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Gene Section
Review

DGKA (diacylglycerol kinase, alpha 80kDa)

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Abstract

Review on DGKA, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: DAGK, DAGK1, DGK-alpha

HGNC (Hugo): DGKA

Location: 12q13.2

Local order

GSTP1-WIBG-**DGKA**-PMEL-CDK2.

Note

Diacylglycerol kinase alpha (DGKA) is a lipid kinase that phosphorylates the lipid diacylglycerol (DAG), transforming it into phosphatidic acid (PA). DGKA is classified as a type I DGK, characterized by possessing EF-hand motifs, which allow calcium mediated regulation. DGKA has been characterized as a negative regulator of Ras-MAPK pathway in T lymphocytes.

DGKA has a dual role in cancer; it exhibits properties similar to a tumor suppressor and has also a positive role in the maintenance of cancerous states.

DGKA function might be crucial in the genesis and development of several pathologies.

DNA/RNA

Note

DGKA gene is highly expressed in thymus, spleen, testis and lung (Sanjuan et al., 2001). DGKA displays alternative splicing; numerous splice variants are predicted, including truncated forms of the protein as well as RNAs with introns retained (Martínez-Moreno et al., 2012). The expression of some of these transcripts might be related to certain pathologies (Batista et al., 2013).

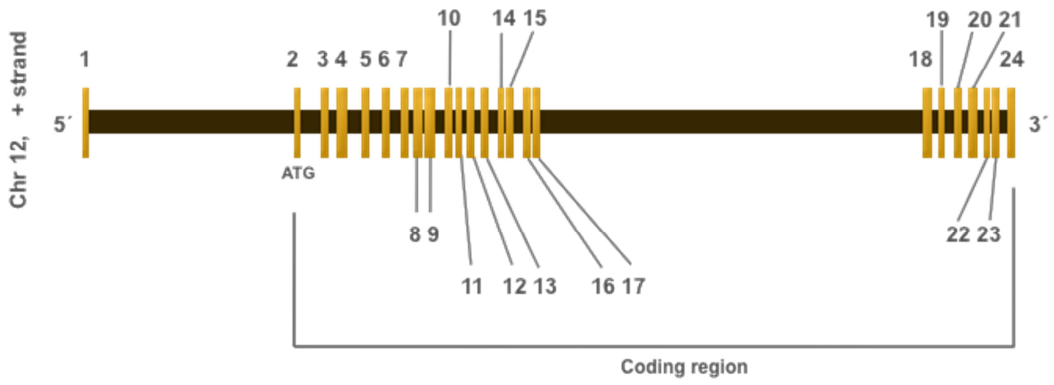

Figure 1. The DGKA gene is located at chromosome 12. It contains 24 exons and the translation initiator ATG is located at Exon 2.

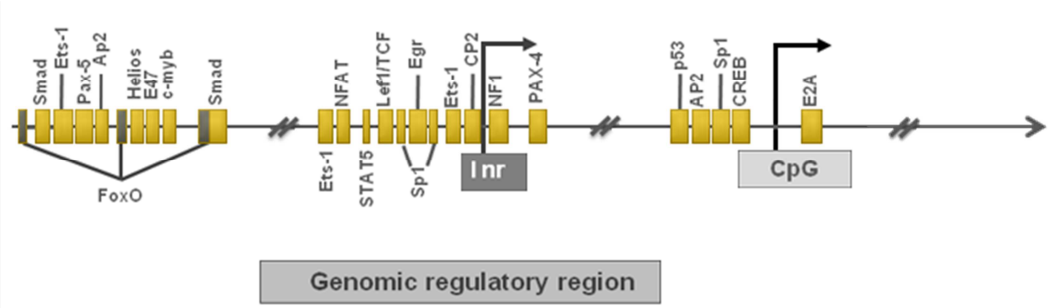

Figure 2. Putative regulatory elements in the DGKA gene. Transcription initiation sites are indicated (arrows). The +1 position was assigned in the Inr element. Putative binding sites for transcription factors are indicated by rectangles; FoxO sites are gray (Adapted from Martinez-Moreno et al., 2012).

Transcription

The DGKA gene encodes a protein of 80 KDa. Presence of regulatory regions in the gene was early suggested to restrain the expression of DGKA to certain tissues (Fujikawa et al., 1993).

DGKA gene displays alternative use of promoter regions, in homology with the mouse gene at least two alternative promoters likely exist.

The regulatory gene region contain several binding motifs for transcription factors including FoxO, p53, Egr, Smad, etc, which allow the coupling of DGKA expression with several signaling pathways. Identification of DGKA as a gene regulated by FoxO has contributed to explain its transcriptional downregulation in response to antigen stimulation and interleukin 2 (IL2) (Martinez-Moreno et al., 2012).

Protein

Note

The protein encoded by the DGKA gene (2.7.1.107) belongs to the eukaryotic diacylglycerol kinase family.

It attenuates the second messenger diacylglycerol, that activates C1-containing proteins like members of the classical and novel PKCs, PKD, RasGRP and chimaerin families.

It also produces phosphatidic acid, another lipid mediator that participates in the resynthesis of phosphatidylinositols and activates different proteins like mTOR or atypical PKCs.

Description

- The diacylglycerol kinases (DGK) are a family of signaling proteins that modulate diacylglycerol levels by catalyzing its conversion to phosphatidic acid (Merida et al., 2008). DGK belongs to a superfamily that also includes the recently identified bacterial DgkB as well as the sphingosine kinase (SPK) and ceramide kinase (CERK) families. Proteins in this superfamily share a common catalytic domain (DAGKc: Pfam00781).
- In addition to the catalytic region, all DGK family members have at least two protein kinase C-like type 1 (C1) domains that, except for the first C1 domain in DGKB and DGKG, lack the key residues that define a canonical phorbol ester/DAG-binding C1 domain (Shindo et al., 2003).
- Mammals express ten DGK isoforms grouped into five subtypes; each DGK subtype has distinct regulatory motifs that suggest the existence of diverse regulatory mechanisms and/or participation in different signaling complexes.
- Diacylglycerol Kinase alpha (DGKA) together with the beta (DGKB) and gamma (DGKG) isoforms represent the type I DGK, whose signature is the presence at the N-terminal region of a recoverin-like domain (RVH) and a tandem of EF hand motifs, characteristic of Ca^{2+}-binding proteins.

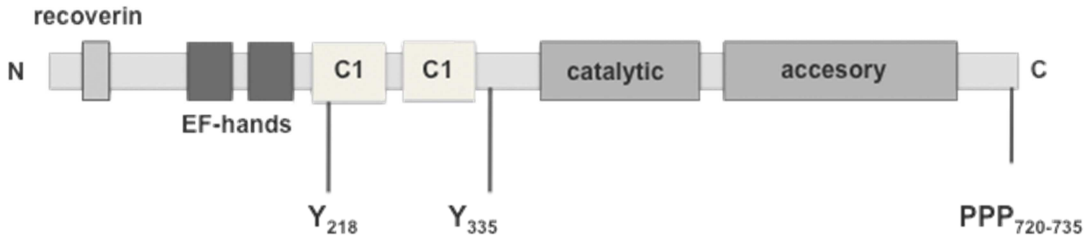

Figure 3. Distribution of conserved and specific regions in DGKA. C1, conserved protein kinase C-type 1 regions. Y218, Tyrosine phosphorylated by c-Abl. Y335, Tyrosine phosphorylated by Src and Lck. PPP Pro-rich region proposed to interact with Src.

Species Gene ID	Symbol	xref	Ortholog Gene ID	Ortholog Symbol
Human/Chimp	1606	DGKA	HGNC:2849 451976	DGKA
Human/Macaque	1606	DGKA	HGNC:2849 710559	DGKA
Human/Mouse	1606	DGKA	HGNC:2849 13139	Dgka
Human/Rat	1606	DGKA	HGNC:2849 140866	Dgka
Human/Cow	1606	DGKA	HGNC:2849 506348	DGKA
Human/Horse	1606	DGKA	HGNC:2849 100051662	DGKA
Human/Dog	1606	DGKA	HGNC:2849 474393	DGKA
Human/Dog	1606	DGKA	HGNC:2849 100855691	DGKA
Human/Platypus	1606	DGKA	HGNC:2849 100084397	
Human/Chicken	1606	DGKA	HGNC:2849 424839	DGKG
Human/Zebrafish	1606	DGKA	HGNC:2849 564739	dgka
Human/Zebrafish	1606	DGKA	HGNC:2849 724010	dgkaa
Human/C.elegans	1606	DGKA	HGNC:2849 186262	dgk-3
Human/Drosophila	1606	DGKA	HGNC:2849 35738	Dgk

Expression

- DGKA is the only DGK isoform particularly enriched in the thymus and peripheral T lymphocytes. DGKA levels are tightly coupled to the differentiation and proliferation state of T lymphocytes. Quiescent, naïve T lymphocytes express high levels of DGKA that decrease rapidly in response to antigenic and IL2-derived signals (Martinez-Moreno et al., 2012). DGKA was identified as an anergy-induced gene (Macian et al., 2002). Anergy represents an unresponsive state in T cells that is vital in immune system homeostasis and constitutes a means for avoiding response to self and thus, for preventing autoimmunity. Tumors also induce anergic-non responsive states in T cells. In agreement with this finding, DGKA-overexpressing lymphocytes are "anergic" and no longer respond to antigenic stimuli (Zha et al., 2006). On the contrary, T cells from DGKA deficient mice are resistant to anergy induction (Olenchock et al., 2006).
- Recent studies have characterized miR-297 as a highly cytotoxic microRNA expressed in glioblastoma, with minimal cytotoxicity to normal astrocytes. DGKA is shown to be a miR-297 target with a critical role in miR-297 toxicity. These studies identify miR-297 as a novel and physiologic regulator of cancer cell survival, largely through targeting of DGKA (Kefas et al., 2013).

Localisation

- DGKA is a cytosolic enzyme that translocates to the membrane to phosphorylate diacylglycerol. The N-terminal region of DGKA, encompassing the Ca^{2+} regulatory elements has a negative regulatory role in enzyme activation and receptor-induced membrane localization, as shown by enhanced activity and constitutive plasma membrane localization of a mutant lacking this region (Sanjuan et al., 2001). In addition to Ca^{2+} generation, activation of Tyr kinases is required for membrane stabilization of DGKA (Sanjuan et al., 2001). Tyr335 in the human sequence, located at the hinge between the C1 and the catalytic domains, was recently identified as an Lck-dependent DGKA phosphorylation site in T lymphocytes (Merino et al., 2008).
- Membrane localization of DGKA in non-T cells requires Src-family tyrosine kinase activity and involves the association of DGKA with Src via a proline-rich sequence (Baldanzi et al., 2008). DGKA membrane localization and activation is required for cell motility, proliferation and angiogenesis, acting as a rheostat that sets the thresholds required for growth factor-induced migratory signals.
- Recent reports have suggested nuclear localization for DGKA following serum starvation and demonstrated that DGKA relocates back to the cytosol in response to serum re-addition. Serum-induced export requires c-Abl mediated Tyr-218 phosphorylation (Matsubara et al., 2012).

Function

- The best characterized function for DGKA as a negative modulator of diacylglycerol-based signaling has been demonstrated in T lymphocytes. DGKA acts as a "switch-off" signal for Ras activation, mediated by localization to the membrane of Ras-GRP1 a GDP-exchanger for Ras

with a DAG-binding domain (Sanjuan et al., 2001; Sanjuan et al., 2003).
- Contrary to its negative contribution to T cell responses, high DGKA expression in tumors appears to have a positive role in neoplastic transformation.
DGKA-dependent PA generation contributes to melanoma survival through activation of the NFKB pathway (Yanagisawa et al., 2007).
- DGKA mediated PA generation has been reported to participate in tumor migration and invasion. Generation of PA downstream of DGKA is essential to facilitate the Rab coupling protein (RCP)- mediated integrin recycling that is required for tumor cell invasion (Rainiero et al., 2012).

Mutations

Note
V379I mutation in DGKA identified as a putative driver mutation for pancreatic cancer.

Implicated in

Lymphoma

Note
DGKA was found to be constitutively activated in nucleophosmin/anaplastic lymphoma kinase (NPM / ALK) fusion in malignant lymphomas, where inhibition of DGKA significantly reduced tumor growth (Bacchiocchi et al., 2005).

Melanoma

Note
DGKA has been implicated in suppression of TNF-alpha induced apoptosis of human melanoma cells via NF-KB (Yanagisawa et al., 2005).

Hepatocellular carcinoma

Note
DGKA is absent in hepatocytes but it is expressed in different hepatocellular carcinoma cell lines. DGKA is found expressed in cancerous tissue but not in the adjacent non-cancerous hepatocytes.
High DGKA expression associates with high Ki67 expression and a high rate of HCC recurrence (p=0.033) following surgery.
In multivariate analyses, high DGKA expression is found as an independent factor for determining HCC recurrence after surgery (Takeishi et al., 2012).

Pancreatic carcinoma

Note
Using CHASM (Cancer-specific High-throughput Annotation of Somatic Mutations) V379I mutation in DGKA was found as a putative driver mutation for pancreatic cancer (Carter et al., 2010).

Glioblastoma

Note
Recent studies have described DGKA as an important component of malignant transformation in glioblastoma (Dominguez et al., 2013).
Impaired DGKA activity through siRNA targeting or the use of small-molecule inhibitors induced caspase-mediated apoptosis in glioblastoma cells, but lacked toxicity in noncancerous cells.

Lung cancer

Note
Survival trees in a study involving the expression profiles of 3588 genes in 211 lung adenocarcinoma patients identified DGKA as a marker for good survival in a group of advanced-stage patients with remarkably good survival outcome (Berrar et al., 2005).

X-linked proliferative disease

Note
Studies have reported DGKA inhibition by the adaptor protein SAP (Baldanzi et al., 2011). Loss-of-function SAP mutations cause X-linked lymphoproliferative disease (XLP), an immune disorder characterized by a deregulated immune response to Epstein-Barr virus, susceptibility to lymphoma and defective antibody production. Impaired regulation of DGKA activity in SAP-deficient lymphocytes may contribute to their defective TCR-induced responses, suggesting that pharmacological inhibition of DGKA could be useful in the treatment of certain manifestations of XLP.

CD8 tumor infiltrates

Note
DGKA was found to be more highly expressed in CD8-tumor infiltrates T cells (TILs) in renal carcinoma that in circulating CD8 cells (Prinz et al., 2012).
Low dose treatment of TILs with IL2 reduced DGKA protein levels, improved stimulation-induced ERK and AKT phosphorylation, and increased the number of degranulating CD8-TILs. DGKA inhibition could be a novel strategy to enhance anti-tumor CD8 T cells response and may help prevent inactivation of adoptively transferred T cells improving therapeutic efficacy.

Localized aggressive periodontitis (LAP)

Note
Localized aggressive periodontitis (LAP) is a familial disorder characterized by destruction of the supporting structures of dentition.
Microarray and kinetic-PCR analysis revealed

diminished RNA expression of DGKA in neutrophils from LAP patients compared with asymptomatic individuals (Gronert et al., 2004).

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