

Investigating the role of HSP90 in cancer cell phenotypic plasticity

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Abstract

"What are the mechanisms driving tumor evolution under the selective pressure of chemotherapeutics?" The emerging importance of epigenetic gene regulation in cancer progression necessitates not only our understanding of which genes are potential targets but also what mechanisms are employed in targeting those genes. Understanding the mechanisms that promote the evolution of the normal genome and epigenome is central to understanding how cancer cells adapt to chemotherapy. Our previous investigations have shown that heat shock protein 90 (HSP90) has a critical role in epigenetic gene regulation through histone acetylation and phenotypic plasticity. We recently extended these results in an A549 lung cancer model to test the role of HSP90 in the plasticity of cells regarding multi-drug resistance and epithelial-to-mesenchymal transition phenotypes. HSP90 is over-expressed in multiple cancers with poor prognosis. We propose that inhibition of HSP90 results in lower phenotypic plasticity of cancer cells making them more susceptible to chemotherapeutic intervention. Here we review the context of our results in the broader field of evolution of these phenotypes.

Keywords: Epigenetic, Cancer, HSP90, Histone Acetylation, Phenotypic Plasticity, Multi-drug Resistance, Cellular Stress

Introduction

Life finds a way to survive, even malignant life. Viewing cancer as a Darwinian struggle between the body's defense mechanisms and a rogue cell is an apt description of the process of oncogenesis. It also allows us to apply evolutionary biology principles to understand and design treatment strategies for those suffering from this malady. In particular, lung cancer with its high recurrence rate and early metastasis continues to plague therapeutic efforts [1]. Both metastasis and recurrence processes depend upon phenotypic change of cancer cells to adapt to new environmental conditions. The building blocks of evolution in these contexts is the genetic and epigenetic changes that different groups of cells can acquire after the initiation events of premalignancy. Recently, we have provided evidence showing that transient inhibition of Heat Shock Protein 90 (HSP90) by AUY-922 can inhibit epithelial-to-mesenchymal transition (EMT) associated with invasion and metastasis, as well as the up-regulation of drug transporters to a multi-drug resistant (MDR) phenotype associated with the emergence of chemotherapy-resistant cells [2]. In this review, we will show how this evidence supports the theory in the field.

HSP90 and EMT

EMT is an important biological process involved with embryonic development and tissue regeneration. Epithelial cells will gain migratory and invasion abilities while losing cell polarity and cell-cell adhesion molecules [3]. This process is normally highly regulated. However, cancer cells will utilize EMT to take on more mesenchymal phenotypes. They become stem cell-like, able to dedifferentiate and self-renew. They lose E-cadherin, a cell adhesion molecule and powerful tumor suppressor. Thus, EMT allows cancer cells to proliferate rapidly and invade other tissues. EMT is a contributing etiology in many types of cancer, including breast, lung, prostate, and liver cancer.

Increased EMT in tumors is associated with greater metastatic capacity, therapy resistance, and poor prognosis. The switch between epithelial and mesenchymal states is deregulated in cancer, and often, tumor cells remain in a hybrid epithelial-mesenchymal state [4]. Interestingly, breast tumors expressing both E-cadherin (an epithelial marker) and vimentin (a mesenchymal marker) yielded the worst survival rates. These transient changes contribute to a cancer cell's phenotypic plasticity; the cell can cycle through various differentiation phenotypes based on environmental conditions [5]. In our experiments with A549 cells, we showed that cellular plasticity associated with the acquisition of EMT was inhibited by transient inhibition of HSP90 [2].

The process of EMT depends on genetic and epigenetic factors. EMT is initiated by signals from molecules such as Transforming Growth Factor- β (TGF- β), Wingless Integrin (WNT), and Phosphoinositide 3-kinase (PI3)/ Protein kinase B (AKT). In our original experiments with HSP90 inhibition, we found that HSP90 inhibition triggered dysregulated expression of WNT in *Drosophila* [6]. The molecules activate pathways that govern the activity of several transcription factors (TFs), such as Snail 1/2, Twist, and Zinc finger E-box-binding homeobox (Zeb) 1/2. TGF- β and WNT directly regulate TF expression through Smad 2/3 (small" worm phenotype and Mothers Against Decapentaplegic protein family) and β -catenin interactions respectively. PI3/Akt can promote metastasis and chemoresistance through Twist phosphorylation. There is extensive crosstalk between the TFs to repress genes responsible for epithelial phenotypes while activating genes responsible for mesenchymal phenotypes. Among their functions, Snail 1 is partially responsible for the MDR phenotype through P-gp activation, Zeb 1 directly inhibits E-cadherin, and Twist up-regulates N-cadherin. These TFs are also under microRNA control. The binding of certain miRNA (mi-R) molecules to TF genes represses TF activity. Down-regulation of these miRs can result in upregulation of TF expression. Other microRNAs, such as mi-R155 and mi-R24, can act farther down EMT pathways to disrupt tight junctions and adherins. The aforementioned molecules are under TGF- β control as well [7]. Chromatin effectors also play a role in EMT induction. Snail 1/2 and Zeb 1 can recruit histone deacetylases (HDACs) and histone methyltransferases to epithelial genes to decrease their expression. One histone methyltransferase recruited is the Enhancer of Zeste Homeobox 2 (EZH2) complex, which represses the E-cadherin gene through inhibitory modification H3K27me3 at its promoter. Snail activity is also partially under epigenetic regulation, with Lysine demethylase 6B inducing its expression by removing repressive modifications from the Snail gene. EMT can also be induced by DNA methyltransferase 1 (DNMT1) and EZH2 as an early precursor to the activation of certain oncogenes like KRAS [8].

HSP90 contributes to cancer development through the promotion of EMT. HSP90 is up-regulated in malignant cells, and greater HSP90 levels in tumor cells correlate to lower survival rates [9]. HSP90 can epigenetically regulate EMT modulators to increase the incidence of EMT. Secreted HSP90 can signal the upregulation of EZH2 through the Extracellular Signal-regulated Kinase (ERK) pathway. The resulting signaling cascade suppresses E-cadherin, promotes EMT, and improves cancer cell migration. HSP90 can also activate TGF- β signaling through its client proteins Matrix Metalloproteinase-2 (MMP-2) and MMP-9 [10]. Interactions between HSP90 and Low-density Lipoprotein Receptor-related Protein 1 (LRP1) in various pathways can also trigger EMT. In

colorectal cancer cells, HSP90 with LRP1 triggers the expression of Transcription factor 12 (TCF12), increasing fibronectin and decreasing E-cadherin [11]. In breast cancer cells, HSP90 and LRP1 work synergistically with clusterin to activate Akt, ERK, and Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells (NF- κ B), leading to EMT and increased metastatic capacity. HSP90 can also increase the expression of Snail 1/2, Twist, and Zeb 1/2 [12]. Multiple *in vitro* studies have shown that HSP90 inhibitors can suppress EMT, diminishing cancer cell growth and metastatic potential. Thus, there is great interest in utilizing HSP90 inhibitors as oncological therapeutics to combat EMT in tumors [13-15].

MDR and Epigenetic Gene Regulation

MDR is understood as the nonreceptivity of a single cancer cell line to an assortment of anti-cancer drugs that vary in structure and function. MDR phenotypes within cancer cells can be demarcated into two categories: primary resistance and acquired resistance phenotypes. Primary resistance is associated with MDR abilities inherently found in a cell line before exposure to anti-cancer treatments, while acquired resistance transpires after exposure [16]. Cell expression of MDR can function by a variety of different processes, including elevated drug metabolism, heightened cellular efflux, growth factors, the increased ability to repair damaged DNA as well as a variety of other genetic factors [17]. It is these factors that have led to the attribution of over 90% of deaths in patients receiving chemotherapy and other anti-cancer drugs to MDR. In our experiments with A549 cells, we showed that cellular plasticity associated with the acquisition of MDR by heightened cellular efflux was inhibited by transient inhibition of HSP90 [2].

Of the different mechanisms of MDR, cellular efflux is of great interest. Efflux is defined as the ability of cells to transport hazardous chemicals out through transporters within the cellular membrane. An example of transporters associated with MDR include ATP-binding cassette (ABC) proteins, which include the Breast Cancer Resistance Protein (BCRP) and P-glycoprotein (P-gp) which is coded for on the ABC subfamily B member 1 gene (ABCB1) [17]. ABC transporters are membrane-spanning proteins participating in cholesterol homeostasis, transport of molecules in and out of cells and organelles, immune recognition, oxidative stress, and drug efflux. ABC transporters are considered the main arbiters of multidrug resistance [18]. P-gp is overexpressed in about 50% of human cancers and this overexpression can be exacerbated by certain chemotherapies such as paclitaxel [17]. In our experiments, we found that ABCB1 and ABCC1 were up-regulated in response to paclitaxel and that this process was inhibited by prior transient inhibition of HSP90 [2].

One of the suspected causes of MDR is epigenetic alterations. Mechanisms such as hyper- and hypomethylation are associated with increased cellular access to oncogenes and decreased access to suppressor genes allowing for the continual proliferation of invasive cancer cells [16,19]. Previous work has shown that demethylation of the ABCB1 gene leads to a decrease in the amount of chemotherapy that is able to accrue within the cell [17]. Additionally, histone deacetylase inhibitors (HDACi) have been shown to modify the composition of transporters on the surface of some cancerous and noncancerous cells. HDACi have demonstrated the ability to increase acetylation and transcription factors within certain cells, which in turn have up-regulated of tumor suppressors and up-regulation of cell transporter expression, indicating that histone acetylation plays

a role in ABC transporter regulation [18]. Our previous experiments were the first to link HSP90 to epigenetic dysregulation and histone acetylation in *Drosophila* which we later showed to be present in mammalian systems [6,20].

HSP90 is a cellular chaperone protein associated with epigenetic modification, and phenotypic change, and is often up-regulated within cancer cells. HSP90 is known for its ability to epistatically subdue or enable the expression of different genetic variants [21]. The level of the protein in cancer cells is associated with patient outcomes. High levels of the protein are correlated with high malignancy and less drug response [22]. In a study examining HSP90 in A2780 ovarian-originated cancer and its paclitaxel and cisplatin-resistant sublines, it was found that inhibiting HSP90 increased the susceptibility of the drug resistance cancers to paclitaxel and cisplatin. It was also found that silencing HSP90 decreased the level of P-gp and BCRP within the A2780 cells, suggesting that ABC transporters are associated with or involved in HSP90-induced resistance to paclitaxel in ovarian cancer cells [23].

HSP90 and Histone Acetylation

HSP90 and other heat shock proteins are overexpressed in a range of cancer cells [24]. We were the first to connect HSP90 function to epigenetic mechanisms, specifically to histone acetylation [6]. The expression of genes is partially regulated by histone modifications (e.g. acetylation) as a part of chromatin remodeling. Oncogenes or tumor-suppressor genes expression can be modified by changes in histone acetylation [25]. Tumor cells often lose p53 function and have higher expression of proto-oncogenes such as Human Epidermal Growth Factor Receptor 2 (HER2) and c-Myc [24]. Hsp90 is a molecular chaperone that involves itself with the post-translational processing, folding, stabilization, and maturation of various client proteins, including histone-modifying proteins. Several HDACs, which are enzymes responsible for removing acetyl groups from histones [26], and histone acetyltransferases (HATs), which are enzymes that add acetyl groups to histone proteins, are clients of HSP90. Since these are clients of HSP90, the regulation of HSP90 alters the balance of histone acetylation in cells. A multitude of histone modifications have been shown to be affected when HSP90 is inhibited in bladder cancer cells [27].

Cancer is highly adaptive, with a heterogeneous population that quickly responds to stress. This adaptability is crucial for cancer cells to survive and thrive in diverse environmental conditions, including those that would normally induce cellular stress and apoptosis. The heat stress response of cancer has been extensively studied, and it is becoming increasingly clear that cancer cells hijack normal cellular protective processes to survive [28,29]. A common feature of any cellular stress response is the effort to recover from protein misfolding through increased expression of molecular chaperones like HSP90. These responses to stress alter many cellular processes involved in malignancy (like the cases of EMT) [30].

Furthermore, the interplay between HSP90 and histone acetylation extends beyond individual gene regulation. Our results provide evidence that it contributes to the broader phenotypic plasticity seen in cancer cells, allowing them to switch between different states in response to varying environmental cues. As a key chaperone, heightened levels of HSP90 allow for the excessive accumulation and function of its client proteins [31]. It is common for proteins to require assistance to form their functional three-

dimensional conformation when they are translated, but a subset of proteins have a significant amount of conformational instability in their mature state and require perpetual and ongoing chaperone assistance to avoid denaturation. Many of these “less stable” proteins are expressed in various cancer cells, and the higher levels of HSP90 expressed in cancer cells allow for their continued function. In addition, mutations that alter the three-dimensional structure of proteins, make malignant cells more reliant upon chaperone functions creating an addiction to high-level expression of HSP90.

Phenotypic Plasticity and HSP90

The first researchers to connect HSP90 to evolutionary biology did so in a variety of organisms including *Arabidopsis* and *Drosophila* [32,33]. We later showed that these mechanisms, at least partially, occur through epigenetic mechanisms involving histone acetylation [6]. It was later shown that HSP90 could inhibit the evolution of resistance to hormonal therapies in breast cancer [34]. This was an exciting discovery as it suggested that evolutionary principles such as canalization, which have been associated with HSP90 since Suzanne Rutherford and Susan Linquist linked HSP90 with evolution, could be applied to cancer biology. It is interesting to note that Conrad Waddington, the researcher who first coined the term epigenetics, also was the first to posit the process of canalization. The predominant success of the complex process of development despite the necessity of high precision in cell fate decisions and spatial relationships suggests a mechanism for buffering for minor changes. Canalization theory states that this is the result of canalization of the preferred normal phenotype of the species during development (**Figure 1**). The expression patterns of genes from among organisms in a particular species are diverse enough to give a wide range of phenotypes that are not present in the population (depicted on the left with a y-axis of phenotypic range). The present morphology of the species is favored and variations in gene expression that would result in deviation from this model are compensated for by canalizers (or capacitors) present in the system. In this context, HSP90 stores genetic and epigenetic variation, until stress releases that change allowing for rapid adaptation to the environment. In effect, HSP90 restricts the production of phenotypic diversity (canalization) to the normal distribution of phenotypes under non-stressful conditions.

The attribute of phenotypic plasticity, where an organism or cell can change its characteristics is antithetical to canalization that restricts variability in phenotype. If you apply the principles of canalization to oncogenesis as has been commonly done with the Darwinian evolution paradigm (**Figure 1**), HSP90 becomes an important factor in the molecular evolution of malignant cells. When canalization theory is applied to malignancy, where genetic mutation and the epigenetic changes are acquired by cells to increase variability, the associated stress can release canalization and promote the acquisition of the Hallmarks of Cancer [35,36]. However, because mutation is a stochastic process, in which deleterious mutations accumulate and hinder the cell's viability. To compensate for the protein folding problems associated with these mutations, malignant cells commonly up-regulate HSP90 expression 2-10 fold. Through this process, these cells acquire an addiction to HSP90 and an increased canalization capacity, though this capacity is often occupied in these cells (the ratio of complexed: uncomplexed HSP90 is much higher in malignant cells compared to normal cells) [37].

Our experiments were designed to test the effects of inhibition

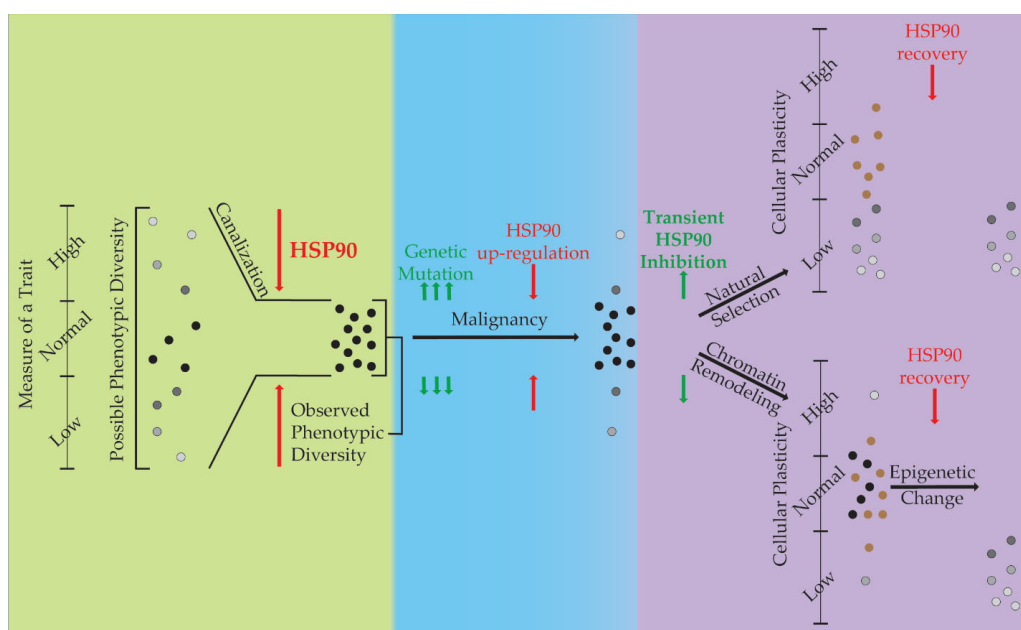


Figure 1. The Role of HSP90 in Phenotypic Diversity and Plasticity. This diagram describes the role HSP90 performs in canalization of phenotypes during evolution (green), its role in restriction of phenotypes during malignancy (blue), and two hypotheses for its role in our experiments with regards to phenotypic plasticity (purple). Phenotypic variance is displayed vertically with HSP90 restricting its expression through canalization. Cells that exist within the ‘normal’ phenotypic range are in black, while others are shown in grayscale. Cells shown in brown are those that die during inhibition by HSP90.

of HSP90 on phenotypic plasticity associated with the acquisition of the MDR and EMT phenotypes. These phenotypes are a form of cellular adaptation through plasticity. Two hypotheses that explain our results are presented (**Figure 1**). While understanding that these are not mutually exclusive, there is support for both. If natural selection is causing the change in cellular plasticity, then selection after transient treatment with an HSP90 inhibitor results in a pool of surviving cells that have less cellular plasticity. This could be due to the Darwinian selection of cells that have a higher free HSP90 level (and thus a higher canalization ability) and are thus less susceptible to inhibition. When HSP90 levels are restored, the increased canalization ability of the malignant cells exerts itself and restricts phenotypic plasticity when the cells are induced to undergo EMT or MDR. Alternatively, epigenetic changes also associated with HSP90 inhibition may result in a pool of surviving cells with less phenotypic plasticity. A multitude of histone modifications have been shown to be affected when HSP90 is inhibited in bladder cancer cells [27]. In addition, we found that the application of HDACi was able to reverse HSP90-mediated phenotypic effects in *Drosophila* and murine stem cells [6,20].

Conclusions

If loss of phenotypic plasticity through HSP90 inhibition prevents the emergence of chemotherapy resistance, then a new mechanism for treating cancers will have been discovered. Our data show that some epigenetic impacts of HSP90 inhibition are conserved in mammalian systems and offer a mechanism for the loss of phenotypic plasticity. Since epigenetic changes occur in most forms of cancer and phenotypic plasticity is reliant upon them, further elucidation of the connections between epigenetic gene

regulation, HSP90, and phenotypic plasticity could have clinical implications on treating advanced cancers. This would provide new treatment strategies in clinical studies using HSP90 inhibitors, particularly as adjuvant therapies to prevent the evolution of therapy resistance.

Eighty-five percent of lung cancers are non-small cell lung cancers (NSCLC) [38], with metastasis and ABC transporter-driven chemotherapeutic resistance as common features of these cancers either at the time of diagnosis or manifesting during the treatment process [39-44]. The development of drug resistance is a frequent problem in the management of breast cancer [45]. Many patients’ tumours are resistant to the therapeutic agents by the time of disease recurrence, leading to the average five-year survival rate of patients with metastatic breast cancer of 31% [46]. The recent evidence that some treatment approaches may incidentally enable the metastatic cascade [47-49] and the persistence of drug-resistant relapse after current treatment methods [50] demand new, rational, treatment strategies that can curtail the emergence of metastatic and drug-resistant cancer phenotypes simultaneously. Therefore, discovering ways to limit metastasis and chemotherapeutic resistance in cancer will benefit many patients.

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