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Mini Review

What's in my BAG-1? The Various and Complex Roles of the Co-Chaperone

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Abstract

The Bcl-2-associated anthanogene-1 (BAG-1) is a multifaceted pro-survival co-chaperone possessing critical functions in cellular pathways. In recent years the interaction potential of BAG-1 with the family of Heat Shock Protein 70 (Hsp70) has been documented. The BAG family provides important functions, given its impact on many different disease models, which are described in the recent literature. Neuroprotective BAG-1 effects have been shown in disease models for Parkinson's disease, Huntington's disease and frontotemporal lobar degeneration. But reality is much more complex than theory. Contemporary publications show another side of this co-chaperone: In models for Alzheimer's disease, BAG-1 leads to enhanced tau pathology and thus to a deterioration of the disease. Thinking outside the box, BAG-1 is also an important player in hematology and oncology. Given all the information so far, is BAG-1 friend or foe in terms of neurodegenerative as well as hematological and oncological disease models? What conclusions can be drawn for a potential role for BAG-1 as biomarker or even as therapeutic agent?

Keywords: BAG-1; Chaperone; Tau pathology; Neurology, Hematology, Oncology

Introduction

Have you ever wondered where the name "chaperone" comes from?

Based on the etymology, the word "chaperone" characterizing a woman accompanying and guiding a younger, unmarried lady in public has evolved in the 18th century in France. The French word "chaperone" also means "protector" [1].

Molecular co-chaperones are proteins which regulate chaperones by binding to specific sites leading to activation or inhibition. Thus, they assist proteins for appropriate folding which is the basis for their specific functionality [2]. Molecular chaperones are protectors because they prevent protein aggregation. Aggregation can be caused by intracellular stress like toxic chemicals, inflammation, oxidative stress and even induced by heat-shock [3].

BAG-1 A Molecular Co-chaperone with an Antiapoptotic Function

Bcl-2-associated athanogene-1 (BAG-1) is an antiapoptotic protein. It was the first identified member of the BAG family which consists of six members (BAG 1-6). With exception of BAG-5, all BAG family members share the evolutionary highly conserved BAG domain near the C terminus [4-6].

Through this BAG domain it binds to the ATPase domain of Hsp70, stimulating its ATPase activity [7-9]. BAG-1 contains an N-terminal ubiquitin-like motif and was found to bind to the proteasome and to the E3 ligase carboxyl terminus of Hsc70-interacting protein (CHIP) [6,10,11].

BAG-1 exerts Neuroprotective Functions in Neurological Disease Models

The function of BAG-1 has been investigated in several disease models and its neuroprotectivity is of particular interest as different

outcomes have been shown. In Table 1, studies reporting a neuroprotective effect of the molecular co-chaperone BAG-1 are listed.

Disease model	Reference	Notes
n/a Over-expression of BAG-1 in immortalized neuronal CSM14.1 cell	[12,13]	BAG-1 stimulates neuronal differentiation and fosters neuronal survival
Stroke	[12]	BAG-1 is neuroprotective against stroke induced by middle cerebral artery occlusion in transgenic mice overexpressing BAG-1
Ischemia	[14-16]	BAG-1 overexpression protects against various apoptotic insults
Axonal lesion	[17]	BAG-1 enhances axonal regeneration in mice
Huntington's disease	[9]	BAG-1 overexpression prevents protein aggregation
Parkinson's disease	[18,19]	BAG-1 overexpression prevents protein aggregation

Table 1: The protective role of BAG-1 in neurological disease models.

The neuroprotective role of the co-chaperone even goes far beyond: Götz et al. described in 2005 that BAG-1 is essential for differentiation and survival of hematopoietic and neuronal cells and a lack of this co-chaperone leads to cell death [20]. BAG-1 overexpression leads to deterioration of tau levels and tau aggregates in Alzheimer's disease models [21-22]. In a comparative study, BAG-1 likely acts as protective factor for sporadic frontotemporal lobar degeneration (FTLD), but not for Alzheimer's disease (AD), suggesting its specific role in tau pathology in this disease model [23]. These results were quite surprising and contrasting other disease models in which BAG-1 appears to act as neuroprotective factor.

Is the Dichotomous Role of BAG-1 just found in Tau Pathology Models?

Tau inclusions are classic hallmarks of many neurodegenerative diseases including Alzheimer's disease [24]. Since Elliott et al. and our group investigated the influence of BAG-1 in a model for Alzheimer's disease focusing on tau pathology the question arose whether BAG-1 does lead to deterioration in a disease model where tau is involved [6,21]. Conflicting results could be found in the forementioned study by Venturelli et al. who examined the role of BAG-1 in a comparative study on two models of tau pathology. The protective role could be seen in sporadic FTLD while deteriorating effects had to be documented in AD [23].

BAG-1 influences crucial intracellular pathways in Alzheimer's disease models leading to increased toxicity

Recently it has been shown that there is an increase in levels of the BAG-1M isoform in the hippocampus of AD patients. The co-localization of BAG-1 with both tau tangles and intracellular amyloid underlines the hypothesis that BAG-1 may play a significant role in the pathology of AD [22]. In table 2, the non-protective function of BAG-1 are summarized.

Disease model	Reference	Notes
Alzheimer's disease	[21]	BAG-1 overexpression induced increased tau levels, which is shown to be due to an inhibition of protein degradation
Alzheimer's disease	[23]	BAG-1M is up-regulated in hippocampus of Alzheimer's disease patients and associates with tau and APP proteins
Alzheimer's disease	[6]	BAG-1 stabilizes high molecular tau fragments and enhances the formation of tau aggregates

Table 2: The non-protective role of BAG-1 in Alzheimer's disease models.

Does BAG-1 act like a molecular switch in tau pathology?

Since we work back from effect to cause – what exactly does BAG-1 in tau pathology? In the AD disease model this has not been found yet since its overexpression led to an increased amount of intracellular high molecular tau protein in timeline experiments where the expression of high molecular tau protein could be detected after a few hours and was increasing by time [6]. Thus, this effect of BAG-1 is not based on a certain time point or to a distinct amount of tau protein. This proves that the co-chaperone BAG-1 is not a molecular switch in tau pathology. Given all the published studies on BAG-1-tau interaction, the deterioration of tau pathology is its originally function. Can at al. already pointed out the potential role of BAG-1 in the funneling of chaperone clients into the proteasome for degradation [25].

BAG-1 is a Potential Biomarker for Early AD and Hematological/Oncological diseases

Biomarkers in neurodegenerative diseases are becoming increasingly important for differential diagnosis. Nowadays, the levels of analysis of beta-Amyloid-1-42, Tau, beta-Amyloid-1-42, phospho-Tau, Huntingtin and alpha-Synuclein are analyzed in cerebrospinal fluid and more recently in serum as biomarkers reflecting neuronal damage and loss [26]. The search for early biomarkers not only in AD is still ongoing. Currently, neurofilaments as well as glial markers like the Glial Fibrillary Acid Protein (GFAP) are discussed vividly as indicators for early neuronal loss [27]. The fact that the isoform BAG-1M is up-regulated in the hippocampus of Alzheimer's disease patients [22] could be used for further studies. While BAG-1 has been proven to accelerate tau aggregation from the beginning, the question remains if the co-chaperone can be detected in early AD stages. Investigations of cerebrospinal fluid levels of BAG-1M in pre-dementia and dementia patients would be the next step.

On the contrary, the relevance of BAG-1 as a biomarker has already been established in hematology and oncology [25,28-32]. Xerri et al. already described in 1999, that apoptotic factors like BAG-1 are expressed in human biopsy samples from patients suffering from B cell non-Hodgkin's lymphoma [33]. Deregulation of the molecular co-chaperone BAG-1 also plays an important part in acute myeloid leukemia (AML) where it acts like a sentinel for apoptosis [34]. In B-cell acute lymphoblastic leukemia (B-ALL), BAG-1 isoform expression and intracellular localization were investigated. Interestingly, BAG1 levels decreased during disease remission, and showed a drastic increase at relapse [35].

Kitada et al. made a similar observation as they stated that BAG-1 may provide prognostic information about clinical responses to chemotherapy in previously untreated B-CLL (B-cell chronic lymphocytic leukemia) patients. Higher levels of BAG-1 were associated with failure to achieve complete remission [36]. Besides blood cancer, the role of the co-chaperone BAG-1 has also been investigated in various solid tumors. A special role of BAG-1 as biomarker has been described in breast cancer. Namely, the prognostic value of the BAG-1L isoform specifically binding to the transcriptional activity of estrogen in breast cancer cells has been pointed out in a recent meta-analysis [37]. In a current publication, BAG-1 has additionally been identified as one of five autophagy-related genes that are of substantial prognostic value in breast cancer [38].

Moreover, expression of BAG-1 has been identified in primary and metastatic human melanoma cells. These findings indicate not only a diagnostic but also prognostic potential for BAG-1. Analyzing the HPA database [39] resulted in a higher survival probability of patients showing low BAG-1 expression in their melanoma cells [40]. The interaction of the BAG1S isoform with the HSP70 chaperone complex selectively mediated cell survival in MYC overexpressing osteosarcoma cells. The authors stated the high importance due to the fact that most human cancers show a MYC overexpression indicating a possible treatment option [41]. There is also a role for BAG-1 in lung cancer [42-44]. Silencing of BAG-1 may lead to sensitized cisplatin-induced apoptosis [45]. BAG-1 polymorphisms might even act as important predictive markers for platinum-based chemotherapy efficacy, indicating a crucial role for sensitivity and survival in patients with advanced non-small cell lung cancer (NSCLC) [46]. The effects of apoptotic factors on prostate cancer have been recently explored, Intriguingly, BAG-1 can alter the function of the androgen receptor via nuclear signaling [47]. Further encouraging results for an important role of BAG-1 in solid malignancies are described in the entities renal cancer [48], esophageal cancer [49], colon cancer [50], glioblastoma [51,52] and soft-tissue sarcoma [53].

Discussion

BAG-1 – Even a Potential Treatment Strategy?

Besides its role as biomarker for diagnosis and prognosis in hematological/oncological diseases, its role as a target for potential treatment options has been discussed for neurological indications. The wide landscape with different functions of the co-chaperone BAG-1 are summed up in Figure 1.

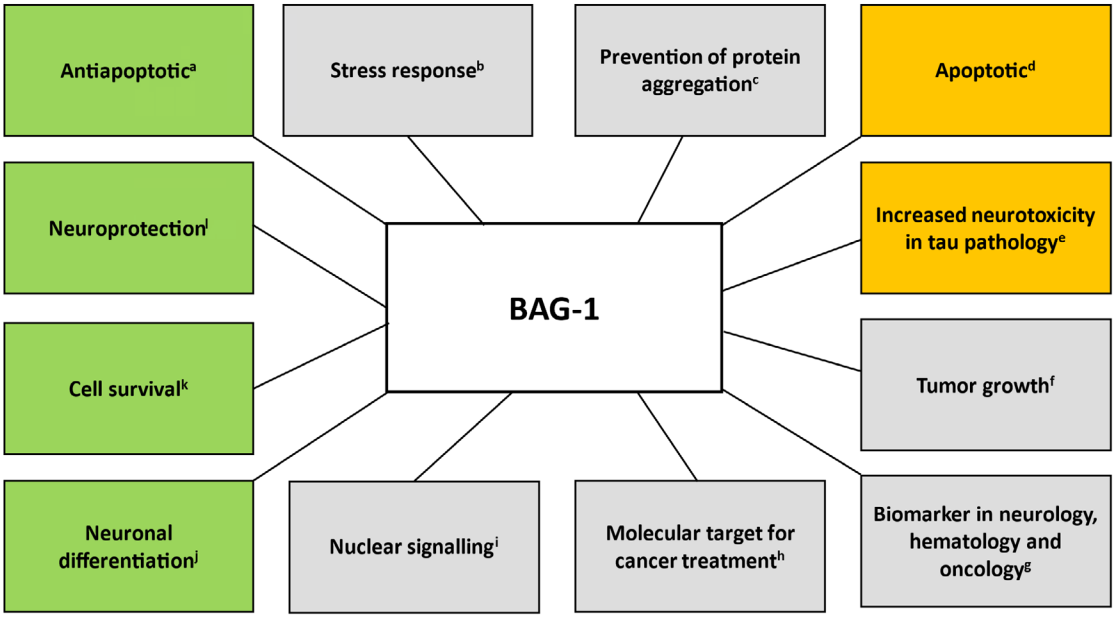

Figure 1: Multiple functions of the co-chaperone BAG-1.

- a: Takayama and Reed 2001; Liman et al. 2005; Hohfeld and jentsch 1997; Takayama et al. 1997; Sroka et al. 2009; Lueders et al. 2000; Demand et al. 2001; Götz et al. 2005.
- b: Garrido et al. 2001.
- c: Garrido et al. 2001; Sroka et al. 2009; Deeg et al. 2010; Kermer et al. 2015.
- d: Xerri et al. 1999; Liu et al. 2020.
- e: Signore et al. 2021; Elliott et al. 2007; Elliott et al. 2009; Venturelli et al. 2011.
- f: D'Arcangelo et al. 2018.
- g: Can et al. 2021; NIH National Instititute of Ageing 2024; Alberti et al. 2003; DaCosta et al. 2010; Mariotto et al. 2020; Sharp et al. 2004; Galmiche et al. 2007; Xerri et al. 1999; Aveic et al. 2011; Kitada et al. 1998; Du et al. 2020.
- h: Götz et al. 2004.
- i: Kuznik et al. 2022.
- j: Kermer et al. 2002; Götz et al. 2008; Götz et al. 2005.
- k: Götz et al. 2005.
- l: Sroka et al. 2009; Kermer et al. 2022; Götz et al. 2008; Takayama et al. 1995; Kermer et al. 2003; Townsend et al. 2003; Planchamp et al. 2008; Deeg et al. 2010; Kermer et al. 2015.

Therapies involving molecular co-chaperones which induce refolding of misfolded proteins have already been established and approved for Gaucher's disease [54] and transthyretin-mediated amyloidosis [55]. Recently, small molecules are attracting increasing attention because they are able to pass the blood-brain barrier and represent novel and promising treatment approaches. Small molecules with chaperone/co-chaperone interactions are currently investigated as therapeutic approach in neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [56,57].

The interaction of BAG-1 with Hsp70 requires an intact C-terminal domain. We showed *in vitro* in an AD model that the deletion mutant BAGΔC was not capable of stabilizing high-molecular tau fragments [6]. Specifically blocking the C-terminal domain of BAG-1 with a small molecule would be an interesting approach. Moreover, it would not restrict the physiological function of Hsp70 and thus the physiological degradation of other proteins. BAG-1 expression is frequently altered in human cancers. Reduced BAG-1 expression specifically targets tumor cells to apoptosis and impairs tumorigenesis suggesting BAG-1 as a potential molecular target for cancer treatment [43].

Conclusion

Let's resume: Is BAG-1 friend or foe?

Further investigations in neurological, hematological and oncological diseases are necessary to answer the question above. Certainly, BAG-1 can be seen as "foe" in the reviewed AD disease models because of increased toxicity. However, supposing BAG-1 as a potential biomarker puts into perspective the term "foe" and should foster further research dealing with BAG-1 as prognostic and therapeutic agent.

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