SIPA1 (signal-induced proliferation-associated 1)

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Published in Atlas Database: May 2010

Online updated version: http://AtlasGeneticsOncology.org/Genes/SIPA1ID46282ch11q13.html

DOI: 10.4267/2042/44969

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Identity

Other names: MGC102688, MGC17037, SPA1
HGNC (Hugo): SIPA1
Location: 11q13.1

DNA/RNA

Note
History and nomenclature: SIPA1 gene, originally referred to as SPA-1, was first isolated in 1995 as the secondary response gene transcriptionally induced in the lymphoid cells by the stimulation with mitogenic cytokines or cross-linking antigen receptors.

Description
The SIPA1 gene spans 12.8 kb of the genome and is characterized by 16 exons; exon 1, 91 bp of exon 2 and the 3’ 205 bp of exon 16 are untranslated. The figure shows the general structure of the gene.

Transcription
A 3.6 kb transcript is detected preferentially in lymphohematopoietic tissues and certain cancer cells. Two alternatively spliced variants encoding the same isoform have been characterized to date.

Protein

Description
The SIPA1 protein, SPA-1, contains 1042 amino-acids (130 KDa); contains Rap GTPase-activating (GAP) domain (350-539), PDZ domain (685-759) and leucine zipper like domain (964-1042) which resembles myosin tail.

Expression
SPA-1 is most abundantly expressed in lymphohematopoietic tissues including bone marrow, thymus and spleen.

Localisation
Localized in various intracellular compartments, such as actin cytoskeleton, plasma membranes, and possibly nuclei, depending on the cell type and specific protein interaction via the PDZ domain.

Function
SPA-1 exhibits a specific GAP activity for Ras-related regulatory proteins Rap1 and Rap2, but not for Ran or other small GTPases. SPA-1 overexpression (abrogating the endogenous Rap1 activation) induced rounding and eventual detachment of inherently adherent cells from extra-

Structure of the SIPA1 gene.
cellular matrix, indicating that Rap1 signals are involved in the regulation of cell adhesion and SPA-1 functions as a negative regulator of cell adhesion.

**Homology**

SPA-1 is highly homologous to human rap1GAPs (RapGA1, RapGA2) at a catalytic domain called the GAP-related domain (GRD) (43% identical amino acids). So far, three homologous molecules of SPA-1 except human rap1GAPs have been reported; SPA-1-like (SPA-L1) (also called E6TP1 or SPAR), SPA-L2, and SPA-L3, all of which share a PDZ domain in addition to a GRD.

**Mutations**

**Note**

SPA-1-deficient (Spa-1<sup>-/-</sup>) mice also develop age-dependent progression of T-cell unresponsiveness, preceding the overt development of leukemia described as follows. Such Spa-1<sup>-/-</sup> T cells show defective Ras-mediated ERK activation in response to TCR-stimulation. Stimulation of the Spa-1<sup>+</sup> T cells by TCRs results in the persistence of a high level of Rap1 activation.

Spa-1<sup>-/-</sup> mice exhibit increased basal Rap1GTP selectively in the progenitor population of bone marrow cells, and this is associated with a progressive increase in the hematopoietic stem-cell population as the mice aged. After a long latent period, virtually all of the Spa-1<sup>-/-</sup> mice develop overt leukemia, which can be classified into several distinct types. A proportion of them show a marked increase in the number of blood leukocytes with only a few blast cells, extensive enlargement of the liver and spleen, and hypercellular bone marrow. The increased leukocytes are predominantly mature granulocytes, or small lymphoid cells bearing an IgM<sup>+</sup> CD5<sup>+</sup> CD11b<sup>-</sup> phenotype with monoclonal immunoglobulin gene-rearrangement patterns, closely resembling human chronic myelogenous leukemia (CML) in the chronic phase, or chronic lymphocytic leukemia (CLL), respectively.

Both types of disease can be successfully transferred into severe combined immunodeficient (SCID) mice, indicating that the abnormal proliferation is myeloid progenitor cell autonomous. A minor portion of Spa-1<sup>-/-</sup> mice show decreased leukocyte numbers with dysplastic myeloid cells accompanied by severe anemia, being reminiscent of the human myelodysplastic syndrome (MDS).

Finally, the majority of Spa-1<sup>-/-</sup> mice develop aggressive lethal leukemia with abundant blast cells of either myeloid or erythroid lineage, which extensively infiltrate into all the vital organs, probably representing the blast crisis of CML in the chronic phase. Blast crisis represents a blastic transformation of leukemia cells that invariably occurs in the course of human CML, and is associated with signs and symptoms of acute leukemia, often with extramedullary disease.

In addition to CML-like leukemia, around 15% of over 100 Spa-1<sup>+/+</sup> mice developed B-lineage cell leukemia. The majority of B220<sup>+</sup> leukemic cells exhibited CD5 and Mac1 expression, apparently corresponding to B1 cells. Indeed, the majority of Spa-1<sup>-/-</sup> mice show a progressive increase in their B1 cell populations in the peritoneal cavity as they aged; this was associated with the generation of anti-dsDNA antibody and lupus-like glomerulonephritis. Many of the Spa-1<sup>-/-</sup> mice with B1 cell-type leukemia also show a hemolytic autoantibody; this feature highly resembled human B cell chronic lymphocytic leukemia (CLL).

Sip1α is a candidate gene for the Mtes-1 locus which is involved in controlling lung metastasis of mammary tumors in mouse model. In mice, there is a nonsynonymous polymorphism in the Sip1, either alanine (A) or threonine (T) at the amino acid position 741 in the PDZ domain; all the strains with a Sip1/741A allele showed high metastatic tendency, whereas those with a Sip1/741T allele reveal less lung metastasis. Sip1/741A shows higher Rap1GAP activity than Sip1/741T in cancer cells, probably due to the altered binding affinity of the PDZ domain for the interacting proteins. In agreement, overexpression of wild type Sip1α in mammary tumor cells markedly enhanced the lung metastatic activity, whereas knockdown of the endogenous Sip1α reduces the activity.

No pathological mutations have been detected in any leukemia cases.

**Implicated in**

**Breast cancer**

**Note**

Several studies have shown that germline polymorphisms in SIPA1 are associated with metastasis of breast cancer (Crawford et al., 2006; Hsieh et al., 2009). Crawford et al. examined three SNPs within SIPA1 (one within the promoter (-313G>A: rs931127) and two exonic (545C>T: rs3741378 and 2760G>A: rs746429)). The population (n=300) consisted of randomly selected non-Hispanic Caucasian breast cancer patients using SNP-specific PCR. They showed that the variant 2760G>A and the -313G>A allele were associated with lymph node involvement (P=0.0062 and P=0.0083, respectively), and the variant 545C>T was associated with estrogen receptor negative tumors (P=0.0012) and with progesterone negative tumors (P=0.0339). Associations were identified between haplotypes defined by the three SNPs and disease progression. Correlation of SIPA1 SNP rs3741378 with breast cancer susceptibility was also confirmed by Hsieh et al.
References


This article should be referenced as such:
