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Clinical Reviews and Case Reports

Houhong Wang*

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Review Article

AMP-Activated Protein Kinase: Structure, Function, Role in Diseases and Therapeutic Prospects

Houhong Wang

Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China.

***Correspondence Author:** Houhong Wang, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China.

Received Date: January 19, 2026 | Accepted Date: January 30, 2026 | Published Date: February 02, 2026

Citation: Houhong Wang, (2026), AMP-Activated Protein Kinase: Structure, Function, Role in Diseases and Therapeutic Prospects, *Clinical Reviews and Case Reports, 5*(1); **DOI:**10.31579/2835-7957/151

Abstract

AMP-activated protein kinase (AMPK) is a master regulator of cellular energy homeostasis. Sensing changes in the cellular energy status, AMPK activates catabolic pathways and inhibits anabolic processes to restore energy balance. Beyond energy metabolism, AMPK is involved in diverse physiological processes, including autophagy, cell growth, and inflammation. Dysregulation of AMPK has been closely associated with various diseases, such as metabolic disorders, cancers, and neurodegenerative diseases. This review comprehensively summarizes the structure, biological functions, roles in disease pathogenesis, and current therapeutic strategies related to AMPK. In-depth understanding of AMPK's mechanisms provides a solid foundation for the development of effective therapeutic approaches targeting related diseases.

Keywords: amp-activated protein kinase; energy metabolism; metabolic disorders; cancer; neurodegenerative diseases; therapeutic strategies

1.Introduction

Maintaining cellular energy homeostasis is essential for the proper functioning of cells and organisms. AMP-activated protein kinase (AMPK) serves as a key sensor and regulator of cellular energy status. When the cellular AMP/ATP ratio increases, indicating energy depletion, AMPK is activated. Once activated, AMPK phosphorylates a wide range of substrates, initiating a series of cellular responses that enhance energy production and reduce energy consumption. AMPK is involved in multiple physiological and pathological processes, making it an important target for understanding disease mechanisms and developing therapeutic strategies. In recent years, extensive research has been conducted on AMPK, uncovering its complex functions and potential applications in various diseases. This review aims to summarize the latest findings regarding AMPK, covering its structure, functions, roles in diseases, and current therapeutic approaches.

2. Structure of AMPK

2.1 Subunit composition

AMPK is a heterotrimeric complex composed of an α-catalytic subunit and β- and γ-regulatory subunits. There are two isoforms of the α-subunit (α1 and α2), three isoforms of the β-subunit (β1, β2, and β3 in some species), and four isoforms of the γ-subunit (γ1, γ2, γ3, and γ4). Different combinations of these subunits result in the formation of various AMPK heterotrimers with distinct tissue distributions and functions. The α-subunit contains a kinase domain at the N-terminus, which is responsible for the catalytic activity of AMPK, and a regulatory domain at the C-terminus that interacts with the β- and γ-subunits. The β-subunit has a glycogen-binding domain, which may play a role in the regulation of AMPK activity in response to changes in glycogen levels. The γ-subunit contains four cystathionine-β-synthase (CBS) domains that form two Bateman modules, which are crucial for sensing the cellular AMP/ATP, ADP/ATP ratios and allosterically activating AMPK [1].

2.2 Structural insights from crystallography

X-ray crystallography and cryo-electron microscopy studies have provided detailed structural information about the AMPK complex. These structural analyses have revealed the precise interactions between the subunits and how the binding of AMP or ADP to the γ-subunit induces conformational changes, exposing the activation loop of the α-subunit for phosphorylation by upstream kinases, such as liver kinase B1 (LKB1) and calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2). The structural insights help in understanding the molecular mechanisms of AMPK activation and regulation, and also serve as a basis for the design of small molecule activators or inhibitors that can modulate AMPK activity [2].

3. Biological functions of AMPK

3.1 Regulation of energy metabolism

One of the primary functions of AMPK is to regulate cellular energy metabolism. When energy is scarce, AMPK activates catabolic pathways, such as glucose uptake, fatty acid oxidation, and mitochondrial biogenesis, to generate ATP. For example, in skeletal muscle, AMPK activation promotes the translocation of the glucose transporter GLUT4 to the cell membrane, enhancing glucose uptake. In the liver, AMPK stimulates fatty acid oxidation and inhibits gluconeogenesis by phosphorylating key enzymes involved in these processes, such as acetyl-CoA carboxylase (ACC) and phosphoenolpyruvate carboxykinase (PEPCK). At the same time, AMPK inhibits anabolic processes, including protein synthesis, lipid synthesis, and glycogen synthesis, to conserve energy. By phosphorylating mammalian target of rapamycin complex 1 (mTORC1), a major regulator of protein synthesis, AMPK reduces protein synthesis under energy-deprived conditions [3].

3.2 Regulation of autophagy

AMPK is an important regulator of autophagy, a cellular process that degrades and recycles damaged organelles and proteins. Activated AMPK phosphorylates and activates Unc-51-like autophagy-activating kinase 1 (ULK1), a key protein in the initiation of autophagy. This phosphorylation event promotes the formation of the ULK1 complex, which then initiates the autophagy process. Through the regulation of autophagy, AMPK helps cells to adapt to stress conditions, such as nutrient deprivation, and maintain cellular homeostasis [4].

3.3 Other functions

AMPK is also involved in regulating cell growth, proliferation, and differentiation. By inhibiting mTORC1, AMPK can arrest the cell cycle and inhibit cell growth. Additionally, AMPK has been implicated in the regulation of inflammation. It can phosphorylate and regulate various inflammatory signaling molecules, such as nuclear factor kappa-B (NF-κB), to modulate the inflammatory response. In addition, AMPK plays roles in processes like angiogenesis, neuronal function, and insulin sensitivity, highlighting its broad influence on cellular and physiological functions [5].

4. AMPK in diseases

4.1 Metabolic disorders

Dysregulation of AMPK is closely associated with metabolic disorders, such as type 2 diabetes and obesity. In type 2 diabetes, insulin resistance and impaired glucose metabolism are key features. Reduced AMPK activity in insulin-sensitive tissues, such as skeletal muscle, liver, and adipose tissue, contributes to the development of insulin resistance. Activation of AMPK can enhance glucose uptake and utilization, improve insulin sensitivity, and reduce blood glucose levels. In obesity, AMPK activation can promote fatty acid oxidation and inhibit lipid synthesis, helping to reduce fat accumulation. However, in some cases, chronic overactivation of AMPK may also lead to adverse effects, such as increased appetite, which needs further investigation [6].

4.2 Cancers

The role of AMPK in cancer is complex. On one hand, activation of AMPK can inhibit tumor growth by suppressing mTORC1-dependent protein synthesis and promoting autophagy, which can eliminate damaged or abnormal cells. On the other hand, in certain contexts, AMPK activation may also promote cancer cell survival and adaptation to stress conditions, such as hypoxia. For example, under low-energy or hypoxic conditions, AMPK activation can help cancer cells to switch to alternative energy sources and survive. Moreover, different tumor types may respond differently to AMPK activation or inhibition, making the targeting of AMPK in cancer therapy a challenging but promising area of research [7].

4.3 neurodegenerative diseases

In neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, AMPK dysregulation has been reported. Activation of AMPK may have neuroprotective effects by promoting autophagy, reducing protein aggregation, and modulating inflammation. For instance, in Alzheimer's disease, AMPK activation can enhance the clearance of amyloid-β peptides and tau proteins, which are associated with the pathogenesis of the disease. In Parkinson's disease, AMPK activation may protect dopaminergic neurons by promoting mitochondrial function and reducing oxidative stress. However, the exact mechanisms and the optimal modulation of AMPK activity in neurodegenerative diseases still need to be further explored [8].

5. Therapeutic strategies targeting AMPK

5.1 Small molecule activators

Small molecule activators of AMPK have been actively investigated as potential therapeutic agents. Metformin, a widely used drug for the treatment of type 2 diabetes, activates AMPK through multiple mechanisms, including inhibition of complex I in the mitochondrial respiratory chain, leading to an increase in the AMP/ATP ratio and subsequent AMPK activation. Other small molecule activators, such as AICAR (5-aminoimidazole-4-carboxamide ribonucleotide), directly mimic the effects of AMP and allosterically activate AMPK. These activators have shown potential in preclinical and clinical studies for the treatment of metabolic disorders, cancers, and neurodegenerative diseases, but also have limitations, such as off-target effects and limited bioavailability [9].

5.2 Small molecule inhibitors

In some cases, small molecule inhibitors of AMPK may also be useful. For example, in certain cancer types where AMPK activation promotes tumor cell survival, inhibiting AMPK may enhance the efficacy of chemotherapy or radiotherapy. Compound C is a well-known AMPK inhibitor that blocks AMPK activation by inhibiting the upstream kinase LKB1. However, like activators, inhibitors also face challenges, such as specificity and potential side effects, and their development requires careful consideration [10].

5.3 Combination therapies

Combination therapies that target AMPK along with other pathways are being explored. For example, combining AMPK activators with drugs that target other aspects of metabolic dysregulation in type 2 diabetes may have synergistic effects. In cancer therapy, combining AMPK inhibitors with traditional chemotherapy or targeted therapies may overcome resistance and improve treatment efficacy. Additionally, in neurodegenerative diseases, combination therapies that modulate AMPK activity along with other disease-modifying agents may offer more comprehensive treatment options [11].

6. Challenges and future directions

Despite the progress in understanding AMPK and developing AMPK-targeted therapies, several challenges remain. One major challenge is the complexity of AMPK’s functions in different tissues and cell types. The diverse roles of AMPK in various physiological and pathological processes mean that a one-size-fits-all approach to AMPK modulation may not be effective. Developing more tissue-specific or cell type-specific AMPK activators or inhibitors is crucial. Another challenge is the potential off-target effects of AMPK modulators. Since AMPK is involved in

multiple signaling pathways, modulating its activity may lead to unexpected consequences. Future research should focus on improving the specificity of AMPK-targeted drugs. Additionally, understanding the crosstalk between AMPK and other signaling pathways, as well as the role of AMPK in different disease stages, will be important for the development of more effective therapeutic strategies. The application of advanced technologies, such as single-cell sequencing and gene editing, may help to further elucidate the functions of AMPK and accelerate the discovery of novel AMPK-targeted therapies.

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