Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

PKM2 (pyruvate kinase isoenzyme type M2)

Sybille Mazurek, Ferdinand Hugo, Werner Zwerschke

Institute for Biochemistry & Endocrinology, Veterinary Medicine, University of Giessen, Frankfurter Strasse 100, 35392 Giessen, Germany (SM), ScheBo Biotech AG, Netanyastrasse 3, 35394 Giessen, Germany (SM), Institute of Medical Microbiology, Medical Faculty, University of Giessen, Frankfurter Strasse 107, 35392 Giessen, Germany (FH), Cell Metabolism and Differentiation Group, Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Rennweg 10, 6020 Innsbruck, Austria (WZ)

Published in Atlas Database: May 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/PKM2ID41728ch15q22.html
DOI: 10.4267/2042/44450

Identity

Other names: CTHBP; OIP3; PK2; PK3; PKM; TCB; THBP1
HGNC (Hugo): PKM2
Location: 15q22

DNA/RNA

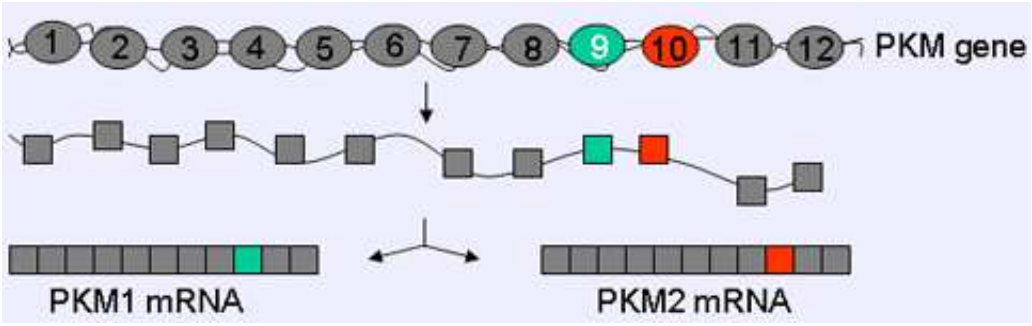
Note
Pyruvate kinase isoenzyme type M2 (alias M2-PK, alias PKM2) is one of four pyruvate kinase isoenzymes which differ widely in their occurrence according to the type of tissue, their kinetic characteristics and regulation mechanisms. The three other pyruvate kinase isoenzymes are type M1, type L and type R. The PKM-gene encodes for pyruvate kinase isoenzyme type M2 as well as pyruvate kinase isoenzyme type M1.

Description

The human PKM gene is 32,315 kb long and consists of 12 exons and 11 introns.

Transcription

Pyruvate kinase isoenzymes type M1 and type M2 are different splicing products of the PKM gene (exon 9 for M1-PK and exon 10 for M2-PK). Both mRNAs are 1593 base pairs long and differ from another within 160 nucleotide residues from 1143-1303. The PKM gene is induced by hormones, mitogenic pathways and nutrients. The thyroid gland hormone triiodothyronine (T3) induces PKM gene expression in rat pituitary cells and the monomeric form of the PKM protein has been identified as T3-receptor. Interleukin 2 stimulates PKM transcription in proliferating thymocytes, resulting in increased PKM2 mRNA and protein levels in the S phase of the cell cycle. In NIH3T3 L1 adipocytes PKM gene expression is induced by insulin. Evidence for a role of hypoxia, and the key nutrients glucose and glutamine, in the regulation of PKM gene expression has also been reported. The regulation of the PKM gene at the promoter level is, however, not well understood. The PKM gene contains putative DNA-consensus binding sites for the transcription factors Sp1 and Sp3 (GC-boxes)



Exon/intron structure of the PKM gene and the PKM1 and PKM2 mRNAs derived by alternative splicing.

and Sp1/Sp3-dependent stimulation of PKM gene transcription has been demonstrated. The GC-boxes appear to also play a role in glucose-dependent PKM-gene induction. A carbohydrate-response element (ChoRE), which integrates regulation of many glycolytic genes in response to changes in glucose concentration, has not yet been precisely localized in the PKM promoter region. However, putative consensus DNA-binding elements for USF (Upstream stimulating factor), a transcription factor which is involved in glucose-response, HIF-1alpha (Hypoxia-inducible factor) and the oncogenic transcription factor Myc are present within the PKM promoter region. The USF-box (5'-CACGTG-3'), the HIF-1alpha DNA-binding consensus element (5'-RCGTG-3') as well as the MYC consensus element (E-box; 5'-CACGTG-3') match the consensus core DNA-binding sites (5'-CACGTG-3') of the ChoRE. However, direct evidence for a role of these transcription factors in the stimulation of PKM gene expression has bot been obtained.

Pseudogene

No Pseudogenes.

Protein

Note

In various references pyruvate kinase isoenzyme type M2 (abbreviations M2-PK or PKM2) has been termed type III, type A, type B, type K or type K4.

Description

Each monomer of PKM2 consists of 531 amino acids and can be subdivided into four domains: the N-domain (aa 1-43), the A-domain (aa 44-116 and 219-389), the B-domain (aa 117-218) and the C-domain (aa 390-531). The molecular weight of the M2-PK monomer is 58 kD. In contrast to the other PK isoenzymes which are characterized by a tetrameric quaternary structure, M2-PK occurs in a tetrameric as well as dimeric form. The dimeric form of M2-PK is the result of intracellular contact between the A-domain of two monomers. The tetrameric form occurs by association of the interface of the C-domains of two dimers. The C-domain contains 44 amino acids of the 56 amino acid stretch (aa 378-434) which differs between M1 and M2-PK-isoenzymes and is responsible for the different kinetic characteristics and regulation mechanisms found for M1 and M2-PK, i.e. fructose 1,6-P2 activation and interaction with different oncoproteins. The cleft formed between the A- and B-domain is the location of the active site of the enzyme. The C-domain (aa 393-531) comprises an inducible nuclear translocation signal.

Expression

Pyruvate kinase isoenzyme type M2 is expressed in some differentiated tissues, such as lung, fat tissue, retina, pancreatic islets as well as in all cells with a high rate of nucleic acid synthesis, which include all proliferating cells, such as normal proliferating cells, embryonic cells, adult stem cells and especially tumor cells. In healthy tissues all pyruvate kinase isoenzymes consist of four subunits whereby hybrids of the different forms can also occur. Hybrids between M1 and M2-PK were found in the oesophagus and the stomach. L-PK and M2-PK hybrids were found in the jejunum, colon and rectum. During differentiation of embryonic cells M2-PK is progressively replaced by the respective tissue specific isoenzyme. Conversely, during tumorigenesis the tissue specific isoenzymes disappear and M2-PK is expressed.

Localisation

Pyruvate kinase type M2 is found predominantly in the cytosol and to a minor extent in the nucleus. Cytosolic M2-PK is associated with other glycolytic enzymes, i.e. hexokinase, glyceraldehyde 3-P dehydrogenase, phosphoglycerate kinase, phosphoglyceromutase, enolase and lactate dehydrogenase in a so-called glycolytic enzyme complex.

Function

Pyruvate kinase (ATP: pyruvate O^{2-}phosphotransferase; EC 2.7.1.40) catalyzes the last step within glycolysis, the dephosphorylation of phosphoenolpyruvate (PEP) to pyruvate while producing one mole of ATP per mole of PEP. Depending upon the tetramer to dimer ratio M2-PK plays a bi-functional role within tumor metabolism. The tetrameric form of M2-PK favors the degradation of glucose to pyruvate and lactate with regeneration of energy due to a high affinity to its substrate PEP. The dimeric form is characterized by a low PEP affinity and is nearly inactive at physiological PEP concentrations.

Molecular structure of the human PKM2 protein. NLS = nuclear localization signal.

This leads to an expansion of all phosphometabolites above the pyruvate kinase reaction and an increased channeling of glucose carbons into synthetic processes, i.e. DNA, phospholipid and amino acid synthesis. Tumor cells contain high levels of dimeric M2-PK, which has therefore been termed 'Tumor M2-PK'.
The M2-PK tetramer to dimer ratio fluctuates in tumor cells depending upon the concentrations of signal metabolites. High fructose 1,6-P2 levels induce the association of the inactive dimeric form of M2-PK to the highly active tetrameric form. When FBP levels drop below a critical value the tetrameric form dissociates to the dimeric form. Dimerization of M2-PK is induced by direct interaction with different oncoproteins, i.e. pp60v-src, A-Raf and HPV-16 E7. The importance of M2-PK for oncogenesis is further underlined by the impairment of the oncogenic activity of activated A-Raf (gag-A-Raf) by a kinase-dead mutant of M2-PK and the enhancement of the transforming activity of gag-A-Raf by ectopically expressed wild type M2-PK. Similarly, a knockdown of M2-PK expression by short hairpin RNA and replacement with M1-PK led to a reduction in tumor growth rate. Peptide aptamers which specifically bind to M2-PK and not to the 96% homologous PK isoenzyme type M1 were found to avoid re-association of M2-PK to the tetrameric form thereby reducing ATP levels and decelerating tumor cell proliferation.
Recent work has shown that the binding of cytosolic promyelocytic leukemia (PML) tumor suppressor protein to M2-PK leads to inhibition of the activity of the tetrameric form of M2-PK which results in a suppression of lactate production. The interaction of M2-PK with HERC-1, PKCdelta and tumor endothelial marker TEM8 has also been reported; however, the physiological functions of these findings are not yet well understood.
Regarding the function of M2-PK in the nucleus both pro-proliferative, but also pro-apoptotic stimuli have been described. Thus, interleukin-3-induced nuclear translocation of M2-PK stimulated cell proliferation, whereas nuclear translocation of M2-PK induced by TT232, H2O2 or UV-irradiation was linked to the induction of caspase independent programmed cell death. Nuclear M2-PK was found to participate in the phosphorylation of histone H1 by direct phosphate transfer from PEP to histone H1. Furthermore, M2-PK was shown to interact with Oct-4 and stimulates transactivation by the transcription factor; however, the functional consequences of these findings have not been elucidated.
The interaction between PKM2 with gonococcal Opa proteins points to a physiological role of M2-PK in bacterial pathogenesis.

Homology

It is assumed that M1 and M2-PK diverged shortly before the evolution of fish. The pyruvate kinase amino acid sequence is highly conserved. The homology between human M1-PK and human M2-PK is 96%. Comparison of the M2-PK amino acid sequence between different species revealed the following homologies: human and rat: 93%; human and mus musculus: 93 %; rat and mus musculus 98%; human and S. cerevisiae: 50%.

Mutations

Note

There is one report which describes a missense mutation and a frame shift mutation in exon 10 of the M gene in three B-lymphoblastoid cell lines established from three Bloom syndrome patients. Exon 10 encodes for the intersubunit contact domain of the M2-PK protein. These mutations have a dominant negative effect leading to inactivation of M2-PK. However, the relevance of these mutations has not yet been determined.

Implicated in

Note

M2-PK is overexpressed in all tumor entities thus far investigated, such as gastrointestinal tumors, melanoma, tumors of the lung, breast, prostate, ovary and cervix. Tumor M2-PK, the dimeric form of M2-PK, is released from tumors into the blood, and pleural fluid and from tumors of the lower gastrointestinal tract also into the stool of tumor patients. The amount of Tumor M2-PK in plasma and stool was found to correlate with staging and may be used for early detection of tumors and follow up studies during therapy. For some tumor entities correlations with certain oncoprotein expressions have been described.

Renal cell carcinoma

Disease

The term renal cell carcinoma (RCC) comprises different histological types whereby the clear cell renal cell carcinoma is the most common histologic variant, accounting for approximately 70% of all cases. Estimated incidences rank RCC as the 13th most common malignancy in men and 15th in women. In addition to sporadic forms, hereditary forms of RCC also occur, e.g. in a high proportion of patients with von Hippel-Lindau disease (VHL).

Oncogenesis

In patients with von Hippel-Lindau disease and in a high percentage of tumors from patients with sporadic clear cell RCC, one inherited allele of the VHL gene - a master regulator of HIF (hypoxia-inducible factor) - is mutated and the second allele
is deleted. VHL mutations lead to a pseudo-hypoxic state with overproduction of HIF-1a. The PKM promotor contains a binding site for HIF-1. Hypoxia correlates with an increase in PKM2 mRNA.

Tumors of the uterine cervix

Disease

Cervical carcinoma is the 2nd most common cancer in women worldwide. It originates for the most part from the transformation zone of the cervix. The histologic morphology is predominantly of the squamous cell type.

Oncogenesis

Chronic infection with human papillomavirus (HPV) plays a major aetiological role in the evolution of cervical carcinomas. The products of the oncogenes E6 and E7 from HPV 16 are able to form stable complexes with cellular proteins thereby modifying or inactivating their normal functions. It has been shown that the E7 protein physically interacts with and stabilizes the dimeric form of PKM2.

Gastric carcinoma

Note

In different gastric carcinoma cell lines cisplatin resistance was found to correlate with low M2-PK protein levels and activities. Lowering of M2-PK expression through antisense transfection increased cisplatin resistance.

Disease

Stomach cancer is the 4th most common cancer worldwide. Helicobacter pylori infection appears to play a pivotal aetiological role in the induction of the intestinal type of gastric carcinoma, whereby its action is probably indirect by provoking an inflammatory response. Thus, gastritis is usually the first step in cancer induction and may lead to multifocal atrophic gastritis followed by intestinal metaplasia as an important precursor lesion.

Colon and rectum cancer

Disease

Colorectal cancers rank 4th in frequency in men and 3rd in women. Most carcinomas develop from adenomas, which constitute their precursor lesion. These adenomas may occur sporadically or as part of a polyposis syndrome. More than ninety percent of all large bowel tumors are ordinary adenocarcinomas.

Oncogenesis

Inactivating mutations of the adenomatous polyposis coli (APC) gene is an early event and a key molecular step in adenoma formation. Further progression to colon cancer is a multistep process wherein multiple alterations may be relevant, e.g. mutations in the DCC, k-ras, and/or p53 genes; loss of heterozygosity; and DNA methylations. A recent report described the coexistence of mutational activation of the k-ras gene and HPV high risk types infection in colon cancer. It has been shown that the HPV-16 E7 protein, which cooperates with ras in cell transformation, directly binds to PKM2, thereby inducing and stabilizing the dimeric form of this isoenzyme.

References

van Berkel TJ, de Jonge HR, Koster JF, Hülsmann WC. Kinetic evidence for the presence of two forms of M2-type pyruvate kinase in rat small intestine. Biochem Biophys Res Commun. 1974 Sep 9;60(1):398-405

Corcoran E, Phelan JJ, Fottrell PF. Purification and properties of pyruvate kinase from human lung. Biochim Biophys Acta. 1976 Sep 28;446(1):96-104

Tolle SW, Dyson RD, Newburgh RW, Cardenas JM. Pyruvate kinase isozymes in neurons, glia, neuroblastoma, and glioblastoma. J Neurochem. 1976 Dec;27(6):1355-60

Saheki S, Harada K, Sanno Y, Tanaka T. Hybrid isozymes of rat pyruvate kinase. Their subunit structure and developmental changes in the liver. Biochim Biophys Acta. 1978 Sep 11;526(1):116-28

Eigenbrodt E, Glossmann H.. Glycolysis - one of the keys to cancer? Trends Pharmacol Sci 1980 May;240-5.

Presek P, Glossmann H, Eigenbrodt E, Schoner W, Rübsamen H, Friis RR, Bauer H. Similarities between a phosphoprotein (pp60src)-associated protein kinase of Rous sarcoma virus and a cyclic adenosine 3':5'-monophosphate-independent protein kinase that phosphorylates pyruvate kinase type M2. Cancer Res. 1980 May;40(5):1733-41

Reinacher M, Eigenbrodt E. Immunohistological demonstration of the same type of pyruvate kinase isoenzyme (M2-Pk) in tumors of chicken and rat. Virchows Arch B Cell Pathol Incl Mol Pathol. 1981;37(1):79-88

Schering B, Eigenbrodt E, Linder D, Schoner W. Purification and properties of pyruvate kinase type M2 from rat lung. Biochim Biophys Acta. 1982 Aug 6;717(2):337-47

MacDonald MJ, Chang CM. Pancreatic islets contain the M2 isoenzyme of pyruvate kinase. Its phosphorylation has no effect on enzyme activity. Mol Cell Biochem. 1985 Oct;68(2):115-20

Noguchi T, Inoue H, Tanaka T. The M1- and M2-type isozymes of rat pyruvate kinase are produced from the same gene by alternative RNA splicing. J Biol Chem. 1986 Oct 15;261(29):13807-12

Takenaka M, Noguchi T, Inoue H, Yamada K, Matsuda T, Tanaka T. Rat pyruvate kinase M gene. Its complete structure and characterization of the 5'-flanking region. J Biol Chem. 1989 Feb 5;264(4):2363-7

Weernink PA, Rijksen G, van der Heijden MC, Staal GE. Phosphorylation of pyruvate kinase type K in human gliomas by a cyclic adenosine 5'-monophosphate-independent protein kinase. Cancer Res. 1990 Aug 1;50(15):4604-10

Ashizawa K, Willingham MC, Liang CM, Cheng SY. In vivo regulation of monomer-tetramer conversion of pyruvate kinase subtype M2 by glucose is mediated via fructose 1,6-bisphosphate. J Biol Chem. 1991 Sep 5;266(25):16842-6

Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. J Biol Chem. 1991 Mar 15;266(8):4706-12

Eigenbrodt E, Reinacher M, Scheefers-Borchel U, Scheefers H, Friis R. Double role for pyruvate kinase type M2 in the expansion of phosphometabolite pools found in tumor cells. Crit Rev Oncog. 1992;3(1-2):91-115

Gillberg IC, Gillberg C, Kopp S. Hypothyroidism and autism spectrum disorders. J Child Psychol Psychiatry. 1992 Mar;33(3):531-42

Netzker R, Greiner E, Eigenbrodt E, Noguchi T, Tanaka T, Brand K. Cell cycle-associated expression of M2-type isozyme of pyruvate kinase in proliferating rat thymocytes. J Biol Chem. 1992 Mar 25;267(9):6421-4

Brinck U, Eigenbrodt E, Oehmke M, Mazurek S, Fischer G. L- and M2-pyruvate kinase expression in renal cell carcinomas and their metastases. Virchows Arch. 1994;424(2):177-85

Wang Z, Takenaka M, Imai E, Yamada K, Tanaka T, Noguchi T. Transcriptional regulatory regions for expression of the rat pyruvate kinase M gene. Eur J Biochem. 1994 Mar 1;220(2):301-7

Gryfe R, Swallow C, Bapat B, Redston M, Gallinger S, Couture J. Molecular biology of colorectal cancer. Curr Probl Cancer. 1997 Sep-Oct;21(5):233-300

Netzker R, Weigert C, Brand K. Role of the stimulatory proteins Sp1 and Sp3 in the regulation of transcription of the rat pyruvate kinase M gene. Eur J Biochem. 1997 Apr 1;245(1):174-81

Discher DJ, Bishopric NH, Wu X, Peterson CA, Webster KA. Hypoxia regulates beta-enolase and pyruvate kinase-M promoters by modulating Sp1/Sp3 binding to a conserved GC element. J Biol Chem. 1998 Oct 2;273(40):26087-93

Eigenbrodt E, Mazurek S, Friis R.. Double role of pyruvate kinase type M2 in the regulation of phosphometabolite pools. In: Bannasch P, Kanduc D, Papa S, Tager JM (eds). Cell Growth and Oncogenesis. Birkhauser Verlag, Basel 1998: 15-30.

Kress S, Stein A, Maurer P, Weber B, Reichert J, Buchmann A, Huppert P, Schwarz M. Expression of hypoxia-inducible genes in tumor cells. J Cancer Res Clin Oncol. 1998;124(6):315-20

Williams JM, Chen GC, Zhu L, Rest RF. Using the yeast two-hybrid system to identify human epithelial cell proteins that bind gonococcal Opa proteins: intracellular gonococci bind pyruvate kinase via their Opa proteins and require host pyruvate for growth. Mol Microbiol. 1998 Jan;27(1):171-86

Dang CV, Semenza GL. Oncogenic alterations of metabolism. Trends Biochem Sci. 1999 Feb;24(2):68-72

Netzker R, Fabian D, Weigert C, Brand KA. Functional studies by site-directed mutagenesis on the role of Sp1 in the expression of the pyruvate kinase M and aldolase A genes. Biochim Biophys Acta. 1999 Feb 16;1444(2):231-40

Oremek GM, Teigelkamp S, Kramer W, Eigenbrodt E, Usadel KH. The pyruvate kinase isoenzyme tumor M2 (Tu M2-PK) as a tumor marker for renal carcinoma. Anticancer Res. 1999 Jul-Aug;19(4A):2599-601

Steinberg P, Klingelhöffer A, Schäfer A, Wüst G, Weisse G, Oesch F, Eigenbrodt E. Expression of pyruvate kinase M2 in preneoplastic hepatic foci of N-nitrosomorpholine-treated rats. Virchows Arch. 1999 Mar;434(3):213-20

Zwerschke W, Mazurek S, Massimi P, Banks L, Eigenbrodt E, Jansen-Dürr P. Modulation of type M2 pyruvate kinase activity by the human papillomavirus type 16 E7 oncoprotein. Proc Natl Acad Sci U S A. 1999 Feb 16;96(4):1291-6

Lüftner D, Mesterharm J, Akrivakis C, Geppert R, Petrides PE, Wernecke KD, Possinger K. Tumor type M2 pyruvate kinase expression in advanced breast cancer. Anticancer Res. 2000 Nov-Dec;20(6D):5077-82

Mazurek S, Zwerschke W, Jansen-Dürr P, Eigenbrodt E. Metabolic cooperation between different oncogenes during cell transformation: interaction between activated ras and HPV-16 E7. Oncogene. 2001 Oct 18;20(47):6891-8

Le Mellay V, Houben R, Troppmair J, Hagemann C, Mazurek S, Frey U, Beigel J, Weber C, Benz R, Eigenbrodt E, Rapp UR. Regulation of glycolysis by Raf protein serine/threonine kinases. Adv Enzyme Regul. 2002;42:317-32

Schneider J, Neu K, Grimm H, Velcovsky HG, Weisse G, Eigenbrodt E. Tumor M2-pyruvate kinase in lung cancer patients: immunohistochemical detection and disease monitoring. Anticancer Res. 2002 Jan-Feb;22(1A):311-8

Asai Y, Yamada K, Watanabe T, Keng VW, Noguchi T. Insulin stimulates expression of the pyruvate kinase M gene in 3T3-L1 adipocytes. Biosci Biotechnol Biochem. 2003 Jun;67(6):1272-7

Garcia-Gonzalo FR, Cruz C, Muñoz P, Mazurek S, Eigenbrodt E, Ventura F, Bartrons R, Rosa JL. Interaction between HERC1 and M2-type pyruvate kinase. FEBS Lett. 2003 Mar 27;539(1-3):78-84

George DJ, Kaelin WG Jr. The von Hippel-Lindau protein, vascular endothelial growth factor, and kidney cancer. N Engl J Med. 2003 Jul 31;349(5):419-21

Ignacak J, Stachurska MB. The dual activity of pyruvate kinase type M2 from chromatin extracts of neoplastic cells. Comp Biochem Physiol B Biochem Mol Biol. 2003 Mar;134(3):425-33

Anitha M, Kaur G, Baquer NZ, Bamezai R. Dominant negative effect of novel mutations in pyruvate kinase-M2. DNA Cell Biol. 2004 Jul;23(7):442-9

Kaura B, Bagga R, Patel FD. Evaluation of the Pyruvate Kinase isoenzyme tumor (Tu M2-PK) as a tumor marker for cervical carcinoma. J Obstet Gynaecol Res. 2004 Jun;30(3):193-6

Kim JW, Zeller KI, Wang Y, Jegga AG, Aronow BJ, O'Donnell KA, Dang CV. Evaluation of myc E-box phylogenetic footprints in glycolytic genes by chromatin immunoprecipitation assays. Mol Cell Biol. 2004 Jul;24(13):5923-36

Yoo BC, Ku JL, Hong SH, Shin YK, Park SY, Kim HK, Park JG. Decreased pyruvate kinase M2 activity linked to cisplatin resistance in human gastric carcinoma cell lines. Int J Cancer. 2004 Feb 10;108(4):532-9

Dombrauckas JD, Santarsiero BD, Mesecar AD. Structural basis for tumor pyruvate kinase M2 allosteric regulation and catalysis. Biochemistry. 2005 Jul 12;44(27):9417-29

Mazurek S, Boschek CB, Hugo F, Eigenbrodt E. Pyruvate kinase type M2 and its role in tumor growth and spreading. Semin Cancer Biol. 2005 Aug;15(4):300-8

Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005 Mar-Apr;55(2):74-108

Buyru N, Tezol A, Dalay N. Coexistence of K-ras mutations and HPV infection in colon cancer. BMC Cancer. 2006 May 4;6:115

Ahmed AS, Dew T, Lawton FG, Papadopoulos AJ, Devaja O, Raju KS, Sherwood RA. M2-PK as a novel marker in ovarian cancer. A prospective cohort study. Eur J Gynaecol Oncol. 2007;28(2):83-8

Duan HF, Hu XW, Chen JL, Gao LH, Xi YY, Lu Y, Li JF, Zhao SR, Xu JJ, Chen HP, Chen W, Wu CT. Antitumor activities of TEM8-Fc: an engineered antibody-like molecule targeting tumor endothelial marker 8. J Natl Cancer Inst. 2007 Oct 17;99(20):1551-5

Hoshino A, Hirst JA, Fujii H. Regulation of cell proliferation by interleukin-3-induced nuclear translocation of pyruvate kinase. J Biol Chem. 2007 Jun 15;282(24):17706-11

Kumar Y, Tapuria N, Kirmani N, Davidson BR. Tumour M2-pyruvate kinase: a gastrointestinal cancer marker. Eur J Gastroenterol Hepatol. 2007 Mar;19(3):265-76

Mazurek S, Drexler HC, Troppmair J, Eigenbrodt E, Rapp UR. Regulation of pyruvate kinase type M2 by A-Raf: a possible glycolytic stop or go mechanism. Anticancer Res. 2007 Nov-Dec;27(6B):3963-71

Siwko S, Mochly-Rosen D. Use of a novel method to find substrates of protein kinase C delta identifies M2 pyruvate kinase. Int J Biochem Cell Biol. 2007;39(5):978-87

Steták A, Veress R, Ovádi J, Csermely P, Kéri G, Ullrich A. Nuclear translocation of the tumor marker pyruvate kinase M2 induces programmed cell death. Cancer Res. 2007 Feb 15;67(4):1602-8

Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, Fleming MD, Schreiber SL, Cantley LC. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature. 2008 Mar 13;452(7184):230-3

Christofk HR, Vander Heiden MG, Wu N, Asara JM, Cantley LC. Pyruvate kinase M2 is a phosphotyrosine-binding protein. Nature. 2008 Mar 13;452(7184):181-6

Elia S, Massoud R, Guggino G, Cristino B, Cortese C, De Massimi AR, Zenobi R. Tumor type M2-pyruvate-kinase levels in pleural fluid versus plasma in cancer patients: a further tool to define the need for invasive procedures. Eur J Cardiothorac Surg. 2008 Apr;33(4):723-7

Lee J, Kim HK, Han YM, Kim J. Pyruvate kinase isozyme type M2 (PKM2) interacts and cooperates with Oct-4 in regulating transcription. Int J Biochem Cell Biol. 2008;40(5):1043-54

Shimada N, Shinagawa T, Ishii S. Modulation of M2-type pyruvate kinase activity by the cytoplasmic PML tumor suppressor protein. Genes Cells. 2008 Mar;13(3):245-54

Spoden GA, Mazurek S, Morandell D, Bacher N, Ausserlechner MJ, Jansen-Dürr P, Eigenbrodt E, Zwerschke W. Isotype-specific inhibitors of the glycolytic key regulator pyruvate kinase subtype M2 moderately decelerate tumor cell proliferation. Int J Cancer. 2008 Jul 15;123(2):312-21

This article should be referenced as such:

Mazurek S, Hugo F, Zwerschke W. PKM2 (pyruvate kinase isoenzyme type M2). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(4):276-281.