Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

DAPK2 (death-associated protein kinase 2)

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Published in Atlas Database: April 2016
Online updated version : http://AtlasGeneticsOncology.org/Genes/DAPK2ID40263ch15q22.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/66944/04-2016-DAPK2ID40263ch15q22.pdf
DOI: 10.4267/2042/66944

Abstract

Short communication on DAPK2, with data on DNA and on the protein encoded.

Keywords
DAPK2; DRP1; DRP-1; calcium/calmodulin; serine/threonine; kinase; apoptosis

Identity

Other names: DRP1, DRP-1

HGNC (Hugo): DAPK2

Location: 15q22.31

Location (base pair): Chromosome 15:63,907,036-64,072,033 reverse strand. GRCh38:CM000677.2 (Ensembl.org)

DNA/RNA

DAPK2 is a gene that codes for a protein that belongs to the serine/threonine protein kinase family.

Transcription

DPAK2 has 13 transcripts (3 coding), 75 orthologues and 11 paralogues (MYLK4, MYLK3, STK17A, DAPK3, DAPK1, OBSCN, SPEG, TTN, MYLK, STK17B, MYKL2) (ENSG00000035664).

ATGTTCCAGGCCTCAATGAGGAGTCCAAACATGGAGCCATTCAAGCAGCAGAAGGTGGAGGACTTTTATG
ACATCGGAGAGGAGCTGGGGAGTGGCCAGTTTGCCATCGTGAAGAAGTGCCGGGAGAAGAGCACGGGGCT
TGAGTATGCAGCCAAGTTCATCAAGAAGCGGCAGAGCCGGGCGAGCCGGCGCGGTGTGAGCCGGGAGGAG
ATCGAGCGGGAGGTGAGCATCCTGCGGCAGGTGCTGCACCACAATGTCATCACGCTGCACGACGTCTATG
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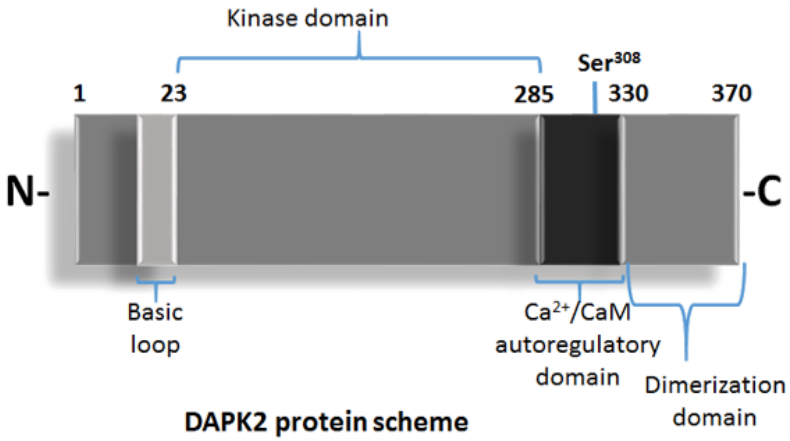
TTCCACACATCAAGCTGATTGACTTTGGTCTGGCTCACGAAATAGAAGATGGAGTTGAATTTAAGAATAT
TTTTGGGACGCCGGAATTTGTTGCTCCAGAAATTGTGAACTACGAGCCCCTGGGTCTGGAGGCTGACATG
TGGAGCATAGGCGTCATCACCTACATCCTCTTAAGTGGAGCATCCCCTTTCCTGGGAGACACGAAGCAGG
AAACACTGGCAAATATCACAGCAGTGAGTTACGACTTTGATGAGGAATTCTTCAGCCAGACGAGCGAGCT
GGCCAAGGACTTTATTCGGAAGCTTCTGGTTAAAGAGACCCGGAAACGGCTCACAATCCAAGAGGCTCTC
AGACACCCCTGGATCACGCCGGTGGACAACCAGCAAGCCATGGTGCGCAGGGAGTCTGTGGTCAATCTGG
AGAACTTCAGGAAGCAGTATGTCCGCAGGCGGTGGAAGCTTTCCTTCAGCATCGTGTCCCTGTGCAACCA
CCTCACCCGCTCGCTGATGAAGAAGGTGCACCTGAGGCCGGATGAGGACCTGAGGAACTGTGAGAGTGAC
ACTGAGGAGGACATCGCCAGGAGGAAAGCCCTCCACCCACGGAGGAGGAGCAGCACCTCCTAA

Blue highlighting indicates alternating exons; Red highlighting indicates amino acids encoded across a splice junction.



Schematic diagram of DAPK2 protein structure. The 42 KDa DAPK2 protein kinase bears three domain structures. A kinase domain on its N-terminal region determines specificity and allows for homodimerization through its basic loop. It is followed by a calcium/calmodulin (CaM)-regulated Serine/Threonine binding domain, which dictates kinase catalytic activity by unblocking substrate access when bound to Ca2+/CaM. Autophosphorylation of S308 decreases DAPK2 activity. The C-terminal dimerization domain allows for homodimerization. (Kawai T et al., 1999; Inbal B et al., 2000)

Protein

Description

DAPK2 encodes a 42 KDa protein kinase (Inbal B., 2000) that belongs to the serine/threonine protein family of five proapoptotic proteins with tumor suppressor activity. DAPK2 is soluble and cytosolic (Inbal B., 2000).

It contains highly-conserved N-terminal kinase catalytic domain, followed by a conserved calcium/calmodulin regulatory binding domain and a C-terminal homodimerization domain encompassing the last 40 aminoacids, predicted to form two helices, which has no sequence homology to known protein sequences.

Autophosphorylation restrains the apoptotic activity of DAPK2 kinase by controlling dimerization and calmodulin binding (Shani G et al., 2001).

DAPK2 is a monomer in its activated state and a homodimer when inhibited by autophosphorylation at Ser-308 (Shani G et al., 2001). The dimers of DAPK2 are formed through the association of two opposed catalytic domains (Patel AK et al., 2001). DAPK2 is negatively regulated by the autoinhibitory CaM-binding domain and this inhibition is removed by the binding of Ca2+/CaM (Inbal B et al., 2000). That is, DAPK2 is activated by CaM in response to Ca^{2+} stimuli, and regulated by a double locking mechanism. DAPK2 is dephosphorylated at Ser-308 in response to activated Fas and TNF-alpha receptors.

UniProtKB: Q9UIK4

Expression

Widespread expression. Strong expression in heart, lung and skeletal muscle, but also expressed in colon, breast, spleen tissue and leukocytes (Kawai T et al., 1999; Inbal B et al., 2000).

In mouse, DAPK2 is strongly and specifically expressed in interstitial cells of the kidney cortex (Guay JA et al., 2014).

Localisation

Cytoplasm (Inbal B et al., 2000), cytoplasmic vesicles, inside autophagic vesicles (Inbal B et al., 2002).

Function

DAPK2 is a regulator of apoptosis, autophagy and inflammation (Geering B 2015).

Apoptosis

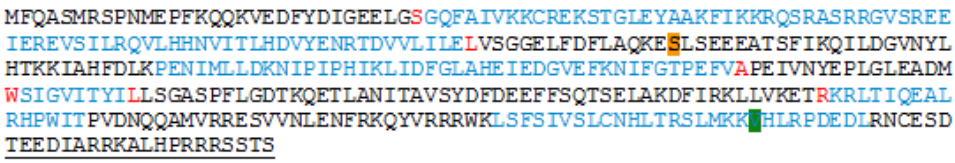
DAPK2 overexpression induces cell apoptosis in 50 to 60% (Inbal B et al., 2000). Depletion of the C-terminal tail of DAPK2 abolishes its apoptotic activity, while further truncation of the CaM-regulatory domain strongly enhances its apoptotic effect (Inbal B et al., 2000).

DAPK2 is a modulator of TRAIL signaling and TRAIL-induced apoptosis. Genetic ablation of DAPK2 causes phosphorylation of NF-KB and its transcriptional activity in several cancer cell lines, leading to the induction of several proapoptotic proteins (TNFRSF10A (DR4) and TNFRSF10B (DR5)) (Schlegel CR et al., 2014).

Autophagy

DAPK2 modulates MTOR activity by directly interacting and phosphorylating mTORC1. This way it suppresses mTOR activity to promote autophagy induction and autophagy levels under stress and steady-state conditions (Ber Y et al., 2015).

Expression of DAPK2 in its activated form triggers autophagy in a caspase independent way. DAPK2 mediates the formation of autophagic vesicles during apoptosis (Inbal B et al., 2002). Expression of dominant negative mutant of DAPK2 reduces autophagy (Inbal B et al., 2002).



Translation (370 aa)

Protein serine/threonine kinase activity
In vitro kinase assays, using myosin light chain (MLC) as substrate, have shown both MLC phosphorylation and DAPK2 autophosphorylation (Kawai T et al., 1999; Inbal B et al., 2000). DAPK2 functions in vitro as a kinase that is capable of phosphorylating itself and an external substrate (Kawai T et al., 1999; Inbal B et al., 2000).

Calmodulin binding
The addition of Ca^{2+}/CaM to in vitro kinase assays using myosin light chain (MLC) as substrate, lead to an increased amount of phosphorylated MLC, suggesting that DPK2 is regulated by binding to CaM (Kawai T et al., 1999; Inbal B et al., 2000). DPAK2 is negatively regulated by the autoinhibitory CaM-binding domain and this inhibition is removed by the binding of Ca^{2+}/CaM (Inbal B et al., 2000).
Truncation of the CaM-regulatory region of DAPK2 enhances the apoptotic effect (Inbal B et al., 2000).

Oxidative stress regulation
DAPK2 regulates oxidative stress in cancer cells by preserving mitochondrial function. Depletion of DAPK2 leads to an increased production of mitochondrial superoxide anions and increased oxidative stress (Schlegel CR et al., 2015).

Cellular metabolism
DAPK2 kinase domain in important to maintain mitochondrial integrity and thus metabolism. Depletion of DPAK2 leads to metabolic alterations, decreased rate of oxidative phosphorylation and destabilized mitochondrial membrane potential (Schlegel CR et al., 2015).

Membrane blebbing
Interaction of DAPK2 with ACTA1 (α-actin-1) at the plasma membrane leads to massive membrane blebbing (Geering B et al., 2015).
Expression of DAPK2 in its activated form triggers membrane blebbing and this process is caspase independent (Inbal B et al., 2002). Dominant negative mutants of DAPK2 reduce membrane blebbing during the p55/TRAF1 (TNF-receptor 1)-induced apoptosis (Inbal B et al., 2002).

Motility
Interaction of DAPK2 with α-actin-1 leads to reduced cellular motility (Geering B et al., 2015).

Intracellular signaling transduction
Depletion of DAPK2 leads to the activation of classical stress-activated kinases, such as ERK,

JNK and p38 (Schlegel CR et al., 2015).

Positive regulation of eosinophil and neutrophil chemotaxis, and granulocyte maturation
DPAK2 inhibition blocks recruitment of neutrophils to the site of inflammation in a peritonitis mouse model.
DAPK2 functions in a signaling pathway that mediates motility in neutrophils and eosinophils in response to intermediary chemoattractants, but not to end-target chemoattractants (Geering B et al., 2014).
DPAK2 regulates granulocytic motility by controlling cell spreading and polarization (Geering B et al., 2014) and may play a role in granulocyte maturation (Rizzi M et al., 2007).

Regulation of erythropoiesis
Among hematopoietic lineages, DPAK2 is expressed predominantly in erythroid cells. DPAK2 is substantially up-modulated during late erythropoiesis (Fang J et al., 2008).
In UT7epo cells, siRNA knock-down of DAPK2 enhanced survival due to cytokine withdrawal, and DAPK2's phosphorylation and kinase activity also were erythropoietin (EPO)-modulated. DAPK2 therefore comprises a new candidate attenuator of stress erythropoiesis (Fang J et al., 2008).
The physiological substrate of DAPK2 is unknown although it is known to phosphorylate the myosin light chain in vitro (Inbal B et al., 2000).

INTERACTION
YWHAB (14-3-3-β) (Yuasa K et al., 2015) and α-actinin-1 are novel DAPK2 binding partners (Geering B et al., 2015).
The interaction of DAPK2 with α-actinin-1 is localized to the plasma membrane, resulting in massive membrane blebbing and reduced cellular motility, whereas the interaction of DAPK2 with 14-3-3- β is localized to the cytoplasm, with no impact on blebbing, motility, or viability (Geering B et al 2015). 14-3-3- proteins inhibit DAPK2 activity and its apoptotic effects (Yuasa K et al., 2015).
DAPK2 also interacts with RAD1, MAPK1 and MLC1 (Steinmann S et al., 2015).

Homology

DAPK3/ZIPK/DLK (Death-related protein 1); STK17A (DRAK1/STK17B (DRAK2) (DAPK-related apoptosis inducing protein kinases 1 and 2) (Shobat G et al., 2002)

Mutations

Germinal

No germline or somatic mutations have been described for DAPK2 gene. There are 4 structural variants are described for DPAK2 gene: nsv1567 and nsv1569 leading to loss (PubMed ID 18451855), and nsv1568 and esv1414761 leading to insertions (PubMed IDs 18451855 and 17803354, respectively) (Database of Genomic Variants).

Somatic

Hypermethylation of the promoter region downregulates DAPK2 expression.

Implicated in

Hematological malignancies

DAPK2 is a tumor suppressor gene. Promoter region hypermethylation is one mechanism of DAPK2 inactivation in Hodgkin lymphoma-derived tumor cell lines (Tur MK et al., 2009).
DAPK2 is up-regulated during normal myeloid differentiation and enhances neutrophil maturation in myeloid leukemic cells (Rizzi M et al., 2007).
Acute promyelocytic leukemia (APL) patients have particularly low levels of DAPK2, where the predominant lesion causing its transcriptional repression isPML-RARA. and SPI1 (PU.1) bind to binding sites in the DAPK2 promoter. Restoring DAPK2 expression can rescue neutrophil differentiation (Humbert M. et al., 2014).
Low DAPK2 expression is associated with CEBPA-mutated AML patients and Humbert et al have found that DAPK2 is induced by the myeloid transcription factors PU.1 and CEBPA during granulocyte differentiation but repressed by PML-RARA in APL patients (Humbert M. et al., 2014).
CEBPA-dependent regulation of DAPK2 during APL differentiation (Humbert M. et al., 2014).

Breast cancer

DAPK2 expression is regulated by MIR520H in breast cancer cells (Su CM. et al., 2016).

Obesity

DAPK2 regulates obesity-related attenuated autophagy in adipocytes – DAPK2 downregulation associates with attenuated adipocyte autophagic clearance in human obesity (Soussi H et al., 2015).

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This article should be referenced as such:

Pinto M, Máximo V. DAPK2 (death-associated protein kinase 2). Atlas Genet Cytogenet Oncol Haematol. 2016; 20(12):587-591.