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Gene Section
Review

HSPB1 (Heat-Shock 27 kDa Protein 1)

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Identity

Other names: HSP27; HSP28; Hsp25; CMT2F; HMN2B; SRP27; HS.76067; DKFZp586P1322

HGNC (Hugo): HSPB1

Location: 7q11.23

Local order: Genes flanking HSPB1 in centromere to telomere direction:
- MDH2 (mitochondrial malate dehydrogenase precursor)
- FLJ37078 (hypothetical protein LOC222183)
- HSPB1
- YWHAG (tyrosine 3-monooxygenase/tryptophan)
- SRCRB40 (scavenger receptor cysteine-rich domain-containing group B protein precursor)

DNA/RNA

Description

The DNA sequence (1.69 Kb) contains 3 exons.

Transcription

The transcript is 847 bp.

Pseudogene

Two pseudogenes have been identified:
- a processed retropseudogene lacking promoter elements on Xp11.23 (Hickey et al., 1996);
- a 5'-truncated semiprocessed retropseudogene on 9q13-9q21 (Kappe et al., 2003).

Protein

Note

HspB1 belongs to the ubiquitous family of small heat shock proteins (sHsps). sHsps are characteri-zed by low molecular mass (12-30 kDa), a conserved C-terminal "a-crystallin" domain and oligomeric structure. sHsps bind denatured proteins and facilitate their refolding by the ATP-dependent molecular chaperones of the Hsp70 family (Haslbeck et al., 2005; Sun and MacRae, 2005).

Description

HspB1 is a protein of 205 amino acids (22783 Da), which can be phosphorylated at serines 15, 78 and 82 by mitogen- activated protein kinases associated protein kinases (MAPKAP kinase 2, MAPKAP kinase 3). Various signals modulate HspB1 phos-phorylation: growth factors, tumor necrosis factor, differentiating agents, heat and oxidative stress (Arrigo et al., 2007). HspB1 forms oligomers up to 1000 kDa, which are dynamic structures. Phospho-rylation results in a decrease size of the oligomers (Kato et al., 1994; Rogalla et al., 1999). Dissocia-tion of the oligomers is required for recognition of protein substrates (Shashidharamurthy et al., 2005).

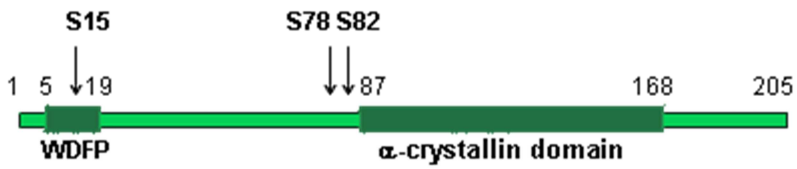


Fig.1. HspB1 contains an N-terminal hydrophobic domain with a WDFP motif and an alpha-crystallin domain at residues Glu87-Pro168. The arrows indicate phosphorylation sites at serines 15, 78 and 82.

It has been reported that HspB1 forms hetero-oligomers with other sHsps: alphaB-crystallin (HspB5) and Hsp20 (HspB6) (Zantema et al., 1992; Sugiyama et al., 2000; Bukach et al., 2009).

Expression

Ubiquitous, produced constutively at high levels in heart and skeletal muscles (Sugiyama et al., 2000); overexpressed in response to a wide variety of physiological and environmental insults; produced at high levels in many tumors (Garrido et al., 2006). Increased expression of HspB1 in response to the aggregation of proteins specific for conformational diseases have been reported by several authors (Outeiro et al., 2006; Vleminckx et al., 2002).

Localisation

Cytosol, nucleus. HspB1 has been identified as a component of the nuclear speckles, structures implied in RNA processing (Bryantsev et al., 2007).

HspB1 interacts with actin, intermediat filaments and microtubules (Landry and Huot, 1995; Mounier and Arrigo, 2002; Lee et al., 2005; Hino et al., 2000; Jonak et al., 2002). During ischemia in muscles, HspB1 is translocated from the cytosol to myofibryls (Golenhoffen et al., 2004).

HspB1 accumulates in protein aggregates associated with conformational diseases: Parkinson's disease (Outeiro et al., 2006; Zourlidou et al., 2004), Alexander disease (Iwaki et al., 1993), Alzheimer's disease (Wilhelmus et al., 2006).

HspB1 was also detected as a surface membrane protein in some cancer cell types (Shin et al., 2003).

Function

HspB1 acts as an ATP-independent molecular chaperone and prevents irreversible aggregation of bound substrates in vitro (Jakob et al., 1993).

HspB1 is involved in the remodeling of cytoskeleton during embryogenesis and protection of the cytoskeleton in cells exposed to various stresses, particularly in the skeletal and cardiac muscles (Mounier and Arrigo, 2002; Sugiyama et al., 2000; Golenhofen et al., 2004; Salinthone et al., 2008). HspB1 phosphorylated by p38 MAP kinase is necessary for migration of vascular smooth muscle cells, neutrophils, fibroblasts and breast epithelial cells (Salinthone et al., 2008).

HspB1 inhibits translation during heat shock by binding eIF4G and facilitating dissociation of cap-initiation complexes (Cuesta et al., 2000).

HspB1 interacts with different proteins of the programmed cell death machinery and thereby blocks apoptosis at distinct key points. It has been demonstrated that HspB1 sequesters cytochrome C and thus, prevents assembly of the apoptosome (Bruey et al., 2000a; Concannon et al., 2001). The release of Smac/Diablo from mitochondria is also blocked by HspB1 (Chauhan et al., 2003). In addition, HspB1 inhibits activation of procaspase-3 by caspase 9 (Garrido et al., 1999; Concannon et al., 2001). HspB1 prevents translocation of pro-apoptotic Bid to mitochondria by stabilization of actin microfilaments (Paul et al., 2002). Havasi et al. (2008) demonstrated that HspB1 inhibits activation of pro-apoptotic Bax protein via a phosphatidylinositol 3-kinase-dependent mecha-nism. In the extrinsic pathway (receptor-mediated cell death) HspB1 prevents interaction of DAXX (death domain associated protein) with Fas death receptor and protein kinase Ask1 in caspase-independent pathway (Charette et al., 2000). It has been reported by Rane et al. (2003) that HspB1 controls apoptosis by binding cytoprotective protein kinase B (Akt). Anti-oxidant properties of HspB1 play an important function in the regulation of apoptosis. HspB1 maintain glutathione in its reduced form and decrease the amount of reactive oxygen species (ROS) produced in cells exposed to oxidative stress or tumor necrosis factor TNFalpha (Arrigo et al., 2007). HspB1 may indirectly affect apoptosis by promoting degradation of death regulatory proteins by ubiquitin-proteasome path-way. Under stress conditions HspB1 stimulates ubiquitination of I-kappaBalpha, an inhibitor of the anti-apoptotic transcription factor NF-kappaB, and Kip1 a cyclin-dependent kinase inhibitor. The HspB1- mediated proteolysis of $p27^{Kip1}$ facilitates progression from G_o/G_1 to S-phase of the cell cycle (Parcellier et al., 2006).

In cancer cells HspB1 participates in oncogenesis and resistance to chemotherapy (see below). It has also been reported that expression of recombinant HspB1 at elevated levels leads to protection of human mammary epithelial cells from doxorubicin. The protection is associated with suppression of the doxorubicin-induced senescence, where HspB1 inhibits p53-mediated induction of p21 (O'Callaghan-Sunol et al., 2007). However, Venkatakrishnan and co-workers (2008) demonstra-ted that HspB1 causes p21 upregulation and G2/M phase cell cycle arrest in doxorubicin-treated fibroblasts.

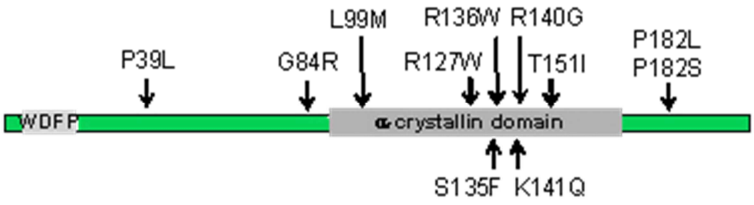
Homology

HspB1 shares homology trough the conserved alpha-crystallin domain with other members of the sHsps family. Eleven human sHsps have been identified so far: HspB1 (Hsp27) HspB2, HspB3, alphaA-crystallin (HspB4), alphaB-crystallin (HspB5), Hsp20 (HspB6), cvHsp (HspB7), HspB8 (H11), HspB9, HspB10 (ODF1) and Hsp16.2 (Kappe et al., 2003; Bellyei et al., 2007).

Mutations

Germinal

Mutations in the HSPB1 gene were found to cause distal hereditary motor neuropathy type II (dHMN II) or Charcot-Marie-Tooth disease type 2F



Gene mutation	Variation of amino acids	Disease	Inheritance	Literature
C116T	P39L	dHMN	AD	Houlden *et al.*, 2008
G250C	G84L	dHMN	AD	Houlden *et al.*, 2008
C295A	L99M	dHMN	AR	Houlden *et al.*, 2008
C379T	R127W	CMT2F	AD	Evgrafov *et al.*, 2004 Tang *et al.*, 2005
C404T	S135F	CMT2F	AD	Evgrafov *et al.*, 2004
		dHMN	AD	Houlden *et al.*, 2008 Chung *et al.*, 2008
C407T	R136W	CMT2F	AD	Evgrafov *et al.*, 2004
C418G	R140G	dHMN	AD	Houlden *et al.*, 2008
A421C	K141Q	dHMN	AD	Ikeda *et al.*, 2009
C431T	T151L	dHMN	AD	Evgrafov *et al.*, 2004
C544T	P182S	dHMN	AD	Kijima *et al.*, 2005
C545T	P182L	dHMN	AD	Evgrafov *et al.*, 2004

Fig2. Distribution of HSPB1 mutations in dHMN II and CMT2F patients.
dHMN: distal hereditary motor neuropathy, CMT: Charcot-Marie-Tooth type 2F disease, AD: autosomal dominant, AR: autosomal recessive.

(CMT2F). Five of the mutations are located in the alpha-crystallin domain (see figure 2).
Dierick and co-workers (2007) identified a HSPB1 promoter variant (c.-217T>C) in an ALS patient, which drastically impaired the HSPB1 heat shock response.

Somatic

Not known.

Implicated in

Various cancers

Disease

Increased levels of HspB1 have been detected in breast cancer, ovarian cancer, osteosarcomas, endometrial cancer and leukemias (Garrido et al., 2006; Ciocca and Calderwood, 2005). It was also reported that the pattern of HspB1 phosphorylation in tumor cells is different from that observed in nontransformed cells (Sarto et al., 2004; Tremolada et al., 2005).

Prognosis

Overexpression of HspB1 correlates with poor prognosis in gastric, liver, prostate carcinoma and osteosarcomas (Glaessgen et al., 2008; Romani et al., 2007; Ciocca and Calderwood, 2005).
Increased IbpB1 expression is associated with a favorable prognosis in schistosomiasis-associated bladder carcinoma (El-Meghawry El-Kenawy et al., 2008), neuroblastoma (Zanini et al., 2007) and non-small cell lung carcinoma (Malusecka et al., 2008).
Patients with reduced HspB1 expression have poorer survival rates in oral squamous cell carcinoma (Lo Muzio et al., 2004) and ovarian carcinoma (Geisler et al., 2004).
Lower lymphocyte HspB1 level is associated with an increased risk of lung cancer (Wang et al., 2008).

Cytogenetics

Not reported.

Hybrid/Mutated gene

Not known.

Abnormal protein
Not known.

Oncogenesis
HspB1 is involved in oncogenesis and resistance to various anti-cancer therapies due to its cytoprotective activities. It is suggested that HspB1 plays a crucial function during metastasis formation (Zhao et al., 2007).
Strategies combining chemo- or radiotherapy with down-regulation of HspB1 have been proposed as effective anti-cancer treatments. The HspB1 knockdown by using small interfering RNA (siRNA) increases sensitivity of human epithelial cells to geldanamycin (McCollum et al., 2006) and pancreatic cancer cells to gemcitabine (Mori-Iwamoto et al., 2007). Blocking HspB1 by antisense RNA restores apoptosis induced by drugs in multiple myeloma cells (Chauhan et al., 2003) and human bladder cancer cells (Kamada et al., 2007). Various cancer cells transfected with antisense Hsp27 cDNA exhibits increased sensitivity to gamma-irradiation (Aloy et al., 2008). Down regulation of HspB1 by interferon C enhances drug sensitivity in oral squamous cell carcinoma (Yonekura et al., 2003). Kim et al. (2007) has demonstrated that a heptapeptide derived from protein kinase C delta (PKC delta)-V5 region sequesters HspB1 and sensitizes human cancer cells to irradiation and cisplatine.

Charcot-Marie-Tooth type IIF disease (CMT-IIF) / distal hereditary motor neuropathy (dHMN)

Note
A number of mutations in HspB1 has been identified that are associated with dHMNII or CMT2F (table of figure 2). The exact pathogenic mechanism of the HspB1 mutations is not yet understood. Expression of the mutant HspB1 (P182S) results in the formation of insoluble aggregates, affects assembly of neurofilament net-work and axonal transport in cortical neurons (Ackerley et al., 2006; Evgrafov et al., 2004; Zhai et al., 2007).

Disease
CMT disease and dHMN belong to a clinically heterogeneous group of disorders characterized by progressive weakness and distal limb muscle atrophy due to nerve degeneration. The neuropathy of CMT affects both motor and sensory nerves. The phenotype of dHMN II resembles CMT2F, but sensory abnormalities are absent in dHMNII.

Conformational disorders

Disease
One of the characteristics of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amylotrophic lateral sclerosis (ALS) and Huntington disease is the formation of protein aggregates. HspB1 and other molecular chaperones are often detected as components of these aggregates.
Cerebral deposits of intracellular neurofibrylllary tangles and extracellular aggregates of amyloid beta peptide (Abeta) are the pathological hallmarks of Alzheimer's disease. Intracellular Lewy bodies associated with Parkinson's disease contain alpha-synuclein. In Huntington's disease (HD), a proteo-lytic fragment of the huntingtin protein that contains an expanded polyglutamine tract (polyQ), misfolds and forms aggregates. Rosenthal fibers of Alexander disease are cytoplasmic inclusions within astrocytes, which contain glial fibrillary acidic protein (GFAP) (Iwaki et al., 1993; Der Perng et al., 2006).
Numerous studies indicate that molecular chaperones associated with intra- and extracellular protein deposits, affects their production and toxicity.
It has been reported that HspB1 inhibits assembly of Abeta fibryls in vitro and reduces cerebrovascular toxicity of Abeta (Wilhelmus et al., 2006). HspB1 also inhibits GFAP polymerization (Der Perng et al., 2006) and toxicity induced by overexpression of alpha-synuclein or polyQ in neuronal cells (Outeiro et al., 2006; Zourlidou et al., 2004; Wyttenbach et al., 2002). It is proposed that the sequestering of HspB1 by Rosenthal fibers diminishes its function as an anti-apoptotic factor which in turn results in astrocytes degeneration (Mignot et al., 2004). Similarly, association of HspB1 with mutated Cu/Zn superoxide dismutase 1 (SOD1) may induce apoptosis (Okado-Matsumoto and Fridovich, 2002). Missense mutations in the gene coding for SOD1 cause familial cases of amyotrophic lateral sclerosis (ALS) characterized by the death of large motor neurons in the cerebral cortex and spinal cord (Rakhit and Chakrabartty, 2006).

Williams syndrome

Note
Stock et al. (2003) used FISH to map the HspB1 gene and they found that the band 7q11.23 also contains the site of the deletion associated with Williams sydrome (WS). The HSPB1 gene was deleted in three out of six WS patients examined in this study.

Disease
Williams syndrome (WS, also known as Williams-Beuren syndrome, WBS) is a rare neurodevelop-mental disorder characterized by multiple anoma-lies including: typical facial dysmorphisms (elfin face), congenital heart defects, infantile hypercalcemia, mental retardation and growth deficiency.

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