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Gene Section
Review

DUSP6 (dual specificity phosphatase 6)

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Identity

Other names: MKP-3, MKP3, PYST1, rVH6

HGNC (Hugo): DUSP6

Location: 12q21.33

DNA/RNA

Description

The human DUSP6 gene is located on chromosome 12q21.33 and consists of 3 exons. The full-length coding sequence of DUSP6 contains 1146 nucleotides. The functional phosphatase domain of DUSP6 is encoded by half of exon 2 and almost the entire sequence of exon 3.

Transcription

DUSP6 gene transcription can start from either the first ATG or alternatively the second ATG (Met14), and therefore two protein products are generated which usually demonstrate a double-band appearance in regular immunoblotting assays (Dowd et al., 1998; Zhang et al., 2010).

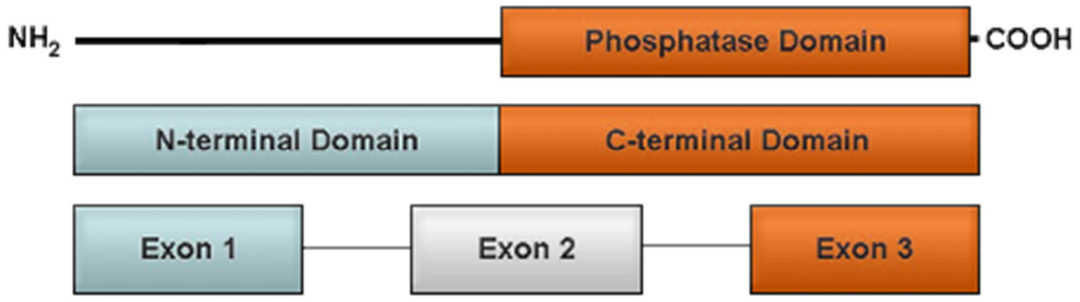
Protein

Description

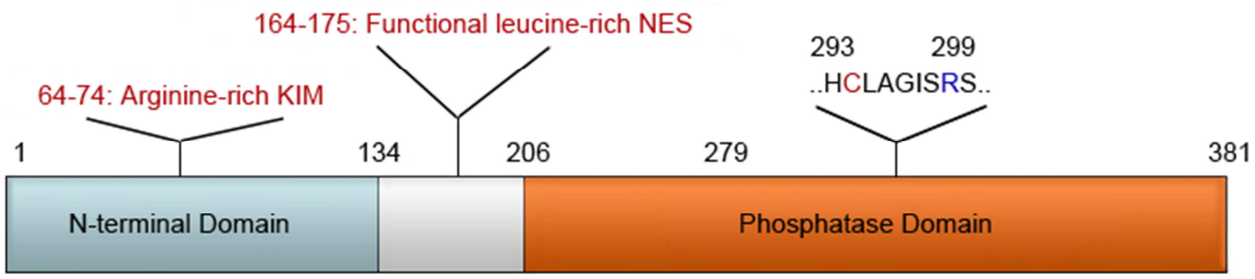
The full-length DUSP6 protein contains 381 amino acids and has a molecular weight of 44 kDa. DUSPs are characterized by a common structure comprising a C-terminal phosphatase domain that are defined by the active-site signature motif HCXXXXXR. The structure of DUSP proteins confers phosphatase activity for both phosphoserine/threonine and phosphotyrosine residues. An enzyme-dead DUSP6 expression construct can be generated via a 293 Cysteine to Serine/Glycine (C293S/G) point mutation (Wishart et al., 1995; Zhang et al., 2010; Zhou et al., 2006).

Expression

DUSP6 is expressed usually at low level in resting, nonstimulated cells in a variety of tissues and is induced as an early response gene after activation of the ERK-MAPK signaling pathway.



The diagram depicts the structure of the DUSP6 gene (bottom) roughly aligned with its corresponding functional protein domains (middle and top). DUSP6 comprises a C-terminal catalytic domain and an N-terminal non-catalytic domain (middle). The 3 exons of DUSP6 (rectangles) are connected with lines representing introns.



The diagram depicts the structural features of DUSP6. The highly conserved C-terminal domain of DUSP6 contains the canonical tyrosine/threonine-specific phosphatase signature sequence HCXXXXXR at the active site, where the cysteine acts as the essential enzymatic nucleophile and arginine interacts directly with the phosphate group on phosphotyrosine or phosphothreonine (Farooq et al., 2001). The amino-terminal domain of DUSP6 contains a specific arginine-rich kinase interaction motif (KIM) (Tárrega et al., 2005) and a leucine-rich nuclear export signal (NES) necessary and sufficient for nuclear export of the phosphatase (Karlsson et al., 2004).

Localisation

DUSP6 is a cytoplasmic dual specificity protein phosphatase.

Function

Mitogen-activated protein kinases (MAPK) constitute a highly conserved family of kinases that relay information from extracellular signals to downstream effectors that control diverse cellular processes such as proliferation, differentiation, migration, survival and apoptosis (Wada and Penninger, 2004). A balance between the activities of upstream activators and various negative regulatory mechanisms of MAPK signaling, which terminate its activation, determines its biological outcomes. DUSP6 is a prototypical member of a subfamily of cytoplasmic MKPs, which includes DUSP7 and DUSP9 as well. These enzymes all display a high degree of substrate selectivity for ERK1 and ERK2 (Keyse, 2008). DUSP6 has been shown to act as a central feedback regulator attenuating ERK levels in developmental programs (Echevarria et al., 2005; Li et al., 2007). The cytoplasmic localization of DUSP6 is mediated by a chromosome region maintenance-1-dependent nuclear export pathway. DUSP6 appears to play a role in determining the subcellular localization of ERK by serving as a cytoplasmic anchor for ERK, thereby mediating a spatio-temporal mechanism of ERK signaling regulation. Cytoplasmic retention of ERK requires both a functional kinase interaction motif and nuclear export site. Defects of these feedback regulation steps are thought to contribute to ERK-MAPK related oncogenesis. An in vivo study has identified DUSP6 as a negative feedback regulator of fibroblast growth factor-stimulated ERK signaling during murine development (Li et al., 2007). Several in vitro studies have demonstrated that DUSP6 acts as a negative regulator of fibroblast growth factor receptor signaling and endothelial cell platelet-derived growth factor receptor signaling via termination of ERK activation (Ekerot et al., 2008; Jurek et al., 2009).

Homology

DUSP6 belongs to a subfamily of ten more closely related dual-specificity MAPK phosphatases (MKPs) within the larger cysteine-dependent dual specificity phosphatase (DUSP) family (Keyse, 2008). While DUSP1 (MKP-1), DUSP4 (MKP-2), and DUSP9 (MKP4) dephosphorylate both ERKs, p38 and JNK, the phosphatases DUSP5 (Hvh-3), DUSP6 (MKP-3), and DUSP7 (MKP-X) exclusively target ERK1/2 MAPKs (Keyse, 2008). The N-terminal domain of all DUSPs has two regions of homology with the Cdc25 cell cycle regulatory phosphatase. The more conserved catalytic domain within DUSPs contains an active site sequence related to the prototypic VH-1 phosphatase encoded by the vaccinia virus. Specificity of MKPs toward MAPKs relies on the KIM domain. Although each MKP targets different subsets of MAPKs, there is an overlap between their specificities (Bermudez et al., 2010).

Mutations

Note

Although DUSP6 has been implicated as a candidate tumor suppressor in several cancer setting, no mutations in the gene have been identified so far.

Implicated in

Various cancers

Note

DUSP6 null mice demonstrate enhanced ERK1/2 phosphorylation leading to increased myocyte proliferation and cardiac hypercellularity (Maillet et al., 2008). DUSP6 has been identified as a potential novel tumor suppressor gene in pancreatic cancer since loss of DUSP6 expression might synergize with activating-mutated k-Ras resulting in increased activation of ERK1/2 MAP kinase and thus contribute to the development of the malignant and invasive phenotype in pancreatic cancer (Furukawa et al., 2003). Loss of

DUSP6 expression caused by oxidative stress-mediated degradation was also noted in ovarian cancer and correlated with high ERK1/2 activity (Chan et al., 2008). DUSP6 has also been identified as one of only three genes which are uniquely expressed in myeloma cells harboring a constitutively active mutant N-ras gene and is also overexpressed in human melanoma cell lines with potent activating mutations in B-raf and in breast epithelial cells stably expressing H-Ras (Bloethner et al., 2005; Croonquist et al., 2003; Warmka et al., 2004), suggesting that the over-expression of DUSP6 seen in response to activating-mutated Ras or Raf might represent a compensatory increase in the negative feedback control of the ERK1/2 MAPK pathway, which lies downstream of these activated oncogenes. In support of this, the tetracycline-induced expression of a functional fusion protein between DUSP6 and green fluorescent protein in H-ras transformed fibroblasts following injection into nude mice resulted in a large delay in tumor emergence and growth as compared to the untreated control group (Marchetti et al., 2004). DUSP6 has been reported to be one of the most highly regulated genes in chronic myeloid leukemia cells upon imatinib treatment (Hakansson et al., 2008) and similarly DUSP6 is overexpressed upon inducible expression of the EGFRvIII oncogene in glioblastoma cells (Ramnarain et al., 2006). DUSP6 has also been demonstrated to be positively correlated with the activity of the oncogenic ERK pathway in non-small cell lung cancer tissue and is an ETS-regulated negative feedback mediator of ERK signaling in lung cancer cells (Zhang et al., 2010).

Prognosis

Elevated DUSP6 RNA expression was reported to be a major negative predictor of survival in patients with resected non-small cell lung cancer as part of a five-gene signature model (Chen et al., 2007).

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