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Regulation and function of the human *HSP90AA1* gene

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Abstract

Heat shock protein 90 α (Hsp90 α), encoded by the *HSP90AA1* gene, is the stress inducible isoform of the molecular chaperone Hsp90. Hsp90 α is regulated differently and has different functions when compared to the constitutively expressed Hsp90 β isoform, despite high amino acid sequence identity between the two proteins. These differences are likely due to variations in nucleotide sequence within non-coding regions, which allows for specific regulation through interaction with particular transcription factors, and to subtle changes in amino acid sequence that allow for unique post-translational modifications. This article will specifically focus on the expression, function and regulation of Hsp90 α .

Keywords

Molecular Chaperone; Heat Shock Protein; Stress Response; Heat Shock Element; Post-translational Modification; Drug Target; Cancer; Gene Ontology; Gene Promoter; Interactome

Introduction

Heat shock protein 90 (Hsp90) is a well-characterized, conserved and essential chaperone protein in eukaryotes. Several cellular proteins, termed ‘clients’, rely on Hsp90 for their function. In humans there are several Hsp90 isoforms including the well-known cytoplasmic Hsp90 α and Hsp90 β , as well as the endoplasmic reticulum and mitochondrial isoforms Grp94 and TRAP1, respectively (Ammirante et al. 2006).

Hsp90 comprises 1–2% of cellular protein in unstressed cells and up to 4–6% in the presence of stress (Picard 2002; Whitesell and Lindquist 2005; Stravopodis et al. 2007; Taipale et al. 2010; Finka and Goloubinoff 2013). The two isoforms of Hsp90 best studied in mammalian cells are the constitutively-expressed Hsp90 β and the stress-inducible Hsp90 α . Hsp90 α and Hsp90 β isoforms are the result of gene duplication approximately 500 million years ago (Gupta 1995). These duplication events suggest the necessity of alternate forms of Hsp90 to perform distinct cellular functions in eukaryotes (bacteria express only one Hsp90-like protein, htpG). Despite sharing 86% amino acid sequence identity, Hsp90 α

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and Hsp90 β have unique functions during embryologic development and in the cell. Given that Hsp90 α upregulation has been correlated with several diseases (see below), it is important to understand its unique functions and regulation.

Despite high amino acid identity, at the nucleotide level Hsp90 α and Hsp90 β differ more dramatically. This is especially true in the 3' and 5' non-coding regions (Rebbe et al. 1989; Zhang et al. 1999). The differences in these non-coding regions allow for specific regulation of Hsp90 α expression by different transcription factors depending on cellular conditions. Further, slight variation in amino acid sequence of the two proteins allows for unique Hsp90 α function. For example, Hsp90 α is required for peptide-loaded MHC1 complex processing in spermatocyte maturation and hERG ion channel maturation (Kunisawa and Shastri 2006; Grad et al. 2010; Peterson et al. 2012). Hsp90 α and Hsp90 β also have opposing effects on the biogenesis of KCNQ4 channels and on endothelial nitric oxide (eNOS) activity (Cortes-Conzalez et al. 2010). Hsp90 contains three conserved domains: the amino-terminal ATP-binding domain, the middle domain, and carboxy-terminal dimerization domain. Each of these domains contain post-translational modification (PTM) sites. Within the Hsp90 α protein, sequence specific post-translational modification sites are found (Taherian et al. 2008; Quanz et al. 2012; Muller et al. 2013). This allows for further regulation of Hsp90 α -specific cellular functions.

Although Hsp90 α has distinct functions from Hsp90 β and its upregulation has been correlated with disease (see below), an Hsp90 α -specific inhibitor has yet to be identified. Therefore, a better understanding of the unique functions of Hsp90 α will be important for future isoform-specific drug design.

HSP90AA1 Gene Structure

Human *HSP90AA1* is encoded on the complement strand of Chromosome 14q32.33 and spans over 59 kbp. Several pseudogenes of *HSP90AA1* exist throughout the human genome located on Chromosomes 3, 4, 11 and 14 (Ozawa et al. 1992; Chen et al. 2005). The *HSP90AA1* gene encodes for two distinct mRNA transcripts initiated from separate transcription start sites (TSS). No mRNA splice variants of *HSP90AA1* have presently been verified. Transcript variant 1 (TV1, NM_001017963.2) encodes the primate-specific 854 amino acid isoform 1 of Hsp90 α (NP_001017963) from a 3,887 bp mRNA transcript containing 12 exons spanning 59, 012 bp (Tripathi and Obermann 2013). Transcript variant 1 is located directly adjacent to the WDR20 gene, which is transcribed from the opposite coding strand. Transcript variant 2 (TV2, NM_005348.3) encodes the well-studied 732 amino acid isoform 2 (NP_005339) from a 3,366 bp mRNA transcript containing 11 exons spanning 6,438 bp (Figure 1). DYNC1H1 encodes the gene product on the other side of *HSP90AA1*, which coincidentally has been found to interact with Hsp90 α (Gano and Simon 2010). Hsp90 α TV1 and TV2 are identical except for an additional 112 amino acids on the N-terminus of isoform 1 encoded by its first 2 exons. The function of the extended N-terminal domain on isoform 1 is currently not understood. This information was gathered from both NCBI Gene and the UCSC Genome Browser.

Hsp90 α expression

Despite sharing similar amino acid sequence, Hsp90 α expression is regulated in a different manner than Hsp90 β . Hsp90 α is the stress-inducible isoform while Hsp90 β is expressed constitutively. Several heat shock elements (HSE's) are located upstream of Hsp90 α allowing for its inducible expression upon binding of heat shock factor 1 (HSF1, the master transcriptional regulator of the heat shock response). Specifically, occupancy of the HSE located at -96/-60 enhances the expression of Hsp90 α , while co-occupancy of the HSE complex at -1031/-1022 is required for a heat shock induction (Zhang et al. 1999; Sreedhar et al. 2004).

In the presence of cellular stress, Hsp90 α levels increase. Hsp90 α is also expressed at differing levels in a tissue-specific manner and is up regulated in several cancers. In leukemia Hsp90 α levels are upregulated and correlated with disease prognosis (Yufu et al. 1992; Tian et al. 2014). Increased levels of Hsp90 α also suggest poor prognosis in breast and pancreatic cancers (Jameel et al. 1992; Gress et al. 1994). In human T-cells, *HSP90AA1* expression is increased by the cytokines IL-2, IL-4 and IL-13 (Metz et al. 1996). Furthermore, Hsp90 α levels are elevated in individuals suffering from chronic obstructive pulmonary disease (COPD) (Hacker et al. 2009). Thus, in some disease instances, elevated expression of Hsp90 α potentially could serve as a prognostic indicator.

HSP90AA1 Promoter

Transcription of the *HSP90AA1* gene is currently understood to be induced by stress through binding of the master transcription factor (TF) HSF1 to the *HSP90AA1* promoter (Ciocca et al. 2013). However, several focused studies of the *HSP90AA1* promoter along with extensive global analysis of the human genome indicate that various other transcription complexes regulate *HSP90AA1* gene expression. Mammalian *HSP90AA1* along with *HSP90AB1* gene expression was first characterized in transformed mouse cells where it was shown that *HSP90AB1* is constitutively expressed 2.5-fold higher than *HSP90AA1* under normal conditions. However upon heat shock, *HSP90AA1* expression increased 7.0-fold while *HSP90AB1* increases only 4.5-fold (Ullrich et al. 1989). Detailed analysis of the *HSP90AA1* promoter shows that there are 2 heat shock elements (HSE) within 1200 bp of the transcription start site (Zhang et al. 1999, Sreedhar et al. 2004). The distal HSE is required for heat shock induction and the proximal HSE functions as a permissive enhancer. This model is supported by ChIP-SEQ analysis of cells under normal conditions where HSF1 is found bound to the proximal HSE and not detected at the distal HSE. The proto-oncogene MYC is also found to induce *HSP90AA1* gene expression and binds proximally to the TSS as verified by ChIP-SEQ. Depletion of Hsp90 α expression indicates that *HSP90AA1* is required for MYC-driven transformation (Teng et al. 2004). In breast cancer cells the growth hormone prolactin induces *HSP90AA1* expression through STAT5 (Perotti et al. 2008). NF- κ B or RELA also induces *HSP90AA1* expression possibly explaining the pro-survival ability of NF- κ B-driven transcription (Ammirante et al. 2008). Conversely, STAT1, the proto-tumor suppressor, is found to inhibit stress induced expression of *HSP90AA1* (Chen et al. 2007). In addition to these findings, ChIP-SEQ analysis of the human genome indicates that at least 85 unique transcription factors bind to the promoter

regions that drive the expression of both *HSP90AA1* transcript variants (Hudson and Snyder 2006; Euskirchen et al. 2007), thus further indicating that *HSP90AA1* gene expression may be highly regulated and complex.

Examination of the *HSP90AA1* gene structure shows that there are 3 separate RNA polymerase II (POLR2A) binding sites (Figure 2). Two of these sites (A and B) are associated with TV2 expression while one site (C) is associated with TV1 expression. Site A overlaps the TV2, TSS by 996 bp indicating that it is the primary site for transcription initiation. Site B is separated from site A by 76 bp and lies 910 bp away from the TSS. Site B also has a smaller footprint with fewer transcription factors associated with it, and therefore might serve as a secondary site for recruiting and pausing POLR2A. Site C overlaps the TSS of transcript variant 1 by 665 bp and does not cover the adjacent TSS of WDR20 which is encoded on the opposite DNA strand. This gene structure is consistent with the likelihood that *HSP90AA1* expression may be regulated by multiple factors.

The UCSC Genome Browser has gathered 161 ChIP-SEQ transcription factor profiles across the entire human genome providing a powerful resource for characterizing gene structure and regulation (Hudson and Snyder 2006; Euskirchen et al. 2007; Wang et al. 2013). Examination of the *HSP90AA1* promoter indicates that 85 different TFs in total bind to one of the three RNA polymerase II (POLR2A) binding site footprints. Each site is bound by a unique set of TFs with site A being bound by 34 unique TFs and sites B and C being bound by 3 and 11 unique TFs, respectively (Figure 2). The unique TF profiles for each POLR2A binding sites suggest that specific biological processes are associated with the initiation of transcription of *HSP90AA1* from each of these POLR2A sites. Using gene ontology, the bioinformatics initiative whose goal is to represent all gene and gene product attributes across all species, the biological processes, molecular functions or cellular components which a set of genes are most strongly associated with in a given context can be predicted. Indeed, gene ontology analysis of the complete TF set associated with each POLR2A site indicates that specific biological processes are related to each POLR2A site (Figure 3; Supplemental Table 1). Site A includes 180 unique gene ontology terms with the highest scoring biological processes terms related to regulation of cell death, apoptosis, viral processing and drug responses. Site B includes 23 unique terms with the highest scoring terms related to late viral transcription, regulation of transcription by glucose and carbon catabolites, nuclear organization and response to insulin. Overall, Site B seems to be influenced by energy supply and other metabolic processes along with viral transcription. Site C includes 31 unique terms with the highest scoring terms mainly related to regulation of cell differentiation and tissue development. This is of interest since site C controls the expression of TV1, which is not observed under most experimental conditions due to it possibly only being expressed in progenitor cells or highly specialized tissue. Together the comparison of the POLR2A binding sites along with all previous studies indicate that *HSP90AA1* expression is associated with a variety of physiological functions and not solely with the heat shock response.

HSP90 α interactome

Combined, Hsp90 α and Hsp90 β are predicted to interact with 10% of the eukaryotic proteome (Zhao et al. 2005). In humans this represents a network of roughly 2,000 interacting proteins. Presently over 725 interactions have been experimentally documented for both Hsp90 α and Hsp90 β (Escheverria et al. 2011). This connectivity allows HSP90 to function as a network hub linking diverse protein interaction networks. Within these networks HSP90 primarily specializes in maintaining and regulating proteins involved in signal transduction or information processing. These include transcription factors that initiate gene expression, kinases that transmit information by post-translationally modifying other proteins and E3-ligases that target proteins for degradation via the proteasome. Indeed a recent study utilizing the LUMIER method has shown that human Hsp90 β interacts with 7% of all transcription factors, 60% of all kinases and 30% of all E3-ligases (Taipale et al. 2014). Other studies have shown that HSP90 interacts with various structural proteins, ribosomal components and metabolic enzymes (Falsone et al. 2005; Skarra et al. 2011). Hsp90 has also been found to interact with a large number of viral proteins including those from HIV and EBOLA (Smith et al. 2010; Low and Fassati 2014). This is not to mention the numerous co-chaperones that modulate and direct Hsp90 activity.

Few studies have focused on discerning the unique protein interactions between Hsp90 α and Hsp90 β (Gano and Simon 2010; Hartson and Matts 2012). Work done in *Xenopus* eggs and yeast has shown that Hsp90 α and Hsp90 β differ in co-chaperone and client interactions (Taherian et al. 2008; Gong et al. 2009). However, little is understood concerning the unique functions delegated to each paralog. Fortunately, the Picard lab has aggregated all available Hsp90 interaction data into the Hsp90Int.DB website (Escheverria et al. 2011). This resource allows for the comparison of Hsp90 α and Hsp90 β interacting networks through its curation of 292 combined PubMed articles on both human paralogs: 128 articles focused on Hsp90 α , 63 articles focused on Hsp90 β and 101 articles covered both paralogs.

Including the massive LUMIER screen that compared the interactions of 630 proteins with only Hsp90 β (Taipale et al. 2014), it can be observed that Hsp90 α and Hsp90 β interact with over 725 different proteins: Hsp90 α exclusively interacting with 135 proteins, Hsp90 β exclusively interacting with 410 proteins and both paralogs sharing 183 proteins (Figure 4). Collection of the gene ontology terms for the whole set of interacting proteins for Hsp90 α or Hsp90 β may allow one to predict the unique functions of each paralog. Comparing each list of gene ontology terms, it can be observed that Hsp90 α is associated with 162 unique terms for biological processes while Hsp90 β is associated with 158 unique terms; both paralogs share 624 terms for biological processes. Thus, although Hsp90 β is currently found to interact with a larger number of proteins, Hsp90 α is associated with a slightly larger number of biological processes. This is a particularly interesting observation in light of the fact Hsp90 α is not required for mammalian viability while Hsp90 β is essential (Voss et al. 2000; Grad et al. 2010; Kajiwara et al. 2012). This supports the idea that the biological processes associated with Hsp90 β are more relevant to maintaining viability, while the processes associated with Hsp90 α are more related to adaptation to stress or other specialized functions. It also demonstrates that Hsp90 α and Hsp90 β are redundant in contributing to a large number of biological functions. This is echoed in profiling the molecular function

terms in which Hsp90 α is associated with 23 unique terms, Hsp90 β is associated with 32 unique terms and both paralogs share 88 molecular functions terms. This distribution further demonstrates that each paralog contributes to a unique set of basic molecular functions while overlapping in a large number of other functions. More telling is the profiling of cellular components terms where Hsp90 α is associated with 20 unique terms, Hsp90 β is associated with 19 unique terms and both paralogs share 64 cellular component terms. This provides information on the temporal-spatial distribution of each paralog within the cell and lends support to the role of Hsp90 α as an extracellular agent (Eustace et al. 2004). Together this analysis demonstrates that HSP90 possesses unique biological functions discernible from Hsp90 β . It also points to the need for a balanced analysis of the Hsp90 paralogs and a comprehensive screening of the Hsp90 α interactome. All lists and terms were generated using Amigo2 and Venny (Supplemental Table 2) (Carbon et al. 2009; <http://bioinfogp.cnb.csic.es/tools/venny/>).

Hsp90 α post-translational modifications

Post-translational modifications have a large impact on Hsp90 function and regulation (Mollapour and Neckers 2012). Phosphorylation, acetylation, S-nitrosylation, oxidation, methylation, sumoylation and ubiquitination are ways in which Hsp90 is modified in order to modulate its many functions. Furthermore, post-translational modification sites are found in all domains of Hsp90, consistent with a functional requirement in different regions of the protein. Twenty-eight sites within Hsp90 α have been identified using site-specific mutation, while many more have been discovered using mass spectrometry (Figure 5). Many of these sites are conserved between Hsp90 α and Hsp90 β . However, there are a few distinctions between the two that allow for specific functions to be performed by Hsp90 α .

Phosphorylation of Hsp90 has been shown to affect its binding to clients, cochaperones and nucleotide (Zhao et al. 2001; Mollapour et al. 2010; Mollapour et al. 2011; Xu et al. 2012; Quanz et al. 2012; Muller et al. 2013). Although Hsp90 α and Hsp90 β have several overlapping phosphorylation sites, some are specific to Hsp90 α . These sites are highlighted in red in Figure 5B. An example of specific sites would be phosphorylation of Threonines 5 and 7 of Hsp90 α . Phosphorylation of these sites happens in response to DNA damage and results in the co-localization of Hsp90 with DNA repair proteins at the sites of damage (Quanz et al. 2012 JBC; Solier et al. 2012). Specific phosphorylation of carboxy-terminal residues in Hsp70 and Hsp90 α also act as a switch for co-chaperone interaction. The phosphorylation status of these residues allow Hop and Chip to recognize and bind or unbind Hsp70 and Hsp90 α . Additionally, phosphorylation of the carboxy-terminus of both Hsp70 and Hsp90 α is increased in primary cancers (Muller et al. 2013). This is not surprising as phosphorylation at this location increases Hop interaction with both proteins, which has been previously linked to faster tumor growth (Kubota et al. 2010; Ruckova et al. 2012).

Additional phosphorylation sites on Hsp90 are shared between the two paralogs, but have Hsp90 α -specific consequences. For example, phosphorylation of Threonine 90 of Hsp90 α increases its translocation to the cell surface and secretion (Lei et al. 2007; Wang et al. 2009). Secretion of Hsp90 α has been suggested to be an essential prerequisite for

proinvasiveness and tumor metastasis (Wang et al. 2009; McCready et al. 2010). Phosphorylation of Hsp90 α at Serines 231 and 263 in the charged linker is found in leukemic cells. Phosphorylation of the same residues in Hsp90 β did not occur in leukemic cells, but rather in untransformed cells (Lees-Miller et al. 1989; Kurokawa et al. 2008).

Hsp90 α function is also regulated by acetylation. Treatment of cells with an HDAC inhibitor revealed seven acetylation sites that were hyperacetylated. The hyperacetylation of these sites increased Hsp90 α secretion, leading to increased tumor invasiveness (Scroggins et al. 2007; Yang et al. 2008).

Hsp90 α and cancer

Over the last two decades HSP90 has emerged as an intriguing target in the war on cancer. HSP90 interacts and supports numerous proteins that promote oncogenesis, thus distinguishing Hsp90 as a cancer enabler as it is regarded as essential for malignant transformation and progression. Moreover, through their extensive interactomes, both paralogs are associated with each hallmark of cancer (Workman et al. 2007; Trepel et al. 2010). However, in contrast to changes in expression of Hsp90 α protein (*vide supra*), the *HSP90AA1* gene is not altered in a majority of tumors according to The Cancer Genome Atlas (TCGA). Currently bladder cancer is found to have the largest number of alterations at 10% of tumors sampled followed by pancreatic cancer at 6.7% (Gao et al. Science Signaling 2013; Cerami et al. Cancer Discovery 2012) (Figure 6). Additionally, whole genome sequencing across all tumor types and cancer cell lines reveals that there are presently 115 different mutations within the *HSP90AA1* open reading frame (Supplemental Table 3). The effects of these mutations on HSP90 α function, however, remain unknown. Remarkably, in a number of tumors the *HSP90AA1* gene is homozygously deleted, suggesting that these tumors may have a reduced level of malignancy. This hypothesis is supported by a comparative genome-wide analysis of 206 gastric cancer patients that reported loss of *HSP90AA1* is indeed associated with favorable outcomes after surgery alone (Buffart et al. 2012), and is in agreement with other studies reporting that the absence of Hsp90 α in tumor biopsies may serve as a biomarker for positive clinical outcomes (Gallegos et al. 2008; Cheng et al. 2012).

Biologically, Hsp90 α differs from Hsp90 β in that Hsp90 α is presently understood to function as a secreted extracellular agent in wound healing and inflammation in addition to its intracellular roles. These two processes are often hijacked by cancer allowing for malignant cell motility, metastasis and extravasion (Eustace et al. 2004). Current research in prostate cancer indicates that extracellular Hsp90 α transduces signals that promote the chronic inflammation of cancer-associated fibroblasts. This reprogramming of the extracellular milieu surrounding malignant adenocarcinoma cells is understood to stimulate prostate cancer progression. Extracellular HSP90 α induces inflammation through activation of the NF- κ B (RELA) and STAT3 transcription programs that include the pro-inflammatory cytokines IL-6 and IL-8 (Bohonowych et al. 2014). Coincidentally NF- κ B also induces expression Hsp90 α (Ammirante et al. 2008), thus providing a model where newly-expressed Hsp90 α would also be secreted from the stimulated fibroblast thereby creating positive autocrine and paracrine feedback loops resulting in an inflammatory storm at the site of

malignancy. This concept requires further attention as it may explain the correlation of increased levels of Hsp90 α in the plasma of patients whose cancers are in advanced stages of malignancy (Wang et al. 2009).

Hsp90 Inhibitors

As mentioned above, Hsp90 is exploited by cancer cells to support activated oncoproteins, including many kinases and transcription factors. These clients are often mutated, amplified or translocated in cancer, and Hsp90 works to buffer these and other cellular stresses induced by malignant transformation (Workman Ann NY Acad Sci 2007; Trepel 2010 Nat Rev Cancer). Inhibition of Hsp90 leads to the degradation or instability of many of its client proteins (Blagg BS Med Res Rev. 2006.). Thus, Hsp90 has become an attractive target for cancer therapy.

As with all ATPases, ATP binding and hydrolysis is essential for the chaperoning function of Hsp90 *in vivo*. Most Hsp90 inhibitors interfere with this cycle at its early stages by replacing ATP in the N-domain ATP binding site, leading to the regulated ubiquitination and proteasome-mediated degradation of most client proteins (Blagg and Kerr 2006.) (Figure 7). As such, the N-domain nucleotide binding pocket remains most amenable to drug targeting (Whitesell et al. 1994; Prodromou et al. 1997; Stebbins et al. 1997; Grenert et al. 1997; Sharma 1998, Schulte et al. 1998; Banerji et al. 2005; Banerji et al. 2005; Chiosis and Tao IDrugs 2006; Eccles 2008; Kummar et al. 2010; Lancet et al. 2010; Pacey et al. 2011; Patel et al. 2011; Jhaveri et al. 2012; Jegu et al. 2013; Taldone et al. 2014). To date, there are 23 active Hsp90 inhibitor oncology trials, and 13 HSP90 inhibitors are currently undergoing clinical evaluation in cancer patients; 10 of these inhibitors have entered the clinic in the past few years (Neckers and Trepel 2014).

While the N-terminal nucleotide-binding pocket of Hsp90 is most widely studied and thus targeted, recent studies have suggested that a second nucleotide-binding site is located in the Hsp90 C-terminus (Marcu J Biol Chem 2001; Garnier J Biol Chem 2002; Soti J. Biol Chem 2002; Soti Eur J Biochem 2003; review by Donnelly et al, Curr Med Chem 2008). Targeting of this region is reported to result in specifically reduced Hsp90-steroid hormone receptor interactions and has been shown to influence Hsp90 binding to the N-domain nucleotide pocket (Sreedhar Biochim Biophys Acta 2004; Rosenhagen Mol Endocrinol 2003).

Although none of the C-terminal Hsp90 inhibitors have yet to enter the clinic, the use of both N- and C-terminal Hsp90 inhibitors in combination represents an exciting new strategy for chemotherapy.

Although many of the previously mentioned inhibitors share the same Hsp90 binding site (either N- or C-terminal), it has been shown that some of these drugs preferentially access distinct Hsp90 populations, which can be differentiated by the extent of their post-translational modification (Moulick Nat Chem Biol 2011; Beebe Oncotarget 2013). Though no published inhibitor has yet to distinguish between Hsp90 α and Hsp90 β , a recent study has shown that phosphorylation of a particular residue in the Hsp90 N-terminus can provide isoform specificity to inhibitor binding (Beebe Oncotarget 2013), thus providing an additional level of regulation for optimal Hsp90 targeting.

Future directions for HSP90 α

In the era of precision medicine, continued investigation of the *HSP90AA1* gene, in terms of function, regulation and drug targeting, should prove beneficial. Further characterization of the *HSP90AA1* promoter could be useful in predicting the expression of Hsp90 α in specific scenarios related to disease. Determining the effects of individual and combined sets of TFs on the transcription of *HSP90AA1* may provide insights into how cancer utilizes Hsp90 α expression to promote malignancy. An investigation into the expression profile of TV1 may also be useful in better understanding *HSP90AA1* biology. Moreover, through the use of advanced proteomic and molecular biology techniques, a better understanding of the Hsp90 α interactome across all tissues and disease states should provide valuable insights into how the stress response is hijacked in cancer and other disorders. This knowledge may also aid in designing drug combinations to combat cancer that anticipate and circumvent the development of drug resistance. Continued examination of the effects of PTMs on Hsp90 α function will yield important information on chaperone regulation and drug specificity in normal and disease states. PTM profiling will also discern what protein populations of Hsp90 α are preferentially targeted by drugs. Conversely, the induction of the stress response, including Hsp90 α expression, may prove useful in addressing neurological pathologies related to protein aggregation and aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Hsp90	heat shock protein 90
Grp94	glucose regulated protein 94
TRAP1	tumor necrosis factor associated protein 1
MHC1	major histocompatibility complex 1
PTM	posttranslational modification
TSS	transcription start site
HSE	heat shock element
TF	transcription factor
HSF1	heat shock factor 1
POLR2	RNA polymerase 2
TV	transcript variant
LUMIER	LUminescence-based Mammalian IntERactome
TCGA	The Cancer Genome Atlas

Research Highlights

- *HSP90AA1* is not only transcriptionally regulated by HSF1 but also by other factors
- *HSP90AA1* and *HSP90AB1* are differentially regulated at the transcriptional level
- The protein products of *HSP90AA1* and *HSP90AB1* are homologs but with unique function
- Hsp90 α and Hsp90 β are differentially regulated by posttranslational modification
- *HSP90AA1* transcript and Hsp90 α protein levels may have prognostic value in disease

Figure 1.
Schematic of the human *HSP90AA1* gene structure. Two transcript variants of Hsp90α protein are encoded on the complement strand of Chromosome 14. Information was obtained from NCBI Gene. Untranslated Region (UTR); ORF, Open Reading Frame (ORF).

Figure 2. Depiction of the *HSP90AA1* transcription start sites. RNA polymerase II binds at three different sites on the *HSP90AA1* gene; two sites associated with Transcript Variant 2 and one site associated with Transcript Variant 1. Information was obtained from UCSC Genome Browser and Encode.

Figure 3.

Gene Ontology (GO) comparisons of the *HSP90AA1* POLR2A binding site profiles: GO terms were computed/gathered by compiling all the transcription factors (TFs) that were found within the POLR2A binding site footprints. The lists of TFs were then searched on Amigo2 Term Enrichment Service powered by PANTHER with the biological process and *H. Sapiens* parameters selected (Carbon et al. 2009). The resulting list of GO terms was ranked by p-value. GO terms that scored $p < 0.05$ were accepted as significant. The resulting lists were then compared using Venny. The top 10 unique GO terms for each POLR2A sites are listed.

Figure 4. Interactomes and Gene Ontology comparisons of *HSP90AA1* and *HSP90AB1*. Venn diagram of the number of overlapping and unique protein interactors and gene ontology terms associated with each Hsp90 isoform is shown. Information was obtained from Hsp90Int.DB, Amigo2 and Venny. These values are expected to change over time as the interactomes of each Hsp90 isoforms are further defined.

Figure 5.

Hsp90 post-translational modification sites. A. Crystal structures of Hsp90 were obtained from RCSB protein databank; 1YET: human Hsp90α N-terminal domain bound to geldanamycin; 2CG9: yeast Hsp90 middle and C-terminal domains from full length structure bound to Sba1. Post-translational modification sites found on the PhosphoSite Plus website (<http://www.phosphosite.org/homeAction.do?sessionId=75252660BD94E928CEA59D49CC039052>) are labeled in red using the PyMOL program. B. Display of Hsp90 post-translational sites. Unique phosphorylation sites for Hsp90α are in red.

Figure 6. Alterations of the *HSP90AA1* gene across cancer. Data accumulated from the genomic characterization and analysis of tumor types according to The Cancer Genome Atlas. Chart was generated by cBioPrtal for Cancer Genomics.

Figure 7.
Hsp90 N-terminal Inhibitors. Hsp90 N-terminal domain interaction with ATP is compared to interaction with Hsp90 inhibitors geldanamycin and radicicol using the PyMol program. 1YET.pdb (adapted from Roe et al. 1999).