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BAG-1 in carcinogenesis

Adam Sharp, Simon J. Crabb, Paul A. Townsend, Ramsey I. Cutress, Matthew Brimmell, Xiu-hong Wang and Graham Packham

BAG-1 is a multifunctional protein that exists as several differentially localised and functionally distinct isoforms. BAG-1 isoforms interact with a diverse array of molecular targets and regulate a wide range of cellular processes, including proliferation, survival, transcription, apoptosis, metastasis and motility. The BAG domain of BAG-1 interacts with chaperone molecules and this is considered important for many BAG-1 functions. The ability of BAG-1 to regulate such a wide variety of cellular processes suggests it might play an important role in many cancer types. For example, regulation of nuclear hormone receptor function and susceptibility to apoptosis might have a major impact on cancer development, progression and response to therapy. There is also increasing evidence that BAG-1 expression is altered in a variety of human malignancies relative to normal cells, and with further understanding of BAG-1 function it might become a powerful prognostic/predictive marker in human cancer. This review describes the structure and function of BAG-1 isoforms and the potential clinical implications of their expression in tumour cells.

BAG-1 (Bcl-2-associated athanogene 1) was discovered in 1995 by two independent research groups searching for novel interaction partners for the anti-apoptotic Bcl-2 protein and the activated glucocorticoid receptor (GR), respectively (Refs 1, 2). Since then, BAG-1 has been demonstrated to exist as multiple isoforms, and to interact with a wide range of cellular targets (Refs 3, 4, 5, 6). Many of the activities of BAG-1 might depend on its ability to bind to and modulate the activity of the heat shock proteins Hsc70 and Hsp70. Via its binding partners,

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BAG-1 modulates growth control pathways important for both normal and malignant cells, such as transcription and apoptosis. Given the ability of BAG-1 to regulate these diverse pathways, there is considerable interest in studying the function and expression of BAG-1 in cancers. Here we describe the expression and function of BAG-1 in cancer cells and the potential clinical implications.

BAG-1 structure and function

BAG-1 isoforms

Cells express multiple BAG-1 isoforms, which can be differentially localised in the cell and functionally distinct. There are three major BAG-1 isoforms in human cells: BAG-1S (~36 kDa), BAG-1M (~46 kDa) and BAG-1L (~50 kDa) (Refs 7, 8, 9). A fourth isoform of ~29 kDa has also been reported, but it is generally expressed at relatively low levels (Ref. 9). Although protein diversity is most frequently generated through alternative splicing, where a single gene gives rise to multiple mRNAs each encoding distinct proteins, these BAG-1 isoforms are generated via alternative translation initiation from a single mRNA (Fig. 1). Translation of the largest BAG-1 isoform, BAG-1L, is initiated from an upstream CUG codon; by contrast, translation of BAG-1S and BAG-1M is initiated at the first and second in-frame AUG codons, respectively. [Although most translation initiates at AUG codons, there is a small but increasing number of proteins for which CUG-initiated isoforms have been described (Refs 10, 11). Many of these proteins, such as c-Myc, play a critical role in cell growth control.] Since these initiation codons are all in the same translational reading frame, BAG-1 isoforms have a common C-terminus and the longer isoforms have unique N-terminal extensions (Fig. 1). The sequence of an alternatively spliced human BAG-1 mRNA, potentially giving rise to additional BAG-1 protein isoforms, has been deposited in the public databases (GenBank accession number AAD25045), but the significance of this remains unclear. Various nomenclatures have been used in the literature to describe BAG-1 proteins, including HAP (heat-shock-associating protein) and RAP (receptor-associating protein) (see Table 1 in Ref. 3).

BAG-1S is generally the most abundant isoform expressed in cells; however, relative expression of the isoforms varies between

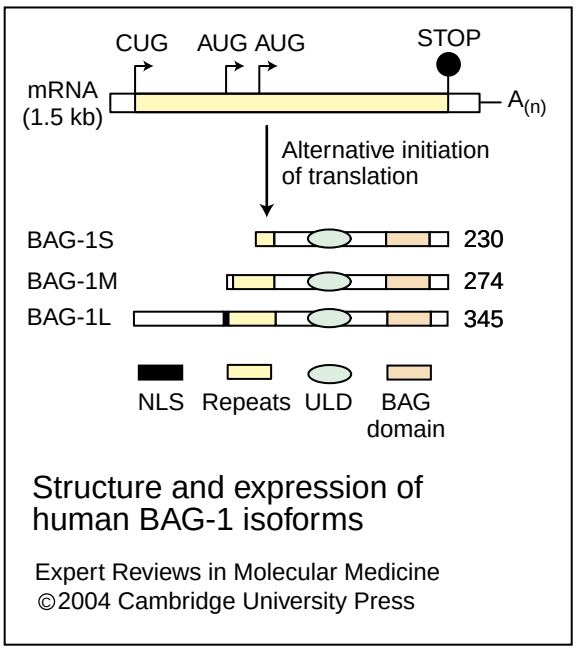

Figure 1. Structure and expression of human BAG-1 isoforms. Three major BAG-1 protein isoforms are generated by alternative initiation of translation from a single BAG-1 mRNA. Whereas translation of BAG-1S and BAG-1M initiates at AUG codons, BAG-1L translation initiates at a noncanonical CUG codon. The lower part of the figure shows the domain structures of the BAG-1 isoforms; the number of amino acid residues of each isoform is shown on the right. BAG-1M translation initiates within the nuclear localisation sequence (NLS) – it is not clear whether the portion retained in BAG-1M constitutes a fully functional NLS. ULD, ubiquitin-like domain.

different cells (Refs 3, 4, 5, 6). Most proteins are generated by cap-dependent translation, where ribosomes access the mature mRNA at the 5' cap structure and scan the mRNA molecule until they encounter a translation initiation codon (Ref. 12). Therefore, the relative abundance of BAG-1S is somewhat surprising, since BAG-1S translation is initiated from what is essentially an internal AUG codon; a scanning ribosome entering at the 5' cap structure of the BAG-1 mRNA would have to disregard several potential translation initiation codons (including those for BAG-1L and BAG-1M) before reaching this site. The abundant expression of BAG-1S might be explained by the presence of an internal ribosome entry sequence (IRES) upstream of the AUG codon. The IRES sequence allows the translation machinery to enter the body of the mRNA molecule to initiate expression of

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BAG-1S (Ref. 13). By contrast to translation of BAG-1S, BAG-1L translation is thought to be mediated by cap-dependent scanning.

The cellular localisation of proteins can play a pivotal role in controlling function, and BAG-1 isoforms can be detected in different subcellular compartments. Variations have been described, but BAG-1L is predominantly a nuclear protein, whereas BAG-1S is predominantly found in the cytoplasm and BAG-1M is found in both the nucleus and cytoplasm (Refs 7, 8, 9, 14). Nuclear localisation of BAG-1L might be due to the presence of a nuclear localisation sequence (NLS) in the N-terminus of this isoform that is absent from BAG-1S and BAG-1M (Refs 7, 15) (Fig. 1). However, it is important to recognise that the localisation of BAG-1 isoforms can be regulated: cellular stress can cause relocalisation of BAG-1S and BAG-1M to the nucleus (Refs 16, 17). BAG-1L has also been demonstrated to locate within the nucleus to nucleoli – the site of rRNA synthesis – but the significance of this remains unclear (Refs 14, 18).

BAG-1 domains and binding partners

In addition to the NLS of BAG-1L, BAG-1 isoforms contain various other functional domains (Fig. 1). At the C-terminus of all BAG-1 isoforms lies a domain of approximately 70 amino acids, termed the BAG domain, which mediates interaction of BAG-1 with the Hsc70 and Hsp70 heat shock proteins (Refs 19, 20). Hsc70 and Hsp70 are molecular chaperones that have multiple functions, including the energy-dependent refolding of newly synthesised or denatured, unfolded proteins (Ref. 21). Hsc70 and Hsp70 comprise a peptide-binding domain that interacts with substrate proteins and an ATPase domain; cycles of ATP hydrolysis and nucleotide exchange provide energy for the refolding reactions. BAG-1 interacts with the ATPase domain of Hsc70/Hsp70, leaving the peptide-binding domain of the chaperone molecule free to bind substrate. The BAG domain comprises a bundle of three α-helices. Two antiparallel α-helices are directly involved in the interaction with Hsc70 and Hsp70 (Refs 19, 20); the third helix might play a role in stabilising this structure and mediating additional protein–protein interactions (Fig. 2). BAG-1 isoforms have been shown to regulate the refolding of denatured substrate proteins by Hsp70 and Hsc70 both negatively and positively (Refs 3, 4, 22). The interaction of BAG-1 with the chaperone molecules is considered critical for at least some BAG-1 functions, since mutation of specific amino acid residues important for binding to chaperone proteins abrogates BAG-1 function (Refs 16, 20, 23, 24).

The BAG domain is also important for interaction with Raf-1. Raf-1 is a serine/threonine protein kinase that plays an important role in transmitting cell growth control signals from the cell surface to the nucleus (Ref. 25). Raf-1 activates mitogen-activated protein (MAP) kinases, resulting in a cascade of phosphorylation events ultimately controlling the function of specific transcription factors. Interestingly, Raf-1 is normally activated by Ras but it seems that BAG-1 can provide an alternative mechanism of activation for Raf-1 that is independent of Ras (Refs 26, 27).

All three isoforms of BAG-1 contain a ubiquitin-like domain (ULD) (Ref. 1). Ubiquitin

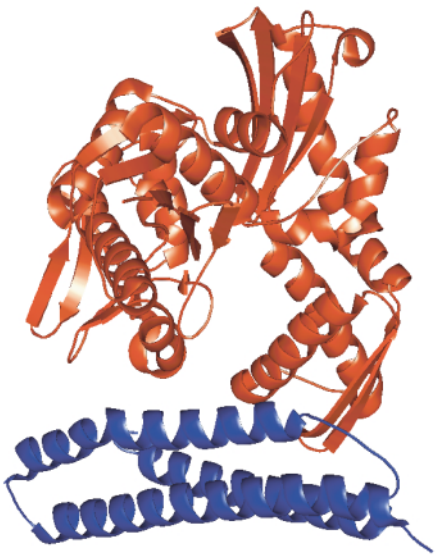

Figure 2. The BAG-1–Hsc70 interaction. The figure shows the interaction of the BAG-1 BAG domain (blue) with the ATPase domain of Hsc70 (red). Note that the molecules interact with a 1:1 stoichiometry and that the BAG domain comprises a tightly packed bundle of three α-helices that makes multiple contacts with the bi-lobed ATPase domain of Hsc70. The figure was drawn from coordinates in Ref. 19.

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is a ubiquitous 76 amino acid residue protein that is covalently attached to proteins to form chains of multiple ubiquitin moieties (Ref. 28). This molecular 'flag' then targets these proteins for degradation by the proteasome, the major nonlysosomal proteolytic complex in cells. Although the ULD of BAG-1 is structurally related to ubiquitin, BAG-1 is not covalently attached to substrate proteins and is generally a stable protein (but see also Ref. 29). By contrast, the BAG-1 ULD appears to be important for complex formation of BAG-1 with the proteasome (Refs 30, 31). Therefore, BAG-1 can simultaneously bind to Hsc70/Hsp70 and the proteasome, and coordinating the function of chaperones and the proteasome might be important for some BAG-1 functions (Ref. 30).

BAG-1 proteins contain variable numbers of repeats rich in acidic amino acid residues. BAG-1S contains three copies, whereas BAG-1M and -1L contain nine copies. The role of the repeats remains elusive; there are conflicting data on the importance of these domains for regulation of the GR (Refs 23, 24). Moreover, overlapping repeat elements create a consensus recognition site for phosphorylation by creatine kinase 2, and although BAG-1M is phosphorylated, the significance of this phosphorylation and the effects on cellular function are not understood (Ref. 32).

In addition to the binding partners described above (Hsc70, Hsp70, Raf-1 and the proteasome), a wide range of additional BAG-1 interaction partners has been described (Table 1). These include nuclear hormone receptors (NHRs), proteins important for cell survival and cell cycle control (Bcl-2 and the retinoblastoma tumour susceptibility protein, Rb), regulators of translation (GADD34), cell-surface receptors (platelet-derived growth factor and hepatocyte growth factor receptors) and growth factors (heparin-binding epidermal-growth-factor-like growth factor), and enzymes involved in catalysing ubiquitylation reactions (Siah and CHIP) (Refs 3, 4, 6, 33, 34). BAG-1M and BAG-1L also bind to DNA nonspecifically and this might contribute to the effects of BAG-1 on survival and NHR functions (Refs 17, 24, 35) (Table 1). Thus, via these diverse binding partners, BAG-1 has the potential to impact on multiple functions important for normal and malignant cell growth, including apoptosis, proliferation, transcription,

Table 1. BAG-1 interaction partners[a]

Binding partner role	Binding partner	Refs
Growth factor signalling molecule	Heparin-binding EGF-like growth factor	69
	Hepatocyte growth factor receptor	70
	Platelet-derived growth factor receptor	70
	Raf-1	26, 27
Transcription modulator	Nuclear hormone receptors	See Table 2 for details
	Retinoblastoma susceptibility protein	33
Translation regulator	GADD34	34
Chaperone	Hsc70 and Hsp70	19, 20
Protein degradation effector	Siah	40
	CHIP	42
	Proteasome	30
Apoptosis modulator	Bcl-2	1

[a] Note that it is not clear to what extent many of the interactions are direct; Hsc70/Hsp70 might mediate interaction of BAG-1 with some partner proteins. The functional significance of many of these interactions also remains unclear.
Abbreviations: Bcl-2, B-cell CLL (chronic lymphocytic leukaemia/lymphoma)-2; CHIP, C-terminus of Hsc70-interacting protein; EGF, epidermal growth factor; GADD34, growth arrest and DNA-damage-inducible protein; Hsc70, constitutive heat shock protein 70; Hsp70, inducible heat shock protein 70; Siah, human homologue of the *Drosophila* seven in absentia (Sina).

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metastasis and cell motility. However, it is important to note that the biological significance of many of these interactions remains unclear. Moreover, since the interaction of BAG-1 with Hsc70/Hsp70 leaves the peptide-binding domain of the chaperone free, it is possible that some of these interactions are indirect.

BAG-1 and cell survival

Apoptosis is a genetically controlled cell suicide pathway important for deleting unwanted cells during development and for maintaining normal tissue homeostasis. Alterations in susceptibility to cell death can contribute to disease and, in particular, resistance to apoptosis is a hallmark of essentially all malignant cells (Ref. 36). A key reason for the interest in BAG-1 in cancer is its ability to suppress apoptosis induced by a wide range of stimuli in a variety of cell types (see Table 3 in Ref. 3). For example, BAG-1 suppresses apoptosis induced by cell-surface death receptors, withdrawal of growth factors, cytotoxic anticancer drugs and radiation. Where studied, all BAG-1 isoforms appear to possess anti-apoptotic activity. The precise mechanism by which BAG-1 promotes cell survival is unclear, but it is possible to suggest many potential mechanisms. For example, suppression of apoptosis might be mediated by stimulation of Raf-1-mediated survival signalling (Refs 26, 27), regulation of the anti-apoptotic Bcl-2 protein (Ref. 1) or control of NHR function (Ref. 5). However, data linking specific molecular targets to suppression of apoptosis in different systems are generally lacking.

The mechanisms by which BAG-1 promotes cell survival have perhaps been best studied in breast cancer cells. Overexpression of BAG-1 isoforms in human breast cancer cells interferes with apoptosis and growth inhibition induced by cellular stress (heat shock, chemotherapeutics, radiation or hypoxia) (Ref. 16) or by serum withdrawal (Ref. 37). The prosurvival activity of BAG-1 was dependent on amino acid residues in the BAG domain required for interaction with Hsc70/Hsp70 (Ref. 16). Although the requirement for chaperone binding would perhaps suggest that BAG-1 suppresses apoptosis by enhancing refolding of denatured proteins in cells, BAG-1 generally appears to inhibit protein refolding (Refs 22, 38). Inhibition of stress-induced growth inhibition in breast cancer cells also required the BAG-1 ULD, involved in binding to the proteasome (Ref. 16), consistent with the idea that BAG-1 might function (at least to suppress stress-induced apoptosis) by linking the chaperone system and the proteasome (Ref. 30). In addition to its role in protein refolding, Hsc70 is required for ubiquitin-dependent degradation of certain protein substrates in vitro (Ref. 39), and BAG-1 also interacts with Siah and CHIP (Refs 31, 40, 41, 42), which are E3 ligase enzymes that catalyse one of the final steps in a cascade of reactions leading to transfer of ubiquitin moieties to substrate proteins destined for destruction. Taken together, these observations suggest a model for BAG-1 function whereby BAG-1 might promote cell survival by simultaneously modulating chaperone activity and acting as a scaffold to build a proteolytic complex containing chaperones, ubiquitylating enzymes and degradation machinery to control protein turnover.

BAG-1 and NHRs

A second key target of BAG-1 isoforms are the NHRs (Refs 3, 5). NHRs are ligand-dependent transcription factors. Ligand binding promotes either homo- or heterodimerisation, allowing these receptors to bind to specific DNA sequences in the promoter regions of target genes, to increase or repress transcription. NHR target genes are involved in a wide range of cellular processes, controlling cell growth, motility, cell division, apoptosis, differentiation and morphology (Ref. 5). Interestingly, heat shock proteins are known to play an important role in controlling the activity of NHRs, for example by facilitating conformational changes following ligand binding, and this therefore provides a potential mechanism by which BAG-1 might modulate NHR activity (Ref. 5). Since the initial identification of BAG-1 in a screen for GR-binding proteins (Ref. 2), BAG-1 has been shown to interact with and modulate other NHRs, including the oestrogen receptors (ERs), androgen receptor (AR), retinoic acid receptor (RAR), thyroid receptor, progesterone receptor and vitamin D3 receptor (VDR) (Table 2). Here we focus on the effects of BAG-1 on two NHRs that play a critical role in the development and response to therapy of cancers: the ERs and AR.

Oestrogens are critical mitogenic factors for normal breast epithelium, premalignant states such as ductal carcinoma in situ (DCIS) and a major proportion of breast cancers, promoting both proliferation and cell survival (Ref. 43).

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Anti-oestrogens, including the selective oestrogen receptor modulators (SERMs) such as tamoxifen, which interfere with ER function, and the aromatase inhibitors, which interfere with the synthesis of oestrogens, are key therapeutic agents for hormone-dependent breast cancers (Ref. 44). The action of oestrogens is mediated by two receptors: ERα, and the more recently identified ERβ. BAG-1 interacts with ERα and ERβ (Refs 35, 45) both in vitro and in intact cells, and stimulates the ability of the receptors to increase target gene expression in response to oestrogens (Ref. 45). In vitro, the interaction of BAG-1M with ERα is dependent on the BAG domain and appears to be mediated by heat shock proteins (Ref. 46). By contrast, in intact cells, only BAG-1L, but not BAG-1S or BAG-1M, interacts with ERα and ERβ and stimulates the transcriptional activity of these receptors (Ref. 45). It is likely that the specific activity of BAG-1L in intact cells is dependent on its preferential nuclear localisation. However, targeting BAG-1S to the nucleus with a heterologous NLS does not confer on BAG-1S the ability to modulate ERα function. This might in some part be due to the observation that BAG-1L is present in the nucleoli of the nucleus whereas BAG-1S tagged with a NLS is not (Ref. 45). Alternatively, additional functional domains present in BAG-1L and absent from BAG-1S might be required. Further preclinical evidence regarding the relevance of BAG-1 to ER functional modulation by SERMs and aromatase inhibitors would be of great interest.

Androgens stimulate proliferation and survival of normal prostate epithelium and most prostate cancers, and the AR is similarly stimulated by BAG-1L but not other BAG-1 isoforms (Refs 15, 47). Overexpression of BAG-1L also reduced the inhibitory effect of cyproterone acetate, an anti-androgen routinely used in prostate cancer therapy, on AR-mediated transcription. Specific mutations within the BAG domain that prevent association with chaperones interfered with the ability of BAG-1L to regulate the AR (Ref. 20). Similar to the case for ERα, nuclear localisation per se is not sufficient to confer AR-regulatory activity on BAG-1S, and other sequences in the N-terminus of BAG-1L are thought to be required (Refs 15, 48).

Although the binding and modulation of chaperones presents a potential mechanism by which BAG-1 might regulate the function of molecules such as the ERα and AR, it is unlikely that a single mechanism of action underlies the effects of BAG-1 on all NHRs (Table 2). First, specific isoforms modulate particular NHRs; for example, whereas only BAG-1L impacts on ER and AR activity, both BAG-1M and BAG-1L regulate GR function (Ref. 23), and BAG-1S is sufficient to modulate RAR-mediated transcription (Ref. 49). Second, BAG-1 can negatively or positively regulate NHR function; for example, in contrast to its stimulatory effect on the ER and AR, BAG-1L inhibits the transcriptional regulation and growth-repressing activity of the GR (Ref. 23). Third, BAG-1 has been demonstrated in separate studies both to inhibit ligand binding to the GR (Ref. 50) and to inhibit the binding of the GR to DNA-response elements (Ref. 23). These differing effects might not be mutually exclusive and might be explained by variable cellular levels of BAG-1 isoforms (which might be deranged in malignancy). Finally, although available data are generally consistent with a role for chaperones in BAG-1 modulation of NHR activity, the BAG domain is not required for modulation of the RAR (Ref. 49), suggesting an alternative mechanism independent of

Table 2. Effect of BAG-1 on nuclear hormone receptors

Receptor	Effect of BAG-1 overexpression	Active BAG-1 isoforms	Refs
Androgen receptor	Activates	BAG-1L (not BAG-1S/M)	15, 47
Vitamin D receptor	Activates/inhibits	BAG-1L (not BAG-1S/M)	51, 52
Glucocorticoid receptor	Inhibits	BAG-1M/L	23
Retinoic acid receptor	Inhibits	BAG-1S	49
Thyroid hormone receptor	Inhibits	BAG-1S	49
Oestrogen receptor (α and β)	Activates	BAG-1L (not BAG-1S/M)	45

Accession information: DOI: 10.1017/S1462399404007537; Vol. 6; Issue 7; 22 March 2004

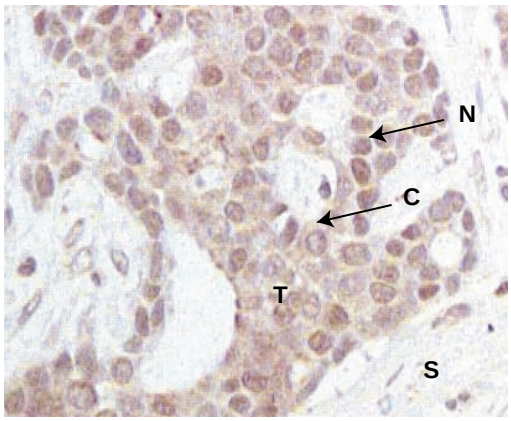
Hsc70/Hsp70. In some cases, nonspecific DNA binding of BAG-1 isoforms might also play a role (Ref. 24). In addition to the potential mechanistic differences described above, the effects of BAG-1 might be cell-type dependent: in human embryonal kidney 293T and COS7 cells, BAG-1 stimulates VDR-dependent transcription (Ref. 51), whereas in U87 glioblastoma cells stably transfected with BAG-1L, binding to the VDR response element and growth suppression induced by vitamin D3 were inhibited (Ref. 52).

BAG-1 expression in human cancer

Given the ability of BAG-1 to modulate critical cell growth control pathways, such as apoptosis and NHR function, there has been extensive interest in studying the expression and clinical significance of BAG-1 in cancer. Although some consistent findings are emerging, there are important inconsistencies and contradictions between the published studies (Ref. 53). Moreover, some of the observations appear paradoxical in light of the results of the laboratory-based experiments described above. Further work is required to understand the clinical significance of BAG-1 expression.

Many of the studies describing the clinical significance of BAG-1 expression have focused on breast cancer. BAG-1 is expressed in both normal and malignant breast epithelium, although levels appear to be increased in malignant cells. High levels of BAG-1 expression have also been detected in DCIS, an early pre-invasive state with a high risk of progression to overt malignancy. This suggests that changes in BAG-1 expression might be important at an early stage in carcinogenesis and tumour development (Refs 14, 54). An example of BAG-1 expression in an invasive breast cancer is shown in Figure 3. As expected, BAG-1 can be detected in both the cytoplasm and nucleus, at least in a subset of cancer specimens.

Five large immunohistochemical studies have related BAG-1 expression with clinicopathological and outcome variables in breast cancer in retrospectively analysed patient cohorts (Refs 45, 54, 55, 56, 57). Consistent correlations with clinicopathological parameters have been described, such as an association between lower tumour grade and increased nuclear BAG-1 expression (Refs 45, 55, 56). Three studies have shown BAG-1 expression to be correlated with breast cancer survival rates (Refs 45, 54, 55).



BAG-1 expression in an invasive human breast cancer

Expert Reviews in Molecular Medicine

Figure 3. BAG-1 expression in an invasive human breast cancer. The image shows the expression of BAG-1 in the cytoplasm (C) and nucleus (N) of breast cancer cells, whereas the stroma (S) surrounding the tumour (T) is largely negative for BAG-1 expression. BAG-1 was detected by immunohistochemistry using an antibody that recognises all BAG-1 isoforms (as in Ref. 45). The binding of the antibody is detected by an enzymatic reaction that produces a coloured product.

However, the results of these studies are conflicting (both negative and positive correlations with survival have been described) and, similar to the correlation of increased expression of an anti-apoptotic protein with lower tumour grade, they may appear surprising. Discussion regarding potential mechanisms to explain this apparent paradox is given in the section 'BAG-1 as a predictive/prognostic factor', but this area does require further investigation. First, Turner et al. (Ref. 54) found BAG-1 overexpression correlated with improved distant-metastasis-free and overall survival in a group of patients with early-stage breast cancer treated with variable modalities, which was maintained in multivariate analysis. [Univariate analysis tests whether a variable, such as BAG-1 expression, is correlated with survival. By contrast, multivariate analysis tests whether BAG-1 expression is correlated with survival independently of other variables considered (which might include tumour stage, or size, as examples). Disease

Accession information: DOI: 10.1017/S1462399404007537; Vol. 6; Issue 7; 22 March 2004

markers that maintain their predictive power in multivariate analyses are particularly useful, since they might provide valuable information as to likely outcome that cannot be provided by any other markers.] Importantly in this study, improved survival for patients who overexpressed BAG-1 was maintained in a subset who were axillary-lymph-node-negative, the most important independent marker of outcome in early breast cancer. By complete contrast, however, Tang et al. (Ref. 55) demonstrated that BAG-1 expression was associated with a significantly shorter disease-free and overall survival (i.e. expression was associated with a poor outcome) in multivariate analysis but not after univariate analysis in a cohort of patients with mixed pathological and clinical characteristics (the study included both early-stage and metastatic breast cancer patients treated with variable modalities).

We have reasoned that the impact of BAG-1 expression on outcome might depend on the treatment modality (Ref. 53). For example, cytoplasmic BAG-1S might play an important role in determining response to chemotherapy (via its effects on apoptosis), whereas nuclear BAG-1L might play an important role in determining responses to hormonal therapies such as tamoxifen or the aromatase inhibitors (via effects on ERα). Therefore, differences in patient characteristics between studies might be part of the reason for the discrepancies reported. Unfortunately, detailed patient information is lacking in several of the currently published studies. Therefore, in the third of the studies that show a correlation of BAG-1 expression to survival outcomes we decided to study the impact of BAG-1 in a relatively homogenous patient cohort, where all women had early-stage breast cancer and were treated with surgery followed by hormonal therapy but not chemotherapy. In this cohort, we demonstrated that increased nuclear (but not cytoplasmic) BAG-1 expression correlated with a significantly increased overall survival in univariate analysis. It is possible that this paradoxical correlation reflects the ability of BAG-1L to directly modulate the activity of the ER (as discussed in the section 'BAG-1 as a predictive/prognostic factor') (Ref. 45).

Although studied in most detail in breast cancer, BAG-1 expression has been shown to be altered and to correlate with clinicopathological outcome measures in several other malignancies, which are summarised in Table 3 (Refs 58, 59, 60, 61, 62). As with the data regarding breast cancer, there is difficulty in interpreting some of these studies because of the variability of retrospective data collection, therapeutic intervention and immunohistochemical data analysis. However, taken together, there is a body of evidence demonstrating that BAG-1 expression is altered in range of malignancies and this can correlate with clinical parameters and patient outcome. The impact of BAG-1 on survival (i.e. good versus poor prognosis) and the significance of subcellular distribution (i.e. nuclear versus cytoplasmic) appear to differ both between patient groups and tumour types. Broadly, one can say that nuclear BAG-1 overexpression seems to correlate with poor outcome in several carcinomas, including those of the oesophagus, bowel, and head and neck, as well as chronic lymphocytic leukaemia (CLL), but that cytoplasmic BAG-1 expression appears to improve outcome in non-small-cell lung cancer.

Clinical implications

There are now extensive preclinical data showing the ability of BAG-1 to regulate multiple cell growth control pathways, suggesting that it might have important clinical implications. In this section, we focus on how these biological effects might impact on cancer cell growth, progression and response to therapy.

Development and progression of cancer

BAG-1 might play multiple roles in the development of malignancies. In breast cancer cells, for example, BAG-1 overexpression suppresses stress-induced apoptosis induced by hypoxia (Ref. 16), and thus BAG-1 might allow malignant cells to survive in the poorly vascularised environment that characterises many solid tumours. Although most studies have focused on short-term effects of BAG-1 on cell survival, overexpression of BAG-1 also interferes with growth inhibition in long-term clonogenic assays, where the ability of a single cell to survive and subsequently divide to form a colony perhaps containing hundreds or thousands of cells is measured (Ref. 16). Thus, BAG-1 does not simply delay cell death, but can confer a long-term growth advantage, consistent with the idea that BAG-1 can contribute to the development of a cancer clone. Although functional studies in tumour cell lines are largely based on

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Table 3. BAG-1 expression and clinicopathological variables in cancers other than breast cancer[a]

Cancer type	Notes	Ref.
Oesophageal squamous cell carcinoma	Nuclear BAG-1 expression correlates with depth of tumour invasion and shorter overall survival in univariate analysis	58
Colorectal carcinoma	Nuclear BAG-1 expression correlates with presence of distant metastases and decreased overall survival	59
Non-small-cell lung cancer	Overall and cytoplasmic BAG-1 expression correlates with improved overall survival	60
Chronic lymphocytic leukaemia	Increased BAG-1 expression correlates with failure to achieve complete response to chemotherapy	61
Laryngeal squamous cell carcinoma	Nuclear BAG-1 staining correlates with reduced failure-free survival following radical radiotherapy	62
Oral squamous cell carcinoma	BAG-1 expression correlates with presence of nodal metastases and tumour grade	71

[a] For further discussion of BAG-1 expression in breast cancer, see main text.

overexpression experiments, there are also data confirming that endogenous BAG-1 in tumour cells is an important determinant of cell survival. For example, nonfunctional mutants of BAG-1 appear to act as dominant negative proteins, interfering with the function of endogenous BAG-1 (perhaps by sequestering key binding partners) to decrease cell growth in vitro and in mice, and increase sensitivity to cell stress (Refs 16, 37). Decreasing expression of endogenous BAG-1 in activated T cells via antisense oligonucleotides also increases susceptibility to apoptosis (Ref. 63).

In translating the relevance of these preclinical studies, one can point to the growing body of clinical human cancer data describing the relationship of BAG-1 expression and outcome variables discussed in the section 'BAG-1 expression in human cancer'. It is likely that BAG-1 has influence at multiple points in tumour development. For example, high levels of BAG-1 expression have been detected in DCIS, suggesting that BAG-1 might play a role relatively early in the development of breast tumours (Ref. 14). However, there is evidence that BAG-1 might also contribute to the progression of locally invasive tumours to metastatic cancer, possibly by enhancing cell motility or suppressing cell death triggered by detachment from the normal extracellular environment (Refs 64, 65). Consistent with this, several studies have reported BAG-1 expression and tumour progression to be linked (see section 'BAG-1 expression in human cancer').

BAG-1 as a predictive/prognostic factor

Since BAG-1 can interfere with apoptosis and regulate NHR function, its expression in cancer cells might influence and/or predict the effectiveness of anticancer therapies that target these pathways. For example, life-time exposure to oestrogens is a significant risk factor for breast cancer, and this risk might be increased by the sensitising effects of BAG-1L on ERα and ERβ (Ref. 45). This raises the important question as to whether the direct effects of BAG-1 on ER function might alter the response to hormonal therapies such as tamoxifen. Hormone-sensitive breast cancer, compared to hormone-insensitive disease, has a comparatively good prognosis and this might explain, at least in part, why high levels of nuclear BAG-1 are associated with a good prognosis in women with breast cancer treated with antihormonal therapies, which otherwise remains a rather paradoxical observation (Ref. 45). High levels of nuclear BAG-1 might be associated with active ER function, indicating why these tumours are particularly responsive to the effects of antihormonal agents and therefore that such women are destined to have a better survival

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outcome (Ref. 53). BAG-1L also modulates the function of the AR (Refs 15, 47), which plays a critical role in hormone-dependent prostate cancer, and BAG-1L overexpression suppresses the effects of cyproterone acetate in preclinical models. Although BAG-1 is frequently expressed in prostate cancer, it is not known whether BAG-1 alters responses to hormonal interventions such as cyproterone acetate in a clinical setting.

Aside from hormonal therapy, BAG-1 might be a candidate to improve decision making with respect to the use of cytotoxic therapy (chemotherapy). In the study by Turner and colleagues (Ref. 54) increased cytoplasmic BAG-1 immunostaining indicated improved overall and distant-metastasis-free survival in patients with axillary-lymph-node-negative breast cancer. These early-stage patients present a particularly difficult clinical challenge. Thus, BAG-1 might also have clinical utility to stratify such 'low-risk' patients to determine need for potentially toxic adjuvant chemotherapy following surgery.

Conventional chemotherapeutic agents and radiation kill tumour cells via induction of apoptosis, and it is possible that suppression of apoptosis by BAG-1 might also confer resistance to these agents. In tissue culture experiments, BAG-1 confers resistance to radiation and a wide range of mechanistically diverse anticancer drugs. Therefore, it would be of use to know whether BAG-1 expression has potential as a predictive marker for determining likely outcome for treatments such as adjuvant chemotherapy, which have the potential to increase cure rates but are toxic. A single study exists where investigators assessed retrospectively just under half of the biopsy specimens for a randomised Phase III study looking at second-line docetaxel versus methotrexate and 5-fluorouracil in patients with advanced breast cancer (Ref. 57). They were unable to determine a predictive relationship to the therapeutic interventions in this study for any of the apoptosis regulators that they assessed, including BAG-1, and BAG-1 did not correlate with survival in this cohort. However, the study did not specify for subcellular localisation of BAG-1 staining, which is known to be of critical importance. Further data on BAG-1 as a predictive indicator for therapy are therefore required.

BAG-1 as a therapeutic target

It is also worth considering the future potential benefit of targeting BAG-1 directly in cancer cells. Although our understanding of the mechanism(s) of BAG-1 function is still limited, available data are consistent with the idea that protein–protein interactions are essential for BAG-1 function. For example, suppression of stress-induced growth inhibition in breast cancer cells requires amino acid residues important for interaction with chaperones and the proteasome (Ref. 16). Developing small molecules to interfere with protein–protein interactions is especially demanding, but it might be an attractive strategy to inactivate BAG-1 function. Theoretically, ablating BAG-1 function might simultaneously overcome the effects of BAG-1 on suppression of apoptosis and regulation of NHR function, thereby inhibiting two key pathways for the development and resistance to therapy of cancer cells.

Interestingly, both the chaperone family and the proteasome have already been identified as targets of new classes of mechanistic-based anticancer agents. Bortezomib (Velcade, PS-341) is a potent and selective inhibitor of the proteasome, active against a variety of tumour cell types including myeloma, CLL, prostate cancer and pancreatic cancer. It has recently been licensed by the US Food and Drug Administration for treatment of relapsed drug-resistant myeloma (Ref. 66). 17-AAG, a derivative of the ansamycin compound geldanamycin, is a specific inhibitor of Hsp90 and is in early-phase clinical trials (Ref. 67). Thus, interfering with BAG-1 function, which links these exciting target areas, might be of particular interest.

Future research

Although there is increasing evidence to support the hypothesis that BAG-1 plays an important role in determining cell growth and survival in cancer cells, impacting on patient survival, key questions remain to be answered.

How does BAG-1 regulate apoptosis pathways?

BAG-1 physically and functionally links the chaperone, ubiquitylation and proteasome machinery, and data from breast cancer cells suggest that these interactions are important for the prosurvival effects of BAG-1 in these cells (Ref. 16). It will be important to confirm further the validity of this model, and then to determine whether BAG-1 might influence the turnover of denatured proteins per se, or whether BAG-1

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directs specific protein substrates to the proteasome. For example, the degradation of pro-apoptotic/growth-arrest proteins induced following cellular stress would enable cells to continue to proliferate/survive. Thus, these studies might also shed light on the basic control of cell stress responses. It will also be important to determine whether a single mechanism underlies the ability of BAG-1 to suppress apoptosis induced by diverse stimuli in different cell types. As discussed above, a myriad of potential mediators exist that might explain the effects of BAG-1 on apoptosis and it will be important to determine which of these proteins might also play a critical role.

How does BAG-1 modulate NHR function?

It will also be important to delineate the mechanisms by which BAG-1 modulates the function of NHRs. For example, what is the role of chaperones and DNA binding? What features of the larger BAG-1 isoforms lacking in BAG-1S enable them to regulate NHR functions specifically? It seems unlikely that a single mechanism will account for the effects of BAG-1 on different NHRs: are there multiple mechanisms by which BAG-1 functions or does this reflect differences in the way in which individual NHR functions are controlled? A better understanding of how BAG-1 controls NHR function might lead to more-detailed understanding of the mechanisms that control NHRs in general.

Animal models

Most of the data on BAG-1 are derived from overexpression experiments in established cancer cell lines. Notably, the function of both the proteasome and chaperones are frequently altered in tumour cells, and systems should be developed to study BAG-1 function in primary cells with respect to these mechanisms. Also, the results of deletion of the *BAG-1* gene (i.e. knockouts) or its overexpression (i.e. transgenics) will be particularly informative as to the role of endogenous BAG-1 in development, and the effects of elevated BAG-1 on tumourigenesis, in an intact animal.

Small-molecule inhibitors of BAG-1

Although it is too soon to consider BAG-1 as a high-priority target for drug development, the development of small molecules to interfere with BAG-1 function would be a significant advance. One way to develop these agents would be to select for compounds that interfere with protein–protein interactions important for BAG-1 function, although this is a particularly demanding pathway to drug identification. These agents would be useful tools to determine the relative importance of BAG-1 in, for example, cell survival in normal and malignant cells and the role of specific protein–protein interactions of the endogenous BAG-1 protein, in vitro and potentially in mice. Indeed, these might be useful in further validating BAG-1 as a potential target for future drug development.

Clinical expression studies

There are a number of studies suggesting that BAG-1 might have clinical utility as a predictive/prognostic marker in human cancer (as discussed above), and there is now a need for further investigation of larger and more fully defined patient cohorts with improved immunohistochemical techniques to understand more completely the role of BAG-1 in human cancer. Cohorts with increased patient numbers should allow the analysis of BAG-1 in specific clinically relevant subgroups. BAG-1 can target multiple cellular processes and thus its function might differ in patients receiving different anticancer therapies. Prospective study design remains the gold standard for this method of research but the time and cost implications make this problematic.

Analysis of the BAG family

BAG-1 is the prototypical member of related proteins, conserved throughout evolution, all of which contain a C-terminal BAG domain and appear to bind and modulate Hsc70/Hsp70 function (Ref. 4). There are at least six BAG proteins in humans. Some BAG proteins contain a ULD, whereas others have different protein–protein interaction domains. Therefore, the theme that BAG-1 directs chaperone function to specific cellular targets appears to have been adapted through BAG protein evolution, to allow chaperones to modulate other target proteins. Interestingly, other BAG family proteins might also play a role in cancer; for example, BAG-4 is overexpressed in pancreatic cancer (Ref. 68). Understanding the function and interactions of the family as a whole, in both cell growth control and carcinogenesis, will be important.

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Further reading, resources and contacts

The CancerGene and the GeneCards websites contain information on BAG-1 expression, chromosomal localisation, allelic variants and structure, with extensive links to related websites and databases:

http://caroll.vjf.cnrs.fr/cancergene/CG618.html
http://genecards.bcgsc.ca/cgi-bin/carddisp?BAG1&search=bag-1&suff=txt

The Pfam website for the BAG domain describes the homology of the BAG domain with related proteins:

http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF02179

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