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Gene Section

Review

BAG1 (BCL2-associated athanogene)

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Identity

Other names: BAG-1, HAP, HAP46, RAP46
HGNC (Hugo): BAG1
Location: 9p13.3

DNA/RNA

Description

Centromere to telomerase orientation; 7 exons.

Transcription

5 alternative transcripts; 1079 nucleotides mRNA.

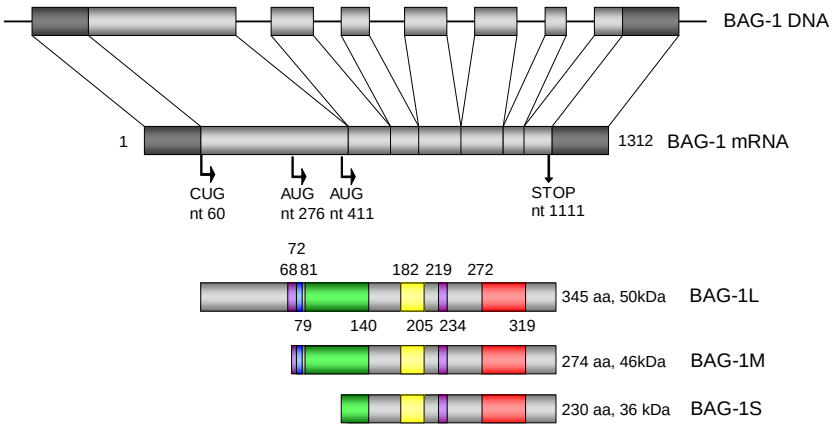
Protein

Description

Three isoforms generated by alternative translation initiation; 50kDa (BAG-1L), 46kDa (BAG-1M) and 36kDa (BAG-1S)(Yang et al., 1998). Each BAG-1 isoform contains a conserved BAG domain and ubiquitin-like domain, with variation in length of their N-terminal sequences.

Expression

Expressed ubiquitously and found to be over-expressed in a number of cancers.



BAG-1 isoforms and their domains. The human BAG-1 gene, located on chromosome 9p12, comprises seven exons which generate an mRNA product of approximately 1.5kb. Three major BAG-1 isoforms are produced from alternative translation start sites within BAG-1 mRNA. The 50kDa BAG-1L isoform is translated from the first in-frame CUG codon by CAP-dependent translation, while BAG-1M and BAG-1S are produced from two downstream AUG codons. BAG-1M is also produced by a CAP-dependent translation mechanism, while BAG-1S is generated by IRES-dependent translation resulting in highest abundance of this short isoform. BAG-1L contains a bipartite nuclear localisation sequence (NLS, purple), the amino-terminal portion of which overlaps with a DNA binding domain (blue). BAG-1M contains a partial NLS, while the NLS is completely absent from BAG-1S. An acidic serine/threonine rich region (green) has been implicated in protein-protein interactions. The ubiquitin-like domain (yellow) and BAG domain (red) are present in all three isoforms.

Localisation

The BAG-1 isoforms differ in their subcellular localisation. BAG-1L is predominantly nuclear, BAG-1M is both nuclear and cytoplasmic and BAG-1S is predominantly cytoplasmic (Packham et al., 1997; Takayama et al., 1998; Yang et al., 1998; Brimmell et al., 1999). However, subcellular localisation can be cell type and context dependent, for example in response to heat shock and hormonal stimulation (Schneikert et al., 1999; Zeiner et al., 1999).

Function

Multifunctional protein: Identified as having a role in many different cellular processes including the regulation of apoptosis, proliferation, transcription, proteasome-mediated degradation and a possible role in motility and metastasis (reviewed in Cutress et al., 2003). BAG-1 affects many cellular processes through interaction with a wide variety of cellular proteins, summarised in the table 1.

Homology

BAG family of proteins that share a common BAG domain. At present six BAG family proteins have been identified in humans: BAG-1 (Rap46) BAG-2, BAG-3, BAG-4 (sodd), BAG-5 and BAG-6 (BAT3).

Mutations

Note

Unknown.

Implicated in

Various cancers

Disease

BAG-1 expression is frequently altered in human cancer (Townsend et al., 2003). It has been shown to be over-expressed relative to normal cells in a number of cancers including breast cancer (Tang et al., 1999), colorectal cancer (Kikuchi et al., 2002;

Interacting protein	Involvement of BAG-1	References
Hsp70 / Hsc70 molecular chaperones	BAG-1 acts as co-chaperone to regulate ATPase activity of heat shock proteins and inhibit chaperone activity	(Takayama *et al.*, 1997)
Raf-1 kinase	Binds to catalytic domain of Raf-1 kinase and activates it independent of Ras	(Song *et al.*, 2001, Wang *et al.*, 1996, Gotz *et al* 2005)
Glucocorticoid recetor (GCR) and other nuclear hormone receptors	BAG-1L interacts with and enhances androgen receptor function BAG-1M negatively regulates GCR- and hormone-induced apoptosis	(Froesch *et al.*, 1998, Kullmann *et al.*, 1998, Zeiner and Gehring, 1995,)
E3 ubiquitin ligases e.g. Siah1 and CHIP	BAG-1 negatively regulates the growth inhibitory ubiquitin ligase, Siah-1 BAG-1 accepts protein substrates from molecular chaperones and presents them to CHIP for ubiqitylation – cooperation to influence protein quality control	(Demand *et al.*, 2001, Matsuzawa *et al.*, 1998)
Proteasome	BAG-1 acts as a link between proteasome and chaperones, Hsp70 / Hsc70	(Luders *et al.*, 2000)
HGF and PDGF receptors	BAG-1 binds to receptor tail via C-terminal domain and enhances HGF- and PDGF-mediated protection against apoptosis	(Bardelli *et al.*, 1996)
DNA	BAG-1L and BAG-1M translocate to the nucleus and bind DNA to activate transcription upon heat shock BAG-1M can bind DNA and Hsp70 simultaneously and form subsequent substrate interactions possibly to act as a bridging molecule with transcription factors	(Niyaz *et al.*, 2001, Zeiner *et al.*, 1999)
Rb	Role for Rb in maintaining nuclear localisation of BAG-1 Nuclear BAG-1 inhibits apoptosis in adenomas to increase survival of colorectal tumour cells in vivo	(Arhel *et al.*, 2003, Clemo *et al.*, 2005, Barnes *et al.*, 2005)
Bcl-2	Association with BAG-1 enhances anti-apoptotic signalling of Bcl-2	(Takayama *et al.*, 1995)

Table 1. Summary of proteins that interact with BAG-1 and some of the reported cellular functions. BAG-1 associates with a wide range of proteins and through these interactions may have multiple cellular effects, any of which might contribute to cancerous cell phenotypes.

Clemo et al. 2008) and human squamous cell carcinoma (Shindoh et al., 2000), endometrial cancer (Moriyama et al., 2004), prostate cancer (Krajewska et al., 2006) and lung cancer (Rorke et al., 2001). Altered expression has been found in pre-malignant lesions (Clemo et al., 2008), implicating a role early in tumour development. BAG-1 has also been suggested to be involved in metastatic disease (Takaoka et al., 1997; Yawata et al., 1998; Hague et al., 2002, reviewed by Sharp et al., 2004).

Prognosis

BAG-1 expression has been shown to be a prognostic factor in a number of cancers. Kikuchi et al (2002) showed in colorectal cancer, that high nuclear BAG-1 expression resulted in a poorer prognosis and a higher risk of metastases. In oesophageal cancer, BAG-1 expression has also been linked to poor prognosis (Takeno et al., 2007). In breast cancer over-expression of BAG-1 has been suggested to be a poor prognostic factor (Krajewski et al., 1999). However, there is conflicting data, with some studies finding increased BAG-1 expression results in a good prognosis (Turner et al., 2001; Nadler et al., 2008), or establishing no link between expression and prognosis (Sjostrom et al., 2002; Tang et al., 2004).

References

Takayama S, Sato T, Krajewski S, Kochel K, Irie S, Millan JA, Reed JC. Cloning and functional analysis of BAG-1: a novel Bcl-2-binding protein with anti-cell death activity. Cell. 1995 Jan 27;80(2):279-84

Zeiner M, Gehring U. A protein that interacts with members of the nuclear hormone receptor family: identification and cDNA cloning. Proc Natl Acad Sci U S A. 1995 Dec 5;92(25):11465-9

Bardelli A, Longati P, Albero D, Goruppi S, Schneider C, Ponzetto C, Comoglio PM. HGF receptor associates with the anti-apoptotic protein BAG-1 and prevents cell death. EMBO J. 1996 Nov 15;15(22):6205-12

Wang HG, Takayama S, Rapp UR, Reed JC. Bcl-2 interacting protein, BAG-1, binds to and activates the kinase Raf-1. Proc Natl Acad Sci U S A. 1996 Jul 9;93(14):7063-8

Packham G, Brimmell M, Cleveland JL. Mammalian cells express two differently localized Bag-1 isoforms generated by alternative translation initiation. Biochem J. 1997 Dec 15;328 (Pt 3):807-13

Takaoka A, Adachi M, Okuda H, Sato S, Yawata A, Hinoda Y, Takayama S, Reed JC, Imai K. Anti-cell death activity promotes pulmonary metastasis of melanoma cells. Oncogene. 1997 Jun 19;14(24):2971-7

Froesch BA, Takayama S, Reed JC. BAG-1L protein enhances androgen receptor function. J Biol Chem. 1998 May 8;273(19):11660-6

Kullmann M, Schneikert J, Moll J, Heck S, Zeiner M, Gehring U, Cato AC. RAP46 is a negative regulator of glucocorticoid receptor action and hormone-induced apoptosis. J Biol Chem. 1998 Jun 5;273(23):14620-5

Matsuzawa S, Takayama S, Froesch BA, Zapata JM, Reed JC. p53-inducible human homologue of Drosophila seven in absentia (Siah) inhibits cell growth: suppression by BAG-1. EMBO J. 1998 May 15;17(10):2736-47

Takayama S, Krajewski S, Krajewska M, Kitada S, Zapata JM, Kochel K, Knee D, Scudiero D, Tudor G, Miller GJ, Miyashita T, Yamada M, Reed JC. Expression and location of Hsp70/Hsc-binding anti-apoptotic protein BAG-1 and its variants in normal tissues and tumor cell lines. Cancer Res. 1998 Jul 15;58(14):3116-31

Yang X, Chernenko G, Hao Y, Ding Z, Pater MM, Pater A, Tang SC. Human BAG-1/RAP46 protein is generated as four isoforms by alternative translation initiation and overexpressed in cancer cells. Oncogene. 1998 Aug 27;17(8):981-9

Yawata A, Adachi M, Okuda H, Naishiro Y, Takamura T, Hareyama M, Takayama S, Reed JC, Imai K. Prolonged cell survival enhances peritoneal dissemination of gastric cancer cells. Oncogene. 1998 May;16(20):2681-6

Brimmell M, Burns JS, Munson P, McDonald L, O'Hare MJ, Lakhani SR, Packham G. High level expression of differentially localized BAG-1 isoforms in some oestrogen receptor-positive human breast cancers. Br J Cancer. 1999 Nov;81(6):1042-51

Krajewski S, Krajewska M, Turner BC, Pratt C, Howard B, Zapata JM, Frenkel V, Robertson S, Ionov Y, Yamamoto H, Perucho M, Takayama S, Reed JC. Prognostic significance of apoptosis regulators in breast cancer. Endocr Relat Cancer. 1999 Mar;6(1):29-40

Schneikert J, Hübner S, Martin E, Cato AC. A nuclear action of the eukaryotic cochaperone RAP46 in downregulation of glucocorticoid receptor activity. J Cell Biol. 1999 Sep 6;146(5):929-40

Zeiner M, Niyaz Y, Gehring U. The hsp70-associating protein Hap46 binds to DNA and stimulates transcription. Proc Natl Acad Sci U S A. 1999 Aug 31;96(18):10194-9

Lüders J, Demand J, Papp O, Höhfeld J. Distinct isoforms of the cofactor BAG-1 differentially affect Hsc70 chaperone function. J Biol Chem. 2000 May 19;275(20):14817-23

Shindoh M, Adachi M, Higashino F, Yasuda M, Hida K, Nishioka T, Ono M, Takayama S, Reed JC, Imai K, Totsuka Y, Kohgo T. BAG-1 expression correlates highly with the malignant potential in early lesions (T1 and T2) of oral squamous cell carcinoma. Oral Oncol. 2000 Sep;36(5):444-9

Demand J, Alberti S, Patterson C, Höhfeld J. Cooperation of a ubiquitin domain protein and an E3 ubiquitin ligase during chaperone/proteasome coupling. Curr Biol. 2001 Oct 16;11(20):1569-77

Lin J, Hutchinson L, Gaston SM, Raab G, Freeman MR. BAG-1 is a novel cytoplasmic binding partner of the membrane form of heparin-binding EGF-like growth factor: a unique role for proHB-EGF in cell survival regulation. J Biol Chem. 2001 Aug 10;276(32):30127-32

Niyaz Y, Zeiner M, Gehring U. Transcriptional activation by the human Hsp70-associating protein Hap50. J Cell Sci. 2001 May;114(Pt 10):1839-45

Rorke S, Murphy S, Khalifa M, Chernenko G, Tang SC. Prognostic significance of BAG-1 expression in nonsmall cell lung cancer. Int J Cancer. 2001 Sep 20;95(5):317-22

Song J, Takeda M, Morimoto RI. Bag1-Hsp70 mediates a physiological stress signalling pathway that regulates Raf-1/ERK and cell growth. Nat Cell Biol. 2001 Mar;3(3):276-82

Turner BC, Krajewski S, Krajewska M, Takayama S, Gumbs AA, Carter D, Rebbeck TR, Haffty BG, Reed JC. BAG-1: a novel biomarker predicting long-term survival in early-stage breast cancer. J Clin Oncol. 2001 Feb 15;19(4):992-1000

Hague A, Packham G, Huntley S, Shefford K, Eveson JW. Deregulated Bag-1 protein expression in human oral squamous cell carcinomas and lymph node metastases. J Pathol. 2002 May;197(1):60-71

Kikuchi R, Noguchi T, Takeno S, Funada Y, Moriyama H, Uchida Y. Nuclear BAG-1 expression reflects malignant potential in colorectal carcinomas. Br J Cancer. 2002 Nov 4;87(10):1136-9

Sjöström J, Blomqvist C, von Boguslawski K, Bengtsson NO, Mjaaland I, Malmström P, Ostenstadt B, Wist E, Valvere V, Takayama S, Reed JC, Saksela E. The predictive value of bcl-2, bax, bcl-xL, bag-1, fas, and fasL for chemotherapy response in advanced breast cancer. Clin Cancer Res. 2002 Mar;8(3):811-6

Arhel NJ, Packham G, Townsend PA, Collard TJ, H-Zadeh AM, Sharp A, Cutress RI, Malik K, Hague A, Paraskeva C, Williams AC. The retinoblastoma protein interacts with Bag-1 in human colonic adenoma and carcinoma derived cell lines. Int J Cancer. 2003 Sep 1;106(3):364-71

Cutress RI, Townsend PA, Sharp A, Maison A, Wood L, Lee R, Brimmell M, Mullee MA, Johnson PW, Royle GT, Bateman AC, Packham G. The nuclear BAG-1 isoform, BAG-1L, enhances oestrogen-dependent transcription. Oncogene. 2003 Aug 7;22(32):4973-82

Townsend PA, Cutress RI, Sharp A, Brimmell M, Packham G. BAG-1: a multifunctional regulator of cell growth and survival. Biochim Biophys Acta. 2003 Mar 17;1603(2):83-98

Moriyama T, Littell RD, Debernardo R, Oliva E, Lynch MP, Rueda BR, Duska LR. BAG-1 expression in normal and neoplastic endometrium. Gynecol Oncol. 2004 Aug;94(2):289-95

Sharp A, Crabb SJ, Townsend PA, Cutress RI, Brimmell M, Wang XH, Packham G. BAG-1 in carcinogenesis. Expert Rev Mol Med. 2004 Mar 22;6(7):1-15

Tang SC, Beck J, Murphy S, Chernenko G, Robb D, Watson P, Khalifa M. BAG-1 expression correlates with Bcl-2, p53, differentiation, estrogen and progesterone receptors in invasive breast carcinoma. Breast Cancer Res Treat. 2004 Apr;84(3):203-13

Barnes JD, Arhel NJ, Lee SS, Sharp A, Al-Okail M, Packham G, Hague A, Paraskeva C, Williams AC. Nuclear BAG-1 expression inhibits apoptosis in colorectal adenoma-derived epithelial cells. Apoptosis. 2005 Mar;10(2):301-11

Clemo NK, Arhel NJ, Barnes JD, Baker J, Moorghen M, Packham GK, Paraskeva C, Williams AC. The role of the retinoblastoma protein (Rb) in the nuclear localization of BAG-1: implications for colorectal tumour cell survival. Biochem Soc Trans. 2005 Aug;33(Pt 4):676-8

Götz R, Wiese S, Takayama S, Camarero GC, Rossoll W, Schweizer U, Troppmair J, Jablonka S, Holtmann B, Reed JC, Rapp UR, Sendtner M. Bag1 is essential for differentiation and survival of hematopoietic and neuronal cells. Nat Neurosci. 2005 Sep;8(9):1169-78

Townsend PA, Stephanou A, Packham G, Latchman DS. BAG-1: a multi-functional pro-survival molecule. Int J Biochem Cell Biol. 2005 Feb;37(2):251-9

Krajewska M, Turner BC, Shabaik A, Krajewski S, Reed JC. Expression of BAG-1 protein correlates with aggressive behavior of prostate cancers. Prostate. 2006 Jun 1;66(8):801-10

Takeno S, Noguchi T, Takahashi Y, Fumoto S, Shibata T, Kawahara K. Assessment of clinical outcome in patients with esophageal squamous cell carcinoma using TNM classification score and molecular biological classification. Ann Surg Oncol. 2007 Apr;14(4):1431-8

Clemo NK, Collard TJ, Southern SL, Edwards KD, Moorghen M, Packham G, Hague A, Paraskeva C, Williams AC. BAG-1 is up-regulated in colorectal tumour progression and promotes colorectal tumour cell survival through increased NF-kappaB activity. Carcinogenesis. 2008 Apr;29(4):849-57

Nadler Y, Camp RL, Giltnane JM, Moeder C, Rimm DL, Kluger HM, Kluger Y. Expression patterns and prognostic value of Bag-1 and Bcl-2 in breast cancer. Breast Cancer Res. 2008;10(2):R35

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