AMP-ACTIVATED PROTEIN KINASE AND INTRACELLULAR SIGNALING IN HEALTH AND DISEASE

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Contents

Summary

The enzyme 5' adenosine monophosphate-activated protein kinase (AMPK) is a critical cellular energy sensor that detects and maintains cellular energy balance. AMPK regulates cellular and whole-body energy homeostasis by stimulating catabolic ATP-producing intracellular signaling pathways and suppressing anabolic ATP-consuming intracellular signaling pathways. There are many molecules that can either activate or inhibit AMPK. In response to starvation, AMPK induces autophagy and inhibits cell growth by regulating specific intracellular signaling molecules. Recent research has shown that AMPK can suppress tumor growth by stimulating cellular processes such as apoptosis, autophagy, and cell growth and proliferation via various signaling molecules. In the pathophysiology of aging and age-related diseases, AMPK plays a crucial role as a regulator of numerous metabolic pathways. AMPK is involved in and plays protective roles in many diseases, including tumors, diabetes, obesity, cardiovascular, and neurodegenerative diseases. This kinase has previously been shown to be involved in the regulation of many different cellular transport proteins that are important for cellular physiology and pathophysiology. Thus, AMPK serves as a vital link between cellular energy metabolism and transport activities. A better understanding of AMPK's role in intracellular signaling under normal and abnormal conditions could pave the way for treatments for many human diseases and disorders in which AMPK plays a role.

This chapter will introduce the reader to numerous intracellular signaling pathways in which AMPK is involved. After a brief introduction to the AMPK, the structure and function of the AMPK as well as its activators and inhibitors will be discussed. Special emphasis is placed on recent advances about the AMPK mechanism of action, particularly its complex intracellular role in autophagy. The chapter continues with the kinase role in health and several diseases and cellular transport regulation. Numerous representative and detailed figures are included to help better and easier understand certain topics. At the end of this chapter is a conclusion and perspective section that will summarize the subject.

1. General Introduction

Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is an enzyme and a critical regulator that recognizes the cell's energy status (Dermaku-Sopjani and Sopjani, 2019). All mammalian cells have this energy-sensing enzyme in their nucleus and cytoplasm. AMPK is activated when cellular energy levels are low, *i.e.*, when the AMP/ATP ratio increases (Dermaku-Sopjani et al., 2014; Sopjani et al., 2010a). Upon activation, AMPK stimulates a number of catabolic processes that increase ATP generation in cells while suppressing a number of anabolic pathways that consume ATP. As a result, it regulates cellular energy homeostasis. This chapter discusses the structure and function of AMPK as well as its therapeutic advantages.

2. AMP-activated Protein Kinase

AMPK is a serine/threonine kinase that is phylogenetically conserved. This widely expressed kinase is a protein complex that monitors the energy status of the cell (Hardie and Alessi, 2013) and plays several important functions in numerous metabolic

processes (Herzig and Shaw, 2018). AMPK is a protein molecule that acts as a cellular fuel sensor, activating when energy is depleted. AMPK regulates energy balance by activating catabolic ATP-generating processes such as glucose absorption, glycolysis, fatty acid oxidation, and mitochondrial biogenesis. In the same way, AMPK inhibits anabolic processes that consume ATP and NADPH (Jeon et al., 2012), such as protein synthesis (Hardie and Alessi, 2013; McBride et al., 2009), glycogen synthesis, gluconeogenesis (Kim et al., 2008), and fatty acid synthesis (Hardie and Alessi, 2013; McFadden and Corl, 2009).

This enzyme has been proposed as an important target for drugs and natural products with effects on several diseases. Metformin is the most often used medicine to treat diabetes mellitus type 2 (DMT2). In other ways, it also helps to protect people against cancer. Metformin and several other natural plant products that pharmacologically activate AMPK have the ability to treat metabolic abnormalities such as DMT2 (Fryer et al., 2002; Langelueddecke et al., 2012), non-alcoholic fatty liver disease (Ix and Sharma, 2010), which is significantly related to insulin resistance and metabolic syndrome (obesity), and malignancies.

Cancer cells require increased glucose uptake and breakdown to produce ATP in order to proliferate rapidly. Cancer cells have an abnormally high energy metabolism. As a result, AMPK as an energy metabolism regulator may be an emerging hallmark and potential target (Imamura et al., 2001; Jones et al., 2005) for application in both cancer prevention and therapy techniques.

2.1. The Structure of the AMPK

In mammals, AMPK is a heterotrimeric (containing three different subunits) protein kinase complex composed of a catalytic subunit (AMPK-α (alpha)) (α1 or α2) containing the kinase domain (KD) and two regulatory β (beta) subunits (β1 or β2) and γ (gamma)) subunits (γ1, γ2, or γ3) (Stapleton et al., 1996; Thornton et al., 1998). Figure 1 shows the AMPK domain structure. In humans, α1 and α2 are encoded by the genes PRKAA1 and PRKAA2 (Stapleton et al., 1996), β1 and β2 are encoded by PRKAB1 and PRKAB2 (Thornton et al., 1998), whereas γ1, γ2, and γ3 are encoded by PRKAG1, PRKAG2, and PRKAG3 (Cheung et al., 2000). In each heterotrimeric AMPK complex, all combinations are feasible, possibly yielding twelve unique AMPK complexes (Ross et al., 2016). It is not clear if these functionally different AMPK heterotrimeric combinations have different ways of recognizing substrates and/or different localizations inside cells.

The α-subunit comprises the serine-threonine kinase domain as well as a crucial residue, Thr^{172}, whose phosphorylation by upstream kinases activates AMPK. The N-terminus of the β subunit contains a glycogen-binding domain (GBD), which permits the enzyme to bind to glycogen. GBD is in charge of directing the kinase to the cell membrane (Warden et al., 2001). The AMPK γ subunits enable the kinase to adapt to changes in the cellular ATP: AMP ratio. It contains four tandem repeat sequences known as cystathionine-synthase (CBS) motifs (Bateman, 1997). CBS domains in γ subunits may bind adenine nucleotides. The binding of AMP and, to a lesser degree, ADP to the AMPK-subunit promotes its activity. CBS acts in pairs. Within an enzyme, pairs of

CBS sequences fold into "Bateman domains" that bind adenosine-containing ligands (Xiao et al., 2007). CBS3 is the primary sensor of adenosine-containing ligands (Xin et al., 2013). Glycogen storage disorders, a hereditary condition in animals, are related to mutations in genes encoding γ subunits (Park et al., 2003; Arad et al., 2002).

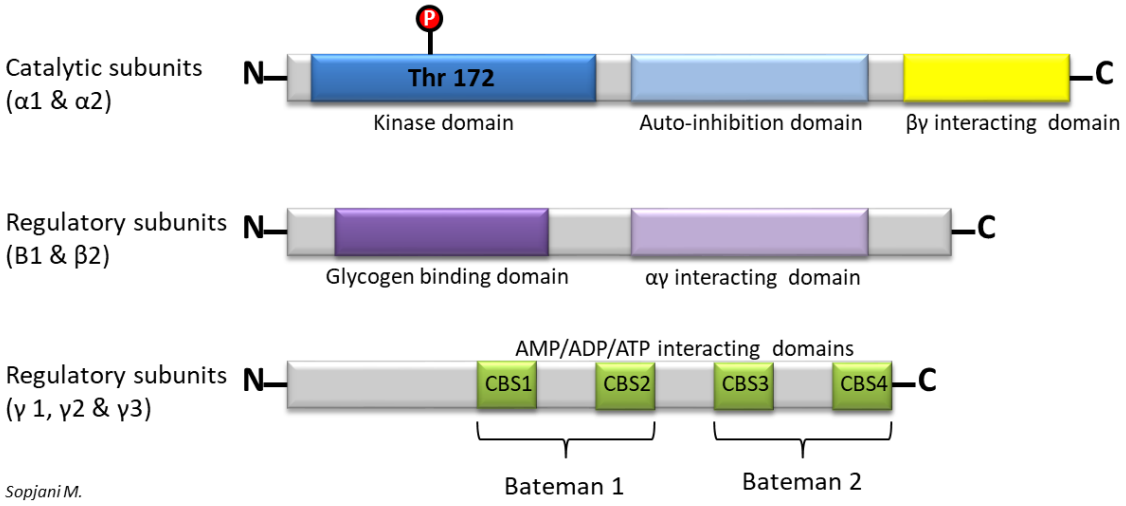

Figure 1. Schematic representation of the AMP-activated protein kinase domain structure (Dermaku-Sopjani and Sopjani, 2019). AMPK is a heterotrimeric complex made up of two regulatory subunits, AMPK-β and AMPK-γ, as well as the catalytic subunit AMPK-α. The catalytic subunit has a conserved threonine residue called Thr-172 in the NH2-terminal region that may be phosphorylated by the protein kinases AMPK kinases (AMPKK). This subunit also features a domain for interacting with the co-functional regulatory subunits β and γ and, as well as a domain for autoinhibition. The AMPK β subunit contains a GBD and an interaction domain for subunits α and γ are located at the N- and C-termini, respectively. The γ subunit has the Bateman domains (CBS1/2 and CBS3/4), which are responsible for competitive binding of the adenosine-containing ligands AMP, ADP, and ATP, and are made up of four tandem repeats of the CBS motif (Xin et al., 2013).

AMPK, the master and primary energy regulator of eukaryotic energy homeostasis, is disrupted in diseases such as diabetes, cancer, obesity, and cardiovascular diseases (Hardie, 2017; Carling, 2017). AMPK has a key role in metabolism. It is a kind of energy switch that links energy metabolism to a number of physiological functions (Dermaku-Sopjani and Sopjani, 2019). Controlling AMPK could be a key part of how diet and exercise improve your health in many ways.

3. Mechanisms of AMPK Activation

All eukaryotes seem to contain AMPK homologs; however, the number of subunits may differ across species. Seven genes encoding AMPK may exist in distinct heterotrimeric subunit compositions in the mammalian genome, allowing unique AMPK complexes to react to diverse kinds of stress stimuli in different cell types (Jensen et al., 2015).

Energy stress activates AMPK in response to increased ATP consumption (*e.g.*, exercise, anabolism, cell proliferation) or reduced ATP generation (*e.g.,* low glucose levels, hypoxia, oxidative stress), which is detected as low ATP to AMP and ADP ratios (Dermaku-Sopjani and Sopjani, 2019). Activated AMPK phosphorylates its downstream targets to affect the activities of rate-limiting metabolic enzymes, proliferation and growth pathways, transcription and translation factors, and epigenetic regulators. This turns up the levels of oxidative phosphorylation, metabolism, glucose and fatty acid absorption, and autophagy while turning down the levels of protein synthesis, fatty acids, cholesterol, ribosomal RNA production, and cell growth and division.

Furthermore, pharmaceutical drugs such as Abbot A769662 and Merck 991 bind to a distant region known as the allosteric drug and metabolite (ADaM) site, which is located at the interface between the KD and the carbohydrate-binding module (CBM) of the subunit β (Kurumbail and Calabrese, 2016). By phosphorylating a residue (Thr^{174} in human α1 and Thr^{172} in human α2) in its kinase activation loop (AL), AMPK is activated 100-fold. Direct allosteric kinase activation has been shown to boost activity by up to 10-fold (Kurumbail and Calabrese, 2016) although it is not clear yet in a cellular context. However, in reconstituted systems, AMP, ADP, and ADaM agonists upregulate AL phosphorylation by stabilizing and maintaining a conformation that restricts phosphatase access to the AL (Scott et al., 2014). Also, binding of AMP, but not ADP or ADaM ligands, further increases AL phosphorylation through maintaining a connection with the tumor suppressor liver kinase B1 (LKB1) (Puustinen et al., 2020), which functions as the primary upstream kinase of AMPK, as well as possibly with additional upstream kinases (Kurumbail and Calabrese, 2016). On the contrary, ATP competes with AMP and ADP at one or more allosteric sites when there is an excess of energy, which prevents AMPK from working. For many years, it has been recognized that adenine nucleotide modulation of AL accessibility represents a major mechanism of AMPK regulation (Carling, 2017; Dermaku-Sopjani and Sopjani, 2019). However, the underlying mechanisms by which adenine nucleotides and ADaM agonists cause conformational changes that influence AL accessibility and how agonists may prevent access to protein phosphatases while not preventing access to AL kinases were unknown. However, a recent study (Yan et al., 2021) reported a multistep mechanism describing how adenine nucleotides and pharmacological agonists affect AMPK activity by modifying AL phosphorylation and accessibility. In general, when there is a lack of energy, AMP stabilizes the active form of AMPK. This protects the kinase AL from protein phosphatases, keeping the AL phosphorylated and the kinase active. Figure 2 shows AMPK regulation and how it is involved in preserving energy balance.

The N-terminus serine/threonine kinase domain of α subunits is only active when phosphorylated at the activation loop by any of many upstream kinases (Hawley et al., 1996). Certain regulators control the activity of AMPK. The key upstream kinase that phosphorylates the serine/threonine kinase domain with subsequent activation of AMPK is the tumor suppressor protein molecule LKB1 (Woods et al., 2003b; Woods et al., 2003a). In turn, this reduces cell growth and proliferation (Woods et al., 2003a). LKB1 is a major upstream kinase of AMPK.

The β subunit has a GBD that mediates binding with glycogen particles, and thus the kinase senses cellular energy status by sensing the structural state of glycogen (Dermaku-Sopjani and Sopjani, 2019; Dermaku-Sopjani et al., 2014). The regulatory γ subunit has two antagonistic nucleotide binding sites for AMP and ATP. When AMP binds to the γ-subunit, AMPK activity could be increased by three distinct mechanisms. 1) Making AMPK a better substrate for the upstream kinases or stimulating the activity of the upstream kinases. 2) Preventing the phosphatases from dephosphorylating the kinase domain in the *α*-subunit due to an AMP-induced conformational shift in the kinase. 3) Increasing the allosteric activation of the activated kinase. Furthermore, AMP binding to the γ-subunit results in a direct allosteric activation of the kinase (Sanders et al., 2007). It should be noted that not only AMP but also ATP may bind to the -subunit CBS domains (Hardie et al., 2011) allowing the kinase to respond to changes in the ATP-to-AMP ratio and thus serve as an energy status sensor that maintains cellular energy balance.

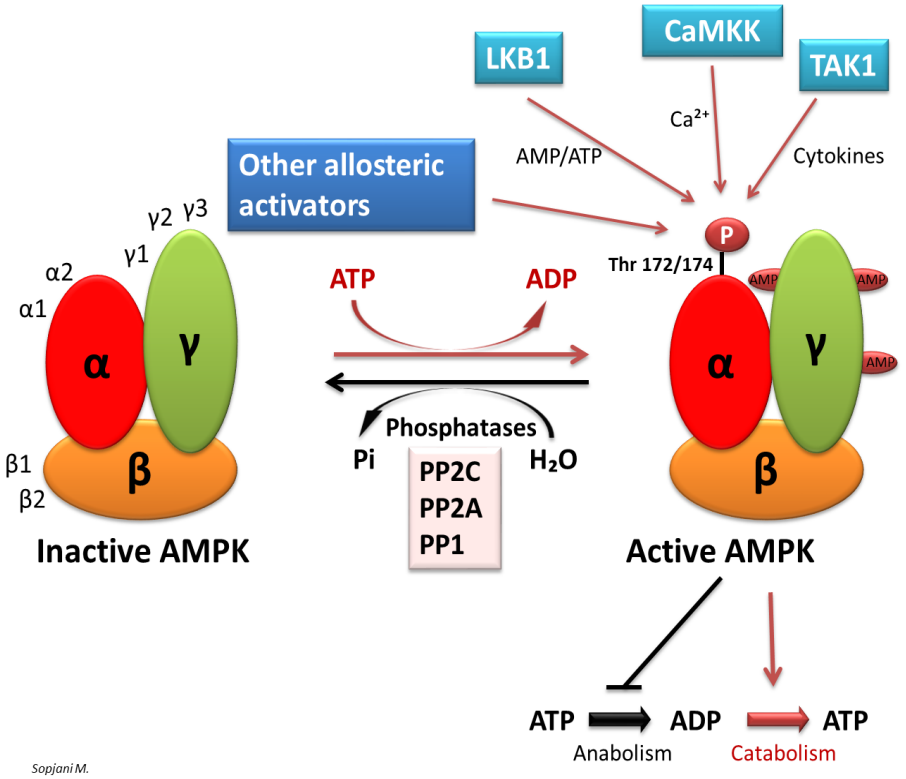

Figure 2. AMPK's composition, regulation, and involvement in maintaining energy balance. AMPK is activated in response to an increase in the AMP/ATP ratio by phosphorylation of threonine (Thr^{172}/$Thre^{174}$ (in human α2 or α1, respectively) within the catalytic-subunit catalyzed by any of the AMPKK, such as LKB1 (for activity, binding of MO25 and STE-20 related adaptor protein (STRAD) forming a heterotrimeric complex is required) or by CaMKK in a Ca^{2+}-dependent manner. TGF-activated kinase 1 (TAK1) is also responsible for AMPK activation, which includes cytokine signaling. AMPK activation affects a wide range of downstream targets, often by inhibiting anabolic signaling pathways while activating catabolic signaling pathways, restoring energy balance. Dephosphorylation of Thr^{172}/$Thre^{174}$ by protein phosphatase 2C (PP2C), PP2A, or protein phosphatase 1 (PP1) inactivates AMPK. More details may be found in the text.

AMPK is activated through phosphorylation by a series of upstream kinases that function in a bi-cyclic protein kinase cascade. The kinase domain of the AMPK is continually phosphorylated by LKB1 within the kinase subunit's activation loop, but it is also quickly dephosphorylated in the absence of AMP. LKB1 mediated AMPK activation results in the inhibition of cell growth and proliferation, actions that seem to be mediated by AMPK (Woods et al., 2003a). The calmodulin-dependent kinase kinase β (CaMKKβ) is another AMPK-regulating upstream kinase that phosphorylates AMPK at the threonine 172 residue when the level of cytosolic Ca^{2+} rises (Hurley et al., 2005). The transforming growth factor-associated kinase 1 (TAK1) (Hardie, 2011) and glucosamine (Kim et al., 2010) are other factors that activate AMPK. Not only have the AMP/ATP ratio and cytosolic Ca^{2+} activity been linked to AMPK stimulation, but also low oxygen (O_2) levels and exposure of skeletal muscle cells to nitric oxide (NO).

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