

Gene Section

Mini Review

RHOBTB1 (Rho-related BTB domain containing 1)

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Identity

Other names: KIAA0740; MGC33059; MGC33841

HGNC (Hugo): RHOBTB1

Location: 10q21.2

DNA/RNA

Description

The RHOBTB1 gene spans over 132 Kpb genomic DNA and consists of 14 exons, 9 coding exons and 5 more exons in the 5'UTR (Figure 1). The coding sequence of RHOBTB1 is 2091 nucleotides long (Ramos et al., 2002). The promoter region has a high GC content with numerous CpG islands.

Transcription

Based on EST sequence analyses there are transcription variants that arise from the use of alternative promoters and alternative splicing, but none of the transcripts affects the coding region.

Protein

Note

RhoBTB1 is one of the three members of the RhoBTB family in vertebrates. The RhoBTB

family was identified during the study of the genes encoding Rho-related proteins in the lower eukaryote *Dictyostelium discoideum* (Rivero et al., 2002). All three RhoBTB proteins may be implicated in tumourigenesis.

Description

RhoBTB1 is 696 amino acids long. All RhoBTB proteins share the same domain architecture: a GTPase domain is followed by a proline-rich region, a tandem of two BTB domains and a C-terminal region (Figure 2).

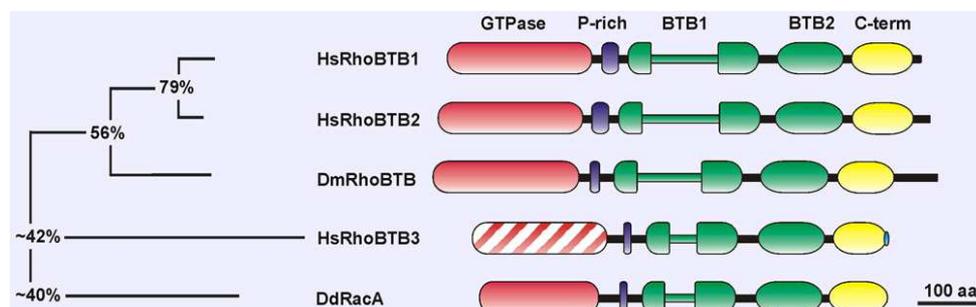
The GTPase domain is Rho-related and contains a Rho insert that is longer than usual, two insertions and one deletion, as well as a few deviations from the GTPase consensus of most Rho GTPases. Consequently, RhoBTB1 would predictably display impaired enzyme activity.

The proline-rich region links the GTPase to the first BTB domain. This region could act as a SH3 domain-binding site.

The BTB domain (broad complex, tramtract and bric-a-brac) is an evolutionary conserved protein-protein interaction domain that participates in homomeric and heteromeric associations with other BTB domains. The BTB domain was also identified as a component of multimeric cullin3-dependent ubiquitin ligase complexes.



Gene structure of RHOBTB1. Boxes represent exons. The coding region is represented in blue. For simplicity very large introns in the 5'UTR have been shortened (indicated by discontinuous lines).



Architecture of RhoBTB proteins. The figure shows the three human (Hs) RhoBTB subfamily members as well as the *Drosophila* (Dm) and *Dictyostelium* (Dd) orthologues. The simplified phylogenetic tree on the left illustrates the relationship among the proteins (overall percentage similarity between branches). The different domains are indicated with colours.

The first BTB domain is bipartite, being interrupted by an insertion of unknown function. The BTB domains of RhoBTB allow the formation of homodimers and of heterodimers with other proteins of the RhoBTB family (Berthold et al., 2008).

The C-terminus is a region conserved in all members of the RhoBTB subfamily. It predictably folds as 4 consecutive alpha-helices and one beta-strand. RhoBTB1 does not bear a CAAX motif that is typical for classical Rho GTPases and serves for localization of the protein to membranes.

Expression

RHOBTB1 is ubiquitously expressed, with high levels detected in skeletal muscle, placenta, stomach, kidney, testis, ovary, uterus and adrenal gland. The gene is also expressed in foetal tissues (Ramos et al., 2002; Nagase et al., 1998).

Expression of RHOBTB1 has been found decreased in kidney, breast and stomach tumours in a cancer profiling array (Berthold et al., 2008) and in 37% of 46 head and neck squamous cell carcinomas (Beder et al., 2006).

Localisation

The localisation of endogenous RhoBTB1 has not been investigated. In cells expressing RhoBTB1 ectopically the protein tends to form aggregates in the cytoplasm (Aspenstrom et al., 2004).

Function

RHOBTB1 has been proposed as a candidate tumour suppressor gene (Beder et al., 2006). The mechanisms by which RhoBTB proteins in general exert this and other roles remain speculative. Much of what we know about RhoBTB2 may be made extensive to RhoBTB1 because of their similarity.

RhoBTB1 binds to cullin3 and by analogy to RhoBTB2 and RhoBTB3 may constitute ubiquitin ligase complexes. RhoBTB proteins appear to exist in an inactive state through an intramolecular interaction of the BTB domain region with the GTPase domain (Berthold et al., 2008).

RhoBTB1, like RhoBTB2, is required for expression of

the chemokine CXCL14 in keratinocytes independently of Cullin3-mediated protein degradation (McKinnon et al., 2008).

RhoBTB1 displays only a moderate influence on the morphology and actin organisation of porcine aortic endothelial cells upon ectopic expression. It does not interact with the GTPase-binding domain of WASP, PAK1 or Rhotekin, which are well-known effectors of many typical Rho GTPases (Aspenstrom et al., 2004).

Homology

There are three RhoBTB proteins in vertebrates: RhoBTB1, RhoBTB2 and RhoBTB3 (Figure 2). RhoBTB1 is very similar to RhoBTB2, while RhoBTB3 displays very low similarity to these. Orthologues have been found in amoebae and in insects but they are absent in plants and fungi.

Mutations

Note

No pathogenic mutations have been identified to date.

Implicated in

Head and neck squamous cell carcinoma

Note

RHOBTB1 resides in a hotspot region with high frequency of allelic loss in HNSCCs. Loss of heterozygosity at the RHOBTB1 locus was identified in 12 of 52 tumour samples. RHOBTB1 showed decreased expression levels in 37% of 46 tumour samples and all informative low-expression samples displayed loss of heterozygosity. Three silent nucleotide changes were found in a mutation analysis (Beder et al., 2006).

Oncogenesis

RhoBTB1, along with RhoBTB2, seems to be required for expression of the chemokine CXCL14 (McKinnon et al., 2008). CXCL14 controls leukocyte migration and angiogenesis and its expression is frequently lost in diverse epithelial tumours, including most HNSCCs.

Various cancers including breast, kidney and stomach

Note

Expression of RHOBTB1 was found moderately but significantly decreased in kidney, breast and stomach tumour samples in a cancer profiling array. The decrease affected to 80% of kidney and to 58% of breast cancer samples. The expression changes correlated with those of CUL3 in the same samples (Berthold et al., 2008).

References

Nagase T, Ishikawa K, Suyama M, Kikuno R, Miyajima N, Tanaka A, Kotani H, Nomura N, Ohara O. Prediction of the coding sequences of unidentified human genes. XI. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. *DNA Res.* 1998 Oct 30;5(5):277-86

Rivero F, Dislich H, Glöckner G, Noegel AA. The Dictyostelium discoideum family of Rho-related proteins. *Nucleic Acids Res.* 2001 Mar 1;29(5):1068-79

Ramos S, Khademi F, Somesh BP, Rivero F. Genomic organization and expression profile of the small GTPases of the RhoBTB family in human and mouse. *Gene.* 2002 Oct 2;298(2):147-57

Aspenström P, Fransson A, Saras J. Rho GTPases have diverse effects on the organization of the actin filament system. *Biochem J.* 2004 Jan 15;377(Pt 2):327-37

Beder LB, Gunduz M, Ouchida M, Gunduz E, Sakai A, Fukushima K, Nagatsuka H, Ito S, Honjo N, Nishizaki K, Shimizu K. Identification of a candidate tumor suppressor gene RHOBTB1 located at a novel allelic loss region 10q21 in head and neck cancer. *J Cancer Res Clin Oncol.* 2006 Jan;132(1):19-27

Berthold J, Schenkova K, Ramos S, Miura Y, Furukawa M, Aspenström P, Rivero F. Characterization of RhoBTB-dependent Cul3 ubiquitin ligase complexes--evidence for an autoregulatory mechanism. *Exp Cell Res.* 2008 Nov 15;314(19):3453-65

Berthold J, Schenkova K, Rivero F. Rho GTPases of the RhoBTB subfamily and tumorigenesis. *Acta Pharmacol Sin.* 2008 Mar;29(3):285-95

McKinnon CM, Lygoe KA, Skelton L, Mitter R, Mellor H. The atypical Rho GTPase RhoBTB2 is required for expression of the chemokine CXCL14 in normal and cancerous epithelial cells. *Oncogene.* 2008 Nov 20;27(54):6856-65

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