Mechanistic Insights and Translational Relevance of Targeting *HSP90* as a Novel Therapy for Cancer

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Abstract

A highly conserved molecular chaperon called *Heat Shock Protein* (*HSP90*) is required for the maturation of freshly generated polypeptides and offers a haven for the refolding or denatured protein turnover. The client proteins of *HSP90* encompass the entire oncogenesis process, which is connected to all cancer hallmarks, in malignancies. The client proteins are directed for proteasomal destruction when their complexes with *HSP90* are broken, according to mounting evidence. As a result, *HSP90* and its co-chaperones have become promising targets for the creation of new cancer treatments. As a result, many natural compounds and their analogues that target *HSP90* have been discovered. Through multiple routes, they have demonstrated a potent inhibitory effect on many cancer types. The inhibitors work by physically attaching to *HSP90*, its co-chaperones, or its client proteins. A number of *HSP90* inhibitors are undergoing promising clinical trials, including shepherdin, geldanamycin, and its derivatives, gamitrinib and shepherdin. Here, we go through *HSP90's* subcellular location, its associated method of action in malignant phenotypes, and new developments in the creation of *HSP90* inhibitors.

Keywords: Heat Shock Protein 90 (*HSP 90*) • Inhibitors

Introduction

In the crowded environment of a single cell, efficient and precise management of the cellular protein pool is essential for homeostasis. One of the heat shock protein subgroups is *HSP90*. *HSP90* shields cells from negative effects when it is functionally increased in response to environmental stress. *HSP90*, which makes up between 1% and 2% of all cellular proteins when cells are not under stress, is universally expressed across all species and is evolutionarily conserved. In a pressured state, it can be raised even higher to around 4%-6%. *HSP90* has been compared to "molecular glue" because of its abundance and adhesion capabilities. The N-Terminal Domain (NTD) of *HSP90*, which has ATPase activity, the Middle Domain (MD), which binds to the client protein, and the primary dimerization C-Terminal Domain (CTD) make up the protein's structure. To maintain its "closed" shape for the binding of client proteins, *HSP90* uses ATP. The immature client proteins continue to fold, which is followed by the release of energy via ATP hydrolysis. After that, *HSP90* transforms into a "open" conformation and releases the matured product. The complex regulation of ATP hydrolysis rates and certain conformational states also calls for co-chaperones. In eukaryotic cells, over 20 co-chaperones of *HSP90* have been identified. These co-chaperones primarily affect *HSP90*'s molecular activity in four ways: Coordinate the interaction between *HSP90* and other chaperone systems, such as *HSP70*; promote or inhibit the ATPase activity of *HSP90*; attract particular classes of clients to *HSP90*; and contribute to various parts of the chaperone cycle through their enzymatic activities.

The HSP90-HSP70-HSP40 complex works cooperatively and successively with the co-chaperones with the TPR domain (i.e., HOP) to mature client proteins. Separately, co-chaperones that increase ATPase activity are thought to be HSP90 conformational cycle activators, whereas those that decrease ATPase activity are more likely to be involved in client loading or the development of mature *HSP90* complexes. In order to determine *HSP90*'s dependence, recently comprehensively screened 2156 clones, including protein kinases, transcription factors, and E3 ligases. They discovered that more than 400 client proteins rely on the *HSP90*-regulated protein folding mechanism to achieve and maintain their active conformations. The *HSP90* client proteins also control a wide range of physiological processes, including signal transduction, protein trafficking, chromatin remodeling, autophagy, and cell proliferation and survival, according to a number of studies. In addition, a lot of *HSP90* client proteins are frequently overexpressed or mutated in cancer cells.

Subcellular localization of *HSP90*

On an evolutionary scale, *HSP90* is a highly conserved molecular chaperone that is constitutively expressed in the majority of organs and tissues. With its ATPase activity, *HSP90* aids in the correct folding, intracellular distribution, and proteolytic turnover of numerous important regulators of cellular homeostasis. Under normal circumstances, HSP90 is primarily found in the cytoplasm, which is also where proteins with abnormal folds are made and polypeptides are generated. *HSP90* was discovered to be expressed "everywhere," including the nucleus, mitochondrion, and plasma membrane, as well as being released into the extracellular matrix, utilizing an *in vivo* PET tracer or in vitro organelle fractionation experiment. Differential subcellular *HSP90* expression may play specific roles in a variety of biological processes, particularly cancer. It's interesting to note that *HSP90* expression patterns differ between healthy cells and malignant cells, with differences only occurring in the mitochondria or extracellular matrix.

Cytosolic localization of *HSP90*

The cytosol component expressed *HSP90*, a crucial homodimer chaperone machinery. It discovered that the C-terminal half of *HSP90* (amino acids between 333 and 664) is important for the cytoplasmic localization by creating several shortened versions of *HSP90* and utilizing confocal microscopy. However, NLS-*HSP90* was preferentially produced in the nucleus by fusing with the Nuclear Localization Signal sequence (NLS). The bulk of *HSP90* in these investigations was likewise primarily confined to the cytoplasm. Perhaps the cytosolic *HSP90* provides a co-chaperone buffering system that significantly aids in the folding and refolding of important oncogenic drivers and pro-survival regulators. The term "molecular glue" has also been used to describe cytosolic *HSP90*, emphasizing both its abundance and its buffering capabilities. The majority of *HSP90*'s client proteins are found in the cytoplasm, where they perform a number of activities including metabolic rewiring, signal transmission, post-transcriptional modification, and cytoskeleton remodeling. Actin filament bundling behavior was recently revealed to be modulated by *HSP90*, and this dynamic interaction between *HSP90* and nearly all cytoplasmic filamentous structures highlights this role. Recently, it was discovered that *HSP90* transiently crosslinks actin filaments in vitro. Additionally linked to *tubulin*, *HSP90* likely guards against heat denaturation of the protein. Similarly, it has been demonstrated that *HSP90* guards against heat stress in myosin. *HSP90* therefore has a functional role in the control of the cytoskeleton.

Nuclear localization of *HSP90*

The nucleus of normal cells showed a low expression of *HSP90* (5% -10% of total cellular *HSP90*). Interestingly, it was discovered that *HSP90* and its co-chaperones concentrate in the nucleus of dormant *Saccharomyces cerevisiae* cells with the help of the importin system, which was strengthened during periods of relative metabolic inactivity.

The nuclear localization sequence is a recognized traditional or alternative nuclear import and export signal, and the HSP90 protein contains sequences that are homologous to these signals. It is significant because HSP90 is linked to a variety of nuclear chaperone clients, such as transcription factors, histone, nucleic acids, and histone modifications. Additionally, HSP90 controls a variety of biological processes in the nucleus, such as RNA synthesis, processing, and other telomerase activities. Steroid receptors, kinases, and FKBP52 control HSP90's nuclear translocation. HSP90 interacts with zinc finger proteins, helix-loop-helix proteins, MyoD1, E12, HIF1, HSF1, and the glucocorticoid receptor. When exposed to a high temperature, HSP90 was found in the nuclear membrane, as demonstrated by the transfection of 3T3 cells with *HSP90* coupled with EGFP. The plasma membrane allows a large number of tiny chemical molecules to reach the cytoplasm, but it has been demonstrated that none of these molecules can penetrate the nucleus, limiting their effectiveness. However, *HSP90* could be translocated from cytoplasm to nucleus, which protects cancer cells from therapeutic pressure. This shows that *HSP90* inhibitors that are nuclear-directed should be taken into account.

Mitochondrial localization of *HSP90*

HSP90 is highly expressed in tumoral mitochondria but hardly expressed in normal tissues, the mitochondrial expression of *HSP90* was unknown. On the back of this groundbreaking breakthrough, a significant amount of research was conducted with the goal of creating *HSP90* organelle-specific small molecule medicines. These inhibitors work together to precipitate a rapid collapse of mitochondrial integrity and death that would only happen in tumor cells. Pancreatic cancer, breast cancer, colon cancer, NSCLC, melanoma, glioblastoma, prostate cancer, lymphoma, and leukemia are just a few cancer types that have been proven to respond favorably to a number of inhibitors that directly target the mitochondrion. By examining the metabolic network in the tumoral mitochondrion that is regulated by *HSP90*, mitochondrial *HSP90* (hereafter mtHSP90), but not cytosolic *HSP90*, binds and stabilizes the electron transport chain complex II subunit Succinate Dehydrogenase-B (SDHB), which keeps cellular respiration under low-nutrient conditions and aids in *HIF1*-mediated tumor. The dynamic interaction between mitochondrial *HSP90* and SDHB folding intermediates was also confirmed by cryo-EM data. It is important to note that while TRAP1 and *HSP90* share 60% of their sequence and have the same NTD, ND, and CTD domains, they have been referred to be different forms of *HSP90*, namely mitochondrial *HSP90*. TRAP1 was almost completely undetectable in normal tissues but consistently raised in primary tumors.

Furthermore, *Cyclophilin D* , a mitochondrial residential protein that protects cells from apoptosis and maintains mitochondrial integrity, was one of the crucial client proteins of TRAP1. Additionally, the *HSP90* and *TRAP1* crystal structures offer additional chemical insights that can be used to create brand-new inhibitors. TARP1 is a promising target for the creation of new cancer treatments when taken collectively.

Membrane and extracellular localization of *HSP90*

Since *HSP90* is highly expressed inside of cells, it was initially thought of as an artefact until it was discovered on the cell surface by a functional screening. After cautious verification, *HSP90* is no longer considered as being exclusively localized within the cell. Additionally, *HSP90* can secrete itself into the extracellular matrix. The malignant stage of the tumor correlates with the cell surface expression of *HSP90*, which is higher on cancer cells than on normal cells.The first evidence for the detection of *HSP90* in the extracellular matrix was implicated in 1986. Extracellular *HSP90* (hence referred to as eHSP90) may function without ATP since the extracellular environment has low levels of ATP due to the absence of an energy source. Environmental stressors and growth factors can cause eHSP90 to secrete, and post-translational chaperone changes like phosphorylation and acetylation can have an impact. Recent studies have also revealed that invasive cancer cells secrete *HSP90* via exosomes, which interacts with plasmin to increase their invasiveness. Cancer cells release both *HSP90* and *HSP90* to interact with MMP2 and MMP9 and increase the invasiveness of tumor cells. Similarly, eHSP90 was found in normal cells only in reaction to stress, while cancer cells consecutively release *HSP90*. Interestingly, eHSP90 promotes the downstream signal transduction linked to tumor development and metastasis, which is similar to the EMT phenotype, by interacting with a number of receptors, including EGFR/HER2/LPR1. Furthermore, across a variety of cancer types, eHSP90 expression is associated with a rise in the risk of metastasis and a decline in the immune response. Cancer cells release both *HSP90* and *HSP90* in order to interact with MMP2 and MMP9 and increase the invasiveness of tumor cells. Similar to how cancer cells consistently release *HSP90*, normal cells only show signs of eHSP90 in response to stress. Interestingly, eHSP90 promotes the downstream signal transduction linked to tumor development and metastasis, which is similar to the EMT phenotype, by interacting with a number of receptors like EGFR/HER2/LPR1. Additionally, in numerous cancer types, eHSP90 expression, is correlated with a decline in the immune response and an increase in the metastatic potential.

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