

Gene Section

Review

BAG3 (Bcl-2 associated athanogene 3)

Morena d'Avenia, Luana Guerriero, Alessandra Rosati, Maria Caterina Turco

Department of Pharmaceutical and Biomedical Sciences (FARMABIOMED), University of Salerno, Fisciano (SA), Italy (MdA, LG, AR, MCT)

Published in Atlas Database: February 2014

Online updated version : <http://AtlasGeneticsOncology.org/Genes/BAG3ID43160ch10q26.html>
DOI: 10.4267/2042/54128

This article is an update of :

Leone A, Rosati A, Ammirante M, Turco MC. BAG3 (Bcl-2 associated athanogene 3). *Atlas Genet Cytogenet Oncol Haematol* 2008;12(2):87-88.

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2014 *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

Abstract

Bcl2-associated athanogene 3 (BAG3) protein is a member of BAG family of co-chaperones that interacts with the ATPase domain of the heat shock protein (Hsp) 70 through BAG domain. BAG3 is induced by stressful stimuli, mainly through the activity of heat shock factor 1 on bag3 gene promoter.

In addition to the BAG domain, BAG3 contains also a WW domain and a proline-rich (PXXP) repeat, that mediate binding to partners different from Hsp70.

These multifaceted interactions underlie BAG3 ability to modulate major biological processes, that is, apoptosis, development, cytoskeleton

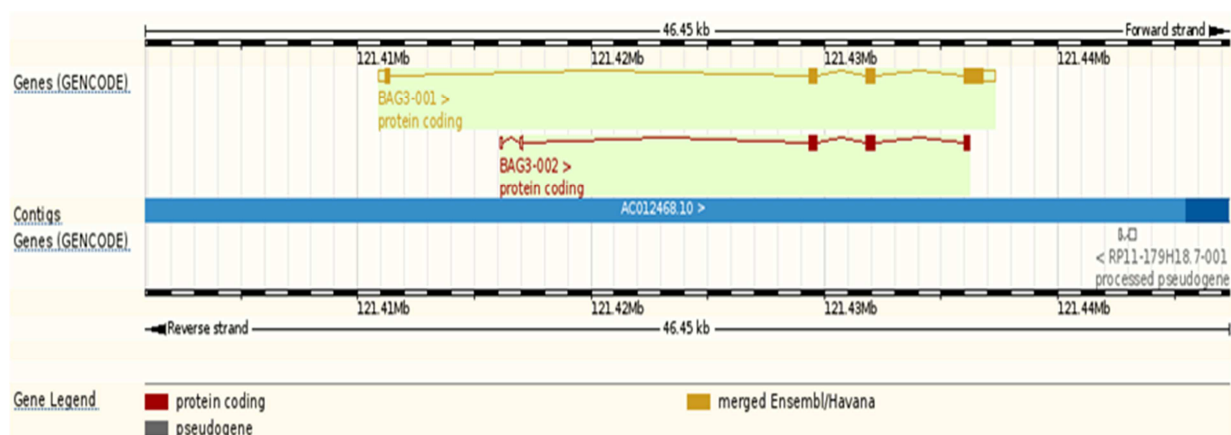
organization and autophagy, thereby mediating cell adaptive responses to stressful stimuli. In normal cells, BAG3 is constitutively present in a very few cell types, including cardiomyocytes and skeletal muscle cells, in which the protein appears to contribute to cell resistance to mechanical stress. BAG3 is expressed also in several tumor types where it sustains cell survival, resistance to therapy, and/or motility and metastatization (Rosati et al., 2011).

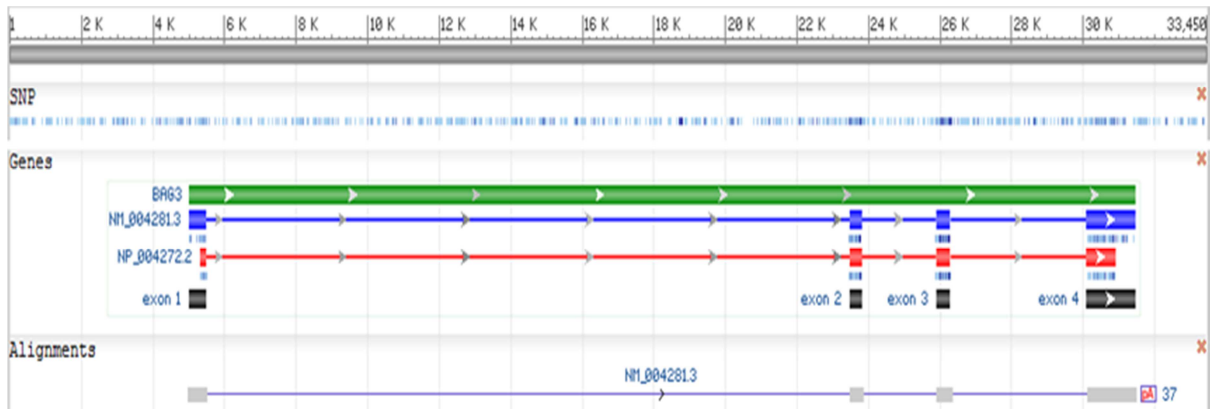
Identity

Other names: BAG-3, BIS, CAIR-1, MFM6

HGNC (Hugo): BAG3

Location: 10q26.11





Green: gene; blue: transcript mRNA; red: coding sequence; black: exons.

DNA/RNA

Description

The gene encompasses 33450 bases, 4 exons.

Transcription

2608 nucleotides mRNA.

Pseudogene

Chromosome 10: 121442639-121443335 reverse strand. Name: RP11-179H18.7-001; transcript: ENST00000441872.

Chromosome 10: 121435973-121436791 forward strand. Name: PGOHUM00000238940; parent protein: ENSP00000358081; parent gene: ENSG00000151929.

Variant: OTTHUMT00000050663. Exons: 5. Transcript length: 1146 bps. Translation length: 325 residues.

Protein

Description

575 amino acids. 74 kDa protein, belonging to the

evolutionary conserved family of BAG domain-containing proteins.

Expression

Under physiological conditions, BAG3 expression appears to be restricted to few cell types including skeletal muscle cells and cardiomyocytes (Hishiya et al., 2010; De Marco et al., 2011; De Marco et al., 2013).

Its expression, however, can be induced in different normal cell types (leukocytes, epithelial, glial and retinal cells) by a variety of stressors, such as oxidants, high temperature, serum deprivation, and it is thought to contribute to stress resistance (Rosati et al., 2007; Pagliuca et al., 2003; Rosati et al., 2009; Ammirante et al., 2010). In contrast to normal cells, BAG3 expression is abundant in several primary tumors or tumor cell lines, where it is thought to give a survival advantage (Rosati et al., 2011). Among those melanoma cells, pancreatic adenocarcinoma cells, colon cancer, liver cancer, T-lymph Jurkat cancer, leukemias, kidney HEK-293, Lung A549, prostate cancer LnCap, cervix cancer Hela, bone cancer U20S, breast cancer cells MCF7.



Localisation

BAG3 is mainly a cytoplasmatic protein, particularly concentrated in the rough endoplasmic reticulum; a slightly different molecular weight, a doublet form or a nuclear localisation can be observed in some cell types and/or following cell exposure to stressors. BAG3 protein is also released from stressed cardiomyocytes and Pancreatic Adeno Carcinoma cells (PDAC) and can be detected in sera of patients with chronic heart failure (HF) or PDAC (De Marco et al., 2013; Falco et al., 2013), as well as in cells supernatants.

Function

Through its BAG domain, BAG3 protein binds with high affinity to the ATPase domain of Hsc70 and regulates its chaperone activity in a Hip-modulated manner; through its PXXP region, BAG3 binds to the SH3 domain of PLC-gamma and forms an epidermal growth factor (EGF)-regulated ternary complex; the proline-rich repeat appears to be involved in regulating cell adhesion and migration, through an indirect effect on focal adhesion kinase (FAK) and its downstream partners; BAG3 knockout mice develop a fulminant myopathy; downmodulation of BAG3 protein levels enhance cell apoptotic response to several inducers, while hyperexpression protects cells from apoptosis. BAG3 levels increase during myoblast differentiation, suggesting that its biological role is relevant for differentiated myocytes and not for immature cells. This is in agreement with the observation that BAG3 deletion causes a lethal cardiomyopathy not in embryos, but in postnatal mice. BAG3 mutations may cause abnormal Z-disc assembly and sensitization to apoptosis in cultured cardiomyocytes. More recently it has been shown that BAG3 is essential for homeostasis of mechanically stressed cells. BAG3 is in fact an important component of the chaperone-assisted autophagy (CASA) pathway leading to selective lysosomal degradation of unfolded proteins. In muscle cells the CASA machinery is located at the Z-disk and appears to be essential for disposal of unfolded mechano-sensors and cytoskeleton proteins resulting from mechanical tension. Impairment of the CASA machinery results in z-disk disruption in contracting muscles (Ulbricht et al., 2013; Ulbricht and Höhfeld, 2013).

Homology

Other members of BAG family.

Mutations

Note

Several reports associate BAG3 mutations with myopathy. A mutated form of BAG3, i.e. heterozygous Pro209Leu, causes childhood

cardiomyopathy and a severe and progressive muscle weakness (Selcen et al., 2009). Non-synonymous BAG3 SNPs or others truncated BAG3 forms were reported to correlate with familiar dilated cardiomyopathy (Villard et al., 2011) and stress-cardiomyopathy also known as Takotsubo cardiomyopathy (Citro et al., 2013). Finally, two heterozygous BAG3 gene mutations, which cause abnormal Z-disc assembly and increased sensitivity to apoptosis in cultured cardiomyocytes, were identified in patients with familial DCM (Arimura et al., 2011).

Implicated in

B-chronic lymphocytic leukaemia

Disease

Expression of BAG3 gene in leukaemic cell samples from a study on 24 B-CLL-affected patients was detected by RT-PCR and immunofluorescence. Downmodulation of its levels by antisense ODNs resulted in enhancing cytochrome c release, caspase 3 activation and appearance of hypodiploid elements in response to fludarabine (Romano et al., 2003).

Childhood acute lymphoblastic leukemia

Disease

Expression of BAG3 gene in leukaemic cell samples from a study on 11 ALL- affected patients was detected by immunofluorescence. Downmodulation of its levels by antisense ODNs resulted in stimulating caspase 3 activity and enhancing by more than 100% the percentages of apoptotic elements in primary cultures, either untreated or incubated with cytosine arabinoside (Romano et al., 2003).

Thyroid carcinomas

Disease

BAG3 was expressed in human thyroid carcinoma cell lines; small interfering RNA-mediated downmodulation of its levels significantly enhanced NPA cell apoptotic response to TRAIL. The protein was not detectable in 19 of 20 specimens of normal thyroid or goiters, whereas 54 of 56 analyzed carcinomas (15 follicular carcinomas, 28 papillary carcinomas, and 13 anaplastic carcinomas) were clearly positive for BAG3 expression (Li et al., 2013).

Pancreatic adenocarcinomas

Disease

BAG3 protein is expressed in PDACs, but is not expressed in the surrounding nonneoplastic tissue. Survival is significantly shorter in patients with high BAG3 expression than in those with low BAG3 expression. Furthermore, BAG3 expression

in PDAC-derived cell lines protects from apoptosis and confers resistance to gemcitabine, offering a partial explanation for the survival data. Indeed BAG3 has a relevant role in PDAC biology, and BAG3 expression level might be a potential marker for prediction of patient outcome (Falco et al., 2013; Rosati et al., 2012).

Colorectal carcinomas

Disease

Bag3 is distinctly expressed in Colo201, Colo205, DLD-1, HCT-15, HCT-116, HT-29, KM-12, SW480, SW620, and WiDr at both mRNA and protein levels.

Carcinoma shows stronger Bag-3 expression than adjacent NNM by IHC and Western blot. Metastatic carcinoma more frequently expressed Bag-3 mRNA in lymph node and liver than in primary carcinoma. Immunohistochemically, Bag-3 expression is seen to gradually decrease from carcinoma, adenoma to NNM.

There is a positive correlation between Bag-3 expression and TNM staging and GRP94 expression, but no relationship to patient age or sex, tumor size, depth of invasion, lymphatic or venous invasion, lymph node metastasis, differentiation or prognosis of colorectal carcinomas. Aberrant Bag-3 expression might be involved in colorectal adenoma-adenocarcinoma sequence and subsequent progression (Yang et al., 2013).

References

- Pagliuca MG, Lerose R, Cigliano S, Leone A. Regulation by heavy metals and temperature of the human BAG-3 gene, a modulator of Hsp70 activity. *FEBS Lett.* 2003 Apr 24;541(1-3):11-5
- Romano MF, Festa M, Petrella A, Rosati A, Pascale M, Bisogni R, Poggi V, Kohn EC, Venuta S, Turco MC, Leone A. BAG3 protein regulates cell survival in childhood acute lymphoblastic leukemia cells. *Cancer Biol Ther.* 2003 Sep-Oct;2(5):508-10
- Rosati A, Leone A, Del Valle L, Amini S, Khalili K, Turco MC. Evidence for BAG3 modulation of HIV-1 gene transcription. *J Cell Physiol.* 2007 Mar;210(3):676-83
- Rosati A, Di Salle E, Luberto L, Quinto I, Scala G, Turco MC, Pascale M. Identification of a Btk-BAG3 complex induced by oxidative stress. *Leukemia.* 2009 Apr;23(4):823-4
- Selcen D, Muntoni F, Burton BK, Pegoraro E, Sewry C, Bite AV, Engel AG. Mutation in BAG3 causes severe dominant childhood muscular dystrophy. *Ann Neurol.* 2009 Jan;65(1):83-9
- Ammirante M, Rosati A, Arra C, Basile A, Falco A, Festa M, Pascale M, d'Avenia M, Marzullo L, Belisario MA, De Marco M, Barbieri A, Giudice A, Chiappetta G, Vuttariello E, Monaco M, Bonelli P, Salvatore G, Di Benedetto M, Deshmane SL, Khalili K, Turco MC, Leone A. IKK(gamma) protein is a target of BAG3 regulatory activity in human tumor growth. *Proc Natl Acad Sci U S A.* 2010 Apr 20;107(16):7497-502
- Hishiya A, Kitazawa T, Takayama S. BAG3 and Hsc70 interact with actin capping protein CapZ to maintain myofibrillar integrity under mechanical stress. *Circ Res.* 2010 Nov 12;107(10):1220-31
- Arimura T, Ishikawa T, Nunoda S, Kawai S, Kimura A. Dilated cardiomyopathy-associated BAG3 mutations impair Z-disc assembly and enhance sensitivity to apoptosis in cardiomyocytes. *Hum Mutat.* 2011 Dec;32(12):1481-91
- De Marco M, Turco MC, Rosati A. BAG3 protein is induced during cardiomyoblast differentiation and modulates myogenin expression. *Cell Cycle.* 2011 Mar 1;10(5):850-2
- Rosati A, Graziano V, De Laurenzi V, Pascale M, Turco MC. BAG3: a multifaceted protein that regulates major cell pathways. *Cell Death Dis.* 2011 Apr 7;2:e141
- Villard E, Perret C, Gary F, Proust C, Dilanian G, Hengstenberg C, Ruppert V, Arbustini E, Wichter T, Germain M, Dubourg O, Tavazzi L, Aumont MC, DeGroot P, Fauchier L, Trochu JN, Gibelin P, Aupetit JF, Stark K, Erdmann J, Hetzer R, Roberts AM, Barton PJ, Regitz-Zagrosek V, Aslam U, Duboscq-Bidot L, Meyborg M, Maisch B, Madeira H, Waldenström A, Galve E, Cleland JG, Dorent R, Roizes G, Zeller T, Blankenberg S, Goodall AH, Cook S, Tregouet DA, Tiret L, Isnard R, Komajda M, Charron P, Cambien F. A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy. *Eur Heart J.* 2011 May;32(9):1065-76
- Rosati A, Bersani S, Tavano F, Dalla Pozza E, De Marco M, Palmieri M, De Laurenzi V, Franco R, Scognamiglio G, Palaia R, Fontana A, di Sebastiano P, Donadelli M, Dando I, Medema JP, Dijk F, Welling L, di Mola FF, Pezzilli R, Turco MC, Scarpa A. Expression of the antiapoptotic protein BAG3 is a feature of pancreatic adenocarcinoma and its overexpression is associated with poorer survival. *Am J Pathol.* 2012 Nov;181(5):1524-9
- Citro R, d'Avenia M, De Marco M, Giudice R, Mirra M, Ravera A, Silverio A, Farina R, Silvestri F, Gravina P, Villa F, Puca AA, De Windt L, De Laurenzi V, Bossone E, Turco MC, Piscione F. Polymorphisms of the antiapoptotic protein bag3 may play a role in the pathogenesis of takotsubo cardiomyopathy. *Int J Cardiol.* 2013 Sep 30;168(2):1663-5
- De Marco M, Falco A, Basile A, Rosati A, Festa M, d'Avenia M, Pascale M, Dal Piaz F, Bisogni R, Barcaroli D, Coppola G, Piscione F, Gigantino A, Citro R, De Rosa R, Vitulano G, Virtuoso N, Manganelli F, Palermo E, Siano F, Rosato G, Hahne M, Tiberti C, De Laurenzi V, Turco MC. Detection of soluble BAG3 and anti-BAG3 antibodies in patients with chronic heart failure. *Cell Death Dis.* 2013 Feb 14;4:e495
- Falco A, Rosati A, Festa M, Basile A, De Marco M, d'Avenia M, Pascale M, Dal Piaz F, Tavano F, Di Mola FF, di Sebastiano P, Berloco PB, Nudo F, Caraglia M, Febbraro A, Barcaroli D, Scarpa A, Pezzilli R, De Laurenzi V, Turco MC. BAG3 is a novel serum biomarker for pancreatic adenocarcinomas. *Am J Gastroenterol.* 2013 Jul;108(7):1178-80
- Li N, Du ZX, Zong ZH, Liu BQ, Li C, Zhang Q, Wang HQ. PKC δ -mediated phosphorylation of BAG3 at Ser187 site induces epithelial-mesenchymal transition and enhances invasiveness in thyroid cancer FRO cells. *Oncogene.* 2013 Sep 19;32(38):4539-48
- Ulbricht A, Eppler FJ, Tapia VE, van der Ven PF, Hampe N, Hersch N, Vakeel P, Stadel D, Haas A, Saftig P, Behrends C, Fürst DO, Volkmer R, Hoffmann B, Kolanus W, Höfeld J. Cellular mechanotransduction relies on

tension-induced and chaperone-assisted autophagy. *Curr Biol*. 2013 Mar 4;23(5):430-5

Ulbricht A, Höhfeld J. Tension-induced autophagy: may the chaperone be with you. *Autophagy*. 2013 Jun 1;9(6):920-2

Yang X, Tian Z, Gou WF, Takahashi H, Yu M, Xing YN, Takano Y, Zheng HC. Bag-3 expression is involved in

pathogenesis and progression of colorectal carcinomas. *Histol Histopathol*. 2013 Sep;28(9):1147-56

This article should be referenced as such:

d'Avenia M, Guerriero L, Rosati A, Turco MC. BAG3 (Bcl-2 associated athanogene 3). *Atlas Genet Cytogenet Oncol Haematol*. 2014; 18(10):704-708.
