RASSF5 (Ras association (RalGDS/AF-6) domain family member 5)

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Identity

Other names: MGC10823, MGC17344, Maxp1, NORE1, NORE1A, NORE1B, RAPL, RASSF3

HGNC (Hugo): RASSF5

Location: 1q32.1

Note

Murine RASSF5 originally named Nore1a. Nore1B independently identified and designated RAPL. Rat RASSF5 also cloned independently and designated Maxp1.

DNA/RNA

Description

The human gene for RASSF5 is 81 kb in length and is located on chromosome 1(q32.1). The gene can produce 4 protein isoforms, two via differential exon usage, a third via differential promoter usage and the genesis of the 4th (which can be found as an EST clone) is not yet clear. The largest isoform, A, is 418 amino acids long and has a molecular weight of about 47 kD. The protein structure of RASSF5A contains a proline-rich region at the N-terminus which contains potential SH3 binding sites and a nuclear localization signal. This is followed by a cystein rich domain, sometimes referred to as a zinc finger. Next is the Ras association domain and this is followed by sequence containing the SARAH motif required for binding to the pro-apoptotic kinases MST1 and MST2. A second nuclear localization sequence has been reported between amino acids 200-260 and a nuclear export sequence between amino acids 260-300.

Figure 1. Isoform A is shown as the longest isoform with 6 exons. Isoform B, without an alternate exon, shows that the frameshift gives a shortened and unique C-terminus. Isoform C is shown with a special 5' UTR and lacks an in-frame coding region leading to a unique N-terminus. The total coding sequence for Isoform A is about 1260 bases with the other isoforms being smaller.
Figure 2. A figure showing the processed mRNA as well as the amino acid sequence for isoforms A-D followed by motif explanation of isoform A (Nore1a).
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Protein

**Description**
The full length cDNA (for isoform A) encodes for a 47-kDa protein which contains a proline-rich region at the N-terminus followed by a putative diacylglycerol/phorbol ester binding domain. This is followed by the Ras association (RA) domain and then the domain containing a SARAH motif. This later is the diacylglycerol/phorbol ester binding domain. This is responsible for binding to the pro-apoptotic kinases MST1 and MST2.

**Expression**
Nore1a mRNA is expressed in the lung, kidney, liver, brain, spleen, thymus and heart.

**Localisation**
It can be detected on microtubules, in the centrosome, but appears most obvious in the nucleus.

**Function**
RASSF5A is a pro-apoptotic Ras effector that can bind and relocalize the pro-apoptotic MST kinases in the presence of activated Ras. It can also promote cell cycle arrest and modulate the activity of p53 by regulating its' nuclear localization. Knockdown of RASSF5A promotes cellular proliferation and soft agar growth. Thus, RASSF5A appears to function as a Ras regulated tumor suppressor. Analysis of human tumors has found little evidence of somatic mutation but the gene is frequently inactivated by promoter methylation in a broad range of human tumors. RASSF5C (also known as Nore1b or RAPL) has been reported to modulate cellular adhesion and to be regulated by the Ras related protein Rap1a. RASSF5C has also been implicated as serving as an adaptor protein to facilitate the interaction of Ras and CARMA1.

Mutations

**Note**
No tumor mutations yet reported.

Implicated in

**Clear cell renal carcinoma**

**Note**
RASSF5 is frequently down-regulated by promoter methylation in a variety of tumors including clear cell renal carcinomas. Moreover, a rare hereditary form of kidney cancer has been reported that maps with a translocation inactivating the RASSF5 gene.

**Various cancers**

**Note**
Nore1a is frequently inactivated by promoter methylation in renal carcinoma, breast cancer, lung cancer, liver cancer and neurological tumors.

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