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Gene Section
Mini Review

PDZK1IP1 (PDZK1 interacting protein 1)

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Identity

Other names: DD96; MAP17; RP1-18D14.5; SPAP

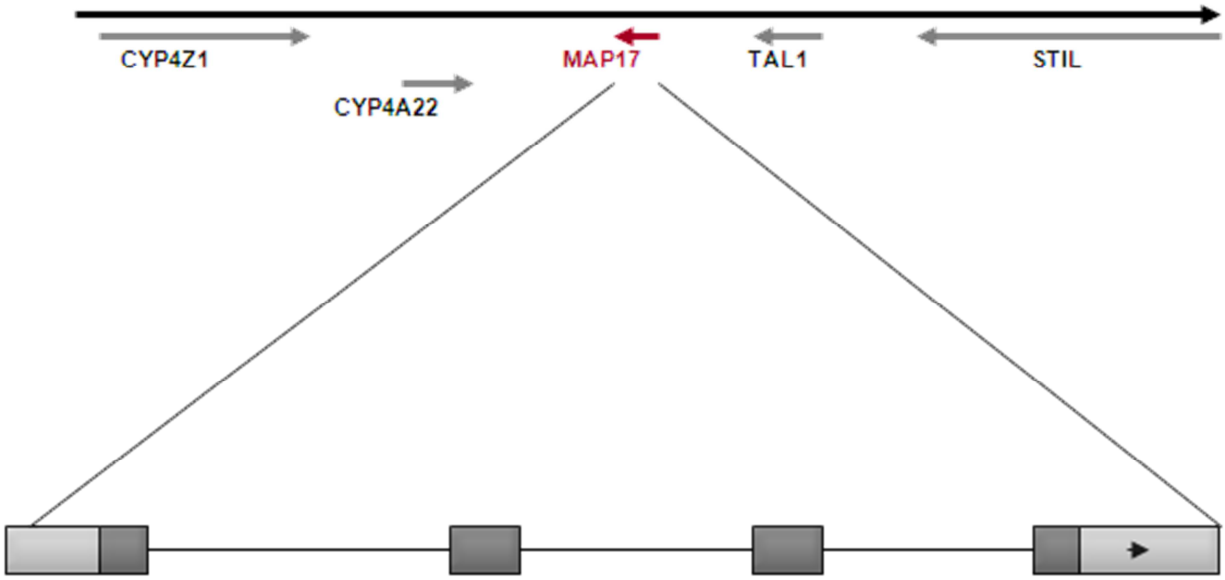
HGNC (Hugo): PDZK1IP1

Location: 1p33

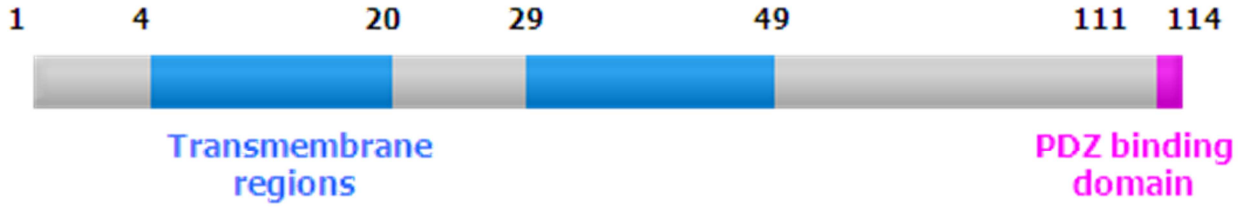
DNA/RNA

Transcription

Four coding exons produce a 600 bp transcript only expressed in proximal tubule kidney cells. PDZK1IP1/MAP17 mRNA is overexpressed in a great variety of human carcinomas and strongly correlates with tumoral progression (P<0.0001). Many tumor cells also express MAP17 and its expression does not correlate with expression of SCL (TAL1) a neighbor gene reported to be co-expressed in some hematopoietic cell lines. SCL neither is expressed in most MAP17 positive tumors, indicating the independent transcription of MAP17, at least in carcinomas. MAP17 promoter is activated by oncogenes.



Scheme of the PDZK1IP1/MAP17 locus and transcript.



Scheme of the PDZK1IP1/MAP17 protein. Blue barrs indicate transmembrane regions. Pink barr indicates PDZ-binding domain.

Protein

Description

MAP17 is a small, non-glycosylated membrane-associated protein of 17 kDa, which is located on the plasma membrane and the Golgi apparatus. The protein sequence possesses a hydrophobic amino-terminus containing 13 amino acids that encodes a PDZ-binding domain and two transmembrane regions. MAP17 binds several PDZ domain-containing proteins, including PDZK1, NHERF proteins, NaPiIIa and NHe3. Together with NHRF3 and NHRF4, overexpression of MAP17 in opossum kidney cells leads to internalization of NaPilla to the trans-Golgi network. In normal tissue MAP17 is only expressed in the proximal tubules of kidney cells. The physiological role of MAP17 in proximal tubules is not known, but it stimulates specific Na-dependent transport of mannose and glucose in Xenopus oocytes and some mammary cells.

Expression

MAP17 protein is overexpressed in a great variety of human carcinomas. Immunohistochemical analysis of MAP17 during cancer progression shows, at least in prostate and ovarian carcinomas, that overexpression of the protein strongly correlates with tumoral progression (P<0.0001). Many tumor cells also express MAP17 protein.

Localisation

Apical end of proximal tubule cells in kidney.

Function

MAP17 binds several PDZ domain-containing proteins, including PDZK1, NHERF proteins, NaPiIIa and NHe3. Overexpression of MAP17 into opossum kidney cells participates, together with NHRF3 and NHRF4 in NaPiIIa internalization to the transgolgi network. The physiological role of MAP17 in proximal tubules is not known but it stimulates specific Na-dependent transport of mannose and glucose in Xenopus oocytes and in mammary cells.

Homology

Higly conserved protein troughout the evolution.

Mutations

Note

Described mutated in malignant mesothelioma tumors with a change of aminoacid (T to I). The functional effect of the change is not known.

Somatic

c403t.

Implicated in

Cancer

Disease

Carcinomas of different origin, melanoma, etc.

Prognosis

Expression levels increase with stage in most carcinomas.

Oncogenesis

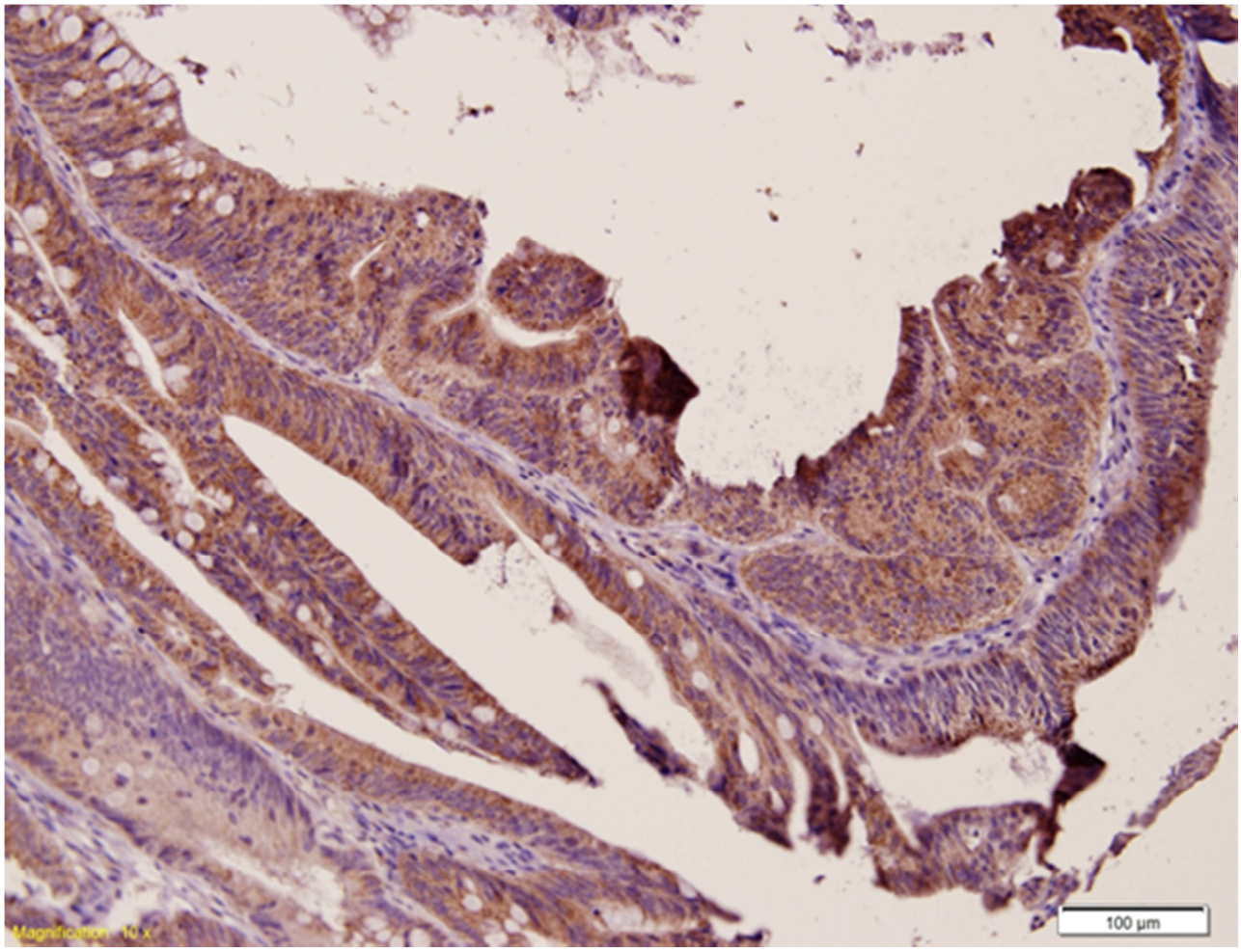
MAP17 (PDZK1IP1, DD96) enhances tumorigenic properties of melanoma cells through ROS increase (Guijarro et al., 2007b). Tumor cells that overexpress MAP17 show an increased tumoral phenotype with enhanced proliferative capabilities both in presence or absence of contact inhibition, decreased apoptotic sensitivity and increased migration. MAP17-expressing clones also grow better in nude mice. The increased malignant cell behavior induced by MAP17 are associated with an increase in ROS production, and the treatment of MAP17-expressing cells with antioxidants results in a reduction in the tumorigenic properties of these cells. Treatment of melanoma cells with inhibitors of Na^+-coupled co-transporters lead to an inhibition of ROS increase and a decrease in the malignant cell behavior in MAP17-expressing clones. Finally, we show that MAP17-dependent ROS increase and tumorigenesis are dependent on its PDZ-binding domain, since disruption of its sequence by point mutations abolish its ability to enhance ROS production and tumorigenesis.
At the molecular level MAP17 protects Rat1a fibroblasts from Myc-induced apoptosis through ROS-mediated activation of the PI3K/AKT signalling pathway (Guijarro et al., 2007d). A fraction of PTEN

undergoes oxidation in MAP17-overexpressing cells. Furthermore, activation of AKT by MAP17 as measured by Thr308 phosphorylation was independent of PI3K activity. Importantly, modulation of ROS by antioxidant treatment prevented activation of AKT, restoring the level of apoptosis in serum starved Rat1/c-Myc fibroblasts (Guijarro et al., 2007d).
MAP17 is overexpressed in a great variety of human carcinomas (Guijarro et al., 2007c). Immunohistochemical analysis of MAP17 during cancer progression shows in prostatic and ovarian carcinomas that overexpression of the protein strongly correlates with tumoral progression (Guijarro et al., 2007c).

Skin diseases

Disease

Abnormal keratinocyte differentiation.
In the meta-analysis of public microarray databases for different skin diseases, Noh and cols (Noh et al., 2010) revealed that MAP17 is commonly up-regulated suggesting that may be potentially associated with the abnormal keratinocyte differentiation. MAP17 was significantly up-regulated in response to interferon-gamma, interleukin 4 (IL-4), IL-6, IL-17A or IL-22 in normal human epidermal keratinocytes (NHEK). Interestingly, the PDZK1 gene is localized within the atopic dermatitis-linked region on human chromosome 1q21. In an attempt to evaluate whether MAP17 regulates the expression of cornified envelope-associated genes at the 1q21 locus, such as filaggrin, loricrin and involucrin, these authors found that the over-expression of MAP17 in HaCaT keratinocytes significantly decreased the expression of filaggrin, a cornified envelope-associated gene. Taken together, the Th cell cytokine-induced up-regulation of MAP17 expression may be linked to the down-regulation of filaggrin, which may be associated with the abnormal epidermal differentiation observed in the dermatological diseases (Noh et al., 2010).



Overexpression of MAP17 in colon carcinoma.

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