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CELL SCIENCE AT A GLANCE

BAG3-mediated proteostasis at a glance

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ABSTRACT

Cellular and organismal survival depend on the ability to maintain the proteome, even under conditions that threaten protein integrity. BCL2-associated athanogene 3 (BAG3) is essential for protein homeostasis (proteostasis) in stressed cells. Owing to its multi-domain structure, it engages in diverse processes that are crucial for proteome maintenance. BAG3 promotes the activity of molecular chaperones, sequesters and concentrates misfolded proteins, initiates autophagic disposal, and balances transcription, translation and degradation. In this Cell Science at a Glance article and the accompanying poster, we discuss the functions of this multi-functional proteostasis tool with a focus on mechanical stress protection and describe the importance of BAG3 for human physiology and pathophysiology.

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Introduction

Living organisms maintain their proteome in a dynamic equilibrium by balancing gene expression, protein translation and protein degradation (Balch et al., 2008; Hartl, 2016). Coordinated changes of this equilibrium enable the organism to adapt to abiotic factors and physiological cues. At the same time, the proteome is threatened by mutations, transcriptional and translational errors, and proteotoxic stress (Balchin et al., 2016; Sala et al., 2017). Disturbing the structural integrity of proteins results not only in

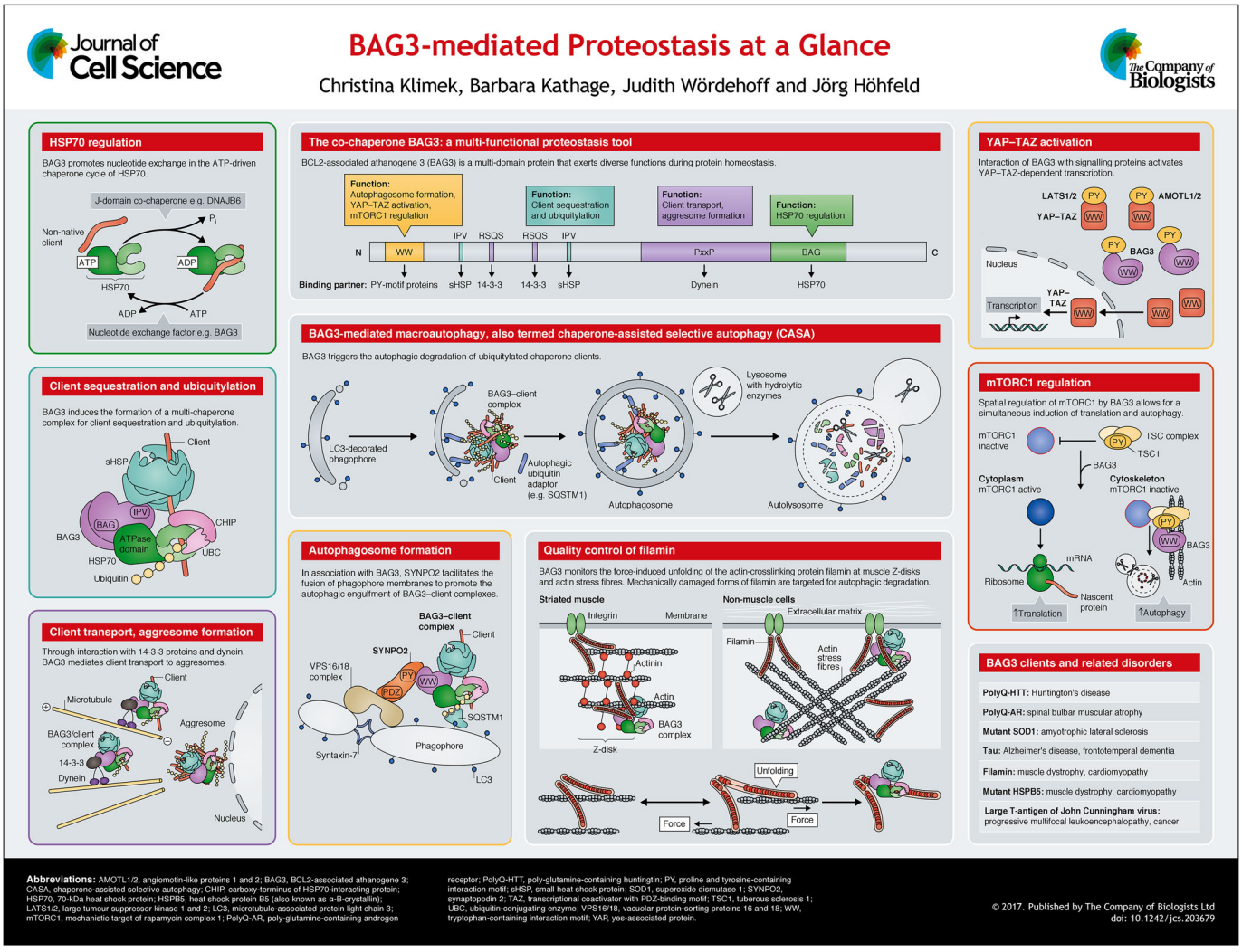

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Table 1. Integration of BAG3 in the cellular chaperone and co-chaperone network

Network protein	Role	References
Chaperone and co-chaperone partners of BAG3		
HSPA8 (HSC70, HSP73)	Constitutive member of the HSP70 family member in the mammalian cytosol and nucleus, cooperates with BAG3 in client processing and autophagic degradation	Rauch and Gestwicki, 2014; Arndt et al., 2010; Gamerdinger et al., 2009
HSPA1A (HSP72)	Main stress-inducible HSP70 family member in the mammalian cytosol and nucleus, cooperates with BAG3 in proteostasis under stress conditions	Rauch and Gestwicki, 2014; Minoia et al., 2014
DNAJA1, DNAJA2, DNAJB1, DNAJB4	Stimulate ATP hydrolysis on HSP70, cooperate with BAG3 in the HSP70 chaperone cycle	Rauch and Gestwicki, 2014
DNAJB6	Stimulates ATP hydrolysis on HSP70, cooperates with BAG3 in muscle proteostasis	Sarparanta et al., 2012
CHIP (STUB1)	HSP70-associated ubiquitin ligase, cooperates with BAG3 during cargo selection for autophagic degradation	Ulbricht et al., 2013; Arndt et al., 2010; Zhang and Qian, 2011; Crippa et al., 2010
Parkin (PRKN)	HSP70-associated ubiquitin ligase, cooperates with BAG3 in mitophagy	Tahrir et al., 2017
HSPB2, HSPB5, HSPB6	Small heat shock proteins that bind with weak or moderate affinity to BAG3	Rauch et al., 2017; Fuchs et al., 2010
HSPB8	Small heat shock protein with high affinity for BAG3, cooperates with BAG3 in muscle proteostasis and stress granule organization	Rauch et al., 2017; Ganassi et al., 2016; Arndt et al., 2010; Fuchs et al., 2010, Carra et al., 2008;
CCT/TRiC	Cytosolic chaperonin, cooperates with BAG3 in actin folding	Fontanella et al., 2010
Competitors of BAG3		
BAG1	Competes with BAG3 for binding to the HSP70 ATPase domain, nucleotide exchange factor (NEF) of HSP70, stimulates proteasomal degradation, changing the cellular BAG1/BAG3 ratio provides a switch between chaperone-assisted proteasomal and autophagic degradation	Rauch and Gestwicki, 2014; Minoia et al., 2014; Gamerdinger et al., 2009; Sondermann et al., 2001; Lüders et al., 2000
BAG2	Competitive binding to the HSP70 ATPase domain, NEF, inhibits HSP70-assisted protein degradation	Rauch and Gestwicki, 2014; Arndt et al., 2005:
BAG4	Competitive binding to the HSP70 ATPase domain, NEF, regulates apoptotic cell death and participates in P-body organization	Taipale et al., 2014; Briknarová et al., 2002
BAG5	Competitive binding to the HSP70 ATPase domain, NEF, inhibits HSP70-assisted protein degradation	Kalia et al., 2011; Briknarová et al., 2002
HSPBP1	Competitive binding to the HSP70 ATPase domain, NEF, inhibits HSP70-assisted degradation	Alberti et al., 2004
HSP105 (HSPH1), APG-1 (HSPA4L) and APG-2 (HSPA4)	members of the HSP110 chaperone family, competitive binding to the HSP70 ATPase domain, NEF, prevent client aggregation and promote refolding	Rauch and Gestwicki, 2014;
HIP (ST13)	Competitive binding to the HSP70 ATPase domain, antagonizes NEF activity, stabilizes the ADP-bound state of HSP70 to promote client binding	Höhfeld et al., 1995; Kanelakis et al., 2000

the loss of individual functional entities, but can also generally impair cellular and organismal health. Misfolded polypeptides often sequester other essential proteins into aggregates, thereby causing severe pathology as observed in many neurodegenerative diseases (Olzscha et al., 2011; Woerner et al., 2016). Consequently, all organisms have protein quality control systems, which recognize non-native proteins and facilitate protein folding or – if the damage is terminal – mediate protein degradation. Molecular chaperones and their regulating co-chaperones are key players in these quality control systems (Balchin et al., 2016). They bind non-native proteins, prevent aggregation and promote folding, whenever possible. Moreover, driven by specialized co-chaperones, some chaperones cooperate with degradation machineries to initiate the disposal of damaged proteins (Kettern et al., 2010). Here, we discuss the importance of the co-chaperone BCL2-associated athanogene 3 (BAG3) for protein homeostasis in mammalian cells and tissues.

BAG3 promotes chaperone activity

BAG3 is closely integrated in the cellular chaperone network, in which competition and cooperation among co-chaperones is essential for the formation of functionally distinct chaperone complexes (Alberti et al., 2004; Arndt et al., 2005; Fontanella et al., 2010; Höhfeld et al., 1995; Kalia et al., 2011; Kanelakis et al., 2000; Kettern et al., 2010; Lüders et al., 2000; Rauch and Gestwicki, 2014; Taipale et al., 2014) (Table 1). BAG3 belongs to a family of co-chaperones that possess a BAG domain for binding to the N-terminal ATPase domain of 70 kDa heat shock proteins (HSP70s) (Bracher and Verghese, 2015; Briknarová et al., 2002; Takayama et al., 1999) (see poster). HSP70s are highly versatile chaperone proteins that recognize non-native proteins through an ATP-regulated transient association with exposed hydrophobic regions (Kityk et al., 2015; Rüdiger et al., 1997). BAG domain co-chaperones operate as nucleotide exchange factors (NEFs) of HSP70 to promote client release and to accelerate the chaperone cycle together with J-domain co-chaperones, such as DNAJB6 (Bracher and Verghese, 2015; Brehmer et al., 2001; Kityk et al., 2015; Rauch and Gestwicki, 2014; Sarparanta et al., 2012; Sondermann et al., 2001). Importantly, BAG3 exerts its HSP70-regulating activity within multi-component chaperone complexes (Arndt et al., 2010; Carra et al., 2008; Fontanella et al., 2010; Rauch et al., 2017) (see poster). Two IPV motifs mediate binding of BAG3 to small heat shock proteins (sHSPs), such as HSPB6 and HSPB8 (Carra et al., 2008; Fuchs et al., 2010; Morelli et al., 2017). sHSPs form oligomeric assemblies, which sequester misfolded proteins in

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a state that allows refolding or further processing (Haslbeck et al., 2005; Ungelenk et al., 2016; Żwirowski et al., 2017). The interaction of sHSPs with BAG3 provides the means to couple their holding function with the folding activity of the versatile HSP70s (Arndt et al., 2010; Crippa et al., 2010; Rauch et al., 2017). Recent work illustrates the importance of this coupling for stress recovery by showing that BAG3 stimulates the cooperation between HSPB8 and HSP70 during the disassembly of stress granules (Ganassi et al., 2016).

BAG3 facilitates aggresome formation

The concentration and sequestration of misfolded proteins represents an important cellular defence strategy against the toxic consequences of protein aggregation (Escusa-Toret et al., 2013; Kaganovich et al., 2008; Miller et al., 2015). BAG3 contributes to this sequestration not only through regulation of sHSPs, but also by promoting the intracellular trafficking of misfolded proteins (Gamerdinger et al., 2011; Xu et al., 2013; Zhang and Qian, 2011). Two RSQS motifs and a proline-rich PxxP domain contribute to association of the co-chaperone with the microtubule-motor dynein; this involves 14-3-3 adaptor proteins and appears to be regulated by co-chaperone phosphorylation (Gamerdinger et al., 2011; Xu et al., 2013). Association with the dynein motor enables BAG3 to induce the retrograde transport of HSP70 clients along microtubules to perinuclear sites, so called aggresomes (see poster). The deposition of misfolded conformers in aggresomes minimizes toxic interference with essential cellular processes and promotes efficient aggregate clearance through macroautophagy (Chin et al., 2010; Kawaguchi et al., 2003; Kopito, 2000; Minoia et al., 2014).

BAG3 initiates a macroautophagy pathway

Macroautophagy (hereafter called autophagy) is a pathway for the degradation of surplus or damaged cell components by lysosomal hydrolytic enzymes (Lamb et al., 2013; Yorimitsu and Klionsky, 2005). Cellular content becomes engulfed by double membranes, leading to the formation of autophagosomes, which ultimately fuse with lysosomal vesicles to achieve content degradation. Autophagy was first identified in starving cells as a rather unselective process (Ohsumi, 2014). However, in recent years, more and more selective autophagy pathways have been described, which rely on the specific selection of cargo for autophagic delivery to the lysosome (Khaminets et al., 2016). Selection often involves an initial labelling of cargo with the degradation marker ubiquitin and its subsequent recognition by autophagic ubiquitin adaptors that provide a link to autophagosome precursor membranes, so called phagophores. BAG3 induces such a selective, ubiquitin-dependent autophagy pathway for the disposal of chaperone clients in cooperation with the HSP70-associated ubiquitin ligase CHIP (also known as STUB1) (Arndt et al., 2010; Carra et al., 2008; Gamerdinger et al., 2009; Zhang and Qian, 2011) (see poster). CHIP interacts with the C-terminus of HSP70, which covers the peptide binding site of the chaperone, and cooperates with ubiquitin-conjugating enzymes (UBCs) in the ubiquitylation of HSP70-bound clients (Jiang et al., 2001; Stankiewicz et al., 2010; Zhang et al., 2005, 2015). In this situation, the chaperone HSP70 is turned into a degradation factor. Indeed, CHIP-mediated ubiquitylation has been shown to direct a broad range of HSP70 clients onto diverse degradation pathways (Arndt et al., 2007). Cytosolic clients are usually targeted to the proteasome, a protease complex specialized in the turnover of ubiquitylated proteins (Asano et al., 2015; Esser et al., 2005; Paul et al., 2013; Schmidt and Finley, 2014), whereas plasma membrane proteins are subjected to endocytic uptake and lysosomal degradation following their CHIP-mediated ubiquitylation (Okiyoneda et al., 2010; Tawo et al., 2017). However, when CHIP ubiquitylates clients that are presented by HSP70-BAG3-HSPB8 complexes, their autophagic degradation is favoured (Arndt et al., 2010; Crippa et al., 2010; Zhang and Qian, 2011) (see poster). The reason for this is not completely understood, but efficient recruitment of the autophagic ubiquitin adaptor SQSTM1 (previously known as p62) appears to be a decisive step, which promotes client loading onto phagophore membranes (Carra et al., 2008; Gamerdinger et al., 2009). Of note, other chaperone-associated ubiquitin ligases, such as the quality control ligase parkin (PRKN), may substitute for CHIP during the initiation of autophagy (Imai et al., 2002; Morishima et al., 2008). Indeed, a recent study reveals a cooperation of BAG3 with parkin in the autophagic clearance of damaged mitochondria (Tahrir et al., 2017). It is also important to note that the pathway induced by BAG3 is distinct from chaperone-mediated autophagy (CMA). CMA does not depend on autophagosome formation, but instead involves a direct transfer of HSP70 clients across the lysosomal membrane (Kaushik et al., 2011). To emphasize this distinction, we coined the term chaperone-assisted selective autophagy (CASA) for the BAG3-induced pathway (Arndt et al., 2010).

BAG3 is essential for proteostasis in post-mitotic cells

BAG3-mediated autophagy significantly contributes to protein homeostasis in post-mitotic cells, such as differentiated neurons and muscle cells (Behl, 2016; Ulbricht et al., 2013). In neurons, BAG3 mediates the autophagic degradation of aggregation-prone proteins linked to neurodegenerative diseases (Carra et al., 2008; Gamerdinger et al., 2009, 2011). This includes pathological variants with extended poly-glutamine stretches of the huntingtin protein, which cause Huntington's disease, and of the androgen receptor, leading to spinal bulbar muscular atrophy (Carra et al., 2008; Rusmini et al., 2015). BAG3 promotes the degradation of mutant and misfolded forms of the superoxide dismutase SOD1, which are causative agents of amyotrophic lateral sclerosis (Gamerdinger et al., 2011). Moreover, BAG3 facilitates the clearance of the microtubule-regulating protein tau in primary neurons (Lei et al., 2015), apparently counteracting the accumulation and aggregation of hyper-phosphorylated tau, which is observed in Alzheimer's disease and some other neuropathologies (Krüger and Mandelkow, 2016). Intriguingly, protein clients destined for turnover by the proteasome are directed towards autophagy by BAG3 when proteasome activity becomes limited, as a result of pharmacological intervention or proteotoxic stress (Minoia et al., 2014). Indeed, induction of BAG3 expression and CASA activity in ageing rodent brains provides a switch from proteasomal to autophagic degradation for improved clearance of damaged proteins (Gamerdinger et al., 2009). In contrast, reduced expression of BAG3 contributes to neurodegeneration in cellular models of Alzheimer's disease (Renziehausen et al., 2015). Furthermore, mutations in human BAG3, and its partner proteins HSPB8 and DNAJB6, give rise to motor axonal neuropathy (Echaniz-Laguna et al., 2017; Ghaoui et al., 2016; Jaffer et al., 2012; Kostera-Pruszczyk et al., 2015), emphasizing the central role of BAG3 in neuronal proteostasis.

BAG3 mediates quality control of filamin

Also in muscle cells, BAG3 initiates the autophagic clearance of pathological, aggregation-prone protein variants (Banerjee Mustafi et al., 2014; Nivon et al., 2016; Ruparelia et al., 2016). In addition, the co-chaperone exerts an important housekeeping function by

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monitoring the mechanical unfolding and damage of cytoskeleton components (Fuchs et al., 2015; Ulbricht et al., 2013; Varlet et al., 2017). In striated muscle, BAG3 as well as its *Drosophila melanogaster* counterpart Starvin (Stv) are associated with actin-anchoring structures, so-called Z-disks, which limit the contractile sarcomeric units (Arndt et al., 2010; Homma et al., 2006). Animal models that are deficient for BAG3 or Stv display normal muscle development during embryogenesis, excluding a role in initial muscle assembly. However, when muscles are put to work after birth or eclosion, a rapid, force-dependent deterioration of Z-disks is observed (Arndt et al., 2010; Homma et al., 2006). The resultant muscle weakness leaves mutant fly larvae and knock-out mice unable to take up food, and the mice die shortly after birth because of heart and lung failure. Of note, BAG3 mutations also cause severe muscle weakness in humans, characterized by the deterioration of Z-disks and the accumulation of protein aggregates (Béhin et al., 2015; Kley et al., 2016). For example, a proline to leucine exchange at position 209 gives rise to rapidly progressing muscle dystrophy and cardiomyopathy in children (Kostera-Pruszczyk et al., 2015; Selcen et al., 2009). Thus, it is clear, that BAG3-mediated proteostasis represents an evolutionarily conserved mechanism for muscle maintenance.

The observed contraction-dependent disintegration of Z-disks in the absence of functional BAG3 or Stv points to the existence of at least one Z-disk protein that needs to be recognized by the CASA machinery following mechanical damage, so that it can be released from the actin-anchoring structure and targeted for autophagic degradation to maintain muscle architecture. In an unbiased biochemical approach, in which the BAG3-dependent release of proteins from isolated cytoskeleton was monitored, we identified the actin-crosslinking protein filamin as such a CASA client (Arndt et al., 2010) (see poster). Filamin is a rod-like protein comprising 24 immunoglobulin (Ig) domains and a terminal actin-binding site. It forms large homodimeric complexes ∼250 kDa in size, which crosslink actin filaments at the sarcomeric Z-disk (Nakamura et al., 2011). Importantly, filamin unfolds under mechanical force, which involves the disruption of an interdomain interaction between Ig domains 20 and 21 (Ehrlicher et al., 2011; Nakamura et al., 2014; Rognoni et al., 2012). This unfolding provides the structural flexibility required for maintaining contacts between actin filaments under mechanical strain. BAG3 binds to the mechanosensitive region of filamin and recruits its partner chaperones to monitor the conformational status of the actin crosslinker (Ulbricht et al., 2013). Mechanically damaged forms of filamin are extracted from the Z-disk and targeted for autophagic degradation. Indeed, mice with impaired autophagy, such as those deficient for the lysosomal membrane protein LAMP2, display severe muscle weakness accompanied by filamin aggregation (Arndt et al., 2010; Tanaka et al., 2000).

Our recent study on the physiological responses to strength training in humans confirmed that CASA is a force- and exercise-induced autophagy pathway (Ulbricht et al., 2015). We showed that strenuous resistance exercise leads to an immediate transcriptional induction of filamin, BAG3 and HSPB8 in human leg muscle, while at the same time the corresponding protein amounts in the muscle tissue decrease, consistent with increased turnover. Of note, BAG3 and HSPB8 are degraded together with filamin following the engulfment of client-loaded chaperone complexes by autophagic membranes (Arndt et al., 2010; Ulbricht et al., 2013). We also observed that repeated exercise during four weeks of training resulted in an upregulation of the basal levels of CASA components (Ulbricht et al., 2015). In human skeletal muscle, the autophagy pathway thus appears to act as a central adaptation mechanism, responding to acute and repeated mechanical stimulation. With regard to the underlying molecular mechanisms, it is important to note that BAG3 expression is controlled by the heat shock transcription factor HSF1 (Du et al., 2009; Franceschelli et al., 2008). Accordingly, BAG3 is induced under heat stress or when non-native proteins accumulate, for example, following proteasome inhibition (Minoia et al., 2014). The mechanical unfolding of cytoskeleton proteins constitutes a comparable physiological stimulus, which results in the activation of HSF1 and, in turn, triggers BAG3 expression and CASA activity (Ulbricht et al., 2013). So far, very few publications have described exercise- or force-induced autophagy, and findings have often been attributed to an increased demand for autophagic degradation owing to its contribution to energy metabolism and glucose homeostasis (He et al., 2012; Höhfeld, 2016; King et al., 2011; Wang et al., 2016). Establishing autophagy as an essential quality control mechanism for mechanically damaged cytoskeleton proteins significantly extends our understanding of the physiological importance of this degradation pathway.

BAG3-mediated cytoskeleton maintenance is not restricted to striated muscle

In smooth muscle cells and non-muscle cells, filamin is associated with actin stress fibres that form when force is applied either from outside or generated inside the cells during adhesion and migration (Nakamura et al., 2011) (see poster). Stretching of smooth muscle cells as well as adhesion, spreading and migration of lymphoblasts result in an induction of BAG3 and is accompanied by increased autophagic turnover of filamin (Ulbricht et al., 2013). Moreover, BAG3 is essential for the motility and adhesion of diverse cancer cells (Antonietti et al., 2017; Iwasaki et al., 2007, 2010). Protein quality control mediated by the CASA machinery thus appears to represent a wide-spread and common mechanism to maintain the cytoskeleton in muscle as well as non-muscle cells. Notably, HSPB8 and BAG3-dependent autophagy is also essential in dividing cells at stages when profound changes in cell tension occur, for instance during proper spindle orientation and the disassembly of the actin-based contractile ring during cytokinesis (Fuchs et al., 2015; Varlet et al., 2017). Although it remains to be seen, whether filamin is a relevant target in these processes, the findings emphasize the importance of CASA for quality control of cytoskeleton networks under mechanical strain.

BAG3 coordinates transcription, translation and degradation

To obtain additional insights into BAG3-mediated proteostasis at a molecular level, we performed a screen for human proteins able to interact with its WW domain (Ulbricht et al., 2013). The WW domain is an interaction module that binds PY motifs (Sudol and Harvey, 2010). In vertebrates, about 70 WW domain-containing proteins associate with a plethora of about 2000 PY proteins to establish large signalling and interaction networks (Meng et al., 2015), and BAG3 also utilizes its WW domain to contact multiple PY proteins (Chen et al., 2013; Iwasaki et al., 2010; Merabova et al., 2015; Sariyer et al., 2012; Taipale et al., 2014; Ulbricht et al., 2013). One of these is synaptopodin-2 (SYNPO2, also known as myopodin), another Z-disk protein (Ulbricht et al., 2013). SYNPO2 links BAG3 to a membrane tethering and fusion complex, which includes the vacuolar protein sorting (VPS) factors VPS18 and VPS16 as well as syntaxin-7. This complex facilitates the fusion of phagophores and thereby promotes the

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membrane engulfment of BAG3-containing chaperone complexes (Ulbricht et al., 2013). SYNPO2 is thus an integral part of the Z-disk-associated CASA machinery, which drives autophagosome formation (see poster). Yet, the expression of SYNPO2 is more restricted than that of BAG3, and it is not readily detectable in neuronal cells (www.genecards.org). The close coupling of client recognition and autophagosome formation, which is mediated by SYNPO2 at the actin cytoskeleton, may thus represent a specific adaptation in cells that are particularly exposed to mechanical stress.

Other BAG3-interacting PY proteins are the kinases LATS1 and LATS2, and the angiomotin-like proteins 1 and 2 (AMOTL1/2), which all belong to the growth- and proliferation-regulating Hippo signalling pathway (Salah and Aqeilan, 2011), as well as the mechanistic target of rapamycin (mTOR) inhibitor tuberous sclerosis 1 (TSC1) (Kathage et al., 2017; Ulbricht et al., 2013). Through these interactions, BAG3 participates in the regulation of transcription and translation, thereby significantly extending its proteostasis function. LATS1/2 and AMOTL1/2 possess PY motifs, which contact the WW domain-containing transcriptional coactivators YAP (also known as YAP1) and TAZ (also known as WWTR1) to prevent their nuclear translocation and thereby attenuate transcription (see poster). However, association of the WW domain of BAG3 with the PY motifs of LATS1/2 and AMOTL1/2 abrogates the inhibitory interactions with YAP and TAZ. The coactivators enter the nucleus and stimulate the transcription of their target genes (Ulbricht et al., 2013). Remarkably, filamin is among these targets (Dupont et al., 2011). Therefore, BAG3 not only mediates the autophagic degradation of damaged filamin, but in addition stimulates a compensatory *de novo* synthesis of filamin through YAP–TAZ activation (Ulbricht et al., 2013) (see poster).

The interaction of BAG3 with the mTOR inhibitor TSC1 adds another intriguing aspect to this scenario (see poster). mTOR is a kinase that is present in two distinct complexes: mTORC1 and mTORC2 (Betz and Hall, 2013; Saxton and Sabatini, 2017). mTORC1 acts as a master regulator of anabolic and catabolic processes in mammals. In the presence of nutrients and growth factors, mTORC1 is active and stimulates translation, whereas autophagy is inhibited. In contrast, under starvation or stress conditions, inactivation of mTORC1 causes a shutdown of protein translation and stimulates autophagy (Dunlop and Tee, 2014; Laplante and Sabatini, 2012). Inactivation is brought about by the TSC1-containing TSC complex, which acts as a GTPase-activating factor on the small GTPase RHEB, thereby driving RHEB into the GDP-bound form that inhibits mTORC1 (Menon et al., 2014; Zhang et al., 2003). Notably, TSC1 possesses a PY motif that is recognized by the WW domain of BAG3 (Kathage et al., 2017). In mechanically strained adherent cells, this interaction enables BAG3 to recruit TSC complexes to actin stress fibres, where they inhibit mTORC1 to initiate CASA at sites of filamin unfolding (Kathage et al., 2017). At the same time, BAG3-mediated sequestration of the TSC complex relieves mTORC1 inhibition throughout the remaining cytoplasm, and, as a consequence, protein translation is stimulated (Kathage et al., 2017) (see poster). In contrast to the established mTORC1-mediated 'all-or-none' switch between anabolism and catabolism in response to the nutritional status, the spatial regulation of mTORC1 by BAG3 provides the means to simultaneously induce autophagy and protein translation in mechanically strained cells. Only in this way can autophagic disposal of damaged cytoskeleton proteins be compensated with the synthesis of new functional molecules to maintain the cellular architecture.

Box 1. Role of BAG3 in tumour cells

Since their initial identification as binding partners of the anti-apoptotic protein BCL-2, BCL-2 associated athanogene (BAG) domain co-chaperones have been studied in the context of cell death regulation and tumour progression (Behl, 2016; Takayama et al., 1999). Elevated expression of BAG3 has been observed in different tumour cells, including small-cell lung cancer cells, urothelial cancer cells, pancreatic adenocarcinoma cells and chronic lymphocytic leukaemia cells, and is accompanied by reduced apoptotic cell death, increased resistance to chemotherapy and poor prognosis (reviewed by Behl, 2016; Rosati et al., 2012). BAG3-mediated proteostasis in response to mechanical stress also appears to be relevant for tumour cells that rely on mechanical signals during migration, invasion and metastasis (Antonietti et al., 2017; Iwasaki et al., 2007, 2010). However, other functions of BAG3 beyond protection from mechanical stress are also observed in tumour cells. In breast cancer cells, for example, an estrogen receptor α-induced and BAG3-dependent autophagy pathway provides resistance to oxidative stress (Felzen et al., 2015). Moreover, the HSP70–BAG3 complex exerts anti-apoptotic and pro-survival functions by modulating the activity of diverse transcription factors [e.g. NF-κB and HIF1α (HIF1A)] and cell cycle regulators [e.g. p21 (CDKN1A) and survivin (BIRC5)] (Colvin et al., 2014; Rapino et al., 2015; Rosati et al., 2012). BAG3 even fulfils signalling functions in cell–cell communication, as the co-chaperone was shown to be secreted by adenocarcinoma cells, which activates macrophages and stimulates the secretion of cancer-promoting factors (Rosati et al., 2015). Consequently, BAG3 is considered to be a promising drug target for cancer treatment (Antonietti et al., 2017; Behl, 2016; Rosati et al., 2012; Sherman and Gabai, 2015). Indeed, a small-molecule inhibitor, which disrupts the HSP70–BAG3 interaction, as well as anti-BAG3 antibodies were found to suppress tumour growth in mice (Colvin et al., 2014; Rosati et al., 2015).

Conclusions

The co-chaperone BAG3 acts as a key proteostasis factor because it combines in a unique manner highly diverse activities ranging from the enhancement of chaperone function and the sequestration of misfolded proteins to the balancing of transcription, translation and autophagy. Besides its role in proteostasis, BAG3 has also gained a lot of interest because of its involvement in the regulation of apoptotic cell death and oncogenic transformation (Antonietti et al., 2017; Behl, 2016; Colvin et al., 2014; Felzen et al., 2015; Franceschelli et al., 2008; Iwasaki et al., 2007; Merabova et al., 2015; Rapino et al., 2015; Rosati et al., 2011, 2012, 2015; Sariyer et al., 2012; Sherman and Gabai, 2015) (see Box 1). The BAG3 chaperone machinery thus operates at several protein hubs crucial for cell maintenance and cell fate decisions. Further deciphering the modes of action and areas of operation of this multi-functional co-chaperone will certainly make many more exciting headlines.

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