

Gene Section

Mini Review

PPM1D (protein phosphatase 1D magnesium-dependent, delta isoform)

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Identity

Hugo: PPM1D

Other names: Wip1 phosphatase; PP2C delta (PP2Cd); EC 3.1.3.16

Location: 17q23

Local order: Centromere - USP32- APPBP2 - PPM1D - BCAS3 - telomere.

DNA/RNA

Description

The gene encompasses 64.5 kb of DNA; 6 exons; several SNPs have been found.

Transcription

Transcript length: 3,163 bps. Several splice forms have been predicted.

Wip1 mRNA transcription is induced in a p53-dependent manner after stress, however p53-independent induction of Wip1 mRNA also has been described. For example, E2F1 was shown to regulate Wip1 expression as well.

Protein

Note: Other names: Protein phosphatase 2C isoform delta (EC 3.1.3.16) (PP2C-delta) (p53- induced protein phosphatase 1) (Protein phosphatase magnesium-dependent 1 delta).

Description

605 amino acids; predicted size almost 65 kDa, however overexpressed Wip1 runs at almost 83 kDa.

Expression

Widely expressed (human expression).

Localisation

Primarily nucleus.

Function

Wip1 phosphatase is a weak oncogene that can complement other oncogenes (Hras, Neu) in transformation of primary rodent cells with low efficiency. Does not complement p53-deficient cells. Wip1 phosphatase has broad substrate specificity towards the threonine (p38 and UNG) or the serine residues (ATM, Chk2, p53, H2AX). Deficiency of Wip1 results in activation of p38- and ATM/Chk2-dependent signaling pathways. Inactivation of Wip1 suppresses the ability of mouse embryo fibroblasts undergo transformation in vitro and grow into tumors when explanted into nude mice. Wip1-deficient mice are resistant to multiple types of cancer including breast cancer and B-cell lymphomas.

Homology

Other PP2C phosphatases.

Mutations

Note: Have not been described.

Implicated in

Primary breast cancer

Disease

Wip1 overexpression primarily due to its gene amplification was found in almost 15% of primary breast cancers. Majority of Wip1-overexpressing tumors also have structurally intact p53. Overexpression of Wip1 inversely correlates with the level of active (phospho-) p38 MAPK. Wip1-

overexpressing tumors also exhibited no or low levels of p16, which normally accumulates upon p38 MAPK activation. PPM1D amplification is associated with ERBB2 expression implying that PPM1D overexpression occurs in tumors with poor prognosis.

Prognosis

High expression correlates with poor prognosis.

Neuroblastoma

Prognosis

High expression correlates with poor clinical outcome.

Pancreatic adenocarcinoma

Prognosis

High expression correlates with poor prognosis.

Ovarian adenocarcinomas

Prognosis

High expression correlates with poor prognosis.

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