Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

PRKAB1 (protein kinase, AMP-activated, beta 1 non-catalytic subunit)

Monserrat Sanchez-Cespedes

Molecular Pathology Program, Spanish National Cancer Center (CNIO), Melchor Fernandez Almagro, 3, 28029 Madrid, Spain

Published in Atlas Database: September 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/PRKAB1ID44100ch12q24.html
DOI: 10.4267/2042/38502

Identity

Hugo: PRKAB1
Other names: AMPK; AMPKb; AMPK beta; AMPKbeta1; HAMPKb; MGC17785; NM_006253
Location: 12q24.1
Local order: Centromere-H11-BC040553-PRKAB1-CIT-RAB35-telomere.

DNA/RNA

Description

The PRKAB1 gene, with a total genomic size of 13639 bp, is composed of 7 coding exons of varying lengths.

Transcription

The human PRKAB1 transcript has approximately 2500-bp and contains an open reading frame of 813 bases, resulting in a predicted protein of 270 amino acid residues. PRKAB mRNA is detected in most tissues.

Protein

Description

PRKAB1 has a molecular mass of 30382 Da; This protein constitutes a regulatory subunit of the AMP-activated protein kinase (AMPK).
AMPK is an heterotrimer of an alpha catalytic, a beta and a gamma non-catalytic regulatory subunits, each encoded by two or three distinct genes (AMPKalpha1 – AMPKalpha2; AMPKbeta1 - AMPKbeta2; AMPKgamma1 - AMPKgamma2 - AMPKgamma3) which have varying tissue and subcellular expression.
Post-translational modifications of PRKAB1 include myristoylation and phosphorylation in vivo at Ser24/25, Ser108 and Ser182. Phosphorylation at Ser108 is required for the activation of the AMPK enzyme, whereas phosphorylation at Ser24/25 and Ser182 affects the localization of the complex.

Expression

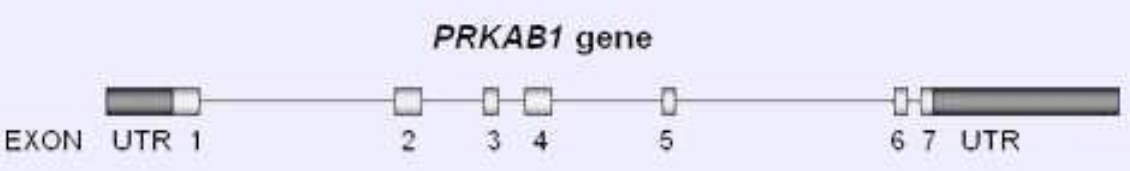
AMPKbeta1 protein expression is highest in the liver, and testis and low in kidney and skeletal muscle. In contrast, expression of PRKAB2, encoded by a different gene, is higher in skeletal muscle. This indicates a tissue specific pattern of expression of these two regulatory beta subunits.

Localisation

AMPKbeta1 localises in the cytoplasm. However nuclear translocation is possible because mutations of Ser24/25 and Ser182 to alanine lead to the redistribution of PRKAB1 to the nucleus.

Function

AMPKbeta1, may act as a positive regulator of AMPK activity and it may serve as an adaptor molecule for the catalytic subunit. It has also been reported that AMPKbeta1 contains a glycogen-binding domain (GBD) that may target the heterotrimer to glycogen storage sites.



PRKAB1 gene structure. UTR: untranslated region.

The heterotrimeric protein AMPK senses low intracellular energy levels upon increased in the AMP/ATP ratio. Binding of AMP results in allosteric activation, inducing phosphorylation on Thr-172 of the AMPKa regulatory subunit (PRKAA) by LKB1 in complex with STE20-related adapter-alpha (STRAD alpha). AMPK activation leads to the modulation of the activity of multiple downstream targets to normalize ATP levels.
Among these substrates is the tuberin protein, the product of the tuberous sclerosis complex 2 gene (TSC2) that upon activation by AMPK represses the activity of the mammalian target of rapamycin, mTOR.
It has been reported that PRKAB1 and PRKAB2 contain a glycogen binding domain that targets AMPK to glycogen.
Moreover, it has been shown that expression of PRKAB1 and PRKAB2 genes, in human cells, may be mediated by p53.

Homology

There is a AMPKbeta1 isoform, designated AMPKbeta2, encoded by the PRKAB2 gene. The N-terminal region of beta2 differs significantly from that AMPKbeta1 isoform, suggesting that this region could play a role in isoform-specific AMPK activity.
The AMPKbeta subunit is the mammalian homolog of the S. cerevisiae Sip1p/Sip2p/Gal83p family of proteins that interact with the AMPKa homolog, Snf1p, and are involved in glucose regulation of gene expression.

Mutations

Note: No germ-line or somatic mutations have been reported in the PRKAB1 gene.

To be noted

Note: Although PRKAB1 itself does not seem to be directly implicated in human disease, there is an indirect relationship between AMPKbeta and heart disease and cancer due to the implication of other subunits of the AMPK complex or to the implication of other related kinases:
- AMPK in heart disease:
Mutations at the PRAAG2 (encoding the gamma2 subunit of AMP-activated protein kinase) causes glycogen overload, Wolff-Parkinson-White syndrome, arrhythmias, and heart failure.
- AMPK in cancer:
LKB1 is a serine/threonin kinase that phosphorylates and activates AMPK. Germ-line mutations at LKB1 lead to the cancer-prone syndrome Peutz-Jeghers syndrome whereas somatic mutations are implicated in the development of non-small cell lung cancer.

References

Gao G, Fernandez CS, Stapleton D, Auster AS, Widmer J, Dyck JR, Kemp BE, Witters LA. Non-catalytic beta- and gamma-subunit isoforms of the 5'-AMP-activated protein kinase. J Biol Chem 1996;271:8675-8681.

Mitchelhill KI, Michell BJ, House CM, Stapleton D, Dyck J, Gamble J, Ullrich C, Witters LA, Kemp BE. Posttranslational Modifications of the 5 -AMP-activated Protein Kinase beta 1 Subunit. J Biol Chem 1997;272:24475-24479.

Stapleton D, Woollatt E, Mitchelhill KI, Nicholl JK, Fernandez CS, Michell BJ, Witters LA, Power DA, Sutherland GR, Kemp BE. AMP-activated protein kinase isoenzyme family: subunit structure and chromosomal location. FEBS Lett 1997;409:452-456.

Thornton C, Snowden MA, Carling D. Identification of a novel AMP-activated protein kinase beta subunit isoform that is highly expressed in skeletal muscle. J Biol Chem 1998;273:12443-12450.

Warden SM, Richardson C, O'Donnell J Jr, Stapleton D, Kemp BE, Witters LA. Post-translational modifications of the beta-1 subunit of AMP-activated protein kinase affect enzyme activity and cellular localization. Biochem J 2001;354:275-283.

Hardie DG. Minireview: the AMP-activated protein kinase cascade: the key sensor of cellular energy status. Endocrinology 2003;144:5179-5183.

Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Mäkelä TP, Alessi DR, Hardie DG. Complexes between the LKB1 tumor suppressor, STRADalpha/beta and MO25alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2003;2:28.

Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell 2003;115:577-590.

Li J, Jiang P, Robinson M, Lawrence TS, Sun Y. AMPK-beta1 subunit is a p53-independent stress responsive protein that inhibits tumor cell growth upon forced expression. Carcinogenesis 2003;24:827-834.

Polekhina G, Gupta A, Michell BJ, van Denderen B, Murthy S, Feil SC, Jennings IG, Campbell DJ, Witters LA, Parker MW, Kemp BE, Stapleton D. AMPK beta subunit targets metabolic stress sensing to glycogen. Curr Biol 2003;13:867-871.

Woods A, Johnstone SR, Dickerson K, Leiper FC, Fryer LG, Neumann D, Schlattner U, Wallimann T, Carlson M, Carling D. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. Curr Biol 2003;13:2004-2008.

Woods A, Vertommen D, Neumann D, Turk R, Bayliss J, Schlattner U, Wallimann T, Carling D, Rider MH. Identification of phosphorylation sites in AMP-activated protein kinase (AMPK) for upstream AMPK kinases and study of their roles by site-directed mutagenesis. J Biol Chem 2003;278:28434-28442.

Feng Z, Hu W, de Stanchina E, Teresky AK, Jin S, Lowe S, Levine AJ. The regulation of AMPK beta1, TSC2, and PTEN expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res 2007;67:3043-3053.

Sanchez-Cespedes M. A role for LKB1 gene in human cancer beyond the Peutz-Jeghers syndrome. Oncogene 2007 Jun 18;[Epub ahead of print].

This article should be referenced as such:

Sanchez-Cespedes M. PRKAB1 (protein kinase, AMP-activated, beta 1 non-catalytic subunit). Atlas Genet Cytogenet Oncol Haematol. 2008;12(2):151-152.