Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

HSPB8 (heat shock 22kDa protein 8)

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Published in Atlas Database: March 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/HSPB8ID43743ch12q24.html
DOI: 10.4267/2042/54369

Abstract

Review on HSPB8, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CMT2L, DHMN2, E2IG1, H11, HMN2, HMN2A, HSP22

HGNC (Hugo): HSPB8

Location: 12q24.23

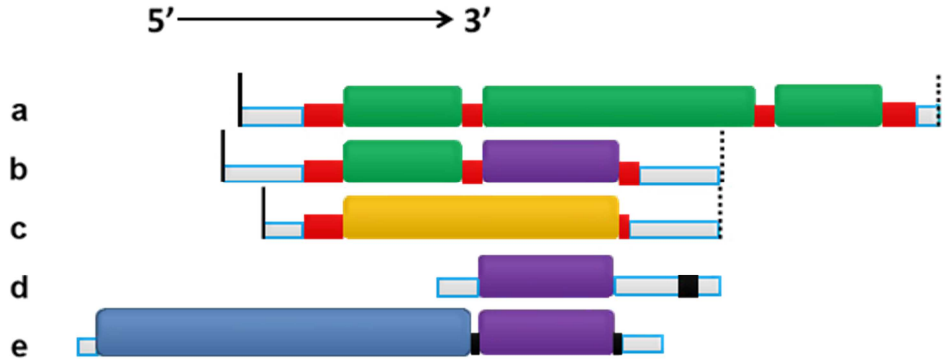
DNA/RNA

Description

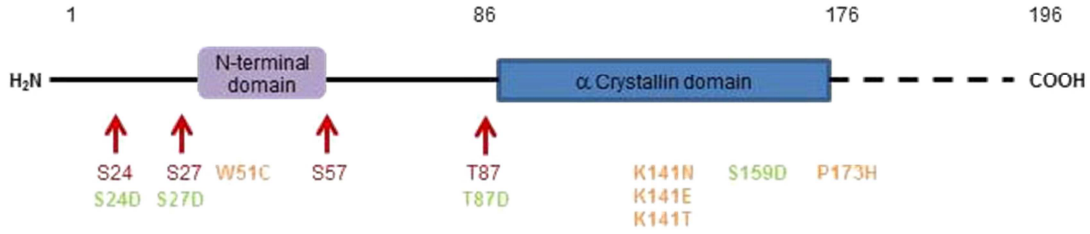
HspB8 maps on chromosome 12, at 12q24.23, spanning 40.2 kb from 119611731 to 119658934. Transcription produces 5 alternatively spliced mRNAs ranging from 244 aa to 27 aa in length, only 3 of which contain an α-crystallin domain and are coding. There are 3 probable alternative promoters and 2 non-overlapping alternative last exons.

Transcription

Transcription produces 5 alternatively spliced mRNAs, which differ by truncation of the 3' end and the presence or absence of a cassette exon. See below the features of the splice variants.
A: Accessions from pericardium, thalamus, caudate nucleus, placenta, and subthalamic nucleus. Complete mRNA, 1526 bp long, predicted protein is 244 aa, contains one α-crystallin domain.
B: Accessions from placenta cot, placenta, brain and eye. Complete mRNA, 2154 bp long, predicted protein 196 aa, contains one α-crystallin domain.
C: Accessions from placenta and placenta cot. Complete mRNA, 1795 bp long, predicted protein 130 aa, contains one α-crystallin domain.
D: Accessions from liver, spleen, head, and lung. Partial mRNA, 1337 bp, best predicted protein would have 60 aa, appears to be non-coding.



The 5 mRNA splice variants of HspB8. The empty light blue boxes represent the untranslated regions, the red boxes are exons, and the wide colored boxes are introns. Exon size is proportional to length. Introns of the same color are identical. The purple introns are upstream open reading frames. The solid black vertical lines indicate validated cap sites at the 5' end and the dotted black lines indicate validated polyadenylation sites at the 3' end.



Schematic representation of the HspB8 protein, highlighting its phosphorylation sites (red arrows), naturally occurring mutations (orange type) and mutations that do not occur in nature (green). See the Mutation section below for more information on mutations.

E: Partial mRNA, 382 bp, best predicted protein would have 27 aa, appears to be non-coding.

Pseudogene

Unknown.

Protein

Description

HspB8 is a relatively new member of the family of mammalian small heat shock proteins (sHsps), a distinct family subset with monomer molecular masses generally in the 12-43 kDa range. HspB8 is one of 10 sHsps identified so far in the human genome (Kappé et al., 2003). It was cloned in 2000 from human melanoma and cervical cancer cells based on its homology to the protein kinase (PK) domain of the large subunit of herpes simplex virus type 2 (HSV-2) ribunucleotide reductase (R1), known as ICP10PK, and was named H11. The molecular mass of HspB8 is 22 kDa. It shares with the other sHsps, a conserved amino acid sequence, called the 'α-crystallin domain' that is located in the C-terminal part of the molecule. However, HspB8 also classifies as an atypical serine/threonine protein kinase (PK). Its catalytic core retains motifs I-III that are required for kinase activity. The invariant Lys residue (motif II) is at position 113 and its mutation abrogates kinase activity. Like its homologue, ICP10PK, the HspB8 autokinase activity favors Mn^{2+}ions (Smith et al., 2000).

Physicochemical properties

Circular dichroism spectroscopy suggests that HspB8 is an intrinsically disordered protein (IDP), meaning that it does not fold into a stable tertiary structure and has a flexible conformation. It contains many Pro residues, which enable formation of a polyproline type II (PPII) structure that contains 2-3 PXXP/PXP repeats. It is rather resistant to thermal denaturation and is very susceptible to proteolysis, consistent with theoretical predictions of disorder probability. Ultracentrifugation in glycerol gradients indicates that HspB8 is an extended monomer (Chowdary et al., 2004), a viewpoint embraced in the UniProtKB/Swiss-Prot database. This suggests that HspB8 differs from other sHsps that tend to form dimers or high-order oligomers. Additional properties that distinguish HspB8 from the other sHsps include theoretical predictions that its structure is enriched in β-strands and unordered structures and it lacks the so-called β2 strand seen in many other sHsps (reviewed in Mymrikov et al., 2011).

Autokinase activity

HspB8 is an atypical serine/threonine PK that resembles the HSV-2 kinase ICP10PK used in its cloning. In immunocomplex kinase assays, HspB8 undergoes autophosphorylation and it phosphorylates exogenous protein substrates. Specificity is underscored by the finding that HspB8 phosphorylates some (viz. myelin basic protein), but not other (viz. a-casein or histone IIIS) substrates. The definitive proof of intrinsic autokinase activity is provided by the loss of phosphorylation upon mutation of the invariant Lys at position 113, which is required for ATP binding (catalytic domain II). This loss of kinase activity is not due to a nonspecific conformational alteration, because it does not occur upon mutation of the adjacent Lys residue at position 115 (Smith et al., 2000; Aurelian et al., 2001; Depre et al., 2002). Further investigations performed on the isolated protein confirmed that HspB8 undergoes autophosphorylation (Chowdary et al., 2004). The rate and extent of phosphorylation are relatively low (Kim et al., 2004). However, both are significantly increased by mutations that cause physichochemical structural change, as exemplified by the significantly higher autokinase activity of the HspB8 mutant W51C, which has 7 additional β turns (Gober et al., 2003; Gober et al., 2004; Gober et al., 2005).

Phosphorylation by other PKs

Protein kinase C (PKC) phosphorylates HspB8 at Ser14 and Thr63, ERK1 at Ser27 and Thr87, and casein kinase 2 at a number of unidentified sites (Benndorf et al., 2001). cAMP-dependent PK phosphorylates HspB8 at Ser57. Phosphorylation of Ser57 (S57D) or Ser24 (S24D) or mutation that mimics phosphorylation at these sites affects the quaternary structure and chaperone-like activity of HspB8 (Shemetov et al., 2008). Proteomic studies have shown in vivo phosphorylation at Ser24 and

Thr87 (Dephoure et al., 2008). However, this may be cell type and tissue specific, as phosphorylation at Tyr118 was also reported in another tissue (Rikova et al., 2007). The conditions that favor the distinct phosphorylation patterns and their effect on the structure and function of HspB8 are still unknown.

Interactome: sHsps and other proteins and affected functions

HspB8 interacts with most sHsps, but the stability and stoichiometry of the complexes are still unknown. All methods revealed tight interaction with HspB7, but cross-linking and immunoprecipitation failed to reveal a tight interaction with HSPB1 (Hsp27). Interaction with HspB1 and HspB6 is affected by their mutation at sites that mimic phosphorylation (Ser15 and Ser16, respectively) (Sun et al., 2006). HspB8 mutation at position 51 interferes with its ability to interact with HspB1 (Smith et al., 2000). The functions regulated by HspB8 interaction with the sHsps are largely unknown, but interaction with HspB1 appears to affect NK activity (reviewed in: Hu et al., 2007; Mymrikov et al., 2011; Arrigo, 2013).

HspB8 also interacts with other proteins. HspB8 residues 62-133 interact with the RNA-binding protein Sam68 that is involved in transportation and processing of RNA (Badri et al., 2006). Because Sam68 interacts with Src-kinase at an overlapping site, its interaction with HspB8 during mitosis may indirectly regulate the intracellular localization and/or activity of Src-kinase, thereby affecting gene expression (transcription/translation). Ribonucleoprotein processing is likely affected by the interaction between HspB8 and Ddx20 (gemin3, Dp120), a protein that has ATP-dependent RNA unwinding (helicase) activity and is involved in spliceosome assembly and RNA processing (Sun et al., 2010). HspB8 also interacts with Destrin (DSTN) a cytoskeleton structural and fibrillar protein, thereby affecting actin depolymerization. It inhibits Rho GTPase and thereby functions in tachycardia remodeling, providing a protective function. It is suggested that the unique ability of HspB8 to inhibit stress fiber formation may be connected with its function in autophagy activation, which in turn acts as a trigger in RhoA pathway initiation (Ke et al., 2011). HspB8 interacts with aggregation-associated proteins, such as α synuclein, SOD1, TDP-43 and PolyQ, thereby inhibiting aggregation or fostering aggregate degradation. It is also a Toll-like receptor-4 (TLR-4) ligand causing dendritic cell activation and immunomodulation and it interacts with the cytokine-induced apoptosis inhibitor CIAPIN1, but the resulting functional modulation is still unclear (reviewed in: Arrigo, 2013). Finally, HspB8 binds Akt and 5'-AMP-activated PK, thereby promoting their nuclear translocation and cell survival (Depre et al., 2006), and it interacts with Bag-3 to regulate autophagy and with eukaryotic initiation factor 2 (eIF2) to inhibit translation (Carra, 2009).

Expression

Expression in human tissues

HspB8 is predominantly expressed in human skeletal and smooth muscle, heart, and brain. Lower expression levels are seen in prostate, placenta, lung, kidney, and skin and there is no expression in ovaries, testes, liver, pancreas, and spleen (Yu et al., 2001). Its expression may be altered in tumor as compared to normal tissues (Gober et al., 2003). In human skin, HspB8 is expressed in basal keratinocytes with long-term in vitro growth potential, which are considered the epidermis stem cells, and it is required for their proliferation (Aurelian et al., 2001).

Stress-induced expression

HspB8 has two heat-shock transcription factor-(HSF-) binding sites, 1000 bases upstream of the translation initiation site. However, its expression is not always heat inducible and it can be upregulated by diverse stress conditions. For example, HspB8 expression is not heat-inducible in melanocytes (Smith et al., 2011) and it is upregulated by sublethal sodium arsenite and oxidative and hyperosmotic stress in neurons, where it likely contributes protective activity (Bartelt-Kirbach and Golenhofen, 2014).

DNA methylation and the regulation of expression/function

HspB8 differs from other Hsps in that its expression in human cells is subject to methylation-associated repression. It has a CpG island at the 5'UTR, 216 bp upstream of the transcription start site and is silenced by aberrant DNA methylation in some tumors, notably melanoma, prostate cancer, Ewing's sarcoma and hematologic malignancies (viz. leukemia, lymphoma). In these tissues/cells, restored HspB8 expression has anti-proliferative and pro-apoptotic activity (Smith et al,. 2000; Gober et al., 2003; Li et al., 2007; Cui et al., 2012). However, HspB8 is overexpressed in breast cancer, particularly estrogen receptor (ER)+ breast cancer and in these cells/tissues, DNA methylation contributes to the development of resistance to anti-estrogen treatment (Fan et al., 2006). High throughput cell-based screens recognized 31 kinases, including HspB8, that confer resistance to tamoxifen therapy. They identified HspB8 as the expression signature which, by itself, predicts poor clinical outcome through inhibition of tamoxifen-induced autophagy (Gonzalez-Malerva et al., 2011). This appears to be facilitated by Lemur tyrosine kinase 3 (LMTK3), a serine/threonine kinase which functions as a regulator of the ERα and increases the levels of HspB8 (Stebbing et al., 2013). The mechanisms responsible for the cell type specificity

of the HspB8 DNA methylation patterns are still unclear. Also unclear is the relationship between methylation and accessibility to expression regulatory factors, such as HSF or estrogen (Charpentier et al., 2000; Sun et al., 2007).

HspB and co-variant genes in differentiation/development

HspB8 is expressed in the adult mouse and rat hippocampus, but expression is modest or absent at the embryonic and postnatal stages (Kirbach and Golenhofen, 2011). In vitro expression during the differentiation of neuronal precursor cells confirmed that HspB8 promotes neuronal, but not astrocytic differentiation and increases cell survival without affecting proliferation. Two groups of genes were found to co-vary with HspB8. In the positively correlating group, enrichment was seen for the categories "regulation of growth" (Hopx, Ddr1, Fgfr1, and Ngf) and "regulation of apoptosis" (Bag3, Fgfr1, Ngf, and Ticam1). The negatively correlating group showed enrichment for the categories "intracellular signaling" (Arhgef9, Rab14, Rap2a, Gnaq, Plcb1, Gm266, Spred2, and Usp8), "apoptosis" (Bcl2l11, Fem1b, and Peg3) and "tissue morphogenesis" (Acvr1, Fem1b, and Serpinb5). The STRING online database tool identified a cluster based around the nerve growth factor family, which contained members that positively correlate with HspB8, and another cluster that was primarily composed of apoptotic proteins which interact with the HspB8/Bag-3 complex (Ramírez-Rodríguez et al., 2013).

Localisation

While it is predominantly detected in the cytoplasm, HspB8 also interacts with the plasma membrane. In human neuroblastoma SK-N-SH cells, it forms tight complexes with phospholipids located in the intracellular membrane leaflet. HspB8 has two myristoylation motifs (at residues 62 and 132) and one N-glycosylation motif that likely facilitate membrane-binding and surface localization. It also co-localizes with cell surface aggregates formed by partially denatured or improperly folded proteins, for example in Alzheimer's or Huntington disease. Unlike other Hsps, it does not always translocate to the nucleus upon heat shock stress. This is likely due to leucine-rich nuclear export signal (NES) motifs that favor cytosolic localization and are located at the N- (residues 21-31) and C- (residues 157-166) termini (Smith et al., 2000; Aurelian et al., 2001; Yu et al., 2001; Gober et al., 2003; Gober et al., 2004; Chowdary et al., 2007).

Function

Chaperone activity

HspB8 overexpression prevents the formation of aggregosomes containing desmin and the R120G mutant of αB-crystallin (HspB5) that correlate with the development of desmin-related cardiomyopathy and improve cardiac function (Chowdary et al., 2004; Kim et al., 2006; Sanbe et al., 2009). HspB8 also interacts with the αB-crystallin mutants Q151X and 464delCT that form aggregates associated with the development of myofibrillar myopathy (Simon et al., 2007), and amyloid β-peptides (Aβ1-42 and Aβ1-40), thereby reducing the accumulation of amyloid peptides on the cell surface and inhibiting the death of cardiovascular cells induced by Dutch-type Aβ1-40 (Wilhelmus et al., 2006). It prevents in vivo aggregation of polyglutamine containing proteins, such as a fragment of huntingtin that contains 43 Gln and the androgen receptor that contains 65 Gln residues (Wilhelmus et al., 2006; Rusmini et al., 2013) and it is upregulated in neurons exposed to sublethal sodium arsenite or oxidative and hyperosmotic stress, contributing chaperone-related protection (Bartelt-Kirbach and Golenhofen, 2014). Quantitation of the in vitro chaperone-like activity of HspB8 using model substrates and size exclusion chromatography showed that HspB8 undergoes dynamic molecular transition in solution, existing in a dynamic equilibrium between various oligomers; predominantly octamers in a nonphysiological solution and mainly tetramers in a physiological solution (pH 7.4) (Yang et al., 2012).

The Lys141 residue in the HspB8 α-crystallin motif is a mutational hot spot for the development of peripheral neuropathy. Two natural missense mutations, K141E and K141N, were associated with distal hereditary motor neuropathy type II (dHMN) and autosomal dominant Charcot-Marie-Tooth disease type 2L (CMT2L) in a large Chinese family (Irobi et al., 2004; Tang et al., 2005) and another mutation, K141T, was described in a Korean patient with Charcot-Marie-Tooth disease (Nakhro et al., 2013). The mutants cause neurite degeneration in motor but not sensory and cortical neurons (Irobi et al., 2010), which is apparently related to decreased chaperone-like activity measured on polyglutamine proteins as in vivo substrates (Carra et al., 2005). Ddx20 mutants fail to interact with HspB8, potentially causing different forms of inherited motor neuron diseases (Sun et al., 2010), but K141N can also cause cardiomyopathy, which is associated with the formation of perinuclear HspB8-positive aggregates that contain amyloid oligomer intermediates (Sanbe et al., 2013).

Inhibition of unfolded protein response (UPR)

HspB8 contributes to the proteolytic degradation of unfolded proteins, involving proteosomes or autophagy regulation. By affecting proteosome stability and intracellular localization, HspB8 induces the degradation of proteins, such as Foxo3 that prevent cardiac hypertrophy under normal

conditions (Hedhli et al., 2008). By interacting with the co-chaperone Bag-3 at the hydrophobic pocket formed by the β4- and β8-strands, it forms a complex with a 1:2 stoichiometry of Bag-3 to HspB8 (Fuchs et al., 2009) that fosters interaction with Hsc70, thereby giving rise to the multiheteromeric chaperone-assisted selective autophagy (CASA) complex. Together with the chaperone-associated ubiquitin ligase CHIP, this complex functions to remove misfolded proteins. It enables the ubiquitylation of the mutant superoxide dismutase (mSOD1) protein that is implicated in the development of amyotrophic lateral sclerosis (ALS), promoting its autophagic removal (Crippa et al., 2010a; Crippa et al., 2010b; Rosati et al., 2011; Vos et al., 2011). HspB8/Bag-3 interaction also has an important role in the protection of astrocytes against different protein aggregation diseases, apparently through autophagy-related aggregate clearance (Seidel et al., 2012) and it may contribute to chaperone-assisted selective autophagy in limb-girdle muscular dystrophy type 1D (LGMD1D), a myopathy caused by mutations of the Hsp40 family member DNAJB6 (Sato et al., 2013). During recovery from heat shock, the transcription factor nuclear factor-kappa B (NF-κB) activates selective removal of misfolded or aggregated proteins by controlling the expression of HspB8 and Bag-3 and increasing HspB8/Bag-3 complex formation, thereby increasing cell survival (Nivon et al., 2012). The CASA complex is also involved in mechanical tension, a physiological stimulus required for the development and homeostasis of locomotory, cardiovascular, respiratory, and urogenital systems and it contributes to stem cell differentiation, immune cell recruitment, and tumorigenesis. It senses the mechanical unfolding of the actin-crosslinking protein filamin, and together with CHIP, it initiates the ubiquitin-dependent autophagic sorting of damaged filamin to lysosomes for degradation (Ulbricht et al., 2013). HspB8 is also involved in spinal and bulbar muscular atrophy (SBMA), which is an X-linked neuromuscular disease characterized by the loss of motoneurons in the spinal cord and bulbar regions of the brain stem. Here, neuronal toxicity results from protein misfolding and aggregation of androgen receptor mutants that contain an elongated N-terminal polyglutamine tract (ARpolyQ) and are apparently dependent on autophagic flux failure. HspB8 restores the normal autophagic flux in motoneurons expressing ARpolyQ by exerting anti-aggregation and/or pro-degradative activity on ARpolyQ (Rusmini et al., 2013). Finally, HspB8 is upregulated in rat models of diabetes mellitus, where it is believed to play a key role in recovery and the prevention of disease-associated complications (Karthik et al., 2012; Reddy et al., 2013). However, studies of mSOD1 transgenic animals have shown that the HspB8-dependent autophagic response is much higher in muscle than spinal cord, potentially identifying a mechanism other than degradation of misfolded proteins (Crippa et al., 2013). Indeed, the HspB8/Bag-3 complex can activate phosphorylation of the α-subunit of the translation initiator factor eIF2, resulting in the general inhibition of protein synthesis and stimulating autophagy, independent of Hsc70 (Carra, 2009; Carra et al., 2009).

Signaling: stem cells, cancer and apoptosis

HspB8 has both pro- and anti-proliferative (pro-apoptotic) activity and it is cell type specific. Proliferative activity was seen in stem cells and in some cancers. For example, in human skin, HspB8 is expressed in basal keratinocytes with stem cell potential and is required for their proliferation (Aurelian et al., 2001). HspB8 is also expressed in breast cancer, glioblastoma, stomach tumors and rat pheochromocytoma (PC12) cells (Gober et al., 2005) and its expression is further increased in breast cancer cells treated with 17- β estradiol (Yang et al., 2006). In these tumors HspB8 demonstrates proliferative and anti-apoptotic properties. In breast cancer and glioblastoma cells, HspB8 functions in cell cycle regulation to prevent apoptosis, potentially through activation of the growth-associated transcription factor E2f and the cyclin-dependent kinase cdk4. HspB8 might also regulate expression of Sam68 thereby modulating the proliferative potential of the glioblastoma cells (Modem et al., 2011). Analysis of tissues from patients with breast ductal carcinoma in situ and invasive ductal carcinoma compared to normal matched controls, confirmed increased expression of HspB8 in invasive lesions, and showed that HspB8 induces anchorage independence and increases cell proliferation (Yang et al., 2006). Moreover, HspB8 overexpression was shown to increase radiation sensitivity, whereas its inhibition with siRNA was accompanied by decreased radiation sensitivity (Trent et al., 2007). In melanoma and cervical cancer, HspB8 mutation has been associated with sustained expression and the acquisition of proliferative anti-apoptotic activity as evidenced by the W51C mutant that has dominant cytoprotective activity and blocks apoptosis induced by wild type HspB8. The W51C cytoprotective activity is through activation of the B-Raf/ERK1/ERK2 survival pathway and it is associated with a 5-6-fold higher autokinase activity than that of the wild type protein (Gober et al., 2003).

By contrast, HspB8 has pro-apoptotic activity in other tumor cells. It's expression is reduced in melanoma, prostate cancer, Ewing's sarcoma and hematologic malignancies through aberrant DNA methylation. The levels of inhibition strongly

correlate with those of DNA methylation ($p < .001$), suggesting that HspB8 may serve as a marker for de-methylating therapeutics (Smith et al., 2011). In these tumors, restored HspB8 expression induces cell death and inhibits tumor growth in xenograft models (Gober et al., 2003; Gober et al., 2005; Li et al., 2007; Cui et al., 2012). HspB8-induced melanoma cell death is through the activation of line-specific death pathways that culminate in apoptosis and initiate with the activation of the MAP3K family member TGF-beta-activated kinase 1 (TAK1). In some of the tumor lines/xenografts, apoptosis is caused by the activation of the TAK1/p38MAPK/caspase-3/caspase-7 pathway. In others, apoptosis is through the activation of novel TAK1-dependent signaling pathways. These include (i) ASC-mediated caspase-1 activation independent of the inflammasome, (ii) Beclin-1 upregulation through mTOR phosphorylation at S2481 which is the site of intrinsic mTORC1-specific catalytic activity, and (iii) apoptosis caused by caspase-1-mediated Beclin-1 cleavage and its translocation to the mitochondria (see attached diagram below). These findings identify HspB8 as a regulator of TAK1 and mTORC1 pathways that function independent of Akt and involve inflammation-unrelated caspase-1 mediated modulation of the haploinsufficient tumor suppressor Beclin-1 (Smith et al., 2012).

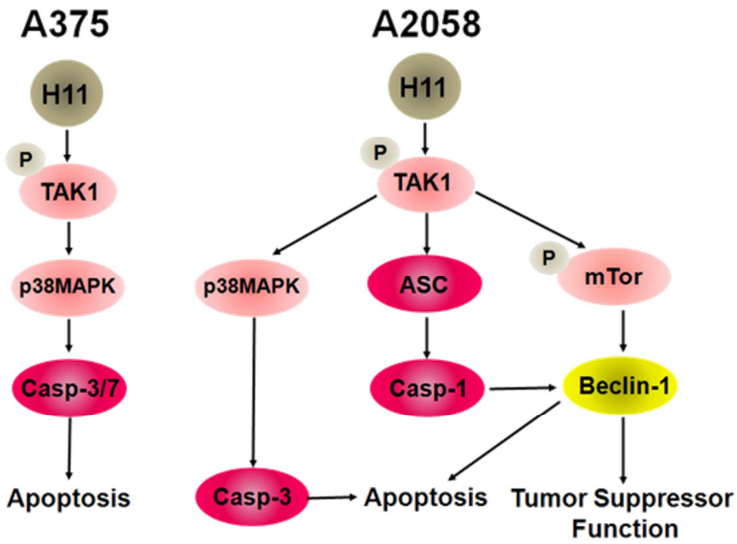
Signaling: cardiac cell hypertrophy and survival

HspB8 expression is increased in transient ischemia, likely indicating its involvement in cell survival (Depre et al., 2001), and it has a protective role in reversible, but not irreversible myocardial injury (Depre et al., 2004). Transgenic mice with a 7-fold increase in HspB8 expression evidence significant myocardial hypertrophy accompanied by activation of Akt and p70S6 kinase (Depre et al., 2002). These mice are characterized by increased expression of glucose transporter GLUT1 in the myocytes plasma membrane, as well as increased glycogen content and phosphoglucomutase activity in the heart, suggesting that HspB8 functions in the cardiac adaptation to stress by coordinating cell growth, survival, and metabolism (Wang et al., 2004). Cell survival in this system is due to anti-apoptotic activity resulting from the direct interaction of HspB8 with Akt (Hase et al., 2005). In addition, HspB8 has metabolic and survival properties that seem to be due to direct interaction and activation of AMP-dependent protein kinase, which is responsible for increased translocation of GLUT1 to the plasma membrane and increased myocardial glycogen content (Depre et al., 2006; Danan et al., 2007). In transgenic mice with cardiac-specific HspB8 overexpression, HspB8 activates the "canonical" bone morphogenetic protein (BMP) pathway, where interaction of BMP with its receptors (BMPR-II) and Alk3 results in Smad1/Smad5/Smad8 phosphorylation. HspB8 also activates the "noncanonical" BMP pathway, promoting activation of TAK1/PI3-K/Akt and TAK1 interaction with Alk3 and BMPR-II (Sui et al., 2009). Myocardial hypertrophy results from HspB8-mediated activation of the PI3-K/Akt pathway independent of its autokinase activity (Depre et al., 2002; Sui et al., 2009). However, high dose HspB8 induces autokinase-dependent apoptosis through the inhibition of casein kinase 2 activity (Hase et al., 2005). HspB8 upregulation by ischemia/reperfusion provides cardioprotection through enhanced mitochondrial production of nitric oxide (NO), which stimulates oxidative phosphorylation in normoxia and decreases oxidative phosphorylation and reactive oxygen species production after anoxia. The upregulation of HspB8 is correlated with increased expression of the inducible isoform of nitric oxide synthase (Laure et al., 2012). HspB8 deletion decreases the phosphorylation of the transcription factor, STAT3, impairs transactivation of the stress response genes regulated by STAT3, and causes a significant decrease in both mitochondrial STAT3 translocation and respiration. In addition, HspB8 deletion interferes with the activation of cell survival pathways, including Akt, ERK, and iNOS (Qiu et al., 2011). In rats with induced myocardial infarction the mitochondrial translocation of HspB8 is reduced, potentially contributing to the impaired mitochondrial energy-producing ability that leads to heart failure after a myocardial infarction (Marunouchi et al., 2013).

Tumor suppressor

HspB8 has tumor suppressor activity. It is expressed in human melanocytes, where it functions as a cell cycle regulator and causes growth arrest through β-catenin phosphorylation at the transcriptional activity site Ser(552) and inhibition of the cell-cycle regulatory proteins cyclin E/Cdk2 that control G1 to S transition (Smith et al., 2011).

In melanoma and other cancers, its expression is inhibited through aberrant DNA methylation and restored expression through treatment with de-methylating agents causes cell death and inhibits tumor growth (Li et al., 2007; Smith et al., 2012; Cui et al., 2012). Tumor cell death is through the activation of death pathways that lead to apoptosis and activation of additional tumor suppressor functions that include the haploinsufficient tumor suppressor Beclin-1 (Smith et al., 2012). Supporting the interpretation that HspB8 has tumor suppressor function is the finding that it is highly expressed in glioblastoma cells, where its inhibition is associated with increased cell proliferation (Modem et al., 2011).



Schematic representation of the death pathways induced by HspB8 in different cells. A2058 and A375 are melanoma cells in which HspB8 signals through distinct pathways to cause cell death. While both pathways initiate with TAK1 activation, the contribution of p38MAPK and the caspases differs. In A375 cells, the TAK1/p38MAPK pathway activates caspases 3 and 7 to cause apoptosis. In A2058 cells, the TAK1/p38MAPK pathway activates caspase-3, but TAK1 also activates caspase-1 through ASC upregulation and upregulates Beclin-1 through mTOR phosphorylation at S2481. Caspase-1 cleaves Beclin-1 to promote apoptosis, but Beclin-1 also contributes to cell death through still unknown tumor suppressor functions. In both cell types, the HspB8 mutant W51C has dominant proliferative potential through its ability to trigger a B-Raf/ERK survival pathway that appears to be dependent on autokinase activity.

The cell-cycle regulatory potential of HspB8 in normal cells, its dysfunctional state in cancer cells, and its ability to induce tumor cell death, identify HspB8 as a tumor suppressor. Also characteristic of tumor suppressors, such as p53, is the cell-type specificity of the HspB8 effects and the finding that it can undergo single-site mutation to lose its activity or to acquire neoplastic potential. This is respectively exemplified by the natural mutants P173H, which is inactive, and W51C, which has proliferative (anti-apoptotic) activity (Gober et al., 2003; Smith et al., 2011; Smith et al., 2012). However, the frequency of such naturally occurring mutations is still unknown.

Inflammation and autoimmunity

HspB8 activates antigen-presenting dendritic cells through a TLR-4-dependent pathway and it is abundantly expressed in synovial tissues from patients with rheumatoid arthritis, potentially contributing to autoimmunity (Roelofs et al., 2006). It also induces interleukin-6 (IL-6) production in cultured pericytes and astrocytes, potentially contributing to local inflammation in Dutch type amyloidosis (Wilhelmus et al., 2009). HspB8 is upregulated in synovial fibroblasts exposed to 5% cigarette smoke extract and in synovial tissues of smokers with rheumatoid arthritis (RA), suggesting that it activates signaling pathways which promote the development of autoimmunity and chronic joint inflammation (Ospelt et al., 2014). Astrocytes are key players in driving CNS inflammation. They respond to insult with a process of cellular activation known as reactive astrogliosis, a key signal of which is activated NF-κB that drives CNS inflammation (Brambilla et al., 2014). Examination of post-mortem brain tissues from patients with protein conformation disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and spinocerebellar ataxia type 3 (SCA3), revealed a strong upregulation of HspB8 and a moderate upregulation of Bag-3 in astrocytes in the cerebral areas affected by neuronal damage and degeneration. This was not the case for neurons, irrespective of their localization or the presence of protein aggregates. These findings were interpreted to suggest that the HspB8/Bag-3 complex enhances the ability of astrocytes to clear aggregated proteins released from neurons in order to maintain local tissue homeostasis and/or modulate the inflammatory response during astrogliosis (Seidel et al., 2012). The ability of HspB8 to regulate inflammatory responses is further supported by our finding that restored HspB8 expression in melanoma cells induces TAK1-dependent activation of receptor-interacting protein 2 kinase (RIP-2) that activates NF-κB and results in increased production of the pro-inflammatory cytokine TNF-α.

Homology

HspB8 has 32% identity and 59% homology with the HSV-2 gene ICP10PK that was used for its cloning (Gober et al., 2005). This level of sequence homology is similar to that seen for viral Bcl-2 homologues and their cellular counterparts, supporting the interpretation that the two proteins

are members of the same family. HspB8 and ICP10PK share multifunctional activities that encompass signaling, UPR, inflammatory responses, and the regulation of life-cycle potential. The contribution that ICP10PK molecular mimicry may have towards the ability of HspB8 to contribute to the development of autoimmune disorders is still unknown (Aurelian et al., 2012). However, if we accept the premise that the presence of an α-crystallin motif, even if degenerate, is a sine qua non criterion for evolutionary-based inclusion into the sHsp family, we must infer that ICP10PK is evolutionarily related to HspB8. According to this interpretation, ICP10PK is likely to have evolved from HspB8, which was originally captured by HSV-2 in order to provide survival advantages such as the inhibition of neuronal apoptosis that is required for virus growth and latency reactivation (Aurelian et al., 2012). Presumably, once it was captured and fused in-frame with the viral R1, HspB8 fell under the control of the R1 promoter, losing the regulatory constraints that define its cell-type-specific death-inducing potential while retaining kinase and ATPase-independent chaperone activity and the ability to inhibit UPR. This interpretation is supported by the recent finding of chimeric genes that consist of in-frame fused genes captured from different sources. Also consistent with this interpretation are the restriction of the homology to HSV-2, but not the closely related virus HSV-1, and the presence of missense mutations that convert HspB8 from a pro-apoptotic to a dominant anti-apoptotic protein. This interpretation is in line with current understanding of virus evolution, which recognizes viruses as "gene robbers" that have evolved after cellular species (Holmes, 2011). However, ICP10PK differs from HspB8 in that it has a transmembrane domain that is required for its kinase activity, and the possibility cannot be excluded that HspB8 evolved from ICP10PK captured by the cell from HSV-2 for an anti-stress function. Indeed, it is becoming increasingly evident that virus sequences can be incorporated into the germ-line DNA of the host, becoming inherited alongside the host sequences and contributing significant functions (Weiss and Stoye, 2013).

Mutations

Germinal

Three naturally occurring missense mutations, K141E, K141N, and K141T, located in the α-crystallin domain of HspB8 result in decreased chaperone-like activity and impaired clearance of aggregated proteins. Their expression has been implicated in the development of Charcot-Marie-Tooth disease type 2L and distal hereditary motor neuropathy (Nakhro et al., 2013).

Mutations of unknown origin: The naturally occurring mutation W51C, results in a protein with 7 additional β turns and significantly higher autokinase activity. The W51C mutation converts HspB8 from a pro-apoptotic to a dominant anti-apoptotic protein that induces cell proliferation through the B-Raf/ERK pathway independent of the cell type. In both W51C and another naturally occurring mutation, P173H, TAK-1 and its downstream pro-apoptotic pathways are not activated (Gober et al., 2003).

Mutations not occurring in nature include S24D, S27D, and T87D, which interfere with the phosphorylation of HspB8. The S159D mutation has no effect on phosphorylation (Shemetov et al., 2011).

Somatic

Unknown.

Implicated in

Melanoma and other cancers

Note

HspB8 is expressed in normal melanocytes, where it causes growth arrest through β-catenin phosphorylation at the transcriptional activity site Ser (552) and inhibition of the Cyclin E/Cdk2 complex.

Like the established tumor suppressors, it is silenced by aberrant DNA methylation in most melanoma tissues and in other cancers (e.g. prostate cancer, Ewing's sarcoma, and hematologic malignancies), and its restored expression induces cell death (Gober et al., 2003; Gober et al., 2005; Li et al., 2007; Cui et al., 2012). Tumor cell death is through the activation of death pathways that lead to apoptosis as well as the activation of additional tumor suppressor functions, including upregulation of the haploinsufficient tumor suppressor Beclin-1 (Smith et al., 2012). The role of HspB8 as a tumor suppressor is further supported by the finding of a pro-tumorigenic mutation associated with increased autokinase activity (W51C). This mutation indicates that the autokinase activity is required for the HspB8 proliferative, but not anti-proliferative (pro-apoptotic) activity (Gober et al., 2003; Smith et al., 2011; Smith et al., 2012).

Charcot-Marie-Tooth disease type 2L (CMT2L)

Note

CMT is an inherited peripheral nerve disorder divided into two types: the demyelinating form (CMT1) and the axonal defective form (CMT2). Three nonsynonymous mutations of the same Lys141 residue (K141E, K141T, K141N) in HspB8 are implicated in CMT2. The lysine residue is located in the highly conserved α-crystallin domain,

and mutations in this region interfere with chaperone activity (Nakhro et al., 2013).

Distal hereditary motor neuropathy (DHMN)

Note

DHMN is a motor disorder of the peripheral nervous system that results in atrophy and muscle wasting.

Two naturally occurring missense mutations, K141N and K141E, in the α-crystallin domain have been implicated in DHMN. These mutants cause neurite degeneration in motor but not sensory and cortical neurons (Irobi et al., 2010), which is apparently related to decreased chaperone-like activity measured on polyglutamine proteins as in vivo substrates (Carra et al., 2005).

Spinal and bulbar muscular atrophy (SBMA)

Note

SBMA is an X-linked neuromuscular disease characterized by the loss of motoneurons in the spinal cord and bulbar regions of the brain stem. Neuronal toxicity results from protein misfolding and aggregation of androgen receptor mutants that contain an elongated N-terminal polyglutamine tract (ARpolyQ) and is apparently dependent on autophagic flux failure. HspB8 restores the normal autophagic flux in motoneurons expressing ARpolyQ by exerting anti-aggregation and/or pro-degradative activity on ARpolyQ (Rusmini et al., 2013).

Limb-girdle muscular dystrophy type 1D (LGM1D)

Note

LGMD1D is a form of muscular dystrophy characterized by proximal dominant muscle weakness and atrophy and caused by mutations of the Hsp40 family member DNAJB6. Immunohistochemical analysis revealed co-accumulation of HspB8 and members of the chaperone-assisted selective autophagy complex with DNAJB6 in cytoplasmic inclusions (Sato et al., 2013).

Alzheimers

Note

HspB8 is associated with the senile plaques of Alzheimer's disease patients and the cerebral amyloid angiopathy of patients with hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D), and was shown to directly interact with amyloid-β peptide. HspB8 likely functions in maintaining the balance between production and clearance of amyloid-β, as well as its aggregation (Wilhelmus et al., 2006).

Amyotrophic lateral sclerosis (ALS)

Note

ALS is a neurodegenerative disorder characterized by the accumulation of misfolded proteins. Some familial forms of the disorder have been linked to mutations in the superoxide dismutase 1 (SOD1) gene.

Mutant SOD1 proteins misfold and form aggregates, which impair proteasomal activity. HspB8 has been shown to bind and assist in the clearance of mutant SOD1 aggregates through autophagy (Crippa et al., 2010b).

Heart failure

Note

Expression of HspB8 is induced by cardiac overload. When exposed to pressure overload, mice with a HspB8 deletion experience a faster transition into heart failure and increased mortality compared to wild type controls.

HspB8 deletion decreases the phosphorylation of the transcription factor, STAT3, impairs transactivation of the stress response genes regulated by STAT3, and causes a significant decrease in both mitochondrial STAT3 translocation and respiration. In addition, HspB8 deletion interferes with the activation of cell survival pathways, including Akt, ERK, and iNOS (Qiu et al., 2011).

Diabetes

Note

In a rat model of diabetes mellitus, increased levels of HspB8 have been observed in the blood plasma, where it is believed to play a key role in recovery and the prevention of disease-associated complications (Karthik et al., 2012).

Upregulation of HspB8, as well as other Hsps, has also been seen in the diabetic retina, implicating it in the protection of retinal neurons and prevention of diabetic retinopathy (Reddy et al., 2013).

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This article should be referenced as such:

Bollino D, Aurelian L. HSPB8 (heat shock 22kDa protein 8). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(12):907-918.