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Gene Section
Review

PRKAA1 (protein kinase AMP-activated catalytic subunit alpha 1)

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Abstract

Protein kinase AMP-activated catalytic subunit alpha 1 (PRKAA1), also known as AMPK α1, is an energy sensor that plays a key role in the regulation of cellular energy metabolism. AMPK α1 is the catalytic subunit of the heterotrimeric AMPK protein with a length of 548 amino acids. A key switch to activate this protein is an alteration in the AMP/ATP ratio.

The protein is dysregulated in several human diseases including diabetes and metabolic syndrome, cardiovascular diseases, neurodegenerative diseases and many cancer types (Steinberg and Kemp, 2009). Two isoforms of AMPK exist including AMPK α1 and AMPK α2; however, discrimination between these isoforms for their involvement in certain diseases is currently not possible.

Keywords

AMP-activated catalytic subunit alpha 1, PRKAA1, AMPK α1, diabetes, neurodegenerative diseases, cancer

Identity

Other names: AMPK, AMPKa1, AMPK1, AMPK Alpha 1

HGNC (Hugo): PRKAA1

Location: 5p13.1

Local order

Starts at 40759379 and ends at 40798195 bp from pter (according to hg38-Dec_2013)

DNA/RNA

Detailed genomic configuration of human PRKAA1 gene can be found in https://www.ncbi.nlm.nih.gov/gene/5562.

Description

The human AMPK α1 gene is located on 5p13.1 and spans about 39 kb. It contains 12 exons and 2 promoters named as PRKAA1_1 and PRKAA1_2. The gene has 3 isoforms named as PRKAA1_001, PRKAA1_002 and PRKAA1_003.

Transcription

The human AMPK α1 gene has 9 transcripts: PRKAA1-201 (1134 bp), PRKAA1-202 (1918 bp), PRKAA1-204 (5088 bp) that code for a protein. PRKAA1-203 (425 bp), PRKAA1-205 (919 bp), PRKAA1-206 (1082 bp), PRKAA1-207 (692 bp), PRKAA1-208 (668 bp) and PRKAA1-209 (436 bp) have retained introns. It also has 7 paralogues and 97 orthologues.

Pseudogene

PRKAA1 has one hypothetical pseudogene titled as LOC363815 from Rattus norvegius and is located in 11q23.

Protein

Description

AMPK α1 is the catalytic subunit of the heterotrimeric AMPK protein with a length of 548 amino acids.

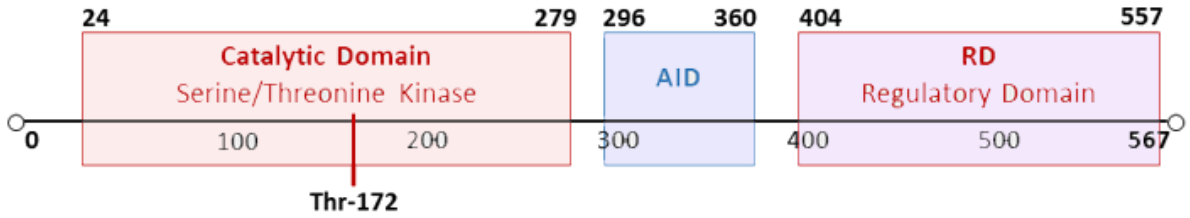

Figure 1. Domains of AMPK-α1. (AID: UBA-like Autoinhibitory Domain)

In response to an increase in the AMP/ATP ratio, AMPK gets activated. AMP binds to the non-catalytic gamma subunit of the AMPK protein and induces phosphorylation of Thr-183 (Lizcano et al., 2004). This residue is present in the T-loop region of the catalytic subunit, AMPK α1 (Bright et al., 2009). There are several known AMPK kinases (AMPKKs). STK11 (LKB1), complexed with STRADA and CAB39 (MO25), is the major upstream regulator of the AMPK, which phosphorylates the AMP bound protein (Shackelford and Shaw, 2009). Ca2+/calmodulin-dependent protein kinase kinase β (CAMKK2 or CaMKKβ) is also known to be an upstream kinase of AMPK (Sundararaman et al., 2016). TGF-beta-activated kinase-1 (MAP3K7 or TAK1) may also phosphorylate AMPK α or at least play a role in its activation as loss of TAK1 leads to impaired AMPK activation (Xie et al., 2006).

The AMPK α1 protein consists of several domains (Figure 1). The N-terminal kinase domain carries out the serine/threonine kinase function. The C-terminus regulatory domain contains an α-RIM sensor loop and a β-subunit interaction domain (Crute et al., 1998). A UBA-like auto-inhibitory domain (AID) is present between the α-RIM sensor loop and the kinase domain. AID is required for allosteric regulation via AMP. Absence of this inhibitory region renders the protein independent of AMP but still requires phosphorylation of the activation loop (Crute et al., 1998).

Expression

AMPK α1 is widely expressed across many tissues such as brain, heart, kidney, liver and lung (Stapleton et al., 1996).

Localisation

It is primarily localized in the cytoplasm, and with HUVEC cells it was shown that AMPK α1 localizes exclusively in the cytoskeleton (Pinter et al., 2012).

Function

AMPK α1, in its active form, phosphorylates many downstream proteins. These phosphorylated target proteins of AMPK regulate metabolism, autophagy, cell growth and proliferation, and cell polarity (Hardie, 2011). AMPK exists as an obligate heterotrimer in cells (Mihaylova and Shaw, 2011), and all the functions that will be mentioned in this section are carried out by the α1 subunit in this obligate heterotrimer complex.

Cellular Metabolism

AMPK is activated when there is energy stress in the cell manifested by an increase in the AMP/ATP ratio. In response to this stress, AMPK activates catabolic pathways while inhibiting anabolic pathways.

Glycolysis

One of the key catabolic pathways for energy generation, glycolysis, is upregulated through AMPK signalling. In order increase glucose uptake to the cell, AMPK activates (induces translocation, short term response) and increases protein expression (longer term response) of SLC2A1 (GLUT1) and SLC2A4 (GLUT4) (Fryer et al., 2002). Also, 6-phosphofructo-2-kinase (PFKFB3 or PFK-2) gets phosphorylated and activated by AMPK which enhances glycolysis (Marsin et al., 2000). Glycogen synthesis (anabolic pathway) is inhibited by the phosphorylation of glycogen synthase.

Gluconeogenesis

Anabolic pathways such as gluconeogenesis that enhance glucose levels are inhibited by repression of transcripts that encode for gluconeogenesis enzymes. CRTC2, coactivator of the cyclic AMP response element-binding protein CREB, gets phosphorylated and inhibited (excluded from the nucleus) by AMPK. This leads to disruption of CREB-CRTC2 complex and inhibition of CREB-dependent gluconeogenesis (Lee et al., 2010). Transcription of mRNAs encoding glucose-6-phosphatase and phosphoenolpyruvate carboxykinase are inhibited via this mechanism. Also, class IIA histones, which can activate the FOXO family of transcription factors via HDAC3 recruitment, gets phosphorylated and excluded from the nucleus. This decrease in activity of FOXO family of transcription factors leads to reduced expression of gluconeogenesis genes (Mihaylova et al., 2011).

Lipid Metabolism

In AMPK activated cells, fatty acid uptake is increased by translocation of fatty acid translocase, CD36 (FAT), to the cellular membrane (Bonen et al., 2007). Meanwhile, acetyl-CoA carboxylase (ACACA ACC1), which catalyses the rate-limiting step of fatty acid synthesis (Hofbauer et al., 2014), gets phosphorylated and this phosphorylation inhibits the enzymatic activity of ACC1.

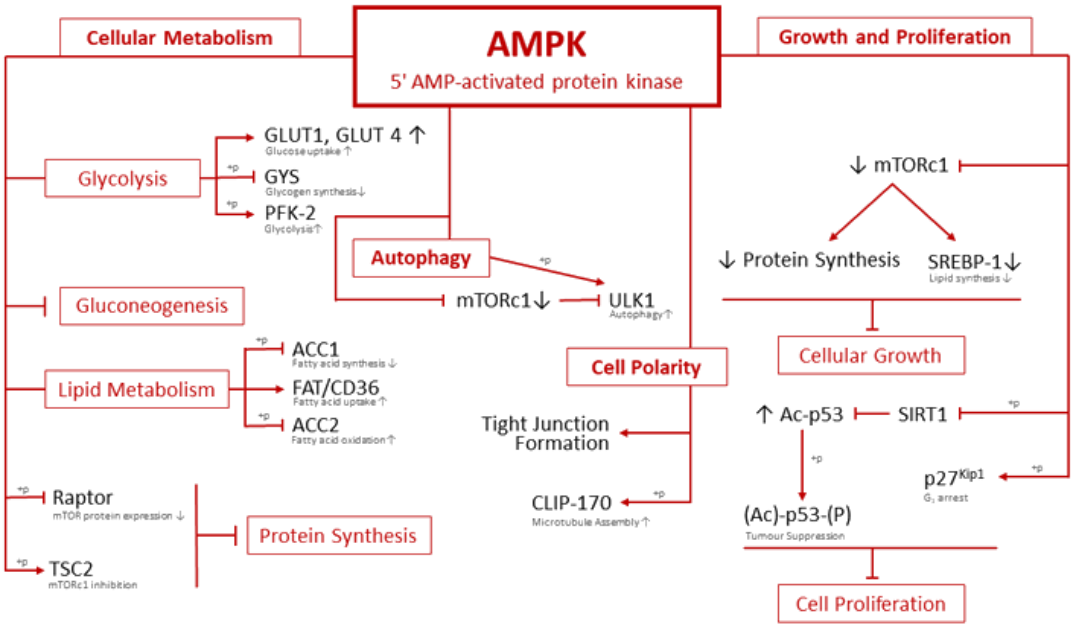

Figure 2. Functions of AMPK

Along with CD36 (FAT) translocation to the membrane, ACACB (ACC2) is also inhibited which leads to increased fatty acid uptake into mitochondria due to decreased amounts of malonyl-CoA in the cell (Merrill et al., 1997).

Protein Synthesis

Synthesis of proteins is an enormous energy consuming process for the cells. MTOR, in its active form, promotes cell proliferation and protein synthesis. Activated AMPK inhibits mTOR via phosphorylation of upstream regulator TSC2 (Huang and Manning, 2008) and its subunit RPTOR (Raptor) (Gwinn et al., 2008). Also, eukaryotic elongation factor 2 (EEF2) is required for the elongation of translation in eukaryotes. EEF2 kinase gets activated by AMPK which inhibits EEF2 via phosphorylation, resulting in inhibition of protein synthesis (Horman et al., 2002).

Autophagy

Excess or dysfunctional organelles get "eaten up" by the cell over time, this process is called autophagy and it can give cells the advantage of recycling important nutrients, especially during starvation. It is known that mTORc1 inhibits autophagy via inhibition of ULK1 (Chan, 2009), and AMPK downregulates mTORc1 via phosphorylation of TSC2 and Raptor. This was thought to be the main mechanism by which AMPK activates autophagy. Recently, it was found that initiator of autophagy, the ULK1 protein kinase, directly interacts with AMPK, and gets phosphorylated and activated by AMPK (Roach, 2011).

Cell Growth and Proliferation

AMPK can act as a metabolic checkpoint via inhibition of cellular growth when energy status in the cell is compromised (Mihaylova and Shaw, 2011).

Processes of cellular growth and proliferation require many events to take place in the cell such as protein and lipid synthesis. As mentioned above, AMPK can decrease the synthesis of proteins and subsequently cell proliferation through the inhibition of mTORc1. mTORc1 also controls lipid biosynthesis via a transcription factor named as sterol regulatory element-binding protein-1, SREBF1 (SREBP-1) (Laplante and Sabatini, 2009). SREBP-1 targets lipogenic genes such as ACC (Brown et al., 2007); fatty acid synthase, FASN (Jung et al., 2012); and stearoyl-CoA desaturase 1, SCD (Mauvoisin et al., 2007). mTORc1 inhibition by AMPK along with the previously mentioned inhibition of ACC1 leads to decreased lipid synthesis in the cell. Other than metabolic effects, AMPK also activates checkpoint regulators such as TP53 via inactivation of SIRT1 (Sirtuin 1) (Lee et al., 2012) and phosphorylation at Ser-15 (Jones et al., 2005), as well as CDKN1B (cyclin-dependent kinase inhibitor p27(Kip1)) via phosphorylation at Thr198 (Liang et al., 2007).

Cell Polarity

LKB1-null and AMPK-null Drosophila models show lethal phenotypes with severe defects in cell polarity and mitosis (Lee at al., 2007). AMPK activation was reported to rescue LKB1-null phenotype while non-muscle myosin regulatory light chain (MRLC) phopshomimetic mutants rescued AMPK-null models (Lee at al., 2007). However, another study reported that in mammalian MDCK cells, AMPK activation did not change phosphorylation of MRLC, rather AFDN (afadin) was identified as AMPK substrate for phosphorylation (Zhang et al., 2011). Activation via AMPK leads to deposition of junction components in the cellular membrane.

Homologs of Human PRKAA1 (AMPK α1)

Gene Name	Organism	NCBI RefSeq	Protein	Length (aa)
PRKAA1	*H. sapiens*	NP_996790.3	5'-AMP-activated protein kinase catalytic subunit alpha-1	574
PRKAA1	*P. troglodytes*	XP_009447514.1	5'-AMP-activated protein kinase catalytic subunit alpha-1	574
PRKAA1	*M. mulatta*	XP_001086410.2	5'-AMP-activated protein kinase catalytic subunit alpha-1	559
PRKAA1	*C. lupus*	XP_022273603.1	5'-AMP-activated protein kinase catalytic subunit alpha-1	573
PRKAA1	*B. taurus*	NP_001103272	5'-AMP-activated protein kinase catalytic subunit alpha-1	458
Prkaa1	*M. musculus*	NP_001013385.3	5'-AMP-activated protein kinase catalytic subunit alpha-1	559
Prkaa1	*R. norvegicus*	NP_062015.2	5'-AMP-activated protein kinase catalytic subunit alpha-1	559
PRKAA1	*G. gallus*	NP_001034692.1	5'-AMP-activated protein kinase catalytic subunit alpha-1	560
prkaa1	*X. tropicalis*	NP_001120434.1	5'-AMP-activated protein kinase catalytic subunit alpha-1	551
prkaa1	*D. rerio*	NP_001103756.1	5'-AMP-activated protein kinase catalytic subunit alpha-1	573
KIN10	*A. thaliana*	NP_001118546.1	SNF1 kinase homolog 10	512
KIN11	*A. thaliana*	NP_974374.1	SNF1 kinase homolog 11	512
Os05g0530500	*O. sativa*	XP_015639849.1	SNF1-related protein kinase catalytic subunit alpha KIN10	505

The microtubule plus-end-tracking protein CLIP1 (CLIP-170) is activated via phosphorylation by AMPK. CLIP-170 phosphorylation is required for microtubule dynamics and the regulation of directional cell migration (Nakano et al., 2010). The same study reported that inhibition of AMPK leads to accumulation of CLIP-170 at microtubule tips and slower tubulin polymerization (Nakano et al., 2010). Thus, AMPK also controls microtubule dynamics through CLIP-170 phosphorylation.

Homology

AMPK α1, with its kinase and regulatory domains, is a very well conserved protein.

Implicated in

Top note

AMPK, a central switch determining the AMP/ATP ratio, is dysregulated in several human diseases including diabetes and metabolic syndrome, cardiovascular diseases, neurodegenerative diseases and several different cancer types (Steinberg and Kemp, 2009). Both isoforms of AMPK: AMPK α1 and AMPK α2 may be involved in these diseases. AMPK was shown to negatively regulate the Warburg effect in genetically ablated AMPK- α1 cancer models in vivo (Faubert et al., 2013); therefore, AMPK can be classified as tumour suppressor although there is also evidence of negative regulation of AMPK by tumour suppressors or proto-oncogenes (Li et al., 2017; Yan et al., 2014).

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disease where the AMPKα1 isoform is known to be activated in the caudate nucleus and frontal cortex of humans.

Activated AMPKα1 was reported to accumulate in the nuclei in these specific regions of the brain of HD patients. Brain atrophy, facilitated neuronal loss and increased aggregation of huntingtin (HTT) protein was observed in a transgenic mouse model with Huntington's disease, which had overactivated AMPKα1. Ameliorated cell death and down-regulation of BCL2 (by mutant Htt) was achieved by prevention of nuclear translocation or inactivation of AMPK- α1 (Ju et al., 2011).

Prostate Cancer

In prostate cancer, the androgen receptor (AR) plays a critical role in the regulation of cell proliferation and death. There is evidence that AR related progression of prostate cancer correlates with activated AMPK levels.

Androgen-mediated AMPK activity was reported to increase the levels of intracellular ATP and PPARGC1A (peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α))-mediated mitochondrial biogenesis.

siRNA-mediated knockdown of AMPKα1, the predominant isoform correlated with poor prognosis in prostate cancer patients, in LNCaP and YCaP human prostate cancer cells reduced the levels of PGC-1α, which is overexpressed in clinical cancer samples (Tennakoon et al., 2015).

5- ATIC (Aminoimidazole-4-carboxamide ribonucleotide (AICAR)), is an AMPK agonist that enhances phosphorylation of AMPK- α1 at Thr-172 and its downstream target ACC at Ser-79. Prostate cancer cell lines infected with lentiviral shRNA against AMPK- α1 were shown to almost block AICAR-induced AMPK phosphorylation. AICAR-induced cytotoxicity in prostate cancer cells was slightly more potent than other AMPK activators such as A-769662 and Compound 13. It has been suggested that AICAR-induced cytotoxicity was not dependent of AMPK activation but might play a pro-survival role in prostate cancer cells (Guo et al., 2016).

Colorectal Cancer

The current literature suggests that activation of AMPK through natural compounds such as berberine, epigallocatechin gallate or quercetin can enhance apoptosis through the upregulation and phosphorylation of TP53 at Ser15, inhibition of COX-2 and mitigation of inflammation as well as delay in cell cycle progression (Sun and Xhu, 2017). AMPKα1 is expressed in almost all colorectal cancer cell lines; however, AMPKα2 expression is limited to some cell lines. Although siRNA-mediated AMPKα1 knock down has no effect on cell death, AMPKα2 depletion was shown to induce cell death in both HCT116 and SW480 cell lines. A competitive inhibitor of AMPK, 5'-hydroxy-staurosporine, was identified by FUSION (Functional Signature Ontology), a method to screen natural compounds for the identification of AMPK inhibitors. Colorectal cancer cell lines were reported to be more sensitive to 5'-hydroxy-staurosporine compared to non-transformed human colon epithelial cells (Das et al., 2018).

Another study suggests that Icaritin (a flavonoid with anti-tumorigenic activity) was reported to induce AMPK signaling in colorectal cancer (CRC) and it also activates autophagy. AMPK-α1 knockdown (shRNA or siRNA mediated) inhibited icaritin-activated autophagy but increased cell death in CRC both in vitro and in vivo (Zhou et al., 2017).

Type 2 Diabetes

AMPK is known to be dysregulated in patients with metabolic syndrome or type 2 Diabetes. Activation of AMPK either through the alteration of the AMP/ATP ratio of by pharmacological agonists can improve insulin sensitivity and metabolic health. In the primary metabolic tissues such as skeletal muscles, cardiac muscle, liver and adipose tissue, activation of AMPK was reported to stimulate glucose uptake, fatty acid oxidation, glucose transporter type (GLUT)4 translocation (in skeletal muscles), mitochondrial biogenesis, while inhibiting gluconeogenesis (in the liver) as well as protein, fatty acid, cholesterol and glycogen synthesis. AMPK is also known to inhibit insulin secretion from pancreatic β-cells and can signals to enhance food intake in the hypothalamus. All of these are beneficial for Type 2 diabetes (Coughlan et al., 2014). In an animal model of type 2 diabetes established by the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, which had chronic and slowly progressive hyperglycemia and hyperlipidemia, overexpression of adenoviral-mediated AMPK-α1 showed a modest decrease in blood glucose level although glucose tolerance was not recovered completely.

Moreover, plasma triglyceride level and hepatic triglyceride contents were also slightly decreased (Seo et al., 2009).

Aging

Dietary restriction (DR), a process of reduced food intake without inducing malnutrition, elicits a low-energy state in the organism, which in turn delays ageing in species ranging from yeast to primates through the activation of nutrient-sensing pathways such as AMPK (Burkewitz et al, 2014). For example, feeding C. elegans 2-deoxy-D glucose leading to the inhibition of glycolysis and glucose metabolism increased the lifespan of the worms in an aak-2 (catalytic subunit of AMPK in C. elegans) dependent manner (Schulz et al., 2007). In rat EDL (extensor digitorum longus) muscle, AMPK-α1 protein level was reported to be higher in older rats compared to younger rats. On the other hand, young rats showed higher expression of AMPK-α2 proteins than the older group. EDL cells treated with AICAR showed increased AMPK-α2 activity in both age groups, while AMPK-α1 activity was increased only in the young group. AMPK-α1 activity was not changed in the EDL muscles that were stimulated by high frequency electrical in the young group (Thompson et al., 2009).

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