



BAG-1 protein prolongs cell survival

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ABSTRACT

BAG-1 (Bcl-2-associated athanogene-1) is a cytoprotective protein that blocks programmed cell death, which may be of paramount importance for human cancerogenesis.

This molecular agent promotes cell survival due to its interaction with Bcl-2 as well as RA-induced decreased level of Bcl-2. To date, BAG-1 expression has been implicated in breast, lung, laryngeal and oral cavity cancers.

It acts cardioprotectively and neuroprotectively whilst increasing the nerve cell survival rate. Its elevated levels accelerate neuronal cell differentiation. Thus its overexpression in brain cells inadvertently protects against brain attack due to its major roles in cell stress induced by hypoxia, radiation and treatment with cytotoxic drugs.

BAG-1 is a potential drug target to reduce the level of brain tissue damage in ischaemic and neurodegenerative disorders.

BAG-1 increases growth factors that aid in liver and blood regeneration (PDGF, HGF).

BAG-1 may represent a significant regulator of cell survival and growth, which contributes enormously to tumorigenesis and resistance to therapy.

Keywords: Bag-1; Coactivator; Nuclear-Targeting, Tumor Cells, Growth Factors

INTRODUCTION

BAG-1 (Bcl-2-associated athanogene-1) is a cytoprotective protein that blocks programmed cell death, which may be of paramount importance for human cancerogenesis. Its coding gene is located on chromosome 9 (9p13.3) that is overexpressed in the heart, retina and peripheral blood mononuclear cells.

On a molecular level, BAG-1 regulates several signaling pathways such as:

- 1) cellular response to heat stress,
- 2) protein processing in endoplasmic reticulum,
- 3) cellular response to stress and

- 4) receptor signaling pathway.

BAG-1 is an anti-apoptotic protein. It binds to bcl-2. It is a multi-functional protein that interacts with a variety of cellular proteins.¹

BAG-1 promotes cell survival due to its interaction with Bcl-2 as well as RA-induced decreased level of Bcl-2. To date, BAG-1 expression has been implicated in breast, lung, laryngeal and oral cavity cancer.²

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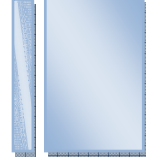
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differentiation. Therefore, its overexpression in brain cells inadvertently protects against brain attack.

Diseases associated with impaired function of BAG-1 coding gene are spindle cell hemangioma and lung cancer. BAG-1 intersperse the molecular pathway related to cellular response to heat stress and androgen receptor signaling pathway. BAG-1 is a potential drug target to reduce the level of brain tissue damage in ischemic and neurodegenerative disorders. Bag-1 can display four different isoforms ranging in size from 29 to 52 kDa. Bag-1L is predominantly a nuclear protein by immunofluorescence microscopy, whilst Bag-1, Bag-1S and Bag-1M are predominantly cytoplasmic.

BAG-1 may play a role in cell stress induced by hypoxia, radiation and treatment with cytotoxic drugs. A specific stress response in eukaryotic cells involves the endoplasmic reticulum (ER), a major storage organelle for calcium and site of synthesis and folding of secretory proteins, cell membrane proteins and lysosomal proteins.

BAG-1 proteins have a role in preventing apoptosis and can also affect transcription either positively or negatively, depending on the cell type and context. BAG-1 increases growth factors that aid in liver and blood regeneration (PDGF, HGF).

BAG-1 is also known as HAP that represents a multifunctional protein. It interacts and affects the activity of various molecular targets. Initially, BAG-1 was identified as a BCL2-binding protein that was involved in the inhibition of apoptosis triggered by staurosporine, Fas or cytotoxic T-lymphocytes in Jurkat cells.

The BAG (bcl-2 associated athanogene) family is comprised of 6 proteins. They act as cochaperons and are involved in protein regulation of proliferation and apoptosis, as well as HSP70, Raf-1, GADD34, bcl-2 and hormone receptors.

BAG molecules are involved in the regulation of survival of cancer cells. They are in the correlation with invasiveness of various tumors. Overexpression

of BAG-1 inhibits trans-RA-induced cancer cell apoptosis and may prevent it.

High levels of BAG-1 protein may contribute to retinoid resistance in certain malignancies. BAG-1 protein levels are elevated in breast and prostate cancers.³

AIM

The purpose of this paper is to evaluate the potential protective roles of BAG-1 in the signaling pathways of the numerous cancer cell biomolecular mechanisms.

BREAST CANCER AND BAG-1

The protein Bcl-2-associated athanogene 1 (BAG-1) is expressed in 3 main isoforms BAG-1S, BAG-1M, and BAG-1L. In addition, it is frequently overexpressed in breast cancer and preinvasive breast disease.⁴

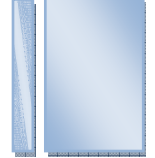
As expression of BAG-1 protein is frequently increased in breast cancer. In certain studies, it has been noted that a certain link might be present between BAG-1 mRNA levels and an overall morbidity and its outcome.

Thus, mRNA was significantly increased in HER2+/ER+ and HER2+/ER- tumors than in other normal breast tissue specimens. The results showed that an overall BAG-1 levels were higher in HER-2 over-expressing cells.

Targeting BAG-1 might therefore constitute a potential therapeutic option for HER2+ breast cancers refractory to trastuzumab.

Consequently, the therapeutic approach may consist of targeting BAG-1 in case of HER2+ breast cancers refractory to trastuzumab. It was shown that a combination of targeted BAG-1 with a selected molecule with a protein-protein interaction inhibitors and HER2 with trastuzumab synergistically lowers the rate of breast cancer cell growth. Such mechanism is followed by the attenuation of protein synthesis as well as induction of G1/s cell cycle arrest along the ERK and AKT pathways.

BAG-1 mRNA is increased in HER2+/ER+ as well as HER2+/ER- breast tumor cells in comparison to



normal breast epithelium, and in HER2+ cell lines, BAG-1 protein expression is elevated. In cases of an increased BAG-1 protein expression, cell viability is promoted by silencing the growth-inhibitory attributes of trastuzumab.

The synergistic effect of BAG-1 and HER-2-targeted therapeutic approach inhibits HER2+ breast cancer cell expansion. BAG-1 appears to be an effective alternative in patients who exhibit de novo resistance to trastuzumab.

It is concluded that increased BAG-1 immunoreactivity represents an independent predictor of outcome especially in node-positive individuals with estrogen receptor (ER) positive breast cancer receiving adjuvant hormonal therapy alone and promotes the predictive value of IHC4 score.⁵

BAG-1 protein levels are increased in some HER2+ breast cancer cell lines, while HER2 gene transfer in MCF7 cells increases expression levels of BAG-1 and its interacting partner Bcl-2.⁶

SIGNALING PROTEINS IN BREAST CARCINOMA

It was noted that bcl-2 was over-expressed in grade 1 and 2 in comparison to grade 3 tumors. Thus, axillary lymph node status represents the most crucial prognostic factors.

In the BAG-1 protein family amongst BAG-1 and BAG-4, known as well as silencer of death domain, SODD and the anti-apoptotic protein bcl-2.⁷

In this study, the therapeutic role of targeting the BAG-1 protein co-chaperone in trastuzumab-responsive or -resistant HER2+ breast cancer cells was documented.

BAG-1 mRNA was significantly elevated in HER2+ breast tumors and predicted overall survival in a multivariate analysis (HR = 0.81; p = 0.022). In a breast cell line panel, BAG-1 protein was increased in HER2+ cells and was required for optimal growth as shown by siRNA knockdown.

Over-expression of BAG-1S in HER2+ SKBR3 cells blocked growth inhibition by trastuzumab, whereas

over-expression of a mutant BAG-1S protein (BAG-1S H3AB), defective in binding HSC70, potentiated the effect of trastuzumab.

BAG-1 has been reported to be a marker of poor survival or improved survival in breast carcinoma, whereas one study failed to find significant association with survival for this molecule.⁸

In contrast, BAG4/SODD expression was significantly related to poor survival in univariate survival analysis, with a trend in multivariate Cox analysis. BAG-4/SODD has not, to the best of our knowledge, been studied in this cancer to date, and our study therefore provides the first data suggesting a prognostic role for this protein in breast carcinoma.

Therefore, targeting BAG-1 mechanisms in combination with anti-HER2 therapy might be of benefit.

Amplification of the human epidermal growth factor receptor 2 (HER2) gene occurs in 15%–30% of breast cancers and results in high levels of HER2 protein expression.

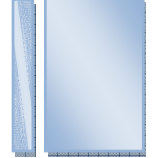
It is followed by an increased HER2 signaling as well as promotion of malignant cell growth and survival.

Thus, patients whose tumors are characterized by HER2 gene amplification and protein overexpression develop a more aggressive type of cancer, which is associated with poor prognosis.⁹

The humanized antibody trastuzumab, which targets the extracellular domain of the HER2 receptor, can prolong overall survival when used as a single agent or when combined with chemotherapy.¹⁰

In the cells, BAG-1 may enhance malignant cell progression characterized by an increased rate of apoptosis. The most important mechanism is chemo-resistance and self-sufficiency in growth factor signals as seen in growth-factor independent survival.

It has been noted that it is possible to limit the rate of breast cancer cells by targeting BAG-1 protein-



protein interactions using synthetic peptides and small molecule components, such as Thioflavin S (Thio-S) and its biologically potent constituent Thio-2.

GASTRIC CANCER MOLECULAR IMPLICATIONS

In gastric carcinogenesis, BAG-1 plays an important role and its abnormal expression and subcellular localization are linked to malignant transformation of gastric epithelial cells.¹¹

BAG-1 may represent a significant regulator of cell survival and growth, which contributes enormously to tumorigenesis and resistance to therapy.¹²

In a certain study it was explored the correlation of BAG-1 in the scenario with clinical characteristics of esophageal cancer.

In this study the main goal was to detect the correlation of BAG-1 linked to the malignant esophageal carcinoma. It has been shown that BAG-1 posses the role in the proliferation, invasion and apoptosis in the esophageal tumor cell line Eca109.

In the aforementioned study the siRNA vector of BAG-2 was integrated and transfected into the Eca109 cell line. Afterwards, fluorescence microscopy was applied to evaluate the transfection efficiency.

The apoptosis rate was assessed by flow cytometry. In case of investigating the Bcl-2 gene, Western blotting is used.

The results showed that BAG-1 expression was significantly decreased in the adjacent non-cancerous esophageal tissue. On the contrary, its expression was increased in the esophageal malignant tissues.

In addition, BAG-1 protein was detected in the cytoplasm and nuclei in greater concentrations. It was shown in the form of yellow or brown staining.

The results showed that the level of BAG-1 in the esophageal carcinoma individuals was not linked to the patient age, gender and tumor location.

Due to BAG-1-siRNA therapy protocol the number of Eca109 cells decreases. Consequently, it leads to the conclusion that BAG-1 is an important factor in cell cycle progression and cell survival.

Upon the transfection of Eca109 cells with BAG-1-siRNA, the cells were lacking their natural proliferation and invasive attributes. Thus, the rate of apoptosis increased significantly.

In case down-regulation of BAG-1 in the Eca109 cell line, the expression of Bcl-2 was significantly decreased.

Apoptosis rate is increased upon transfection. Apoptosis is defined as a cell death due to the interaction of various genes. In the emerging oncologic therapy, there are certain candidates such as apoptosis-related factors.

Down-regulation of the expression of bcl-2 by ribozymes or antisense oligonucleotides results in apoptosis.

BAG-1 is involved in the suppression of the apoptosis in conjunction with bcl-2.

Over-expression of BAG-1 may promote cell motility in human gastric and cervical cancerous cells.¹³

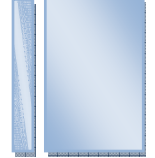
In certain studies, BAG-1 has been shown to be highly expressed in esophageal cancer specimen when compared to the normal tissue samples.

Such data indicate that BAG-1 might be linked to invasion and metastasis of esophageal cancer.

LUNG CANCER

In the study of Liu et al. the BAG-1 was knocked down in cancer cell lines A549 and L9981 of respiratory tissue. Consequently, the most notable changes were in expression of apoptosis-related genes and sensitization of A549 and L9981 cells to cisplatin-induced apoptosis.¹⁴

There are certain indications that targeting BAG-1 may be the novel strategy of esophageal carcinoma treatment.



In the setting of a decreased BAG-1 level, the bcl-2 level decreased in the esophageal cancer tissues. If the total concentration of bcl-2 is decreased, the cell apoptosis rate increases significantly. In most cases, such reaction may cause decreased cell proliferation and differentiation rates.

Such mechanism of the BAG-1 effect on esophageal cancer differentiation, invasion and apoptosis. It has been concluded that BAG-1 is linked to the pathogenesis and development of esophageal carcinoma most commonly via bcl-2.

Apoptosis-related factors are candidates for cancer therapy.

Down-regulation of the expression of bcl-2 by ribozymes or antisense oligonucleotides was found to result in apoptosis.¹⁶

Esophageal carcinoma is a malignant digestive tract tumor and is associated with a poor prognosis.

In most cases, esophageal carcinoma exhibits no symptoms until the cancer is at an advanced stage. The overall survival rate still remains low, and less than 20% of patients survive for more than 5 years.¹⁷

Thus, the main mechanism in this study was to explore the expression of BAG-1 in esophageal carcinoma and adjacent normal tissues. RNA interference (RNAi) provides a new approach in the gene functions.¹⁸

This method leads to the down-regulation of BAG-1 expression. The siRNA vector of BAG-1 was constructed and transfected into the Eca109 cell line to down-regulate the expression of BAG-1 and investigated its role in cell proliferation, invasion and the apoptosis of esophageal carcinoma.

HUMAN CITOMEGALOVIRUS AND BAG-1

Bag-1 is up-regulated in a MAPK/ERK-dependent fashion in CMV infected cells. Depletion of Bag-1 suppresses the anti-apoptotic effect of HCMV.

Taken together, these data indicate that Bag-1 up-regulation is required to maintain apoptosis resistance in HCMV infected cells.

Signaling pathways are associated with apoptotic machinery, for example, activation of the MAPK/ERK signaling pathway is associated with increased expression of anti-apoptotic proteins such as the Mcl-1 and Bag-1.¹⁹

Bag-1 includes at least three isoforms, Bag-1S (p36), Bag-1M (p46), and Bag-1L (p50). Cells express Bag-1 isoforms via alternate translation mechanisms from the same mRNA.

Bag-1M can not only bind transcription factors such as CREB, but enhance transcriptional activity of HCMV early gene promoter reported Bag-1 is up-regulated about 4.5-folds in HCMV infected cells at 24 h post-infection.

Bag-1 is up-regulated in a MAPK/ERK-dependent fashion in HCMV infected cells. Depletion of Bag-1 suppresses the anti-apoptotic effect of HCMV. These data indicate that Bag-1 up-regulation is required to maintain apoptosis resistance in HCMV infected cells.

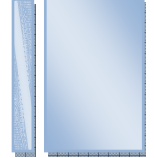
HCMV induces Bag-1 expression by activating the MAPK/ ERK signaling pathway. Bag-1 Expression is required for survival of HCMV infected HEL fibroblasts.

In the present study, we demonstrated that Bag-1 is up-regulated in a MAPK/ERK dependent fashion and is associated with antiapoptotic activity of HCMV.

The expression of Bag-1 was up-regulated at 4 h post-infection in HCMV infected cells, and continued to increase as the infection progressed. Bag-1 is required to prevent apoptosis in HCMV infected cells.

Thus, Bag-1 is associated with the anti-apoptotic activity of Chlamydia trachomatis and herpes simplex virus type 2.²⁰

BAG-1 also interacts with steroid hormone receptors, including the androgen, estrogen and glucocorticoid receptors and the retinoic acid receptor.²¹



BAG-1 influences transcriptional activation and apoptosis induced by steroid hormones and retinoids.²²

BAG-1 binds certain tyrosine kinase growth factor receptors (the hepatocyte growth factor and platelet derived growth factor receptors) and enhances the ability of such receptors to suppress apoptosis.²³

It may can bind and activate the RAF-1 serine/threonine kinase. BAG-1 interacts with the human homologue of *Drosophila* seven in absentia (Siah) and inhibits p53-mediated growth arrest.²⁴

Finally, BAG-1 binds directly and tightly to HSP/HSC70 heat shock proteins and modulates their chaperone activity.²⁵

It is possible that binding to some BAG-1 partners, for example, the estrogen receptor (ER), may be mediated by heat shock proteins, since HSP70 has been identified in ER complexes. Thus, BAG-1 potentially regulates several important cell growth control pathways.

In breast epithelial cancers, BAG-1 may cooperate with relatively low levels of BCL-2 to provide effective protection from apoptosis. BAG-1 may also influence the response of cells to estrogens by direct effects on ER function.

Cells showed a predominantly cytoplasmic or cytoplasmic plus nuclear distribution of BAG-1 staining. BAG-1 expression was also detected in associated benign lesions, including sclerosing adenosis.

Positive effects of p50 BAG-1 isoforms on androgen receptor dependent transcription and negative effects of p46 BAG-1 on glucocorticoid receptor-dependent transcription have been described.²⁶

BAG-1 isoforms may also contribute to or modulate ER responsiveness of breast epithelial cells, possibly via effects on 70-kDa heat shock proteins which are detected in ER complexes.

BAG-1 may also function by directly influencing apoptosis of breast cancer cells in a BCL-2-dependent manner. BCL-2 proteins are thought to function, at least in part, by inserting into membranes and contributing to the formation or regulation of channels.

BAG-1 binds and modulates function of hepatocyte growth factor receptor.²⁷ Over-expression of BAG-1 may therefore contribute to development of some ER-positive breast cancers.

BAG-1 EXPRESSION IN THE NEURONAL TISSUE

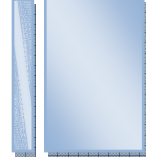
It is known that over-expression of BAG1 results in enhanced tumour cell proliferation, increased cell motility and resistance to apoptosis. Neuroprotective effects were observed in transgenic mice over-expressing BAG1 in neurons, which show a reduction in ischaemic lesion volume following middle cerebral artery occlusion.

BAG1/ mice die during embryogenesis due to failed neurogenesis, suggesting an important role for BAG1 in neuronal differentiation and neuronal survival.²⁸ BAG1 acts in a dual way by inhibiting lesion-induced apoptosis and enhancing axonal growth via suppression of ROCK signaling, making it a promising molecule for neurorestorative approaches in the CNS.²⁹

The over-expression of BAG-1 in well differentiated neuronal cells may significantly reduce ROCK activity by 50% in comparison to wild type cells. Thus, it was shown that BAG-1 over-expression stimulates neuronal outgrowth and regulates growth cone morphology by increasing growth cone region and the number of filopodia.

BAG1-over-expression induces Raf-1 translocation from a membrane-associated localization to the cytoplasm and ROCK2 translocation from the membrane to the perinuclear region respectively. over-expression of BAG1 triggers Raf-1 translocation, recruiting Raf-1 to a functionally different cellular compartment.

BAG1 thus simultaneously exerts cytoprotective effects, increases intrinsic axonal regenerative



potential and reduces inhibitory axonal signaling via ROCK, making it a promising candidate for future therapeutic approaches targeting CNS regeneration *in vivo*.

EFFECTS OF BAG-1 IN BONE DISORDERS

Cartilage is a specific connective tissue occupying about 10% of the total body tissue volume, and serves multiple functions in the developing embryo and in postnatal life.³⁰

This tissue contains a single cell type, the chondrocyte, which is responsible for both synthesis and turnover of the abundant extracellular matrix (ECM). Chondrocytes experience a variety of stresses, such as osmotic stress, oxidative stress and mechanical stress.

Suppression of BAG-1 expression results in decreased chondrocyte growth. Over-expression of BAG-1 results in increased steady-state levels of collagen II under non-stress conditions and down-regulation of collagen II in chondrocytes exposed to ER stressors. BAG-1 is critical for maintaining collagen II expression in chondrocytes.

In case when chondrocytes initially develop ER stress, BAG-1 can protect cells from losing collagen II expression. There has been a decrease in the expression of collagen type II in BAG-1 deficient chondrocytes, while over-expression of collagen II resulted in the increased over-expression of collagen II.

Chondrocytes are the only resident cell in the cartilage, and are critical for maintaining the normal function of cartilage. Cartilage, as an avascular tissue, is exposed to a variety of stressors and ER stress has been linked to impaired chondrocyte function.

BAG-1 is down-regulated at both the transcriptional and protein level in chondrocytes during ER stress induced by both physiological signals and pharmacological agents. BAG-1 might act as a general ER stress modulator and plays an important role in the cellular response to multiple stress stimuli.

BAG-1 is defined as anti-apoptotic protein. It has an ability to bind to Bcl-2, HSP70-family molecular

chaperons and nuclear hormone receptor family members. There are 2 BAG-1 isoforms, BAG-1L and BAG-1S expressed in murine growth plate and articular chondrocytes.

It is known that long bone formation is detected in the growth plate cartilage by the regulated process of endochondral ossification. Subsequently, growth plate chondrocytes differentiate, proliferate, mature and undergo hypertrophy.³¹

Once fully differentiated, hypertrophic chondrocytes participate in mineralization of the cartilaginous matrix and undergo cell death. Bcl-2, an anti-apoptotic molecule, is expressed in the growth plate in late proliferative and prehypertrophic chondrocytes, while expression decreases in hypertrophic chondrocytes.³²

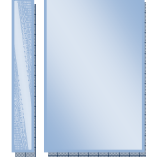
Bag-1 expression is not detected in the cartilaginous anlagen and is down-regulated in the mesenchymal tissues programmed to undergo apoptosis i.e. in the interdigital spaces.³³

BAG-1 knock-out mice are characterized by significant cell death in the embryonic liver, defective hematopoiesis and severe defects in the differentiation and survival of neuronal cells, resulting in their death between E12.5 and E13.5.³⁴

BAG-1 plays an important role in the process of endochondral bone development. BAG-1 functions as an anti-apoptotic defence against heat-shock in chondrocytes. Previous studies have elucidated the anti-apoptotic function of BAG-1 in a number of cell types namely, photoreceptors, cardiac myocytes, neurons and hematopoietic cells.^{35, 36}

Due to aging process, it is of vital importance to maintain an adequate chondrocyte phenotype as well as to prolong the onset of terminal differentiation and apoptosis of chondrocytes.

Bcl-2 is important for maintaining chondrocyte phenotype and delaying terminal differentiation and apoptosis of chondrocytes.



CARTILAGE MATRIX PROTEINS

In case of down-regulated Bcl-2 expression, chondrocytes are hypertrophic and enter the apoptotic mechanism. Thus, the cartilage is being replaced by bone.

Bcl-2 is required to maintain the expression of genes coding for hyaline cartilage matrix proteins.^{37, 38} It has been shown that the anti-apoptotic activity of Bcl-2 is enhanced⁴² by the Bcl-2-binding protein Bag-1.^{39, 40}

Bag-1 proteins also bind to a variety of protein tyrosine kinase receptors and nuclear hormone receptors.⁴¹ It has been noted that BAG-1 is being expressed by a large number of cells, including chondrocytes, both infantile and adult.

Bag-1 is widely expressed by mesenchymal cells in the developing limb, then later down-regulated in the cartilaginous anlagen as well as in the mesenchymal tissues that are programmed to undergo apoptosis, i.e., in the interdigital spaces.⁴⁴

Bag-1 may be a critical regulator of apoptosis and other cellular processes in hyaline cartilage. Once the long bones have reached maturity and the growth plate is no longer active, Bag-1 expression appears to be maintained in the residual population of chondrocytes with no appreciable decrease in aged animals.

The decreased Bag-1 protein level slows chondrocyte growth in vitro. Thus, chondrocytes require an adequate level of Bag-1 protein in order to maintain growth. Bag-1 over-expression in B-cells regulates growth by both increasing proliferation and decreasing apoptosis.⁴⁴ BAG-1 is decreased with aging.⁴⁵ There are decreased expression of collagen type II in BAG1 deficient chondrocytes.

All BAG-1 proteins have a 50 amino acid "BAG domain" near the C-terminus through which BAG-1 binds and activates the Hsp70 family of molecular chaperones.⁴⁶

BAG-1 may play a role in cell stress induced by hypoxia, radiation, and treatment with cytotoxic drugs. BAG-1 proteins have a 50 amino acid "BAG domain" near the C-terminus through which BAG-1

binds and activates the Hsp70 family of molecular chaperones.

All BAG-1 isoforms contain an ubiquitin-like domain (ULD) which serves as an integral sorting signal to mediate the interaction between BAG-1 and the proteasome.⁴⁷

BAG-1 may play a role in moderating cell stress through multiple mechanisms including interaction with Raf-1 kinase and Hsp70, binding to Gadd34 and regulation of protein folding and degradation.

Suppression of BAG-1 expression results in decreased chondrocyte.⁴⁸ Over-expression of BAG-1 results in increased steady-state levels of collagen II under non-stress conditions

In order to establish that the reduced BAG-1 expression was related to ER stress and not simply due to glucose withdrawal, we treated chondrocytes with two other additional ER stress inducers, tunicamycin, and thapsigargin. BAG-1 was down-regulated by 48 h of exposure to all three ER stress inducers compared to control.

BAG-1 might play a role in regulating the expression of cartilage matrix proteins.⁴⁹ These results imply that down-regulation of BAG-1 is an earlier event than loss of Bcl-2 in chondrocytes, and that losing the expression of BAG-1 may sensitize cells to stress-induced apoptosis.

Knocking down BAG-1 by RNAi results in chondrocyte apoptosis. BAG-1 can be regarded as a candidate protein with important functions in cartilage.

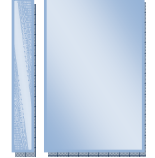
CONCLUSION

Consequently, it is proposed that BAG-1 might play an important role in regulating collagen II expression through both transcriptional regulation and possibly stabilizing the processing of procollagen in the ER. Additionally, BAG-1 may represent a significant regulator of cell survival and growth, which contributes enormously to tumorigenesis and resistance to therapy.

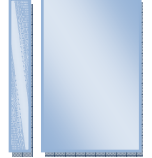


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