CHAPTER

Hsp90 and Developmental Networks

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Abstract

The most abundant cytoplasmic chaperone of eukaryotic cells, Hsp90 is a hub in developmental regulatory networks and the first example described of the phenomenon of molecular buffering. As a chaperone for many different signaling proteins, Hsp90 maintains the clarity and strength of communication within and between cells, concealing developmental and stochastic variations that otherwise cause abrupt morphological changes in a large variety of organisms, including *Drosophila* and *Arabidopsis*. The chapter provides a framework for understanding how Hsp90 controls the sudden appearance of novel morphologies. We start with a discussion of the longstanding problem of hidden polygenic variation and then introduce the idea of signal transduction thresholds in mediating the effect of Hsp90 on the expression of phenotypic variation. This leads to a discussion of the role of nonlinearity in creating thresholds for sudden changes in cellular responses to developmental signals. We end with speculation on the potentially pivotal role of Hsp90 in controlling the developmental networks that determine morphological stasis and change in evolution.

Introduction

Hsp90 is a hub in developmental regulatory networks. By maintaining the activity of over 150 signal transduction proteins in many different developmental pathways, the Hsp90 chaperone controls the strength of signaling, not only by its client proteins, but through the pathways in which they reside. Hsp90 target pathways regulate multiple processes including cell cycle and transcriptional control, as well as chromatin remodeling, growth control, apoptosis, stress responses and response to differentiation signals.[1-3] Many Hsp90-dependent pathways are both ancient and conserved. For example, Hsp90 controls the activity of four of eight ancient signaling pathways that arose before the protostome-deuterostome split. These pathways form a "basic evolutionary toolkit"[4] that is thought to have enabled the evolution of most of biletarian diversity (Table 1). It is not yet understood how the same genes and pathways produce such dramatically different morphologies. One possibility is that evolution occurs via small changes in the structure and connectivity of signal transduction networks, the intricate web of cellular communications and responses that orchestrate development.

Perhaps surprising given their intricacy, biological networks are by nature highly error tolerant and self-correcting. Part of this stability has to do with positive and negative feedback and the complexity of inter-connections. In addition, biological networks are "scale-free". The number of interactions between nodes (genes or proteins) follows a power-law distribution - meaning that a few percent of nodes (such as Hsp90) have huge numbers of interactions, but most nodes having very few interactions (~2).[5] The resulting behavior of scale-free networks is

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Molecular Aspects of the Stress Response: Chaperones, Membranes and Networks, edited by Peter Csermely and Laszlo Vigh. ©2007 Landes Bioscience.

Table 1. A conserved group of signaling pathways, believed to have arisen before the protostome-deuterostome split, has been deployed to different ends throughout bilateran development. Shown are the eight major pathways and examples of Hsp90 client proteins imbedded in each.

Pathway	Hsp90 Targets	References
Hedgehog (Hh)	–	–
Wingless related (Wnt)	–	–
Transforming growth factor B	Tak1*	50
Receptor tyrosine kinase (RTK)	IKK; ERB2; AKT	51-54
Notch	–	–
JAK/STAT	Stat1, Stat3	55
Nuclear hormone pathways	Nuclear hormonre receptors	56
Apoptosis	Caspase 9, Bid	57,58

*Tak1 is a noncanonical effector of TGFB signaling.

therefore robust to the random loss of a high percent of nodes.[6] However rare, highly-connected nodes such as Hsp90 are control points whose loss is devastating to network function. The "structural stability, dynamic behavior, robustness and error and attack tolerance" depend on the integrity of highly connected nodes (hubs), particularly those positioned high in the hierarchy of network structure (Fig. 1).[7,8] For example, hubs such as Hsp90 provide a connection between many different modules of the network (meaning clusters of nodes more interconnected among themselves than to nodes in other modules).

Several years ago, one of the authors (S. Rutherford) discovered that modest (≤50%) reduction of Hsp90 uncovers a remarkable reserve of previously hidden morphogenic variation in *Drosophila*.[9] Hsp90-buffered changes are highly dependent on genetic background and results from the segregation, in normal populations, of likely hundreds to thousands of alleles with generally small effects on the strength of signaling through Hsp90-dependent pathways. Normally this genetic variation is hidden, and therefore has neutral effects on fitness. However, when the strength of Hsp90 signaling pathways is reduced beyond critical threshold levels, normally stable phenotypes can abruptly change.[10] Waddington called the error tolerance and self-correcting behavior of developmental processes canalization.[11,12] In line with Waddington's original concept of canalization, Hsp90-dependent changes in morphology are not quantitative in nature, but are either highly discrete or qualitative (Rutherford et al, submitted for publication). Indeed, a characteristic and almost unifying feature of life is its highly discrete nature. From species to individuals, organs, cell types and physiological and sub-cellular systems: perturbations change probabilities of alternative types, but rarely result in the generation of intermediate forms.

Here we present a framework for understanding Hsp90 buffering and variation in development. We begin with a discussion of the longstanding problem of hidden genetic variation. We then cover Hsp90 and signal transduction thresholds, the role of nonlinearity in creating thresholds in development, and end with speculation on Hsp90 potentially pivotal role in controlling the networks that control the balance of developmental stasis and change.

Hidden Genetic Variation

"We are largely ignorant of the answer to a question of fundamental importance: *How much [and which] variation has direct phenotypic or functional effects that influence the survival and reproduction of individuals?*" Quote from special committee charged with evaluating the Human Genome Diversity Project.[13]

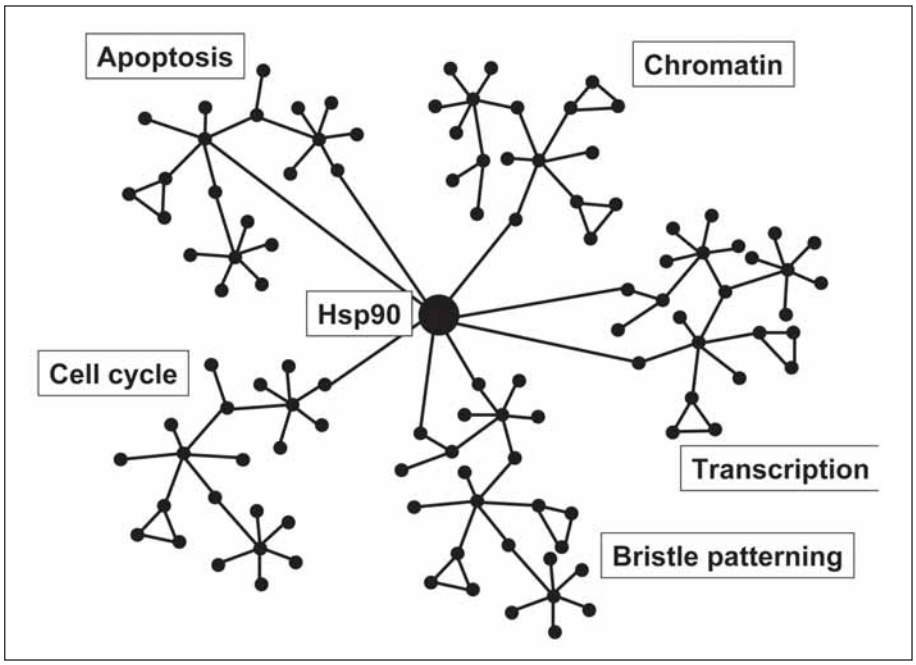

Figure 1. Meta-network of cellular and developmental processes (modules or sub-networks) controlled by Hsp90. A hierarchical network model predicts many properties of Hsp90 buffering, such as control of the modularity, robustness and balance between the functions making up the meta-network of development. Within each module Hsp90 has targets in both activating and inhibitory pathways, suggesting that balance within each module is also maintained.

Estimates of nucleotide polymorphism in *Drosophila* or human populations suggest that there are hundreds of thousands to millions of nucleotide differences between the genomes of unrelated individuals.[14,15] However, extensive surveys of wild populations of flies reveal very little variation in phenotype.[16] Indeed, the Neutral Theory asserts that a large amount of the genetic variation in populations has little or no effect on phenotype.[17] Yet a substantial, if unknown, amount of silent variation is 'conditionally cryptic' and can contribute to phenotypic variance or disease in the appropriate context.[18-20] Many factors allow the accumulation and maintenance of cryptic variation. It has long been known that under differing environmental or genetic conditions, latent genetic variation is expressed.[20] The hidden genetic variance attributable to conditionally cryptic alleles has traditionally been the province of evolutionary and quantitative genetics. For example, dominance interactions between alleles at a given locus, epistatic interaction between alleles at different loci, and genotype-by-environment interactions all buffer the expression of genetic variation.[18] However, the molecular basis of natural quantitative variation, whether conditionally cryptic or not, remains an open question.[21]

Early *Drosophila* geneticists attempted to catalog second-site modifier mutations and environmental effects on mutant phenotypes. However, both expressivity (severity) and penetrance (fraction affected) of mutant phenotypes are altered by so numerous factors it seems likely that their sheer number and the difficulty of their isolation eventually simply overwhelmed the early efforts. The gradual reduction in the phenotypic expression of deleterious mutations by ongoing fitness selection in the mutant stocks has been extensively documented. Perhaps most dramatic is the polygenic suppression of *Drosophila eyeless* (*ey*) mutations. When first isolated, *ey* mutations cause the complete loss of visible eye structures. The *ey* mutations are never-the-less

extremely sensitive to environmental effects, and are easily suppressed by the rapid accumulation of ubiquitous and abundant polygenic modifiers that restore a normal eye structure and vision.[22] Outcrossing these stocks again restores the *ey* phenotype and shows that the mutatation was still present, but "hidden" by modifier alleles. As eye structure is normally invariant, these modifier alleles normally constitute cryptic genetic variation with hidden potential to affect eye development. Perhaps most astounding, ectopic expression of the *ey*/Pax-6 transcription factor drives the formation of *Drosophila* eye structures in multiple tissues of the adult fly (for example on wings, legs, antennae).[23] Because Pax-6 function is both necessary and sufficient for eye development, and is highly conserved throughout evolution, it has been called the "master control gene" for eye development.[24] While Pax-6 may be the one of the best examples of a master control gene, its singularity and importance is questionable as its leading role in this process can be by-passed by polygenic variants and environmental effects.[10] These studies demonstrate the abundance of developmental variation and alternate routes to the development of indistinguishable morphological endpoints.

Conversely, the increased variation in phenotype revealed by major developmental mutations is common and well-documented, and is a form of gene-interaction or epistasis.[10,25] Reducing Hsp90 either genetically, or with an inhibitor, has pleiotropic effects on many morphogenic processes, uncovering variation depending on both Hsp90 reduction and its interaction with trait-specific genetic backgrounds. The diversion of Hsp90 to proteins damaged by heat or other stress provides environmental control of Hsp90-dependent genetic and genotype-by-environment variation. Recent work has shown that other chaperones involved in protein folding, such as Hsp70 and Hsp60 family members, also buffer genetic variation, likely through a direct molecular effect on sequence variants that cannot fold normally without their assistance.[26,27] By contrast, we believe Hsp90 effects are largely indirect.[28] Rather than buffering variant client proteins directly, allowing them to fold, accumulating evidence indicates that Hsp90 acts through enhancing and suppressing effects of genetic variation and the environment on the strength and fidelity of developmental signaling pathways.

Hsp90 and Signal Transduction Thresholds

Our thinking about Hsp90-buffered variation centers on the idea of thresholds for the expression of phenotypes in response to continuously varying strengths of signaling through Hsp90 target pathways. The genetic interactions of Hsp90 with client proteins in signal transduction pathways demonstrate the existence of thresholds, and are easily understood in light of the large body of previous work on the evolutionarily conserved biochemical and genetic requirement for Hsp90 by specific client proteins.[1-3] When Hsp90 levels are decreased by mutation or by inhibitors, signal transduction clients begin to loose activity, and the strength of target pathways becomes severely reduced.[29-31] Threshold trait models were developed in the context of quantitative and population genetics and are often used to describe the genetics of human disease.[32] In development, thresholds are transitions between continuous inputs and discrete outputs. Many binary cell-fate decisions are controlled by thresholds. Specific genetic interactions between Hsp90 and signaling pathways dominantly reveal phenotypic thresholds. Loss of Hsp90 function is lethal to most cells in most organisms, in *Drosophila* heterozygous (recessive) Hsp90 mutations dominantly enhance and suppress sensitizing (cryptic) mutations in many Hsp90 client pathways. Hsp90 heterozygotes fail to complement Cdc37 heterozygous mutations,[33] suppress an over-activated phenotype of the Torso receptor tyrosine kinase,[34] enhance Cdc2 mutant heterozygotes[35] and enhance or suppress under- and over-activated components of the *sevenless* (*sev*) mitogen activated protein kinase (MAPK) pathway.

The well-characterized MAPK signaling pathways initiated at the Drosophila *sev* receptor is a model for Hsp90 interactions with signaling near trait thresholds. High-level activation of the *sev* pathway promotes the normal photoreceptor cell fate, while lower-level activation of the pathway results in a default nonneuronal fate and loss of a photoreceptor. This decision is an all-or-none switch; no intermediate cell-types are found. If signaling is too high or in the

wrong place, extra photoreceptors are produced, giving flies a gain-of-function rough eye phenotype. A series of molecular genetic screens were instrumental in identifying the components of receptor tyrosine kinase signaling pathways. Endogenous members of the *sev* cascade were replaced with marginally over- or under-activated analogs and the temperature adjusted so that flies have normal or gain-of-function phenotypes.[35-37] Heterozygous mutations in other components of the pathway (*m*/+), which are normally 'cryptic' recessive mutations, behave like dominant enhancer or suppressor mutations in the appropriate genetic background. Tellingly, when *sev* signaling is reduced toward a lower threshold, Hsp90 mutations also reduce signaling further, resulting in the loss-of-function phenotype seen with heterozygous mutations in other pathway members.[35,36] Similarly, when the *sev* pathway is over-activated beyond an upper threshold (gain of function phenotype), heterozygous Hsp90 mutations reduce activity and restore a normal, smooth eye phenotype.[38,39] The genetic interaction of Hsp90 in many client pathways shows that it can reduce signaling near thresholds for the expression of mutant phenotypes. If target pathways are sensitive to reduction of Hsp90 client functions, the same result is produced simply reducing Hsp90 activity.

The level of extrinsic or intrinsic noise in signaling and the cell sensitivity could also modulate the expression of phenotypes near signal transduction thresholds. This phenomenon is called either stochastic resonance or stochastic focusing, depending on the whether the noise is extrinsic or intrinsic, respectively. If noise is low, a low level signal may not pass the signal transduction threshold. On the contrary, if the noise is high, the same low level signal will pass the same threshold a higher fraction of the time (Fig. 2).[40,41] By decreasing the "noisiness" of cellular signals, molecular chaperones would also modulate the sensitivities of signal transduction near trait thresholds. When Hsp90 is inhibited, increased developmental and/or purely environmental noise may allow normally-lower signals to pass the same sensitivity thresholds, increasing phenotypic diversity at the whole-cell, or whole-organism level.[42]

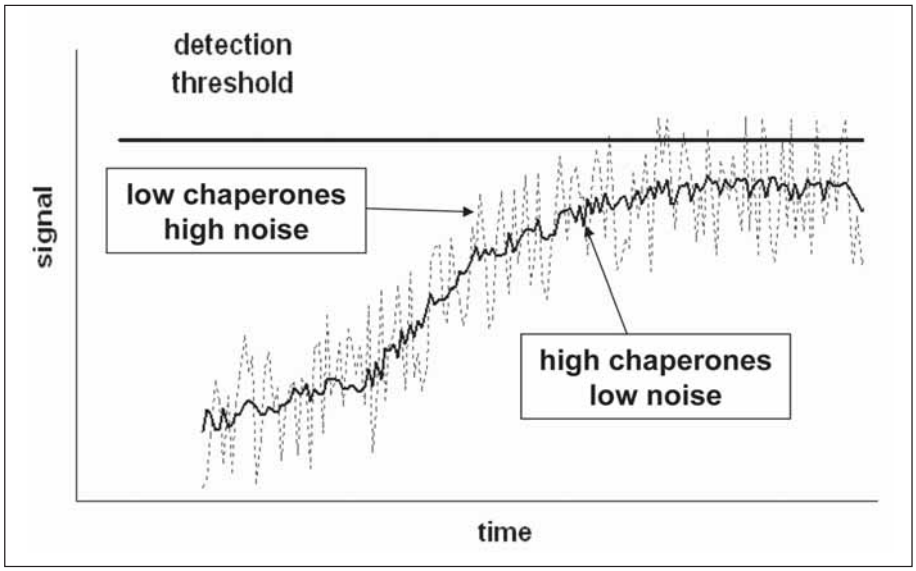

Figure 2. Stochastic resonance as a possible reason for chaperone-induced buffering in the diversity of developmental changes. Stochastic resonance is the phenomenon, where intrinsic or extrinsic noise helps a low level signal to surpass a signal transduction threshold. If molecular chaperones decrease the noise of cellular processes, this may also contribute to their buffering effects of developmental changes by not allowing low-level signals to act.

Nonlinearity in Developmental Responses to Signal Transduction

The ability to produce all-or-none or switch like behavior in response to continuous variation in the strength of the underlying developmental signal may be a common theme in biology.[40,43] For example, the addition of upstream kinases in MAPK signaling creates a sigmoidal (threshold) response over a narrow range.[44] The addition of positive feedback can sharply amplify a graded input to produce a steep and sudden ("switch-like") change in output.[45] We suggest that such nonlinearity in the response of phenotype to underlying developmental signals is a common feature of development, and produces much of the observed discrete behavior of biological systems. Given nonlinearity in Hsp90 target pathways, when Hsp90 is reduced, signaling is reduced. We believe that the sudden changes in morphology, or changes in previously invariant quantitative traits reflects the fact that thresholds have been crossed.

A Pivotal Role for Hsp90 in Network Evolvability?

The activity of signal transduction clients and therefore client pathways decrease sharply with modest decreases in Hsp90 function. Through these target proteins, Hsp90 simultaneously controls output of multiple target pathways imbedded in many different developmental processes such as regulation of cell-cycle, apoptosis or differentiation responses. Each of these processes is controlled by a complex sub-network of signaling pathways that integrate developmental cues to generate appropriate responses. Hsp90 may be uniquely positioned to balance the stability and modularity of the 'meta-network' of processes that make up development, linking network sensitivity and behavior to the environment.

If the meta-network of development were a mobile with groups of hanging objects (nodes), we suggest that Hsp90 would be at the center of the mobile, supporting several groups of objects ('sub-networks' or modules). Linkages between each sub network and Hsp90 are represented by the strings that support the mobile. The effective concentration of Hsp90 available for signal transduction determines the overall height (activity) of the meta-network, and the connectivity or separation of the modules—complete loss of Hsp90 world fragment the modules into isolated sub-networks. By reducing or increasing several target protein functions simultaneously, we suggest that Hsp90 maintains the balance of the system. The overall height (activity) between the subnetworks is shifted ensemble with the degree of environmental stress.

Pushing the metaphor a little further, we suggest that Hsp90 also maintains balance within each sub-network. For example, both cdc28 (a key activator of the cell cycle) and wee1 (an inhibitory kinase that acts on cdc28) are Hsp90 targets. Decreases in both activating and inhibiting pathways would balance out the effect of varying Hsp90 on the rate of the cell cycle. It seems reasonable to expect that in most cases selection has sculpted the set of targets in activating and inhibitory pathways such that the balance of their function is maintained. Normal changes in Hsp90 availability would have no net effect. However, if natural variation or the environment has already destabilized the network balance, bringing an activating or inhibitory pathway close to its threshold, further reduction of signaling by loss of Hsp90 function could result in thresholds being breached and previously hidden phenotypes revealed.

Extending our thoughts beyond the role of Hsp90 to a general molecular buffering effect of chaperones, we have to note that chaperones provide low affinity, transient contacts with other proteins. Weak links are known to help system stability in a large variety of networks from macromolecules to social networks and ecosystems, which may be a general network-level phenomenon explaining many of the genetic buffering effects.[42,46] Besides molecular buffering by Hsp90 and other chaperones, a large number of other mechanisms may also control the diversity of the phenotype.[25,47-49] A single common mechanism, such as involvement in signaling or epigenetic modifications of histones and DNA structure, seems unlikely to explain all of the effects observed. If a general explanation is sought, we believe it is more likely to be related to the overall structure of developmental networks and their emergent properties.

Acknowledgements

Work in the authors' laboratory was supported by research grants from NIH R01 GM068873 the EU (FP6506850, FP6-016003), Hungarian Science Foundation (OTKA-T37357 and OTKA-F47281), Hungarian Ministry of Social Welfare (ETT-32/03), Hungarian National Research Initiative (1A/056/2004 and KKK-0015/3.0).

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