

Gene Section

Mini Review

DMTF1 (cyclin D binding myb-like transcription factor 1)

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Identity

Other names: DMP1, DMTF

HGNC (Hugo): DMTF1

Location: 7q21.12

Local order: Centromere--- GRM3 - KIAA1324L -
DMTF1 - MGC4175 - CROT - ABCB4 - ABCB1 ---
Telomere.

DNA/RNA

Note: There are at least three splicing variants for hDMTF1 alpha, beta and gamma.

Description

20 Exons.

Transcription

Major transcript: 3.9kb (human) (and 3.75kb in the mouse).

Pseudogene

In mus musculus, the pseudogene of Dmtf1 exists on chromosome XE3.

NT 039716, gi:149272292.

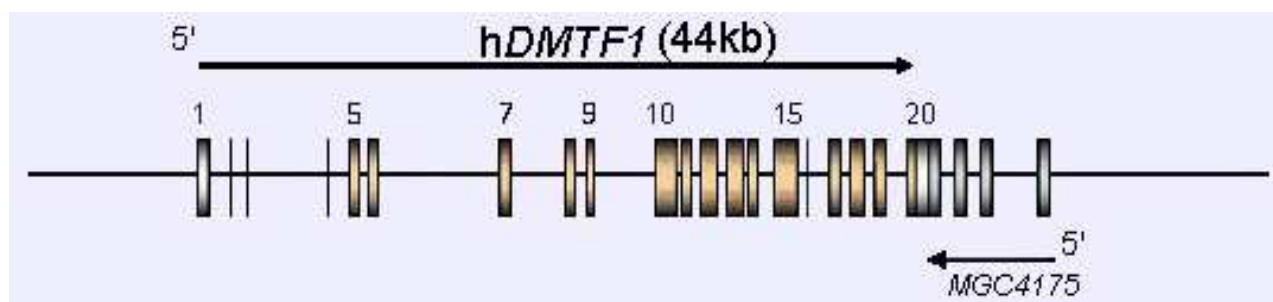
Protein

Note

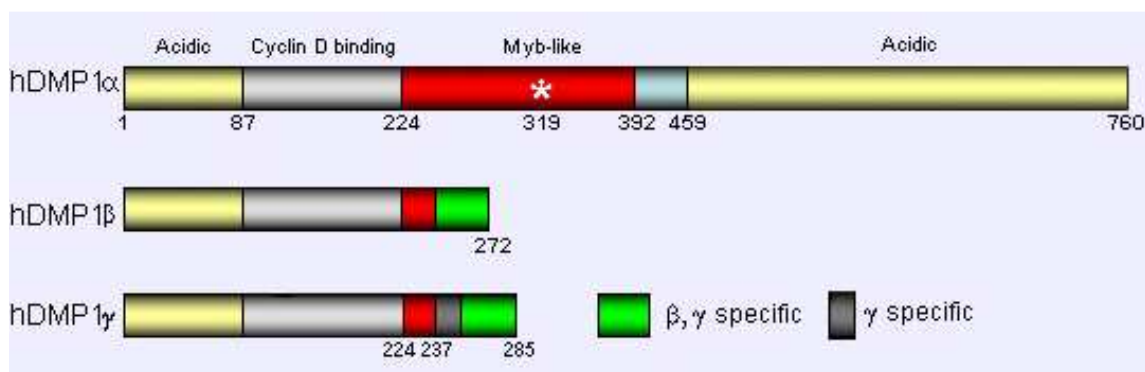
The human DMTF1alpha protein consists of 760 amino acids; DMTF1beta, 272 amino acids; and DMTF1gamma, 285 amino acids. Mouse Dmp1 consists of 761 amino acids.

Description

Dmtf1 is a MYB-like transcription factor isolated in a yeast two-hybrid screen of a mouse T lymphocyte library with cyclin D2 bait. It binds to a consensus sequence CCCG(G/T)ATG(T/C) that is also recognized by Ets family proteins.



The human DMTF1 genomic locus. DMTF1 consists of 20 exons and a gene named MGC4175 is localized at its 3' end in a reverse orientation.



Proteins generated from splicing variants of the human DMTF1 gene. The hDMTF1 beta and gamma isoforms lack most of the Myb-like repeats and the principal transactivation domains, and thus, they do not bind to DNA.

DMTF1 is a novel tumor suppressor that receives signals from oncogenic RAS and activates the ARF - P53 pathway. D-type cyclins antagonize the activity of Dmtf1 when E2F sites are not on the promoter; however, they synergize with Dmtf1 on the Arf promoter. Recent study shows significant involvement of DMTF1 in human non-small-cell lung carcinomas.

Expression

Mouse Dmtf1 protein is expressed in the testis, thymus, spleen, brain, lung, and kidney.

Localisation

Both human and mouse DMTF1 alpha proteins are localized in the nucleus.

Function

Dmtf1-null mice are prone to spontaneous tumor development, which was accelerated when the animals were neonatally treated with ionizing radiation or dimethylbenzanthracene.

Lung adenomas/adenocarcinomas were the most common tumors found in Dmtf1-deficient mice. Eμ-Myc-induced lymphomagenesis was significantly accelerated in Dmtf1-deficient mice. The retention and expression of the wild-type Dmtf1 allele in tumors arising in heterozygotes indicated that Dmtf1 is haplo-insufficient for tumor suppression. The low frequency of Arf deletion and p53 mutation in tumors from Dmtf1-knockout mice suggested that Dmtf1 is a physiological regulator of the Arf-p53 pathway in vivo. The DMTF1 promoter is activated by the oncogenic RAS - RAF - MEK - ERK - JUN pathway, and the induction of ARF by RAS is DMTF1-dependent. Thus, DMTF1 is a critical mediator of p19ARF in response to oncogenic RAS signaling. The importance of dmp1 in P53 regulation was recently demonstrated by crossing Dmtf1-deficient mice with K-ras^{LA} transgenic mice. The Dmtf1 promoter is repressed by overexpression of E2Fs and also by physiological mitogenic signaling. Thus, DMTF1 is a marker of cells that have exited from the cell cycle. The DMTF1 promoter is repressed by genotoxic stimuli mediated by NF-kappa B, and repression of the ARF promoter by genotoxic stimuli is

DMP1-dependent. Very little studies have been conducted on the post-translational modifications for DMTF1.

Homology

Human DMTF1 vs. mouse Dmtf1: 95% (723/761), positives 97% (739/761) at the amino acids level.

Mouse Dmtf1 vs. mouse TTF-1 (transcription termination factor 1): Identities 29% (90/309), positives 47% (148/309).

Mouse Dmtf1 vs. mouse C-myb: Identities 32% (23/71), positives 54% (39/71).

Mouse Dmtf1 vs. mouse A-myb: Identities 29% (31/106), positives 50% (54/106).

Mouse Dmtf1 vs. mouse B-myb: Identities 27% (22/80), positives 53% (43/80)

Mutations

Note

Point mutations for human DMTF1 in human cancer or other human disorders have not been reported.

Promoter hypermethylation for the hDMTF1 promoter is very rare (around 2%) in human non-small-cell lung carcinomas.

Single nucleotide polymorphisms for hDMTF1 are shown in http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=9988.

Germinal

N/A.

Somatic

N/A.

Implicated in

Non-small-cell lung carcinoma

Disease

One report shows that loss of heterozygosity (LOH) for the human DMTF1 gene was found in around 35 % of human non-small-cell lung cancers, especially those without deletions or methylation of p14ARF and/or

mutations of p53. NSCLC with LOH for hDMTF1 showed significantly weaker nuclear staining for DMTF1 protein than tumors without LOH.

Prognosis

The correlation between LOH for hDMTF1 and the prognoses of non-small-cell lung cancer patients has not been reported.

Hybrid/Mutated gene

Not reported.

Abnormal protein

Not reported.

Oncogenesis

N/A.

Hematopoietic malignancies involving chromosome del(7q)

Prognosis

The prognoses of human leukemias with del(7q) abnormalities are generally poor.

Cytogenetics

One allele of the hDMTF1 locus was deleted in 9 of 9 leukemic cells with chromosome 7q abnormalities by FISH analysis, regardless of the detailed karyotype at 7q, suggesting that mono-allelic loss of hDMTF1 could contribute to 7q- leukemias.

Hybrid/Mutated gene

Not reported.

Abnormal protein

Not reported.

Oncogenesis

N/A.

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