Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Review

CHKA (choline kinase alpha)

Ana Ramírez de Molina, María Álvarez-Miranda, Juan Carlos Lacal

Centro Nacional de Biotecnologia (CNB), Darwin 3, 28049 Madrid, Spain (ARM, MÁM, JCL)

Published in Atlas Database: April 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/CHKAID44009ch11q13.html
DOI: 10.4267/2042/44401

Identity

Other names: CHETK-alpha; CHK; CK; CKI
HGNC (Hugo): CHKA
Location: 11q13.2

DNA/RNA

Transcription

The DNA sequence contains 6 exons and the length is of 1374 nt translated to a 457 residues protein.

Protein

Description

Choline Kinase alpha (CHKA, though we have proposed to name it as ChoKα in order to distinguish it from check point kinase CHK) encodes two different isoforms. Choline Kinase alpha isoform a (ChoKαa) has 457 amino acid residues with a molecular mass of approximatively 52 kDa. Choline Kinase alpha isoform b (ChoKαb) has the same N- and C-termini but is shorter compared to isoform a, resulting in a variant of 439 amino acids and a molecular mass of approximatively 50 kDa.

Both isoforms are active only in an oligomeric form (di- or tetrameric) and require ATP and Mg2+ for their catalytic activity (Wittenberg and Kornberg 1953).

ChoKα structure:

Choline Kinase alpha isoform a (NM_001277) has been crystallized in complex with ADP and phosphocholine (referred in the paper as Choline Kinase alpha2). ATP binds in a cavity where residues from both de N and C-terminal lobes contribute to form a cleft, while the choline-binding site constitutes a deep hydrophobic groove in the C-terminal domain with a rim composed of negative charged residues. Upon binding of choline, the enzyme undergoes conformational changes independently affecting the N-terminal domain and the ATP binding loop (Malito et al. 2006).

ChoKα regulation:

Although much work has been made in other organisms (Paddon et al. 1982; Warden and Friedkin 1985; Kim and Carman 1999; Ramirez de Molina et al. 2002; Yu et al. 2002; Choi et al. 2005; Soto 2008), little is known about human ChoKα regulation.

It has been described that in HeLa cells, both EGF and insulin increase ChoK activity promoting the conversion of Cho to PCho, accompanied by an expansion of the PCho pool in treated cells (Uchida 1996). On the other hand, it has been suggested that Hypoxia-Inducible Factor-1α (HIF-1α) regulates ChoKα expression in a human prostate cancer model. An increase in cellular PCho and total Cho, as well as ChoK expression, has been observed following exposure of PC-3 cells to hypoxia. Furthermore, HIF-1α can directly bind to some putative hypoxia response elements (HRE) within ChoKα promoter, suggesting that HIF-1α activation of HREs within the putative ChoKα promoter region can increase ChoKα expression in hypoxic environments (Glunde et al. 2008).

Expression

Choline Kinase is expressed ubiquitously and concurrently (Aoyama et al. 2002). It is a vital enzyme, as homozygous ChoKa knock-out mice is lethal, indicating the indispensable role of ChoKα in early embryogenesis (Wu et al. 2008).

Localisation

ChoKα is found in the cytoplasm.

Function

Choline Kinase activation is necessary for membranes maintenance, cell growth and cell proliferation. It is also necessary for restoring phospholipids degraded

during signal transduction. Consequently, ChoKα has an essential role in growth control and signal transduction and it has been implicated in the carcinogenic process.

Role in metabolic process:

Choline Kinase is the first enzyme in the Kennedy pathway, responsible for de novo synthesis of phosphatidylcholine (PC), one of the major lipid components of plasma membranes in mammal cells, that is also essential for structural stability and cell proliferation. The Kennedy pathway consists of four steps. First Choline Kinase catalyzes choline phosphorylation, then phosphocholine (PCho) cytidylyl-transferase (CCT) catalyzes the formation of CDP-choline from PCho and CTP, and cholinephosphotransferase (CPT) catalyzes the final condensation reaction of CDP-choline with diacylglycerol (DAG) to generate PC. Finally, Phospholipase D (PLD) catalyses the hydrolysis of PC to generate phosphatidic acid (PA) and free choline. ChoKα can also function as an ethanolamine kinase (EtnK) as it is able to phosphorylate ethanolamine. For a long time choline kinase and ethanolamine kinase have been considered as the same enzyme, because ChoK preparations of highly purified or recombinant enzymes from mammalian sources has been shown to have also a significant EtnK activity. Sub-sequently, separate genes that would encode EtnK-specific enzymes were identified (Aoyama et al. 2004).

Role in signal transduction, precursor of second messengers:

PC hydrolysis has been implicated in cell signalling. Due to the relative abundance of PC, its hydrolysis can sustain a prolonged liberation of catabolites without drastic changes in membrane phospholipids content. These long-lasting signals are thought to be important in the acquisition of the transformed phenotype. Under mitogenic stimulation by growth factors or oncogenic transformation, PLD-driven PC hydrolysis gives choline and phosphatidic acid (PA). PA can be hydrolyzed or deacylated to form DAG or lysophosphatidic acid (LPA) respectively, both with mitogenic activity. On the other hand, PCho generated from Cho by ChoK is an essential event for growth factors such as platelet-derived growth factor (PDGF) or fibroblast growth factor (FGF). Furthermore, it has been suggested a mitogenic role for PCho (Lacal 2001; Janardhan et al. 2006).

Role in the regulation of cell proliferation:

The accumulation of PC is necessary for the entrance of S phase of the cycle and cell division. It has been recently proposed that ChoKα participates in the regulation of G1-->S transition of the cell cycle at different levels (Ramirez de Molina et al. 2004). ChoKα over-expression induces the transcriptional regulation of genes involved in cell cycle such as p21, p27, and Cyclin D1 and Cyclin D3, whereas ChoKα specific inhibition reverses this effect on the regulation of cell cycle promoting genes. These results suggest the existence of ChoKα-driven co-regulated mechanism to maintain cell growth through the activation of G1-->S transition of the cell cycle (Ramirez de Molina et al. 2008).

Role in carcinogenesis:

PCho is an important lipid metabolite that is involved in cell proliferation as well as in tumorogenesis (Glunde et al. 2006). A role for ChoK in generation of human tumours has been reported. Studies with nuclear magnetic resonance (NMR) reveals elevated levels of PCho in human tumoral tissues in comparison with normal ones (Ruiz-Cabello and Cohen 1992; Smith et al. 1993). The generation of PCho through Kennedy pathway is considered to be one of the crucial steps in regulating growth factor stimulated cell proliferation, malignant transformation, invasion and metastasis (Lacal 2001; Rodriguez-Gonzalez et al. 2003; Glunde et al. 2006). Confirming the role of ChoK in the generation of PCho in the carcinogenic process, this enzyme has been recently described as a novel oncogene that potentiates the tumorogenic ability of other oncogenes such as RhoA (Ramirez de Molina et al. 2005).

ChoKα is over-expressed in different tumour-derived cell lines as well as in different human tumours including breast, lung, prostate and colorectal colon cancers (Ramirez de Molina et al. 2002; Ramirez de Molina et al. 2002). In addition to ChoKα over-expression, an increased enzymatic activity has been observed in human tumours such as breast (Ramirez de Molina et al. 2002) and colon cancer (Nakagami et al. 1999). Furthermore, ChoKα has been recently described as a new prognostic factor to predict patient outcome in early-stage non-small-cell lung cancer patients (Ramirez de Molina et al. 2007).

Consequently, ChoKα inhibition constitutes an efficient antitumour strategy with demonstrated antiproliferative activity in vitro and antitumoral activity in vivo (Hernandez-Alcoceba et al. 1997; Hernandez-Alcoceba et al. 1999). A dramatic difference in the response to MN58b, a specific ChoK inhibitor, has been observed between normal and tumour cells. Whereas blockage of de novo PCho synthesis by MN58b in primary cells induces pRb dephosphorylation and results in reversible cell cycle arrest in G0/G1 phase, tumour cells suffer a drastic wobble in the metabolism of main membrane lipids PC and sphingomyelin, resulting in a significant increase in the intracellular levels of ceramides that promotes cells to apoptosis (Rodriguez-Gonzalez et al. 2003; Rodriguez-Gonzalez et al. 2004; Rodriguez-Gonzalez et al. 2005).

Mutations

Note

No mutation has been described in ChoKα.

Implicated in

Breast carcinoma

Oncogenesis

Normal and tumoral tissues from patients with breast carcinomas were analysed for ChoKα activity and expression. ChoKα activity was increased in 38.5% of tumoral tissues, whereas ChoKα over-expression determined by WB analysis was found in 17% of the 53 samples analysed (Ramirez de Molina et al, 2002).

Ovarian carcinoma

Oncogenesis

Choline Kinase activity in human epithelial ovarian carcinoma cells (EOC) was 12- to 24-fold higher when compared with normal or immortalized ovary epithelial cells (EONT) (Iorio et al, 2005).

Lung cancer

Oncogenesis

ChoKα mRNA levels were increased in lung tumour cell lines in comparison with human primary bronchial epithelial cells (BEC). This increase was higher in small-cell lung cancer (SCLC) than in non-small-cell lung cancer (NSCLC). Moreover, protein levels and ChoK enzymatic activity were also increased in tumour cells (Ramirez de Molina et al, 2007).

When analysing tissues from patients with NSCLC, ChoKα over-expression was also observed with an incidence of 50%. Furthermore, patients with NSCLC with ChoKα over-expression had worse disease free and overall survival than those patients with normal levels of the enzyme (Ramirez de Molina et al, 2007).

Colorectal cancer

Oncogenesis

Both ChoKα activity and PCho levels were increased in colon cancer and adenocarcinoma tissues when compared with normal tissue. PCho levels in colon cancers were about 1.5 times higher than in normal colon tissue, whereas ChoK activity was 3.7 times higher in tumoral tissues with respect to normal ones (Nakagami et al, 1999).

Prostate cancer

Oncogenesis

Increased ChoKα was found in 48% tumoral prostate tissues when compared with their normal counterparts (Ramirez de Molina et al, 2002).

References

WITTENBERG J, KORNBERG A. Choline phosphokinase. J Biol Chem. 1953 May;202(1):431-44

Paddon HB, Vigo C, Vance DE. Diethylstilbestrol treatment increases the amount of choline kinase in rooster liver. Biochim Biophys Acta. 1982 Jan 15;710(1):112-5

Warden CH, Friedkin M. Regulation of choline kinase activity and phosphatidylcholine biosynthesis by mitogenic growth factors in 3T3 fibroblasts. J Biol Chem. 1985 May 25;260(10):6006-11

Ruiz-Cabello J, Cohen JS. Phospholipid metabolites as indicators of cancer cell function. NMR Biomed. 1992 Sep-Oct;5(5):226-33

Smith TA, Bush C, Jameson C, Titley JC, Leach MO, Wilman DE, McCready VR. Phospholipid metabolites, prognosis and proliferation in human breast carcinoma. NMR Biomed. 1993 Sep-Oct;6(5):318-23

Uchida T. Stimulation of phospholipid synthesis in HeLa cells by epidermal growth factor and insulin: activation of choline kinase and glycerophosphate acyltransferase. Biochim Biophys Acta. 1996 Nov 22;1304(2):89-104

Hernández-Alcoceba R, Saniger L, Campos J, Núñez MC, Khaless F, Gallo MA, Espinosa A, Lacal JC. Choline kinase inhibitors as a novel approach for antiproliferative drug design. Oncogene. 1997 Nov 6;15(19):2289-301

Hernández-Alcoceba R, Fernández F, Lacal JC. In vivo antitumor activity of choline kinase inhibitors: a novel target for anticancer drug discovery. Cancer Res. 1999 Jul 1;59(13):3112-8

Kim KH, Carman GM. Phosphorylation and regulation of choline kinase from Saccharomyces cerevisiae by protein kinase A. J Biol Chem. 1999 Apr 2;274(14):9531-8

Nakagami K, Uchida T, Ohwada S, Koibuchi Y, Suda Y, Sekine T, Morishita Y. Increased choline kinase activity and elevated phosphocholine levels in human colon cancer. Jpn J Cancer Res. 1999 Apr;90(4):419-24

Lacal JC. Choline kinase: a novel target for antitumor drugs. IDrugs. 2001 Apr;4(4):419-26

Aoyama C, Ohtani A, Ishidate K. Expression and characterization of the active molecular forms of choline/ethanolamine kinase-alpha and -beta in mouse tissues, including carbon tetrachloride-induced liver. Biochem J. 2002 May 1;363(Pt 3):777-84

Ramírez de Molina A, Gutiérrez R, Ramos MA, Silva JM, Silva J, Bonilla F, Sánchez JJ, Lacal JC. Increased choline kinase activity in human breast carcinomas: clinical evidence for a potential novel antitumor strategy. Oncogene. 2002 Jun 20;21(27):4317-22

Ramírez de Molina A, Penalva V, Lucas L, Lacal JC. Regulation of choline kinase activity by Ras proteins involves Ral-GDS and PI3K. Oncogene. 2002 Jan 31;21(6):937-46

Ramírez de Molina A, Rodríguez-González A, Gutiérrez R,

Martínez-Piñeiro L, Sánchez J, Bonilla F, Rosell R, Lacal J. Overexpression of choline kinase is a frequent feature in human tumor-derived cell lines and in lung, prostate, and colorectal human cancers. Biochem Biophys Res Commun. 2002 Aug 23;296(3):580-3

Yu Y, Sreenivas A, Ostrander DB, Carman GM. Phosphorylation of Saccharomyces cerevisiae choline kinase on Ser30 and Ser85 by protein kinase A regulates phosphatidylcholine synthesis by the CDP-choline pathway. J Biol Chem. 2002 Sep 20;277(38):34978-86

Rodríguez-González A, Ramírez de Molina A, Benítez-Rajal J, Lacal JC. Phospholipase D and choline kinase: their role in cancer development and their potential as drug targets. Prog Cell Cycle Res. 2003;5:191-201

Rodríguez-González A, Ramírez de Molina A, Fernández F, Ramos MA, del Carmen Núñez M, Campos J, Lacal JC. Inhibition of choline kinase as a specific cytotoxic strategy in oncogene-transformed cells. Oncogene. 2003 Dec 4;22(55):8803-12

Aoyama C, Liao H, Ishidate K. Structure and function of choline kinase isoforms in mammalian cells. Prog Lipid Res. 2004 May;43(3):266-81

Ramírez de Molina A, Báñez-Coronel M, Gutiérrez R, Rodríguez-González A, Olmeda D, Megías D, Lacal JC. Choline kinase activation is a critical requirement for the proliferation of primary human mammary epithelial cells and breast tumor progression. Cancer Res. 2004 Sep 15;64(18):6732-9

Rodríguez-González A, Ramirez de Molina A, Fernández F, Lacal JC. Choline kinase inhibition induces the increase in ceramides resulting in a highly specific and selective cytotoxic antitumoral strategy as a potential mechanism of action. Oncogene. 2004 Oct 28;23(50):8247-59

Choi MG, Kurnov V, Kersting MC, Sreenivas A, Carman GM. Phosphorylation of the yeast choline kinase by protein kinase C. Identification of Ser25 and Ser30 as major sites of phosphorylation. J Biol Chem. 2005 Jul 15;280(28):26105-12

Iorio E, Mezzanzanica D, Alberti P, Spadaro F, Ramoni C, D'Ascenzo S, Millimaggi D, Pavan A, Dolo V, Canevari S, Podo F. Alterations of choline phospholipid metabolism in ovarian tumor progression. Cancer Res. 2005 Oct 15;65(20):9369-76

Ramírez de Molina A, Gallego-Ortega D, Sarmentero J, Bañez-Coronel M, Martín-Cantalejo Y, Lacal JC. Choline kinase is a novel oncogene that potentiates RhoA-induced carcinogenesis. Cancer Res. 2005 Jul 1;65(13):5647-53

Rodríguez-González A, Ramírez de Molina A, Bañez-Coronel M, Megias D, Lacal JC. Inhibition of choline kinase renders a highly selective cytotoxic effect in tumour cells through a mitochondrial independent mechanism. Int J Oncol. 2005 Apr;26(4):999-1008

Glunde K, Ackerstaff E, Mori N, Jacobs MA, Bhujwalla ZM. Choline phospholipid metabolism in cancer: consequences for molecular pharmaceutical interventions. Mol Pharm. 2006 Sep-Oct;3(5):496-506

Janardhan S, Srivani P, Sastry GN. Choline kinase: an important target for cancer. Curr Med Chem. 2006;13(10):1169-86

Malito E, Sekulic N, Too WC, Konrad M, Lavie A. Elucidation of human choline kinase crystal structures in complex with the products ADP or phosphocholine. J Mol Biol. 2006 Nov 24;364(2):136-51

Ramírez de Molina A, Sarmentero-Estrada J, Belda-Iniesta C, Tarón M, Ramírez de Molina V, Cejas P, Skrzypski M, Gallego-Ortega D, de Castro J, Casado E, García-Cabezas MA, Sánchez JJ, Nistal M, Rosell R, González-Barón M, Lacal JC. Expression of choline kinase alpha to predict outcome in patients with early-stage non-small-cell lung cancer: a retrospective study. Lancet Oncol. 2007 Oct;8(10):889-97

Glunde K, Shah T, Winnard PT Jr, Raman V, Takagi T, Vesuna F, Artemov D, Bhujwalla ZM. Hypoxia regulates choline kinase expression through hypoxia-inducible factor-1 alpha signaling in a human prostate cancer model. Cancer Res. 2008 Jan 1;68(1):172-80

Ramírez de Molina A, Gallego-Ortega D, Sarmentero-Estrada J, Lagares D, Gómez Del Pulgar T, Bandrés E, García-Foncillas J, Lacal JC. Choline kinase as a link connecting phospholipid metabolism and cell cycle regulation: implications in cancer therapy. Int J Biochem Cell Biol. 2008;40(9):1753-63

Soto A, Carman GM. Regulation of the Saccharomyces cerevisiae CKI1-encoded choline kinase by zinc depletion. J Biol Chem. 2008 Apr 11;283(15):10079-88

Wu G, Aoyama C, Young SG, Vance DE. Early embryonic lethality caused by disruption of the gene for choline kinase alpha, the first enzyme in phosphatidylcholine biosynthesis. J Biol Chem. 2008 Jan 18;283(3):1456-62

This article should be referenced as such:

Ramírez de Molina A, Álvarez-Miranda M, Lacal JC. CHKA (choline kinase alpha). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(2):110-113.