, which can result in insulin failure and diabetes, this cross-regulation maintains equilibrium between pancreatic endocrine function and systemic metabolic demands (Cui *et al*., 2024).

In the nervous system, AMPK–mTOR plays a critical role in neuronal energy homeostasis, synaptic plasticity, and cell survival (Garza-Lombó *et al*., 2018). Low-energy AMPK activation promotes autophagy and mitochondrial upkeep, shielding neurons from oxidative damage and ROS buildup (Herzig and Shaw, 2018). In contrast, mTORC1 promotes dendritic development and synaptic protein synthesis when nutrients are adequate, allowing for the best possible learning and cognitive performance (Liu and Sabatini, 2020). Neurodegenerative illnesses like Parkinson's and Alzheimer's are associated with dysregulation of this axis, which throws off the equilibrium between protein production and energy management (Garza-Lombó *et al*., 2018). As shown in Figure 2, the AMPK–mTORC1 axis balances energy and nutrient cues to coordinate cell growth/proliferation, differentiation, cell-cycle control, apoptosis–autophagy decisions, and adaptations in skeletal muscle, liver, pancreatic β-cells, and neurons.

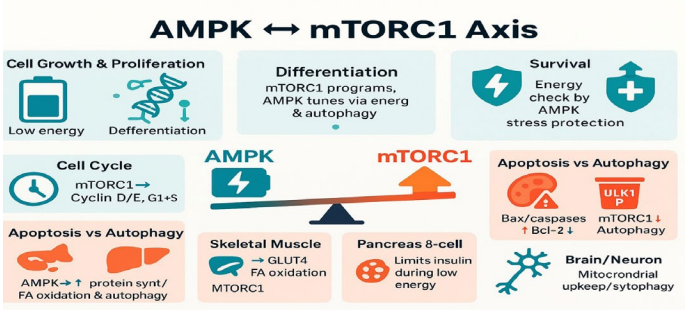

Figure 2. Energy–nutrient signaling via AMPK–mTORC1.

The AMPK–mTOR axis in pathology and therapy

Dysfunction of the AMPK–mTOR axis has been linked to various metabolic diseases, cancers, neurodegenerative disorders, and inflammatory conditions, making it a potential target for precision therapeutic interventions.

AMPK–mTOR dysfunction in metabolic, cancer, neurodegenerative, and inflammatory diseases

Dysfunction of the AMPK–mTOR axis has been shown to play a critical role in the pathogenesis of various metabolic diseases, cancer, neurodegenerative disorders, and chronic inflammatory conditions (Tarasiuk *et al*., 2022). AMPK activity suppression or excessive mTORC1 activation causes fat buildup, insulin resistance, and glucose dysregulation in metabolic disorders such as type 2 diabetes and obesity (Stanciu *et al*., 2024). This raises the possibility of cardiometabolic problems and upsets the balance of energy in the body. Pharmacological drugs like metformin or AICAR can activate AMPK, which can then be used as a potential metabolic therapy technique to reduce excessive mTORC1, increase insulin sensitivity, and restore energy balance (Kazyken *et al*., 2019). Table 2 displays the role of AMPK–mTOR dysfunction in the pathogenesis of various metabolic diseases, cancer, neurodegenerative disorders, and chronic inflammation.

In cancer, dysregulation of the AMPK–mTOR axis promotes uncontrolled cellular proliferation, suppression of apoptosis, and tumor growth (Keerthana *et al*., 2023). Over-activation of mTORC1 promotes the growth of cancer cells by increasing protein synthesis and lipogenesis, whereas AMPK inhibition lowers energy thresholds, enabling tumor cells to endure in nutrient-limited environments (Ling *et al*., 2020). The promise of treatments based on manipulation of this axis has been demonstrated by the use of AMPK activators and mTOR inhibitors, such as rapamycin and its analogs, to limit tumor growth, induce autophagy, and restore cell cycle control (Sadria *et al*., 2022).

In neurodegenerative disorders, such as Alzheimer's and Parkinson's, AMPK–mTOR imbalance disrupts neuronal energy homeostasis and the autophagy process (Cai and Ganesan, 2022). Insufficient AMPK prevents adaptive responses, while excessive mTORC1 activation suppresses autophagy, resulting in the buildup of toxic proteins and damaged organelles (Kazyken *et al*., 2024). Pharmacologically balancing AMPK and mTORC1 activity can improve mitochondrial function, slow the course of neurodegeneration, and increase the breakdown of harmful proteins (Maiese, 2020).

In chronic inflammation, AMPK–mTOR dysregulation affects immune cell activation and proliferation (Sorrenti *et al*., 2022). Pro-inflammatory cytokine production and lymphocyte proliferation are increased when mTORC1 is activated, whereas AMPK suppresses inflammatory pathways and encourages autophagy to alleviate cell stress (Arab *et al*., 2024). AMPK–mTOR-targeting therapeutic strategies can lessen tissue damage, decrease excessive inflammatory responses, and restore immunological homeostasis (Yibcharoenporn *et al*., 2025).

Potential pharmacological interventions

The AMPK–mTOR axis is an attractive therapeutic target because of its broad role in the regulation of metabolism, cell growth, and stress responses (Ashraf and Van Nostrand, 2024). The capacity of AMPK activators, including metformin, AICAR, and berberine, to promote catabolic pathways and indirectly inhibit mTORC1 activity has been thoroughly investigated (Moghaddam *et al*., 2022; Mbara *et al*., 2025). These compounds activate AMPK, which promotes fatty acid oxidation, glucose absorption, and autophagy induction, all of which support cellular energy

Table 2. AMPK–mTOR axis dysfunction and its relationship to disease.

Type of disease	AMPK dysregulation	mTORC1 dysregulation	Physiological / Pathological impact	Therapeutic strategy
Metabolic disease (obesity and type 2 diabetes)	AMPK suppression	Over-activation	Lipid accumulation, insulin resistance, glucose dysregulation, and impaired systemic energy homeostasis	AMPK activators (e.g., metformin and AICAR) to increase insulin sensitivity and suppress mTORC1
Cancer	AMPK suppression → energy checkpoint is disrupted	Overactivation → increased protein synthesis and lipogenesis	Uncontrolled cell proliferation, suppression of apoptosis, and tumor growth	mTOR inhibitors (rapamycin/its analogs) and AMPK activators to limit tumor growth and restore cell cycle control
Neurodegenerative Disorders (Alzheimer's and Parkinson's)	Inadequate AMPK activation	Excessive activation → inhibits autophagy	Accumulation of toxic proteins, damaged organelles, and disruption of neuronal energy homeostasis	Pharmacological modulation to balance AMPK–mTOR improves toxic protein degradation and mitochondrial function
Chronic inflammation	AMPK activation decreases	Overactivation → increased production of proinflammatory cytokines	Excessive lymphocyte proliferation, cell stress, and tissue damage	Targeting AMPK–mTOR to suppress inflammation, increase autophagy, and restore immune homeostasis

homeostasis (Kim *et al*., 2016). AMPK activators have important clinical potential in the treatment of obesity, type 2 diabetes, and metabolic syndrome. They can also lower insulin resistance, inhibit the buildup of hepatic lipids, and enhance blood glucose levels (Tesfa *et al*., 2025).

However, excessive anabolic pathways, including protein synthesis and lipogenesis, are suppressed by mTOR inhibitors, like rapamycin and its analogs (rapalogs), which also promote autophagy (Magaway *et al*., 2019). It has been demonstrated that this treatment is successful in reducing the growth of cancer cells, causing tumor cells to undergo apoptosis, and enhancing the breakdown of harmful proteins in nerve cells (Singh *et al*., 2023). Since mTORC1 inhibition reduces lymphocyte proliferation and the production of proinflammatory cytokines, mTOR inhibitors may also be used to control the immune response in chronic inflammatory diseases (Kezic *et al*., 2018).

The combination strategy, which combines mTOR inhibition with AMPK activation, produces a stronger synergistic effect (Sun *et al*., 2023). This strategy gives cells greater flexibility in regulating growth and metabolism: mTOR inhibition inhibits excessive cellular proliferation and biomolecule synthesis, while AMPK activates catabolic and autophagic pathways to preserve energy (Garza-Lombó *et al*., 2018). This combination approach is being explored in the context of cancer, neurodegenerative diseases, and metabolic disorders, with the goal of restoring the balance between cellular anabolism and catabolism more effectively than single pathway modulation (Sadria and Layton, 2021).

Studies have demonstrated that lifestyle modifications, including exercise, calorie restriction, and intermittent fasting, can physiologically activate AMPK and suppress mTOR in addition to pharmacological therapies, yielding therapeutic outcomes that are on par with those of pharmaceutical therapy (Soomro *et al*., 2025). This strategy highlights how crucial it is to combine molecular and physiological methods for treating illnesses linked to AMPK mTOR axis dysfunction. As shown in Figure 3, an imbalance between decreased AMPK activity and hyperactive mTORC1 suppresses autophagy and skews anabolism, contributing to metabolic disease, cancer, neurodegeneration, and chronic inflammation, while targeted interventions AMPK activators, mTOR inhibitors, combination therapy, and lifestyle measures, help restore anabolic catabolic balance.

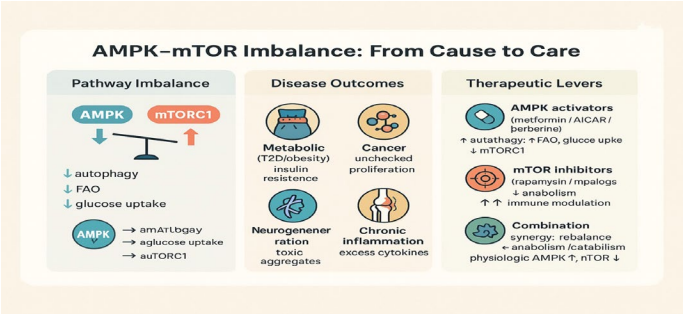

Figure 3. AMPK–mTORC1 dysfunction: Diseases and interventions.

Future perspectives

According to recent research, the AMPK–mTOR axis integrates metabolic, nutritional, and growth factor signals to regulate growth, proliferation, differentiation, autophagy, and stress responses. It also serves as a key regulator of energy balance and cellular physiology (Chun and Kim, 2021). Studies conducted both in vitro and in vivo have highlighted how crucial the balance between AMPK and mTORC1 is in preventing the buildup of damaged proteins and organelles, insulin resistance, glucose dysregulation, lipid accumulation, and aberrant cell proliferation (Ling *et al*., 2020; Szwed *et al*., 2021). AMPK activation inhibits anabolism and stimulates catabolic processes like fatty acid oxidation and autophagy, whereas mTORC1 stimulates the production of proteins, lipids, and organelles under the right nutritional circumstances (Smiles *et al*., 2024). In addition to maintaining energy balance and ensuring cell adaptation to internal and external situations, these dynamic interactions also reduce the likelihood of cellular malfunction, which can lead to metabolic illnesses, cancer, and neurodegenerative disorders (Torre-Villalvazo *et al*., 2019).

Even while science has advanced significantly, there are still a number of unanswered questions. First, the specific mechanisms that regulate AMPK–mTOR interactions in specific tissue contexts and the differences in responses between cell types are still not fully understood (Sukumaran *et al*., 2020). Second, the long-term effects of pharmacological modulation of this axis, including potential resistance, systemic side effects, and cellular adaptation, require longitudinal studies (Arévalo *et al*., 2022). Third, more thorough molecular mapping is still needed to comprehend the intricate regulatory network, including the integration of AMPK–mTOR signaling with other metabolic and stress pathways, including SIRT1, insulin/AKT, and the ROS pathway (Clemente-Suárez *et al*., 2025).

The AMPK–mTOR axis presents a number of promising prospects for therapeutic development, especially when considering metabolic, cancer, and neurological disorders (Zhao *et al*., 2024). Techniques for mTOR inhibition, AMPK activation, or a combination of the two have the potential to enhance autophagy, balance cellular catabolism-anabolism, and enhance organ function (García-Juan *et al*., 2025). The specificity of treatment for particular cell or tissue types, dose optimization to prevent metabolic dysfunction or suppression of normal growth, and the discovery of biomarkers that might forecast a patient's response to therapy are some of the obstacles that must be addressed (Garg *et al*., 2024).

In the future, combining pharmaceutical methods with lifestyle modifications like exercise, calorie restriction, and intermittent fasting may improve physiological AMPK–mTOR modulation, creating chances for safer and more efficient supplemental treatment approaches (Kazeminasab *et al*., 2025). Furthermore, studies employing "omics" technologies and biological systems models can aid in a more thorough mapping of the AMPK–mTOR interaction network, facilitating the creation of precision treatments catered to the genetic and metabolic characteristics of individual patients (Su *et al*., 2024).

Conclusion

The AMPK–mTOR axis balances catabolic and anabolic pathways based on growth factor, nutritional, and energy status, serving as a key regulator of cellular physiology and energy homeostasis. AMPK activation during an energy deficit suppresses anabolism and cell proliferation by inhibiting mTORC1, while promoting catabolic pathways such as fatty acid oxidation, glucose absorption, and autophagy. In contrast, mTORC1 promotes protein synthesis, lipogenesis, and cell growth when nutrient conditions are favorable, thus allowing for optimal metabolic adaptation and growth. The dynamic interplay between AMPK and mTOR guarantees that cells can maintain organelle quality, adapt to stress, and modify their metabolism, differentiation, and proliferation.

The balance between AMPK and mTOR affects glucose metabolism, lipids, protein synthesis, autophagy, and mitochondrial biogenesis in skeletal muscle, the liver, the pancreas, and the nervous system, among other tissues and organs. Pharmacological modulation or lifestyle treatments targeting AMPK–mTOR offer interesting therapeutic methods because disruption of this axis has been clinically linked to inflammatory illnesses, cancer, neurodegenerative diseases, and metabolic diseases. A deep understanding of the mechanisms and regulation of the AMPK–mTOR axis is key to developing precision therapies that balance cellular anabolism and catabolism, improve energy homeostasis, and prevent disease progression.

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Conflict of interest

The authors have declared no conflict of interest.

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