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 (soddl), 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., 1999).

<table>
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<th>Interacting protein</th>
<th>Involvement of BAG-1</th>
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<tr>
<td>Hsp70 / Hsc70 molecular chaperones</td>
<td>BAG-1 acts as co-chaperone to regulate ATPase activity of heat shock proteins and inhibit chaperone activity</td>
<td>(Takayama et al., 1997)</td>
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<td>Raf-1 kinase</td>
<td>Binds to catalytic domain of Raf-1 kinase and activates it independent of Ras</td>
<td>(Song et al., 2001, Wang et al., 1998, Gott et al. 2005)</td>
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<td>Glucocorticoid receptor (GCR) and other nuclear hormone receptors</td>
<td>BAG-1L interacts with and enhances androgen receptor function. BAG-1M negatively regulates GCR- and hormone-induced apoptosis</td>
<td>(Fiosch et al., 1998, Kullmann et al., 1998, Zeiner and Oehring, 1995.)</td>
</tr>
<tr>
<td>E3 ubiquitin ligases e.g. Slit1 and CHIP</td>
<td>BAG-1 negatively regulates the growth inhibitory ubiquitin ligase, Ski-1. BAG-1 accepts protein substrates from molecular chaperones and presents them to CHIP for ubiquitylation - cooperation to influence protein quality control</td>
<td>(Demasi et al., 2001, Matovzova et al., 1998)</td>
</tr>
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<td>Proteasome</td>
<td>BAG-1 acts as a link between proteasome and chaperones, Hsp70 / Hsc70</td>
<td>(Luders et al., 2000)</td>
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<tr>
<td>HGF and PDGF receptors</td>
<td>BAG-1 binds to receptor tail via C-terminal domain and enhances HGF- and PDGF-mediated protection against apoptosis</td>
<td>(Bardelli et al., 1996)</td>
</tr>
<tr>
<td>DNA</td>
<td>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</td>
<td>(Niyaz et al., 2001, Zeiner et al., 1996)</td>
</tr>
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<td>Fb</td>
<td>Role for Fb in maintaining nuclear localisation of BAG-1: Nuclear BAG-1 inhibits apoptosis in adenomas to increase survival of colorectal tumour cells in vivo</td>
<td>(Ahol et al., 2003, Clemo et al., 2005, Barnes et al., 2005)</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Association with BAG-1 enhances anti-apoptotic signalling of Bcl-2</td>
<td>(Takayama et al., 1995)</td>
</tr>
</tbody>
</table>

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 (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


This article should be referenced as such: