RNASET2 (ribonuclease T2)

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Abstract

Review on RNASET2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: RNASE6PL, RP11-514O12.3, bA514O12.3

HGNC (Hugo): RNASET2

Location: 6q27

Local order: Telomeric to RPS6KA2, centromeric to FGFR1OP.

Note: This gene represents the first human member of the Rh/T2/S-glycoprotein family of extracellular ribonucleases. It belongs to the recently defined class of tumor-antagonizing genes, based on its ability to suppress tumor growth in vivo, but not in vitro. It is likely involved in the pathogenesis of several human neoplasias (both solid and hematological) such as ovarian cancer, melanoma and non-Hodgkin lymphoma. Mutations in this gene have also been recently described in children affected by a rare congenital neurological defect. Moreover, GWAS studies have recently reported the association of gene variants mapping close to the RNASET2 gene with susceptibility to a few autoimmune disorders.
The RNASET2 gene has been mapped in the peritelomeric region of the long arm of human chromosome 6 (6q27), which has been consistently reported to be rearranged in several human neoplasias. Its coding region is split in 9 exons, spanning approximately 27 kb of genomic DNA. The translation initiation codon is located in exon 1 and the stop codon in exon 9. Exons III and VI encode the two CAS motifs (Catalytic Active Sites) responsible for the ribonuclease activity of the RNASET2 protein. However, the catalytic activity of the RNASET2 protein is apparently not required for some biological functions, as described for other members of the T2-Rh-S RNase gene family.

**Transcription**

The RNASET2 gene is transcribed in the telomere-to-centromere orientation to produce an ubiquitously expressed mRNA approximately 1.4 kb in length. EST clones representing splice variants of the same gene have been described. Transcription of this gene is rather ubiquitous, with highest expression levels being reported in spleen, pancreas and leukocytes.

**Pseudogene**

A processed pseudogene showing 85% identity with RNASET2 mRNA maps to chromosome 7p11.2. The expression pattern of this pseudogene is not known.

**Protein**

**Description**

The aminoacid sequence of RNASET2 depicts a typical member of the highly conserved Rh7T2/S family of extracellular, acid ribonucleases. The X-ray structure of the protein was recently reported, showing the occurrence of the α+β core fold typically observed in other members of the Rh/T2/S protein family. The catalytic activity of the protein was shown to be significantly inhibited by zinc and copper ions.

**Expression**

In normal human tissues, the RNASET2 protein has been detected in pancreas, stomach, small intestine, colon, salivary glands, liver, thyroid, adrenal glands, lymphoid organs, lungs, melanocytes, ovarian surface and Fallopian tube epithelium. Expression of the RNASET2 protein has also been detected in several human ovarian cancer cell lines and in some melanoma, prostate, pancreatic and breast carcinoma cell lines.

**Localisation**

The full-length RNASET2 protein contains 256 aminoacids and displays an apparent MW of 36 kDa in its secreted form. Two 31 and 27 kDa C-terminal proteolytic products have also been observed intracellularly in several human cancer cell lines.
The extracellular RNASET2 protein is detected in cell culture supernatants as the full length 36 kDa forms. The intracellular localization pattern of the RNASET2 protein suggests a localization in the secretory compartments (endoplasmic reticulum and Golgi apparatus) but also in lysosomes and processing bodies (P-bodies).

**Function**

**Biochemical function:** RNASET2 is an acid ribonuclease with optimal activity at pH 5 and preferential cleavage of poly-A and poly-U homopolyribonucleotides.

**Biological function:** RNASET2 behaves as a tumor antagonizing gene in ovarian cancer models, since experimental manipulation of this gene's expression levels in human ovarian cancer cell lines is associated with a significant change in their tumorigenic and metastasizing potential in vivo. The oncosuppressive role of this protein in ovarian cancer models is associated with a marked recruitment of cells form the monocyte/macrophage lineage within the tumor mass.

In an experimental model of colorectal cancer, recombinant RNASET2 was also found to display a marked oncosuppressive activity. Strikingly, in both models the ribonuclease catalytic activity was apparently dispensable for RNASET2 to play such antioncogenic role.

A role for in vivo tumor suppression for RNASET2 has also been established in a model of malignant melanoma.

Moreover, the human RNASET2 gene has been recently implicated in sperm motility and stress-induced apoptosis in melanocytes.

Recent investigations carried out on RNASET2 orthologs have suggested several additional biological roles for this gene family, such as in vivo priming of dendritic cells for Th2-helper response, inhibition of angiogenesis in vivo, ribosomal RNA decay in plants and CNS physiology.

**Homology**

The primary sequence of RNASET2 shows strong homology to the Rh/T2/S family of secreted ribonucleases.

**Mutations**

**Note**

Epigenetics: The RNASET2 gene has been reported to be frequently down-regulated in several human ovarian cancer cell lines and primary tumors. The underlying molecular mechanism is currently unknown.

**Germinal**

A common exon-9 missense C708T germline mutation has been described but no evidence for an association of this allele with human cancer was found.

A missense mutation (550T>C ; C184R) and a 2.5 kb deletion spanning exon 2 were found to segregate in families affected with cystic leukoencephalopathy.

**Somatic**

A few common polymorphisms in exons 1, 8 and 9 have been described. In general, coding mutations are rarely found in tumor samples.

**Implicated in**

**Ovarian cancer**

**Note**

Loss of expression or downregulation of RNASET2 occurs in a significant fraction of human ovarian cancer cell lines and primary ovarian tumours. Moreover, the genomic region (chromosome 6q27) where the RNASET2 genes maps has been reported to be frequently deleted or otherwise rearranged in a high fraction of ovarian cancer samples. However, no mutation in the RNASET2 gene have been described so far in human ovarian cancer samples. Therefore, this gene seems to be involved in tumor suppression mainly by means of its downregulation at the transcript/protein level in this cancer type.

When overexpressed by gene transfer experiments in human ovarian cancer cell lines displaying a low level of endogenous mRNA, RNASET2 strongly suppresses the tumorigenic and metastatic potential of these cell lines in a murine xenograft model in vivo. The same observation was reported following a complementary experiment, i.e. by knocking-down RNASET2 expression in a poorly aggressive ovarian cancer cell line expressing high levels of endogenous RNASET2.

In both in vivo models, RNASET2-mediated tumor suppression was associated with a marked recruitment of cells from the monocyte/macrophage lineage in the tumor mass. Further experiments have demonstrated a direct chemotactic role for cells from the monocyte/macrophage carried out by the RNASET2 protein. Very recently, downregulation of RNASET2 expression has been associated with resistance to cis-platin and carboplatin in ovarian cancer cells and tissues.

**Malignant melanoma**

**Note**

Besides ovarian carcinoma, the chromosome region 6q27 (where the RNASET2 genes maps) has been reported to be frequently deleted or rearranged in malignant melanoma. Downregulation of RNASET2 has also been reported in cell lines representing this cancer type. Overexpression of RNASET2 in the human melanoma-derived SK-
MEL28 cell line was associated with a significant suppression of tumor growth in vivo (in a xenograft model with immunocompromised mice), but not in vitro, supporting the notion of RNASET2 as a tumor-antagonizing gene whose oncosuppressive action is carried out asymmetrically, i.e. only in the context of a complex tissue architecture where a significant cross-talk between cancer cells and the stromal compartment take place. Moreover, the T2 RNase protein encoded from the Aspergillus niger ortholog gene has been shown to inhibit human melanoma cell growth and metastasis in a xenograft model. The underlying oncosuppressive mechanism in this model was the inhibition of tumor angiogenesis by means of competitive inhibition with angiogenin.

**Colorectal cancer**

**Note**

In an HT29 human colon cancer-derived xenograft experimental model, human recombinant RNASET2 was shown to greatly suppress tumor growth in vivo independent from its catalytic activity. Tumor angiogenesis was mainly affected by recombinant RNASET2 injection in this cancer model.

**Anaplastic large cell lymphoma**

**Note**

More recently, screening of a protein microarray with sera from anaplastic large cell lymphoma (ALCL) patients identified RNASET2 as an ALK-negative ALCL-associated antigen.

**Cystic leukoencephalopathy**

**Disease**

Several loss-of-function mutations have been reported in probands affected by cystic leukoencephalopathy, an autosomal recessive disorder whose clinical and radiological phenotype is indistinguishable with respect to the pattern of brain abnormalities observed in people suffering from congenital cytomegalovirus infection. Affected people develop several neurologic abnormalities in the early post-natal period, including psychomotor defects, seizures and sensorineural hearing impairment, characterized by a diagnostic MRI pattern.

**Cytogenetics**

Six independent mutations in the RNASET2 gene have been reported in both familial and sporadic cases affected by cystic leukoencephalopathy. All mutations are predicted to result in a loss of function phenotype.

**Abnormal protein**

The C184R mutant RNASET2 protein expressed from the 550T>C allele showed defective intracellular trafficking, likely due to impaired protein folding or stability.

**Autoimmune disorders**

**Disease**

Genome-wide association studies have recently implicated the RNASET2 locus in the susceptibility for a few autoimmune disorder, such as vitiligo, Crohn’s disease and Graves’ disease.

**References**


This article should be referenced as such: