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Review:

What we know about ST13, a co-factor of heat shock protein, or a tumor suppressor?*

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Abstract: This article is to summarize the molecular and functional analysis of the gene "suppression of tumorigenicity 13" (ST13). ST13 is in fact the gene encoding Hsp70 interacting protein (Hip), a co-factor (co-chaperone) of the 70-kDa heat shock proteins (Hsc/Hsp70). By collaborating with other positive co-factors such as Hsp40 and the Hsp70-Hsp90 organizing protein (Hop), or competing with negative co-factors such as Bcl2-associated athanogen 1 (Bag1), Hip facilitates may facilitate the chaperone function of Hsc/Hsp70 in protein folding and repair, and in controlling the activity of regulatory proteins such as steroid receptors and regulators of proliferation or apoptosis. Although the nomenclature of ST13 implies a role in the suppression of tumorigenicity (ST), to date available experimental data are not sufficient to support its role in cancer development, except for the possible down-regulation of ST13 in gastric and colorectal cancers. Further investigation of this gene at the physiological level would benefit our understanding of diseases such as endocrinological disorders, cancer, and neurodegeneration commonly associated with protein misfolding.

Key words: ST13, Hip, p48, Hsc/Hsp70, Heat shock protein, Protein folding, Steroid receptor, Tumorigenicity
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INTRODUCTION

In the early 1990's, in an attempt to clone differentially expressed genes in human colorectal cancer, scientists at Zhejiang Medical University (now School of Medicine, Zhejiang University) and Shanghai Cancer Institution implemented a cDNA technology called "subtractive hybridization" (Shi *et al.*, 1992; Zheng *et al.*, 1994; 1997; Mo *et al.*, 1996; Cao *et al.*, 1997). As a result, 46 cDNA clones were isolated and their corresponding genes were identified as "down-regulated" genes in colorectal cancers. These clones were initially named as an "SNC" series (subtracted from normal and cancer tissues), and two of them, SNC6 and SNC19, were deposited at GenBank with full-length cDNA sequences by Zheng *et al.*(1994). SNC6 was then annotated as the "human putative tumor suppressor SNC6" with accession No. U17714. Historically this was the first record of this human gene in public databases. In recent versions of GenBank, U17714 has been replaced by NM_003932 and renamed as "suppression of tumorigenicity 13 (ST13) (colon carcinoma) (Hsp70 interacting protein)". What is ST13 and its function? Is there any implication of this gene in human disease? This paper presents a review on gene ST13, addressing these questions with the information to date available from public databases and literature.

DATA MINING

As an official gene symbol approved by HUGO (Human Genome Organization), "ST13" is currently accessible at multiple public databases, e.g., Entrez Gene: 6767, UniGene: Hs.447477, HGNC (HUGO

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Gene Nomenclature Committee): 11343, OMIM (Online Mendelian Inheritance in Man): 606796, and HPRD (Human Protein Reference Database): 08426. According to these data, ST13, mapped on chromosome 22q13, encodes a 369-amino acid, cytosolic protein. ST13 contains a TPR (tetratricopeptide repeat) domain at its central region and a Sti1 domain (heat shock chaperonin-binding motif) at its C-terminus (Fig.1a). However, there is considerable confusion in the nomenclature of this gene. Besides ST13 and SNC6, it has also designated as Hip (Hsp70 interacting protein), p48 (progesterone receptor-associated p48 protein), or Hop (Hsp70-Hsp90 organizing protein). Databases such as Entrez Gene and OMIM summarize the gene with biographies originally for Hop or for both Hip and Hop. After careful data curation, we identified that Hip and p48 are indeed the same protein, and the correct gene product of ST13. However, Hop, a protein of 543 residues containing 3 TPR domains and one C-terminal Sti1 domain, is encoded by the gene STIP1 (stress-induced-phosphoprotein 1) located on chromosome 11q13. Obviously, Hop has been misplaced and this particular entry calls for database revision. This article accordingly refers to Hip or p48 as the protein product of the ST13 gene.

Cloning

Hip first appeared in the literature as the 48-kDa component, p48, of progesterone receptor (PR)-chaperone complexes found in rabbit reticulocyte lysates (Smith, 1993; Smith *et al*., 1995). Using an antibody developed against the purified rabbit p48 protein, Prapapanich *et al*.(1996a) cloned human p48 cDNA from a HeLa cell cDNA library. The deduced 369-amino acid protein had a calculated molecular mass of ~41 kDa. However, the protein product from the cDNA migrated identically with rabbit p48 by SDS-PAGE and associated with PR in a similar manner (Prapapanich *et al*., 1996a). Independently, around the same time or a little earlier, the cloning of Hip was also accomplished by another two groups: Zheng *et al*.(1994), in the above-described search for genes differentially expressed in colorectal cancer, and Höhfeld *et al*.(1995), in a search for proteins interacting with the 70-kDa heat shock proteins (Hsc/Hsp70). In the latter case, the N-terminal ATPase domain of Hsc70 was used as bait in yeast two-hybrid screening of a rat cDNA library. A cDNA sequence encoding a 41-kDa protein was isolated and designated Hip. Given that the human p48 cDNA and the rat Hip cDNA are over 90% identical, and that they are the presumptive species homologues of each other, in most subsequent publications, including that from Prapapanich *et al*.(1996a), the term Hip has been adopted in place of p48.

Protein structure

In the same report of Hip cloning, Höhfeld *et al*.(1995) demonstrated that Hip regulates Hsc70 activity. Hip binds to the Hsc70 ATPase domain and stabilizes the chaperone in the ADP-bound form having high affinity for polypeptide substrates (see below for details). In order to better understand the function of this novel co-chaperone, structural elements of the protein were characterized based on sequence alignment criteria and mutagenesis studies (Prapapanich *et al*., 1996b; 1998; Irmer and Höhfeld, 1997). As shown in Fig.1a, Hip is composed of an N-terminal region (residues 1~100), a central, TPR domain (residues 114~215) followed by a highly charged region (residues 230~272), and a C-terminal region (residues 283~369) containing GGMP repeats and a Sti1 motif.

Analysis of various Hip mutants encoded by truncated or deleted cDNAs revealed that the Hip TPR domain and flanking highly charged region are required for Hip to bind the Hsc/Hsp70 ATPase domain. The TPR is a protein-protein interaction domain which particularly facilitates interaction with heat shock proteins. The TPR domain had been previously found in Hop and in the Hsp90-binding immunophilins. The N-terminal region is responsible for protein homo-oligomerization, likely dimerization (Velten *et al*., 2000; 2002). However, monomeric Hip is still able to bind Hsp70, suggesting that homo-oligomerization is not required for interaction with Hsp70 (Prapapanich *et al*., 1996b). Another publication reported that truncating the N-terminus demolished Hip's ability to stimulate Hsp70-mediated protein refolding (Nollen *et al*., 2001). As for the C-terminal region, within which the GGMP repeats and the Sti1 motif are known to be shared by Hsp70 and Hop, respectively, the exact function remains unclear. Prapapanich *et al*.(1998) suggested that the C-terminal region of Hip may function in Hsc70-Hsp90 cooperation.

Molecular function

Since Hip was first identified through its interaction with the ATP-binding domain of Hsc70, and found to share structural domains with Hsc70 and other Hsc70/Hsp90-asssociated co-chaperones, it has long been considered as an Hsp70-specific co-chaperone.

The mammalian cytosolic Hsp70 proteins (or Hsc/Hsp70, referring to both the constitutively expressed 70 kDa heat shock cognate protein Hsc70 and the heat-inducible Hsp70) are key chaperones in protein folding, assembly, transport, degradation, and control of the activity of regulatory proteins (e.g., steroid hormone receptors, certain kinases and transcription factors) (Hartl, 1996; Bukau and Horwich, 1998; Esser *et al*., 2004; Mayer and Bukau, 2005). Hsc/Hsp70 appears to function in a dynamic cycle of binding and releasing polypeptide substrate coupled to a cycle of ATP binding and hydrolysis by the intramolecular ATPase. In the ATP-bound state, Hsc/Hsp70 exhibits fast kinetics and low affinity for polypeptide substrates, whereas in the ADP-bound state, Hsc/Hsp70 exhibits slow kinetics and high affinity for polypeptide substrates. Current models of how these cycling states are regulated involve at least five different co-chaperones: Hsp40, Hip, Hop, Bag-1 (Bcl2-associated athanogene 1, or RAP46), and CHIP (carboxy terminus of Hsc70 interacting protein) (Figs.1b).

As shown in Fig.1b, the initial binding of Hsc/Hsp70 to a polypeptide substrate is achieved through cooperation of the chaperone with a member of the Hsp40 family, homologues of the bacterial DnaJ protein (Freeman *et al*., 1995). Hsp40 stimulates the ATPase activity of Hsc/Hsp70 and generates the high affinity, ADP-bound state. However, in the presence of Hsp40 alone, the ADP state of Hsc/Hsp70 is unstable, and the newly formed Hsc/Hsp70-substrate complex may end up with premature dissociation (Höhfeld *et al*., 1995). As described above, the TPR domain of Hip binds to the Hsc70 ATPase domain; this stabilizes the ADP-bound state of Hsc/Hsp70, thus stabilizing the chaperone-substrate complex (Höhfeld *et al*., 1995). Subsequently, another co-chaperone Hop, homologue of yeast Sti1, associates with Hsp70: the Hop TPR domain binds to the Hsp70 C-terminus. Hop is actually an Hsp70/Hsp90-organization protein (as it is named), with its three TPR domains serving as non-overlapping binding sites for both Hsp70 and Hsp90. Interaction with Hop directs Hsp90 to the Hsp70 substrate complex (Frydman and Höhfeld, 1997; Chen and Smith, 1998; Hernandez *et al*., 2002). As Hop can stimulate ADP/ATP exchange by Hsp70, Hop's coupling of Hsp70 and Hsp90 is accompanied by transfer of substrate from Hsp70 to Hsp90, and release Hsp70 chaperone components. This Hsp70-Hsp90 cooperation is considered necessary for the conformational regulation of signaling proteins such as tyrosine kinases and steroid hormone receptors (Frydman and Höhfeld, 1997).

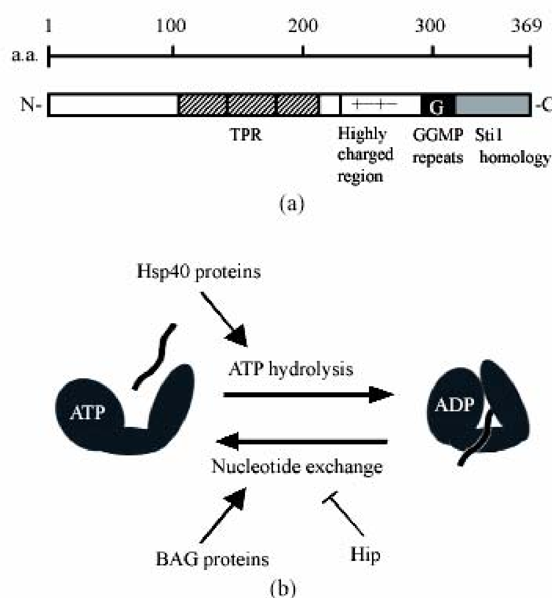

Fig.1 Protein structure and molecular function of Hip. (a) Structurally distinct regions in the Hip protein (see text for details); (b) Conversion of the ATP/ADP-bound states of Hsc/Hsp70 and the interaction of Hsc/Hsp70 with co-chaperones. Hsp40 stimulates the ATPase activity of Hsc/Hsp70 and generates the ADP-bound state with high affinity for a polypeptide substrate. The binding of Hip to the ATPase domain of Hsc/Hsp70 stabilizes the ADP-bound state, preventing the newly formed Hsc/Hsp70-substrate complex from prematurely dissociating. On the other hand, BAG proteins (e.g., Bag-1) competitively bind to the ATPase domain and stimulate the ADP dissociation of Hsc/Hsp70, promoting the release of polypeptide substrates

In addition to these positive regulators of the Hsp70 chaperone, two inhibitory co-chaperones have been identified: Bag-1 and CHIP. Bag-1 was originally discovered as a Bcl2-associated protein. Bag-1 has since been found to bind the ATPase domain of Hsp70 in a manner competitive with Hip (Höhfeld

and Jentsch, 1997; Takayama *et al*., 1999; Alberti *et al*., 2003). In contrast to Hip, Bag-1 stimulates the ADP dissociation rate of Hsc/Hsp70, promoting the release of polypeptide substrates, and thus inhibiting Hsc/Hsp70 chaperone activity. Several Bag-1-related proteins have recently been identified in human cells (Takayama *et al*., 1999). They all share a conserved BAG domain and compete with Hip in binding to the ATPase domain of Hsc/Hsp70 in vitro. Bag-1 also contains an ubiquitin-like domain that is anticipated to mediate the interaction of Bag-1 with the proteasome (Alberti *et al*., 2002). CHIP initially identified as a negative co-factor for human Hsc70, has both a TPR domain and an ubiquitin ligase-related U-box domain (Ballinger *et al*., 1999; Murata *et al*., 2001; 2003). The CHIP TPR domain competes with Hop for binding to Hsc70 and Hsp90, and inhibits Hsp40-stimulated Hsc/Hsp70 ATPase activity. Meanwhile the CHIP U-box domain acts as an E3-ubiquitin ligase to promote the ubiquitination and proteasomal degradation of the Hsc/Hsp70 polypeptide substrates (Murata *et al*., 2001; 2003). Thus, both inhibitory co-factors Bag-1 and CHIP have the potential to shift Hsp70 activity from protein folding to protein degradation. In summary, the chaperone activity of Hsc/Hsp70 is regulated by a network of cooperating and competing co-factors; among these, the ST13 gene product Hip is one of the major positive regulators stabilizing the ADP state of Hsc/Hsp70 and thereby preventing premature release and/or proteolysis of substrate.

Despite considerable progress in understanding the general mode of interaction between Hsc/Hsp70 and these co-chaperones, the exact molecular mechanism by which an individual cofactor, such as Hip, acts toward a specific substrate, such as steroid receptors, is still unclear and somewhat controversial. A model has been proposed in which Hip mediates the transition of PR complexes from early to intermediate stages; this model is based on the observation that C-terminal dominant-negative mutants of Hip cause a dose-dependent inhibition of receptor assembly with Hsp90 (Prapapanich *et al*., 1998). However, other studies suggest that Hip is not essential for the in vitro assembly of the multi-chaperone complexes for either PR or the glucocorticoid receptor (GR) (Kosano *et al*., 1998; Kanelakis *et al*., 2000). Depletion of Hip from the in vitro system or addition of high levels of Hip does not affect the rate of receptor assembly and functional maturation (Kanelakis *et al*., 2000). The same set of data revealed an alternative role for Hip in the regulation of GR signaling. Hip can oppose the inhibition Bag-1 exerts on receptor assembly and activation. In contrast, a more recent report maintains that the functional maturation of GR is directly enhanced by Hip (Nelson *et al*., 2004). It has also been questioned if Hip does stabilize Hsp70 binding to GR (Kanelakis *et al*., 2000), and if binding of Hip to Hsp70 is required for Hip's effect on GR maturation (Nelson *et al*., 2004). Furthermore, new evidence indicates that Hip can directly interact with certain protein substrates (e.g., the membrane chemokine receptor CXCR2) in an Hsp70-independent manner (Fan *et al*., 2002).

Physiological and pathophysiological role

To date, most of our knowledge regarding Hip has been obtained at the molecular level. Very little is known about the function of Hip in vivo. No human hereditary disease has been linked to the gene ST13 (see OMIM link 606796). Neither in vivo transgenic nor knockout studies on this gene have been reported. Based on Hip's function as a positive co-factor for Hsp70, one can speculate that Hip plays a physiological role similar to or overlapping with that of Hsp70. Protein misfolding and aggregation are considered major contributors to neurodegenerative disorders such as Alzheimer's, Huntington's or prion disease. Hsp70 is expected to provide a means of treating these diseases due to the association of Hsp70 with aggregated or misfolded proteins with Hsp70 (Barral *et al*., 2004). Induction of Hsp70 has shown signs of help in neurological diseases and other chronic conditions (Klettner, 2004; Mayer and Bukau, 2005; Sõti *et al*., 2005; Evans *et al*., 2006). However, no experimental evidence has yet linked Hip with these diseases, nor has even an expressional correlation been shown. Another well-recognized function of Hsp70 is the conformational regulation of signal transduction proteins. These proteins, called clients, include nuclear receptors such as PR and GR, kinases such as Raf, eIF2α-kinase, or CyclinB1/Cdk1, and transcription factors such as HSF, c-Myc, or pRb. As mentioned, Hip itself is a component of the PR assembly complex (Smith, 1993; Smith *et al*., 1995; Prapapanich *et al*., 1996a), and may enhance the functional maturation of GR in vitro (Nelson *et al*., 2004). However, data has not confirmed that Hip actually plays a role in the endocrine system in vivo. It is hypothesized that the expression levels of chap-

erones and co-chaperones might be determinants of glucocorticoid resistance in the treatment of acute lymphoblastic leukemia (ALL). Apparently this is not the case, since Tissing *et al*.(2005) found no significant difference in the mRNA levels of these (co)chaperones, including Hip, between glucocorticoid-sensitive and -resistant patients.

On the other hand, much more attention has been paid to the implication of Hsp70 in cancer and cancer therapy. This research focus derives from the following points: (1) Hsp70 has been expected to function in signal transduction, cell cycle regulation, differentiation, and programmed cell death through interacting with its client proteins; (2) over-expression of Hsp70 leads to increased resistance to apoptotic agents (Jäättelä *et al*., 1998; Jäättelä, 1999), whereas selective depletion of Hsp70 results in massive apoptosis of cancer cells (Nylandsted *et al*., 2000); (3) Hsp70 is generally expressed in various human tumors and tumor cell lines, with the level of expression correlating with poor therapeutic outcome in certain cancers (e.g., breast, endometrial, uterine cervical, and bladder carcinomas) (Ciocca and Calderwood, 2005; Ciocca *et al*., 1993; Vargas-Roig *et al*., 1997); and (4) inhibitors of Hsp70's sister chaperone Hsp90, such as 17-AAG, exhibit a broad spectrum of anti-tumor activity and appear promising in clinical trails (Sõti *et al*., 2005; Neckers and Neckers, 2005). But no role in cancer has yet been defined for the chaperone co-factor Hip. So far only a few expression studies have been published, mostly from Zheng Shu's group who originally cloned the ST13 gene. Using Northern blot analysis and quantitative RT-PCR approaches, a decreased level of ST13 mRNA was observed in multiple colorectal cancer samples relative to that in their adjacent normal mucosa (Mo *et al*., 1996; 1997a; 1997b; Li and Zhang, 2000). However, the levels of ST13 mRNA showed no significant correlation with a tumor's differentiation grade, Dukes' stage, invasion depth, lymph node metastasis, or disease-specific survival (Dong *et al*., 2005). Similarly, recent in situ hybridization found that only 3 of 7 colon cancer tissues analyzed were positive for ST13 mRNA, whereas 7 of 7 normal colon tissues were positive (Wang *et al*., 2005).

Nevertheless, caution should be taken in the annotation of ST13 as a gene down-regulated in human cancer. It is necessary to examine gene expression at the protein level as well. In addition, patterns of Hip protein expression among different cancer tissues, and correlation between the protein level and the morphological grade for individual cancers, should also be addressed. If Hip protein expression patterns mimic the data so far obtained at the RNA level, it would spur investigation as to why this Hsp70 cochaperone is down-regulated while the chaperone itself is over-expressed (see above). A recently reported immunohistochemistry study indicated that this down-regulation of Hip protein was likely a special case for gastric and colorectal carcinomas (Zheng *et al*., 2005). Other types of cancers examined in the same study failed to follow this pattern. In contrast, as compared with their adjacent normal tissues, carcinomas of breast, ovary, and endometrium all exhibited increased signal intensity when probed with the anti-Hip antibody (Zheng *et al*., 2005).

SUMMARY

The name of gene ST13 implies a correlation with certain aspects of tumorigenicity. However, so far there is no adequate experimental data to support this, except for the possible decrease in gene expression in merely gastric and colorectal carcinomas. A considerable gap exists between describing this gene as down-regulated in tumors and describing it as a suppressor of tumorigenesis, unless a functional connection or pertinent mutations are found for this gene. The chromosomal region to which ST13 mapped, 22q13 (Zhang *et al*., 1998), has shown frequent loss of heterozygosity in colorectal, breast, and ovarian carcinomas (Castells *et al*., 2000). However, according to a detailed human chromosome map (the Human Genome Project), location of ST13 (22q13.2) is apparently outside the minimal region of deletion that is common for both breast and colorectal cancers (Castells *et al*., 2000). It would be worthwhile to empirically determine whether ST13 is subject to loss of heterozygosity in these carcinomas.

At the molecular level, ST13 is confirmed to be the gene encoding Hip, a positive co-factor of Hsc/Hsp70. Hip may facilitate the chaperone function of Hsc/Hsp70 in protein folding and in controlling the activity of regulatory proteins such as steroid receptors and regulators of proliferation or apoptosis. We recommend future investigation at the physiological level to address its implication in diseases: in protein misfolding-associated neurodegeneration, in endocrinological disorders, and in cancer.

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