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Gene Section
Review

HSPA8 (heat shock 70kDa protein 8)

Tuoen Liu, Shousong Cao

Department of Internal Medicine, Division of Oncology, Washington University School of Medicine, St Louis, Missouri, United States (TL), Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14263, United States (SC)

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Abstract

Review on HSPA8, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: HSC54, HSC70, HSC71, HSP71, HSP73, HSPA10, LAP1, NIP71

HGNC (Hugo): HSPA8

Location: 11q24.1

DNA/RNA

Note

The human HSPA8 gene includes nine exons and eight introns. It is mapped into chromosome 11, 11q23.3-q25 (Sonna et al., 2002). Introns 5, 6 and 8 contain highly conserved repeats about 90 bp which code for U14 snoRNA (Chen et al., 1996). Exons 2, 3, 6, 7, and 9 code for the peptides of extremely uniform length, between 61 and 69 amino acids while exons 4, 8 and 5 code for peptides of 51, 78 and 185 amino acids, respectively. Two 150 bp direct repeats (nt 674 to nt 829 and nt 1783 to nt 1937) are 85% homologous to each other (Dworniczak and Mirault, 1987).

Description

The gene coding for HSC70, HSPA8 affects the posttranscriptional silencing mediated by RNAi and is a component of the RNAi pathway in Drosophila cultured cells (Dorner et al., 2006). The promoter region of the HSPa8 gene includes a TATA box, two CCAAT boxes, two SP1 elements and two sets of heat shock response elements (HSE) where the heat shock transcriptional factors bind (Chen et al., 2002).

Protein

Note

The HSPA8 gene coding for the protein HSC70, also known as HSP73, is a 73 kDa heat shock cognate protein.

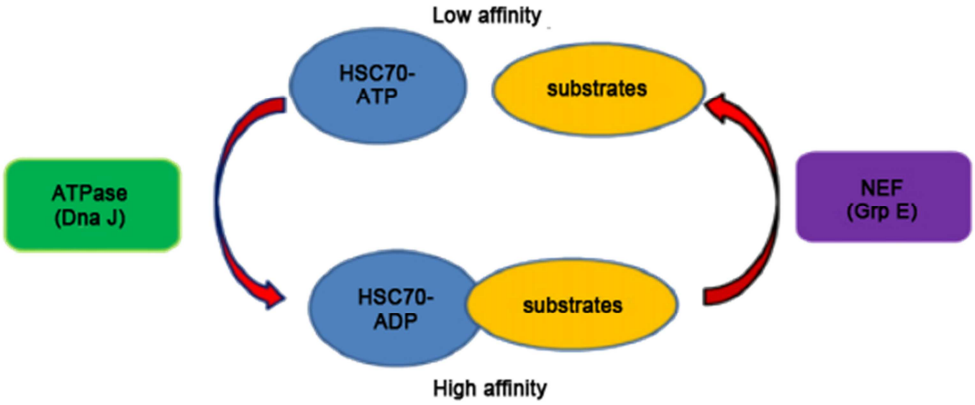
HSC70 is an ATP binding chaperone and has intrinsic ATPase activity which hydrolyzes ATP into ADP (Jakob et al., 1996).

HSC70 hydrolyzing ATP initiates the conformational change of HSC70 and further causes substrate binding by HSC70 (Sullivan and Pipas, 2002).

Description

HSC70, also called HSP73, is a 73 kDa heat shock cognate protein. The basic structure of human HSC70 includes three parts: a 44 kDa amino-terminal adenosine triphosphatase (ATPase) domain (residues 1-384), also known as the ATP-binding domain, an 18 kDa peptide (substrate) binding domain (residues 385-543), and a 10 kDa carboxyl-terminal domain (residues 544-646) which is also designated as the variable or "lid" domain (Smith et al., 1998; Tsukahara et al., 2000; Sullivan and Pipas, 2002).

The carboxyl-terminal amino acid sequence Glu-Glu-Val-Asp (EEVD motif), which is absolutely conserved in all eukaryotic HSC70 and HSP70 family members, is essential for association with some co-chaperones (Mosser et al., 2000).



The model for HSC70 and substrates binding and releasing cycle. In the ATP-bound state, HSC70 has low affinity with the substrates. After hydrolysis of ATP with the ATPase activity, HSC70 in the ADP bound state binds with the substrates with high affinity. Some co-chaperones such as Dna J homologues enhance the ATPase activity of HSC70. Nucleotide exchange factors such as GrpE enhance the dissociation of bound ADP from HSC70 to allow the binding of ATP, resetting the cycle.

Two amino acid sequences have the characteristics of nuclear localization signals in human HSC70 which are involved in nuclear import of HSC70: DAKRL69-73 in the amino-terminal and KRKHKKDISENKRAVRR246-262 in the ATPase domain (Lamian et al., 1996; Tsukahara and Maru, 2004).

Expression

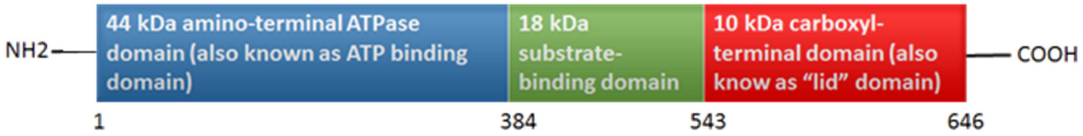
Various conditions and molecules can affect the expression of the HSPA8 gene.
The table below summarizes the factors which affect the expression of the HSPA8 gene (Liu et al., 2012).

Localisation

HSC70 is a major cytosolic molecular chaperone (Place and Hofmann, 2005).
However, HSC70 is also located in various cellular locations such as nuclear and close to cellular membrane (Arispe et al., 2002).
HSC70 can interact with the lipid bilayer in the cellular membrane directly and form ion-conductance channels allowing ion flow through the cellular membrane.
HSC70 is also identified as a tyrosine-phosphorylated protein associated with the nuclear envelope. HSC70 supports the nuclear import of karyophilic proteins and may play a role in nucleocytoplasmic transport (Otto et al., 2001).

Function

1. As a molecular chaperone, HSC70 regulates protein folding, maintains protein normal structure and functions, and protects cells from physical and chemcial damage. HSC70 regulates protein maturation and interacts with nascent polypeptides in the process of new protein synthesis (Beckmann et al., 1990; Beckmann et al.,1992). HSC70 can also regulate the translocation of proteins into different cellular organelles such as endoplasmic reticulum and mitochondria (Chirico et al., 1998, Sheffield et al., 1990).
2. HSC70 was oginally characterized as an uncoating ATPase that dissociates clathrin triskelions from clathrin-coated vesicles. It catalyzes the ATP-dependent uncoating of clathrin-coated pits (chappell et al., 1986; Goldfarb et al., 2005).
3. HSC70 is involved in targeting protein to lysosomes for degradation (Terlecky et al., 1992) and to ubiquitin/proteasome machinery for degradation (Massyuki, 1994).
4. HSC70 regulates cellular signaling and functions such as steroid receptor maturation and Akt signaling pathway (Kimmins and MacRae, 2000; Shiota et al., 2010).
5. HSC70 is important in regulating apoptosis, embryonic development and aging (Beere, 2004; Sreedhar and Csermely, 2004; Kodiha et al., 2005).



The structure of HSC70. The basic structure of human HSC70 includes three parts: a 44 kDa ATPase domain, an 18 kDa peptide (substrate) binding domain and a 10 kDa carboxyl-terminal domain, also known as "lid" domain.

Increase HSPA8 expression	Decrease HSPA8 expression
Stress	Sodium 4-phenylbutyrate
Heat	Butyrate
Organochlorine	Glycerol
Sodium arsenite	Quercetin
Azetidine	Arginase
Heave metals (nickel, cooper, lead, cadmium)	3,3',4,4',5-Pentachlorinateed biphenyls 126 (PCB126)
Exercise	Mitotane (in mitochondria)
Antimony containing drugs	Deoxyspergualin (DSG)
Geranylgeranylacetone	cAMP
Ethanol	D-galactosamine
Phorbol 12-myristate 13- acetate	Lipopolysaccharide
Estrogen	INF-gamma
Progesterone	TNF-alpha
IL-1 beta	Oxymatrine
Krüppel-like factor 4	HSP70 overexpression
Insulin	

Homology

HSC70 belongs to the HSP70 family in which includes other three members: the HSP70, the glucose-regulated protein 78 (GRP78), and HSP75. Human HSC70 shares 85% amino acid similarity with HSP70 (Ali et al., 2003).
They have similar functions and interact with each other in an ATP-dependent manner.
HSC70 can form a stable complex with newly synthesized HSP70 upon heat shock (Brown et al., 1993).

Implicated in

Various cancers

Note

The HSPA8 gene is higher expressed in some cancer cells such as human colon cancer (Kubota et al., 2000).
HSC70 regulates functions of various cancer-related genes and proteins. HSC70 functions as a molecular stabilizer of nonphosphorylated retinoblastoma protein (pRb) by directly binding to it (Inoue et al., 1995).
HSC70 binds to a mutant form of p53 and p73 and links them for degradation.
HSPA8 gene can suppress oncogene (such as mutant p53 and Ras) mediated transformation (Yehiely and Oren, 1992; Gaiddon et al., 2001).

Cytogenetics

Intronic polymorphism (1541-1542delGT) of HSPA8 is associated with decrease of lung cancer risk (Rusin et al., 2004).

Cadiovascular diseases

Note

HSC70 plays a protective role in myocardial injuries. HSC70 is commonly found in atherosclerotic plaques during the atherogenesis and therosclerotic plaque progression and it appears to be a protective factor against cellular stress (Dupont et al., 2008).
HSC70 expression is significantly decreased in diabetic myocardium because of insulin deficiency.
Insulin directly increases the abundance of HSC70 in cultured cardiomyocytes and overexpression of HSC70 leads to protect against stress via suppression of apoptosis signalling (Chen et al., 2006).

Neurological diseases

Note

HSC70 is directly involved in cell survival during neurulation and HSC70 acts as an intrinsic protector of neuroepithelial and neural precursor cells (Rubio et al., 2002).
HSC70 mediates the chaperone mediated lysosomal degradation of α-synuclei which is accumulated in Parkingson's disease and other neurodegenerative diseases (Mak et al., 2010).
HSC70 facilitates degradation of the amyotrophic lateral sclerosis (ALS) -linked mutant SOD1 protein in an ubiquitination-dependent manner (Urushitani et al., 2004; Casoni et al., 2005).
HSC70 mediates the autophagy for the degradation of mutant huntingtin protein which can cause Huntington's disease (Bauer et al., 2010).

Liver diseases

Note

HSC70 has been implicated in the pathogenesis and the pathophysiology of hepatic diseases such as hepatitis B and C, non-alcoholic steatohepatitis autoimmune hepatitis, and primary biliary cirrhosis.
HSC70 plays important role in the replication of hepatitis B virus and hepatitis C virus.
HSC70 could be a novel molecular target for diagnosis and treatment of hepatitis B and C (Wang et al., 2010).

To be noted

Note

HSC70 interacts with many molecules and plays an important role in regulating cellualr functions. As a molecular chaperone, HSC70 interacts with co-chaperones, also called co-factors. Those co-chaperones include auxilin, BAG family members, Hip, Hop, HSPBP1 and CHIP (Liu et al., 2012). In addition to co-chaperones, HSC70 interacts with many other cellular molecules. The cooperation of HSC70 with HSP90 regulates the glucocorticoid receptor activation and signaling pathway (Furay et al., 2006). HSC70 facilitates the heat-shock factor1 mediated cell survival in response to cellular stress (Ahn et al., 2005). HSC70 interacts and forms a complex with histone deacetylase 3 (HDAC3). HSC70 interacts with newly synthesized cyclin D1 and mature cyclin D1/CDK4 holoenzyme complex, thus involved in cell cycle regulation (Diehl et al., 2003). HSC70 interacts genetically with target of rapamycin (TOR) and acts as a regulator of endocytosis (Hennig et al., 2006). HSC70 can regulate the synthesis of GABA by interacting with the rate-limiting enzyme L-glutamic acid decarboxylase (GAD).

Research has been conducted to use HSC70 as a drug target for cancer therapy. A recombinant vaccine composed of CD4+ and CD8+ T cell epitopes fused to HSC70 may prevent tumor growth and metastasis (Mizukami et al., 2008). Fusion the ATPase domain of HSC70 with tyrosinase-related protein-2 acts as a tumor vaccine against B16 melanoma (Zhang et al., 2006).

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