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Gene Section
Review

DAB2 (disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila))

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Identity

Other names: DAB-2; DOC-2; DOC2; FLJ26626

HGNC (Hugo): DAB2

Location: 5p13.1

Local order: The complement factor 9 (C9) gene is located at the 3'-end of the DAB2 gene.

Note
DAB2 was first identified as DOC-2, for differentially expressed in ovarian carcinoma, and subsequently as a protein whose phosphorylation is stimulated by CSF-1.

DNA/RNA

Description

The DAB2 gene consists of 15 exons and 14 introns spanning in a region of 35 kb in size.

Transcription

The putative DAB2 promoter was identified within a 420-bp sequence upstream of the exon1/intron1 junction. DAB2 is alternatively spliced to generate several transcripts and proteins. The transcript has been detected in spleen, thymus, prostate, testis, small intestine, and abundant in ovary.

Protein

Note
DAB2 plays a pivotal role in the control of cellular homeostasis. The adaptor protein DAB2 is implicated in several receptor-mediated signaling pathways, endocytosis, cell adhesive function, hematopoietic cell differentiation, and angiogenesis.

Schematic representation of DAB2 domains. DAB2 possess a highly conserved N-terminal phosphotyrosine-interacting/phosphotyrosine binding domain (PID/PTB), renamed the DAB homology domain, and a C-terminal proline-rich domain (PRD).

Description

770 amino acids, molecular weight 82.5 kDa. DAB2 contains an N-terminal PID/PTB domain (amino acid 42-180) and three C-terminal proline-rich domains (amino acid 619-627, 663-671, and 714-722). A potential actin-binding motif, KKEK is present in the N-terminal domain.

Expression

Widely expressed. Cytoplasmic. DAB2 is expres-sed in many epithelial cell types and was suggested to have a role in epithelial organization. dab2 knock-out mice are embryonic lethal for defective visceral endoderm cell organization. In fact, in dab2 (-/-) mice, the epithelial cells of the early embryos (visceral endoderm) mix within the interior rather then align as a layer covering the inner cell mass. The role of Dab2 in mediating directional trafficking of endocytic proteins to establish apical polarity is suggested as a mechanism for surface positioning of endoderm cells.

Function

The PID/PTB and PRD domains of DAB2 associate with several proteins, and these interactions have been shown to modulate protein trafficking,

cytoskeleton organization, cell adhesion and migration, and cell signaling of various receptor protein-tyrosine kinases.

Cell cycle: DAB2 was identified as a protein phosphorylated in response to mitogenic stimula-tion by CSF-1. In cells, protein phosphorylation of DAB2 modulates its functional activity. Protein kinase C (PKC) and Cdc2 are the two known DAB2 kinases. The major PKC phosphorylation site has been mapped to Ser^{24} and it is essential for the inhibitory function of DAB2 in TPA-induced AP-1 gene transcription. DAB2 is differentially phosphorylated during the cell cycle by cdc2, and its phosphorylation promotes the association of DAB2 with Pin1, that regulates the rate of DAB2 dephosphorylation.

Vesicle traffic: DAB2 plays a role in linking specific extracellular receptors to the endocytic machinery. DAB2 associates with AP-2-positive clathrin-coated structures, together with endocy-tosed trans-membrane proteins such as low-density lipoprotein (LDL) receptors and integrins. DAB2 also binds to the actin-based myosin VI, mediating the attachment of cargos to motor proteins and regulating protein trafficking.

Signaling pathways:

- TGFbeta - Dab2 associates with Smad2 and Smad3, by a direct interaction with the PID/PTB domain of Dab2, and with TGFbeta receptor I and TGFbeta receptor II. Thus Dab2 may be an essential component of the TGFbeta signaling pathway allowing the transmission of signals from the TGFbeta receptors to the Smad family of transcriptional activators.

- WNT - Dab2 associates with Axin and stabilizes its expression by preventing Axin interaction with the LRP5 co-receptor. Thus the interaction of Axin with beta-catenin results stabilized with an increase in beta-catenin degradation and attenuation of Wnt signaling.

- RAS/RAF/MAPK - In cell culture experiments, a Dab2 over-expression leads to suppression of c-Fos expression and cell growth inhibition without affecting MAPK activity. In vivo studies confirmed a Dab2 role in regulating c-Fos expression. A possible molecular mechanism of action is that Dab2 limits the entry of the activated MAPK into the nucleus. DAB2 can also interact with Grb2 through its PRD. Receptor tyrosine kinase activation by growth factors increases the binding of DAB2 to Grb2, which interrupts the binding of SOS to Grb2 and leads to suppression of ERK activation.

Cell adhesion: DAB2 is an adhesion-responsive phosphoprotein and plays a role in cell adhesion and spreading. Ser^{24} phosphorylation promotes membrane translocation of DAB2 and its interaction with beta3 integrin. DAB2 negatively regulates integrin alphaIIbbeta3 activation, leading to the inhibition of alphaIIbbeta3-mediated fibrino-gen adhesion. In cell experiments during TGFbeta-induced epithelial to mesenchymal transdifferen-tiation (EMT), Dab2 expression is increased and Dab2 binds to beta1 integrin. In these conditions, Dab2 silencing leads to a decrease in cell adherence, inhibition of EMT, and apoptosis.

Angiogenesis: DAB2 can bind to Shc3 domain of Src and this interaction results in Src inactivation. DAB2 is expressed in human umbilical vein endothelial cells (HUVEC). By modulating the activation of Src-FAK signaling and MAPK phosphorylation, DAB2 controls endothelial cell migration and differentiation.

Homology

The Disabled proteins are a family of adapters involved in cellular signaling, oncogenesis, and development. DAB2 is related to Drosophila Disabled and mammalian Dab1, which regulate neuronal development. DAB2 shares 81% identity with the mouse p96/Dab2 protein.

Implicated in

Epithelial ovarian cancer

Note

DAB2 was identified due to the loss of its expression in ovarian cancer cells. Ovarian carcinoma cells transfected with DAB2 showed a reduced growth rate and ability to form tumors in nude mice. Loss of DAB2 expression is not correlated with tumor grade, suggesting that loss of DAB2 expression is an early event in ovarian malignancies and DAB2 behaves as a tumor suppressor.

Prostate cancer

Note

DAB2 is a potent growth inhibitor for prostate cancer cells by suppressing several protein kinase pathways. The PRD of DAB2 is the key functional domain responsible for this activity. It was shown that in prostate cancer cells without endogenous DAB2 expression, a functional motif derived from the PRD of DAB2 conjugated with a delivery system is a potent growth inhibitor.

Breast cancer

Note

DAB2 sensitizes breast cancer cells to cell death upon the loss of cell-matrix attachment by targeting the oncogenic activity of ILK.

Various cancer

Note

Urothelial carcinoma of the bladder, esophageal squamous carcinoma, metastatic pancreatic cancer, colorectal cancer, gestational choriocarcinoma.

Disease

DAB2 expression is down-regulated.

Malignant peripheral nerve sheath tumor, invasive cervical carcinoma

Note

Comparative genomic hybridization (CGH) revealed frequent gains of DAB2.

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