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Gene Section
Review

CTDSPL (CTD (Carboxy-Terminal Domain, RNA Polymerase II, Polypeptide A) Small Phosphatase-Like)

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Abstract

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

Identity

Other names: C3orf8, HYA22, PSR1, RBSP3, SCP3

HGNC (Hugo): CTDSPL

Location: 3p22.2

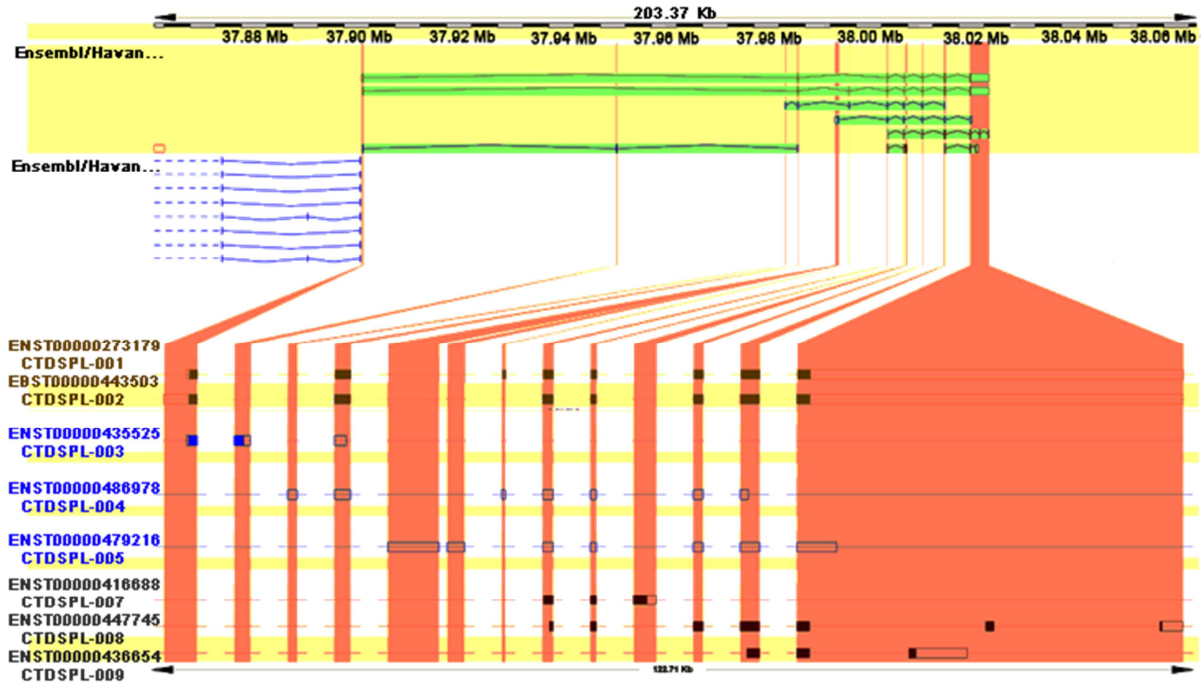
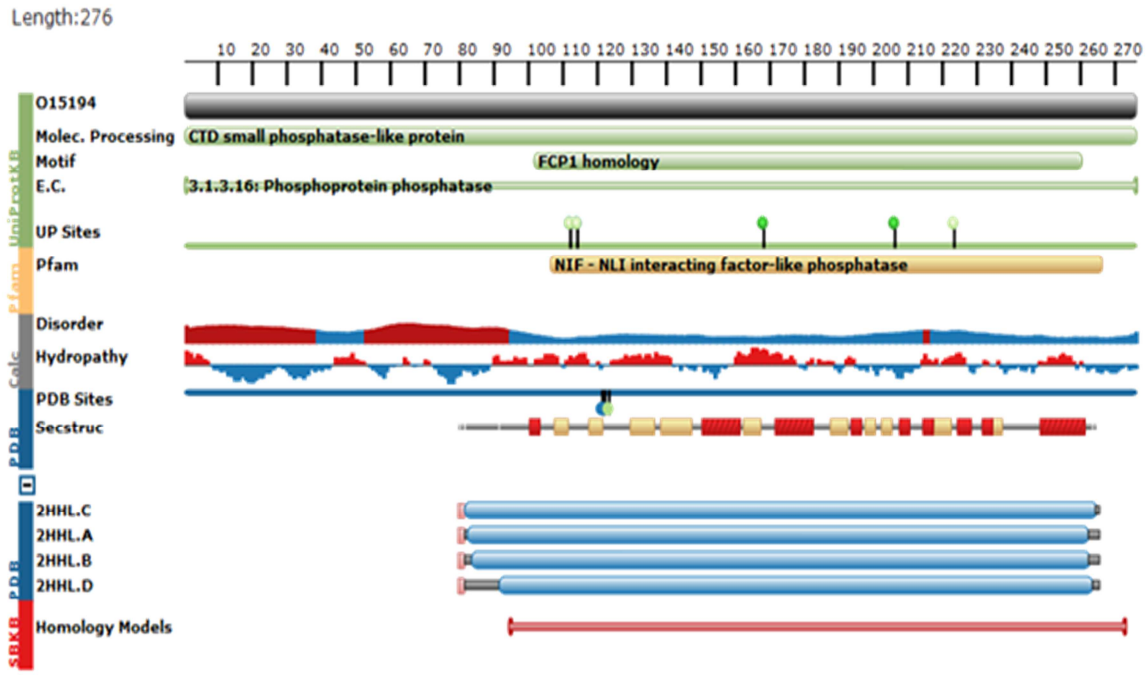


Diagram shows the different transcripts of CTDSPL (Brown, Blue, Grey and Maroon boxes). Beginning of boxes represents transcription start sites. Filled areas represent translated regions. The larger form, CTDSPL B is shown as CTDSPL 001, whereas the smaller form, CTDSPL A is shown as CTDSPL 002. Image adapted from Ensembl.org.



Schematic diagram of full length RBSP3 protein, showing different domains. Adapted from PDB O15194. **Data origin/ Colour codes:** Data in Green originates from UniProtKB; Data in Yellow originates from Pfam, by interacting with the HMMER3 website; Data in Grey has been calculated using BioJava. Protein disorder predictions are based on JRONN, a Java implementation of RONN. (a. Red- Potentially disordered region. b. Blue- Probably ordered region. Hydropathy has been calculated using a sliding window of 15 residues and summing up scored from standard hydrophobicity tables. a. Red- Hydrophobic. b. Blue- Hydrophilic); Data in blue originates from PDB. Secstruc- Secondary structure projected from representative PDB entries onto the UniProt sequence. (a. Red box - Helix. b. Yellow box - Sheet. c. Grey tube- Coil); Data in red indicates combined ranges of Homology Models from SBKB and the Protein Model Portal.

DNA/RNA

Description

Located in the short (p) arm of chromosome 3, the length of the CTDSPL gene is about 122.5 kb, contains 8 exons and is arranged in a telomere to centromere orientation.

Transcription

The full length transcript of CTDSLP is 4459 bp (Ensembl, Transcript ID ENST00000443503). A total of 8 transcripts can be generated, out of which 5 are protein coding, 1 undergoes nonsense mediated decay, while the rest 2 do not code for a protein product. However, two splice variants of CTDSPL, the smaller CTDSPL A (lacking exon 3, therefore short of 33 bp, 11 amino acids) and the full length CTDSPL B were identified by Kashuba et al., 2004.

Interesting observation: The transcription start site for CTDSPL A and CTDSPL B are different (from ensemble.org). While the larger B form has a shorter 5'UTR, the smaller A form has a larger 5'UTR, although their translation start sites remain common. Difference in the size of the 5'UTR may account for differential splicing between the isoforms.

Pseudogene

None reported.

Protein

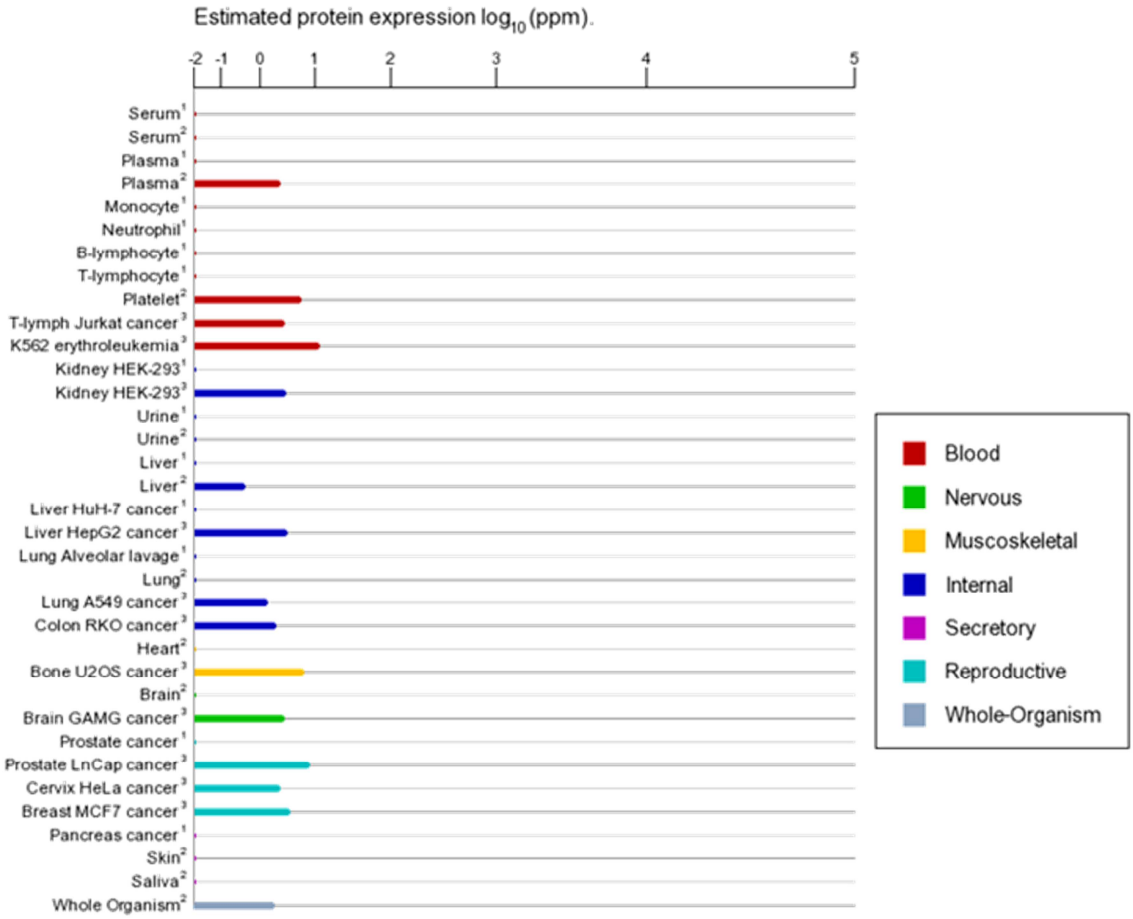
Description

The full length CTDSPL protein (CTDSPL B) is 276 amino acids in length, with a molecular weight of 31 kD.

The smaller protein, CTDSPL A is 265 amino acids in length (amino acids 79- 89 missing) and 29.9 kD in weight. Amino acids 102-260 contain the FCP1 homology domain, which contains an essential protein serine phosphatase that dephosphorylates the C-terminal domain (CTD) of RNA polymerase II.

Localisation

Both nuclear and cytoplasmic (Maiti et al., 2012; Sarkar et al., 2013).



CTDSPL Protein expression data from MOPED[1], PaxDb[2] and MAXQB[3]. 1. MOPED - Eugene Kolker, Bioinformatics & High-throughput Analysis Lab, Seattle Children's Research Institute. **2.** PaxDb - Christian von Mering, Bioinformatics Group, Institute of Molecular Life Sciences, University of Zurich. **3.** MAXQB - Matthias Mann, Department of Proteomics and Signal Transduction, Max-Planck Institute of Biochemistry, Germany. **The data was normalized as follows: 1.** For each sample, ppm protein values were calculated, if not provided so by data sources. For each sample from MAXQB, iBAQ expression values were divided by sum of values of each sample, and multiplied by 1000000. For all samples, data was gene centrically aggregated by summing expression values of all isoforms for each gene. **2.** For better visualization of graphs, expression values are drawn on a root scale, which is an intermediate between log and linear scales as used for our mRNA expression graphs (Safran et al., 2003).

Function

- CTDSPL is a serine phosphatase which regulates cell growth and differentiation. It dephosphorylates RB at serine 807/ 811 (hence called RB1 serine phosphatase from human chromosome 3), thereby increasing RB-E2F interaction and halting the cell cycle at G1/S boundary (Kashuba et al., 2004).
- It also inactivates RNA polymerase-II by preferential dephosphorylation of 'Ser-5' within the tandem 7 residues repeats in the C-terminal domain (CTD) of the largest RNA polymerase II subunit, thus controlling the transcription machinery (hence called carboxy-terminal domain, RNA polymerase II, polypeptide A small phosphatase-like) (Yeo et al., 2003).
- Studies also suggest that CTDSPL/RBSP3 might function as a transcriptional co-repressor, inhibiting transcription of neuronal genes in non-neuronal cells (Yeo et al., 2005), and may also act as a phosphatase of Smad1, Smad2/Smad3 and Snail (Wu et al., 2009; Sapkota et al., 2006).

Homology

Chimpanzee, Rhesus monkey, dog, cow, mouse, chicken, zebrafish, S.cerevisiae, K.lactis, E.gossypii, S.pombe, M.oryzae, and N.crassa show conserved RBSP3 gene (Source NCBI homologene).

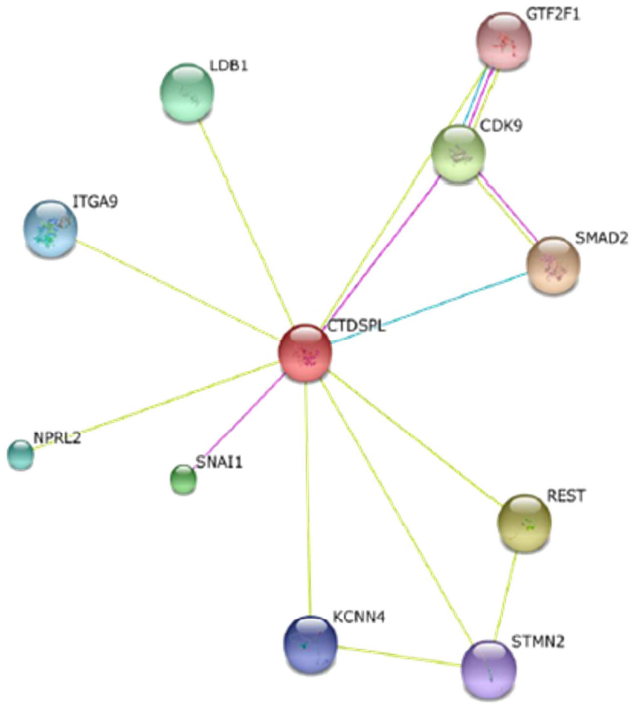
RBSP3 and miRNAs

1. miRNA 100
- RBSP3 is a bonafide target for miRNA 100.
- miRNA 100 binds to the 3`UTR of RBSP3 in regions conserved in humans, rats and mice.
- RBSP3 expression is inversely co-related with the expression of miRNA 100 in 76.5% AML cases.

2. miRNA 26a (has-miR-26a-1)
- miRNA 26a resides in the intron of RBSP3.
- It is concomitantly expressed with RBSP3 during the cell cycle.

ORGANISM	NCBI REFERENCE NO.	CTDSPL HOMOLOGY DOMAIN
CTDSPL, *H.sapiens*	NP_001008393.1	276 aa
CTDSPL, *P.troglodytes*	XP_001170981.1	276 aa
LOC697898, *M.mulatta*	XP_001086442.2	260 aa
CTDSPL, *C.lupus*	XP_851254.2	328 aa
CTDSPL, *B.taurus*	NP_001180010.2	276 aa
Ctdspl, *M.musculus*	NP_598471.3	276 aa
CTDSPL, *G.gallus*	NP_001001316.1	275 aa
ctdsplb, *D.rerio*	NP_001070083.1	266 aa
ctdspla, *D.rerio*	NP_001038912.2	265 aa
PSR1, *S.cerevisiae*	NP_013091.1	427 aa
PSR2, *S.cerevisiae*	NP_013119.1	397 aa
KLLA0F15620g, *K.lactis*	XP_455782.1	414 aa
AGOS_AAL158W, *E.gossypii*	NP_982384.1	478 aa
SPAC2F7.02c, *S.pombe*	NP_592973.1	325 aa
MGG_03646, *M.oryzae*	XP_361103.2	505 aa
NCU08380, *N.crassa*	XP_965283.1	448 aa

Different organisms showing homology in RBSP3 protein.



Predicted Functional Partners:

		Neighborhood	Gene Fusion	Cooccurrence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
SMAD2	SMAD family member 2; Transcriptional modulator activated by TGF-beta and activin type 1 recept [...] (467 aa)						•			0.899
REST	RE1-silencing transcription factor; Transcriptional repressor which binds neuron-restrictive si [...] (1097 aa)							•		0.720
CDK9	cyclin-dependent kinase 9; Member of the cyclin-dependent kinase pair (CDK9/cyclin- T) complex, [...] (372 aa)					•				0.621
SNAI1	snail homolog 1 (Drosophila); Seems to be involved in embryonic mesoderm formation. Binds to 3 [...] (264 aa)					•				0.619
LDB1	LIM domain binding 1; Binds to the LIM domain of a wide variety of LIM domain- containing trans [...] (411 aa)							•		0.551
NPRL2	tumor suppressor candidate 4; Suppresses Src-dependent tyrosine phosphorylation and activation [...] (380 aa)							•		0.540
ITGA9	integrin, alpha 9; Integrin alpha-9/beta-1 is a receptor for VCAM1, cytotactin and osteopontin. [...] (1035 aa)							•		0.517
KCNN4	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; Form [...] (427 aa)							•		0.501
STMN2	stathmin-like 2; May play a role in neuronal differentiation, and in modulating membrane intera [...] (179 aa)							•		0.462
GTF2F1	general transcription factor IIF, polypeptide 1, 74kDa; TFIIF is a general transcription initia [...] (517 aa)							•		0.462

Interacting proteins of RBSP3, using String network.

Tissue	Point Mutations		Copy Number Variation	
	% Mutated	N	Variant %	N
Adrenal gland		23		-
Autonomic ganglia		362		-
Biliary tract		11		-
Bone		75		46
Breast		978		852
Central nervous system		573		411
Cervix		14		-
Endometrium		281		246
Eye		34		-
Haematopoietic and lymphoid		1057		192
Kidney		475		300
Large intestine		610		486
Liver		424		-
Lung		861		476
Meninges		55		-
NS		235		30
Oesophagus		173		-
Ovary		504		462
Pancreas		388		29
Parathyroid		16		-
Prostate		384		-
Salivary gland		49		-
Skin		321		-
Small intestine		42		-
Soft tissue		16		-
Stomach		47		-
Thyroid		17		-
Upper aerodigestive tract		166		-
Urinary tract		103		-

Mutations and copy number variations in different organs. Red bar: Loss. Grey bar: Gain. Adapted from COSMIC gene analysis.

Mutations

Germinal

None reported.

Implicated in

Cervical cancer

Note

- High deletion (48%, 45% cases) and methylation (26%, 25% cases) was seen in CIN and CACX respectively (Mitra et al., 2010).
- Reduced mRNA expression was seen in CACX (Mitra et al., 2010).
- RBSP3B (larger, active isoform) was under-expressed in CACX (Mitra et al., 2010).
- In HPV infected cervical cancer, high deletion (42% cases) was observed, with significant variation ($p<0.05$) between metastatic (64%) and non-metastatic (32%) cases (Anedchenko et al., 2007)
- Altogether, copy number change was seen in 51% cases (Anedchenko et al., 2007).
- Decreased expression was seen in 64% cases, with significant difference between metastatic (83%) and non-metastatic (52%) cases (Anedchenko et al., 2007).
- Increase in expression was also observed in some cases (Anedchenko et al., 2007).
- Altogether, change in expression was in 79% of cases (Anedchenko et al., 2007).

Prognosis

RBSP3 alterations (deletion, methylation) were significantly associated with poor patient outcome and posed 4.5-13 times risk of survival (Anedchenko et al., 2007).

Oncogenesis

Inactivation of RBSP3 was an early event in cervical carcinogenesis (Mitra et al., 2010).

Breast cancer

Note

- Study population was divided into two groups, Group A (≤40 yrs, early onset) and Group B (>40 yrs, late onset) (Sinha et al., 2008).
- High deletion (30%, 24% cases) and methylation (38%, 32% cases) were observed in Groups A and B respectively (Sinha et al., 2008).
- 28.9 ± 39.1 fold reduction in expression of RBSP3 was observed in about 33 - 40% of the tumors (Sinha et al., 2008).
- Homozygous deletion (10-18%) was observed for RBSP3 (Senchenko et al., 2004).

Prognosis

Patients belonging lower to age of onset (≤40 yrs) with alterations of RBSP3 had poor disease outcome (Sinha et al., 2008).

Oncogenesis

Higher alterations of RBSP3 were observed in patients belonging to the lower age of onset (Group A) (Sinha et al., 2008).

Acute lymphoid leukemia (ALL)

Note

Promoter methylation was seen in RBSP3 in 24% of ALL patients.

Prostate cancer

Note

GWAS study using Affymetrix 100K SNP GeneChip with GEE model showed that the SNP, rs9311171 (G/ T), located within RBSP3, had a notable GEE p value ($1.8x\ 10^{-6}$).

Oncogenesis

GEE p value $1.8x\ 10^{-6}$ indicates that this SNP within RBSP3 plays a role in tumor progression.

Non - small cell lung cancer (NSCLC)

Note

- Reduction of expression of RBSP3 was obtained for both adenocarcinoma (AC) and squamous cell carcinoma (SCC) (Senchenko et al., 2008).
- Downregulation was both genetic and epigenetic (Senchenko et al., 2008).
- For ACs, decrease in level of expression was in 88% cases and 70% cases of metastatic and non-metastatic tumors respectively, whereas for SCCs, it was in 88% cases for both metastatic and non-metastatic tumors (Senchenko et al., 2008).
- Decrease in mRNA in ACs was due to deletion (25% cases) and promoter methylation (38% cases), whereas for SCCs, it was in 30% and 80% cases for deletion and methylation respectively (Senchenko et al., 2008).
- Fold decrease in expression of RBSP3 in AC and SCC was 78% and 88% respectively, with overall 85% decrease in expression of RBSP3 in NSCLC (Senchenko et al., 2010).

Oncogenesis

Deletion and methylation of promoter of RBSP3 are responsible for reduction in expression of the protein and play important roles in progression of NSCLC (Senchenko et al., 2008).

Reduction of expression of RBSP3 is required for development of lung adenocarcinomas (Senchenko et al., 2010).

Ovarian cancer

Note

Deletion/Methylation of RBSP3 were observed in 33% cases.

Oncogenesis

RBSP3 deletion/methylation can be used as a biomarker for ovarian cancer in combination with other studied markers.

Head and neck squamous cell carcinoma (HNSCC)

Note

- Deletion of RBSP3 in dysplasia and HNSCC was in 24% and 32% cases respectively (Ghosh et al., 2010).
- Promoter methylation was observed in 39% and 38% cases of dysplasia and HNSCC samples respectively (Ghosh et al., 2010).
- Fold reduction of mRNA in the tumors was 33.6 ± 9.4 (Ghosh et al., 2010).
- While normal tissues expressed the larger RBSP3 B form, tumors either showed no expression of RBSP3, or preferentially expressed the smaller, less active form, RBSP3 A (Ghosh et al., 2010).

Expression of RBSP3 decreases from pre-malignant to malignant lesions (Maiti et al., 2012).

Expression of RBSP3 was seen to be increased from pre-neoadjuvant chemotherapy tumors to post-therapy tumors (Sarkar et al., 2013).

Prognosis

Patients with RBSP3 alterations show poor survival (Ghosh et al., 2010).

Oncogenesis

Early alteration of RBSP3 takes place in head and neck cancers (Ghosh et al., 2010).

Loss of expression of RBSP3 was seen to be required for progression from malignant to invasive cancer (Maiti et al., 2012).

Regain of expression of RBSP3 in post-therapy tumors may be one of the reasons of shrinkage of tumors due to neoadjuvant chemotherapy (Sarkar et al., 2013).

Lung, renal, breast, cervical and ovarian cancers

Note

High frequencies of somatic mutations in RBSP3 in different cancers suggesting it may underlay the mutator phenotype of cancer.

Acute myeloid leukemia (AML)

Note

RBSP3 might have a crucial role in myeloid cell differentiation towards granulocyte/monocyte lineages through pRB-E2F pathway.

Cell lines

Note

Leukemia cell lines RAJI, BJAB (B cell leukemia) and HL-60 (myeloid leukemia) showed hypermethylation of RBSP3 promoter.

Hepatocellular carcinoma (HCC) in mouse model system

Note

RBSP3 shows increase in expression (RNA, protein) upon treatment with the chemopreventive agent Amarogentin.

Oncogenesis

Increase in expression of RBSP3 might play a role in chemoprevention upon treatment with amarogentin.

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