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Review

Regulatory role of the 90-kDa-heat-shock protein (Hsp90) and associated factors on gene expression

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ABSTRACT

The term molecular chaperone was first used to describe the ability of nucleoplasmin to prevent the aggregation of histones with DNA during the assembly of nucleosomes. Subsequently, the name was extended to proteins that mediate the post-translational assembly of oligomeric complexes protecting them from denaturation and/or aggregation. Hsp90 is a 90-kDa molecular chaperone that represents the major soluble protein of the cell. In contrast to most conventional chaperones, Hsp90 functions as a refined sensor of protein function and its principal role in the cell is to facilitate biological activity to properly folded client proteins that already have a preserved tertiary structure. Consequently, Hsp90 is related to basic cell functions such as cytoplasmic transport of soluble proteins, translocation of client proteins to organelles, and regulation of the biological activity of key signaling factors such as protein kinases, ubiquitin ligases, steroid receptors, cell cycle regulators, and transcription factors. A growing amount of evidence links the protective action of this molecular chaperone to mechanisms related to posttranslational modifications of soluble nuclear factors as well as histones. In this article, we discuss some aspects of the regulatory action of Hsp90 on transcriptional regulation and how this effect could have impacted genetic assimilation mechanism in some organisms.

1. Introduction

Upon the onset of environmental stress or due to exposure to damaging or extreme insults, cells dramatically increase the production of a family of proteins that are collectively known as molecular chaperones, heat-shock proteins, or simply, stress proteins. The term "heat-shock protein" (HSP) stems from the original observation that heat-stress greatly enhances the production of this specific set of proteins. Therefore, not all molecular chaperones are HSPs, although HSPs are molecular chaperones. Because HSPs were first identified as the expression product of a number of genes activated by heat-shock, the most frequent collective name for them remains heat-shock proteins [1,2]. They play essential roles in basic cellular events by assisting unfolded or misfolded proteins, which gives the cell the required time to repair or re-synthesize damaged proteins. In addition to regulating the proper folding of a given protein exposed to environmental injury, many chaperones are also related to normal protein trafficking, transcriptional regulation, epigenetic regulation of gene expression and, even more intriguingly, heritable modifications of the state of chromatin [3–5].

The biological relevance of HSPs during the modern times can be traced to the early 1960s when the Italian scientist Ferruccio Ritossa studied the synthesis of nucleic acid in puffs of *Drosophila* salivary glands. A colleague accidentally changed the temperature of the cell incubator and something unexpected was noticed—an incredible transcriptional activity of new chromosomal puffs. New RNAs were detected as soon as 2–3 min after increasing the temperature. The importance of this fortuitous observation was immediately grasped—cells react through the synthesis of some unknown factors in response to elevated temperature [6]. Today, we know that these factors are the HSPs, and this remains to date one of the clearest demonstrations of environmentally induced changes in gene expression. As it often happens, this unanticipated concept was very difficult to accept at the time of discovery. Ritossa's fortuitous but clever observation was systematically rejected from highly prestigious journals with the argument that the finding lacked biological significance.

Perhaps one of the most prominent examples related to the activation of a transcription factor upon the onset of stressing situations is Heat-Shock Factor 1 (HSF-1). HSF-1 is a transcription factor that is inactive under normal conditions and present in a heterocomplex with HSPs. As a consequence of these HSPs having a greater affinity for improperly folded and denatured proteins than HSF-1, the transcription factor is released from the heterocomplex during heat-shock and other types of stresses. This leads to the binding of HSF-1 to specific HSE sequences (or Heat-Shock promoter Elements) in genes encoding

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inducible molecular chaperones, such as Hsp27, Hsp70 and Hsp90, which, in turn, induces a very high level of expression of these proteins [7].

The HSP superfamily comprises five broadly conserved families of proteins—Hsp100s, Hsp90s, Hsp70s, Hsp60s, and the small heat shock protein subfamily that includes Hsp33 as a signature member. It is accepted that exposure of hydrophobic residues is the main mechanism by which HSPs distinguish a partially or globally unfolded protein from the properly folded native protein state. With the biological ability to protect these unfolded proteins from aggregation and degradation, HSPs bind to exposed hydrophobic patches of non-native-folded peptide sequences. HSPs protect client proteins thanks to a controlled binding and release mechanism of non-native-folded proteins, which is usually accomplished by a change in affinity of the chaperone for its substrate.

2. Hsp90 as a potential capacitor of evolutionary processes

Hsp90 is the major soluble protein of the cell and most commonly located in the cytoplasm. A small fraction of Hsp90 is also present in the nucleus where it shows several structural and functional properties. Hsp90 is essential for various cellular processes, such as protein folding, protein degradation, signal transduction cascades, and morphological evolution. Stability of various oncogenic factors is almost entirely dependent on Hsp90 binding, such that cancer cells require this chaperone to survive in the demanding milieu generated by oncogenic transformation [8–10]. Consequently, Hsp90 has become an attractive antineoplastic drug target, and several Hsp90 inhibitors are being currently tested in various stages of clinical trials.

In view of its broad spectrum of biological actions, it is not surprising that Hsp90 is essential for cell survival and has been conserved among species during the course of evolution. Among these prolific biological functions, Hsp90 has been regarded as a key factor at the crossroads of genetics and epigenetics. It has been postulated as a capacitor for phenotypic variation and morphologic evolution, a connection that was first tested in the fruit fly *Drosophila melanogaster* [11]. The results of these first studies were astonishing. When Hsp90 was inactivated by mutations or pharmacological interference with selective disrupting agents, the phenotypic variation of *Drosophila* species affected nearly all adult structures, with particular variants depending on the genetic background of the individuals under analysis. Importantly, various and previously silent genetic determinants generated these variants and were independent of the Hsp90 mutation. This surprising observation led to the hypothesis that *D. melanogaster* had accumulated hidden genetic variations whose phenotypic expression was somehow prevented by Hsp90 [11,12]. It was consequently inferred that when the function of Hsp90 is compromised, its buffering properties are disrupted to the point that previously hidden or repressed phenotypic variants can emerge [5,13,14].

Consistent with these contemporary findings, the British embryologist Conrad Hal Waddington had proposed almost 70 years ago a theoretical mechanism of evolutionary change that was named “genetic assimilation” [15]. The concept supported the idea that environmental and/or genetic factors can disrupt the normally stable course of development in living organisms. Such disruptions may then cause phenotypic variations that allow a given population to persist in a new, relatively hostile environment until new mutations permit the assimilation of the most beneficial phenotypic variants by natural selection.

Since Hsp90 is highly conserved across all species, the finding that these phenotypic buffering properties of Hsp90 are also shown in plant model species such as *Arabidopsis thaliana* was not surprising. It was reported that pharmacological disruption of Hsp90 by specific Hsp90 inhibitors such as geldanamycin or radicicol resulted in unusual phenotypes within a given inbred line [16]. Like *Drosophila*, plants exposed to elevated growth temperatures generated a spectrum of unusual phenotypes in most inbred specimens, whereas the adaptation for growing in the dark (considered a typical instance of phenotypic plasticity) showed varying level of Hsp90 dependence among inbred lines. One important observation was that some of the “new” phenotypes (i.e., leaf morphology and pigment accumulation) were actually beneficial for plants in the new environment.

All these observations support a model where Hsp90 buffers phenotypic variation, transforming this molecular chaperone into an intracellular regulator of adaptation. In short, Hsp90 seems to be responding to the call of Waddington's seminal concept mentioned above. However, the exact mechanism for this peculiar effect of the chaperone remains unclear. How it is that Hsp90 is able to influence this phenomenon, how a given living being is able to evolve after identifying and appraising the proper factors within a stressful environment, or how Hsp90 is able to judge the optimal reaction to a particular stressor is yet to be fully elucidated.

In this article we discuss some aspects of the Hsp90-dependent effects on gene expression under normal and abnormal conditions and how Hsp90-associated epigenetic modifications could affect and regulate the genetic assimilation phenomenon. In order to introduce the reader to the subject, we will first describe the major features of Hsp90 as well as its more frequent posttranslational changes. Then, some aspects of the epigenomic derivations of those modifications will be analyzed.

3. Hsp90 properties

Hsp90 is a highly ubiquitous protein expressed in all organisms, with the exception of most members of unicellular organisms belonging to the domain Archaea [17,18], where only *Methanosarcina mazei* possesses a gene that is well aligned with the HTPG (High Temperature Protein G) bacterial Hsp90 homolog family members [17]. As a general feature, most organisms show two Hsp90 isoforms, which are 85% identical in mammalian cells and the result of gene duplication about 500 mya. The two isoforms include the stress-inducible isoform (Hsp90α) and the constitutively expressed isoform (Hsp90β) [1,19]. In species such as *Saccharomyces cerevisiae*, the sequence homology of the two isoforms is as high as 97% [20]. Organisms including *Caenorhabditis elegans* [21] and *D. melanogaster* [22] have a single Hsp90 gene, whereas some plants such as rice (*Oryza sativa*) have four [23].

Hsp90 accounts for ~2% of the total soluble proteins in resting cells, ~6–7% in cancer cells, and up to 10% in stressed cells or organisms [24–28]. Most of the Hsp90 population is primarily cytoplasmic and exists as homodimers, and a great deal of what is known about Hsp90 interactions with client proteins comes from studies of cytoplasmic Hsp90. A relatively small fraction of the Hsp90 population is nuclear (ranging from 2 to 3% of the total Hsp90 pool in resting cells [29]), and under certain stressing circumstances, this chaperone accumulates in the nucleus [30–32] in an α/β-importin-dependent manner [33]. To date, it is unclear which signaling pathways are responsible for Hsp90 distribution to different cell compartments. While quiescent cells do not export this chaperone, Hsp90α is secreted to the medium in response to tissue injury, wound healing, and cancer, such that extracellular hsp90 could be a useful biomarker for tumor invasion and metastasis.

Hsp90 is a phosphoprotein containing key phosphate groups that affect its association with other co-chaperones and client proteins [34–39]. Hsp90 is subject to post-translational modifications including not only phosphorylation, but also acetylation [40,41], S-nitrosylation [42], oxidation [43], ubiquitination [44], and methylation [45]. Hsp90 is a member of the ATPase/kinase GHKL superfamily (comprising DNA Gyrase, Hsp90, Histidine kinase and MutL proteins), which is characterized by the presence of a unique ATP binding cleft [46].

Compared to other chaperone proteins and chaperonines, Hsp90 has a highly selective substrate recognition and generally low affinity for unfolded proteins [47–49]. The current consensus model is that Hsp90 provides chaperoning activity for client proteins that possess preserved tertiary structure. Rather than acting as an indiscriminant folding factor,

the functions of Hsp90 in the cell seem to act preferentially as a delicate sensor of client protein regulation [4,50].

Most of what is known about the biological role of Hsp90 is due to examining steroid receptor folding, ligand binding, and nuclear translocation. These studies established the critical cooperation of Hsp90 with other chaperones and cochaperones (that show chaperone activity themselves), including Hsp70, Hsp40, p23, Hop (heat-shock organizing protein), and TPR (tetratricopeptide repeat)-domain immunophilins [4]. These chaperone and cochaperones function as a multi-protein machinery that makes vital contributions to the proper assembly and maturation of steroid receptors and protein-kinases [4,51].

It is important to emphasize that when we refer to Hsp90, it is implied that many of these additional chaperones and co-chaperones are present in an Hsp90-associated oligomeric heterocomplex. One particularly important association involves Hsp90 and the small acidic cochaperone protein p23. The p23 cochaperone binding site in an Hsp90 homodimer arrangement comprises the ATP-binding site at the N-termini plus a downstream domain [52]. p23 cochaperone binding to Hsp90 occurs at the later stages of the Hsp90-client protein maturation cycle. Careful studies have demonstrated that p23 serves to enhance Hsp90-client protein stability and, consequently, its biological function. Dimers of Hsp90 are in dynamic equilibrium between two states, the ADP-bound isoform and the ATP-bound isoform (Fig. 1). The ADP-bound Hsp90 shows higher affinity for the TPR-domain-containing cochaperone Hop. Hop brings together Hsp70 and Hsp90. Hop also prevents Hsp90 from effectively chaperoning client proteins whose binding favors a high, sustained level of ATP [53,54]. Hop binding to Hsp90 blocks ATP binding and the ATPase activity of the chaperone, which makes binding of the cochaperone p23 significantly weak or void [55,56]. This ADP-bound conformation of Hsp90 is favored by the Hsp90 disrupting agent geldanamycin, a benzoquinone ansamycin antibiotic that shows high affinity for the nucleotide binding site of the chaperone. In this state, the associations of both p23 and TPR-domain immunophilins to the complex are impaired. On the other hand, when ADP is exchanged with ATP, the ATP-bound isoform of Hsp90 is stabilized by p23 binding, and other TPR proteins such as the high molecular weight immunophilins are efficiently recruited [53,54]. The ATP-bound isoform of Hsp90 is a better modulator of the biological activity of client proteins. It appears that p23 binding to Hsp90 changes the nature of ATP

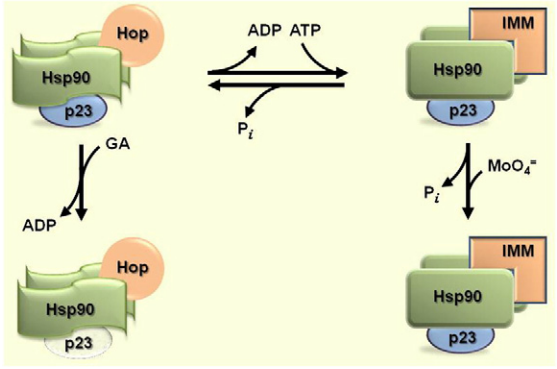

Fig. 1. ATP-dependent conformational states of Hsp90. Dimers of Hsp90 adopt different conformation when ATP or ADP is bound. The best chaperone activity for a given client protein is reached by the ATP form of the dimer, which is also able to interact more efficiently with TPR-domain immunophilins (IMM) and the cochaperone p23. This optimal conformation is stabilized by molybdate, perhaps due to its conformational similarity with the hydrolyzed gamma phosphate of ATP (released by the intrinsic ATPase activity of Hsp90). On the other hand, the ADP-dependent conformation favors the association of the TPR-domain cochaperone Hop rather than IMM binding, and p23 binding is weak or null (which depends on the incubation conditions). This is exemplified by the lighter color of p23. The ADP-dependent conformation of Hsp90 is stabilized by the benzoquinone ansamycin geldanamycin (GA) when the drug displaces ADP from its binding pocket. The ADP-bound form of Hsp90 displays a lower efficiency for client protein binding compared to its ATP isoform and targets the destabilized client protein for refolding or degradation by the proteasome.

binding to Hsp90 and prevents the intrinsic ATPase activity of the chaperone [57], which in turn may affect the biological activity of the Hsp90-bound client factor.

The TPR binding site of the Hsp90 dimer recognizes proteins with degenerate 34 amino acid motives via the conserved pentapeptide MEEVD, located at the C-terminal end of Hsp90. TPR-domain proteins such as FKBP52, FKBP51, FKBP38, CyP40, XAP2, PP5, Hop, WISp39, Tom70, CHIP, and Tah1 bind to this TPR-acceptor site [58,59]. Hsp90 interacts with hundreds of client proteins and other signaling molecules, including steroid receptors, p53, tyrosine-kinases, oncogenes, Stat5, NOS, HSF1, Akt, Chk1, Mdm2, IκB kinases, cytoskeletal proteins, importins, nucleoporins, histones, DNA helicases, telomerase reverse transcriptase, DNA polymerases, SmyD methyltransferases, p300 acetyltransferase, HDAC6, Aha1, SGT1, and Cdc37. In other words, Hsp90 creates a broad scaffold platform for the regulation of signaling cascades, nuclear architecture and cell function [1,50,55]. Table 1 summarizes some examples of Hsp90-modulated proteins classified according to their biological functions. Additionally, the reader may find a comprehensive list of Hsp90-interacting proteins in the web page maintained by the laboratory of Didier Picard (http://www.picard.ch).

4. Modifications of Hsp90

Hsp90 contains several post-translational modifications, including phosphorylation, acetylation, oxidation and S-nitrosylation [34,60]. Phosphorylation was the first characterized Hsp90 modification and has been the most extensively studied to date [35,61]. A number of serines, threonines and tyrosines in Hsp90 have been identified as phosphorylation targets that affect Hsp90-client protein interaction and function [62].

Early studies on pp60v-src tyrosine kinase regulation by Hsp90 reported hyperphosphorylation of Hsp90 in the presence of okadaic acid, a serine/threonine (Ser/Thr)-protein phosphatase inhibitor, which results in a reduced interaction of this client kinase with cell membranes, the functional location for pp60v-src [35]. More recently, inhibition of the steroid receptor-associated phosphatase PP5 was shown to affect the subnuclear localization of this family of ligand-activated transcription factors [63,64]. Also, PP5 is able to dephosphorylate both Hsp90 [65] and the receptor itself [51,66]. On the other hand, phosphorylation of Hsp90 regulates the affinity of Hsp90 for APAF1. In some types of leukemias, reduced phosphorylation in specific Hsp90 serines strengthens Hsp90-APAF1 association, resulting in the abrogation of cytochrome *c*-induced apoptosome assembly and the conferring of chemoresistance [67].

Among the kinase superfamily of Hsp90 client proteins, the first well characterized Hsp90-regulated protein kinase was casein kinase II [68]. Wee1 was also characterized over 20 years ago [69] and is considered one of the most interesting Hsp90-associated kinases, since it is able to regulate the G2/M transition in the cell cycle via a number of signaling cascades. Wee1 phosphorylates a conserved tyrosine residue in the N-terminal end of Hsp90 favoring Hsp90 association with a group of client proteins associated with cancer and include Swe1/Wee1 itself, CDK4, eRBB2, RAF1, pp60*v-src*, and RAF1 [10]. Other Hsp90 client proteins with kinase activity include PKA, which seems to be connected to the mechanisms by which Hsp90α is secreted and involved in tumor metastasis [70,71], B-Raf kinase [72], Akt kinase [73], and DNA-PK (double-stranded DNA protein kinase) [74]. The latter kinase has been shown to phosphorylate the N-terminal domain of human Hsp90α, and cellular DNA damage has been proposed as a mechanism to alter this type of Hsp90 phosphorylation [75].

Acetylation of Hsp90 was first inferred due to the effect of acetylation inhibitors, demonstrated after discovering that the chaperone binds HDAC6 (histone deacetylase 6) [40,41,76–78]. Hsp90 undergoes hyperacetylation in at least eleven lysine residues, which impairs ATP binding and abrogates the association of p23 and several other client

Table 1
Partial list of Hsp90-interacting proteins.

Client protein	Biological consequence of Hsp90-binding	References
Transcription factors/cofactors		
Steroid receptors	Steroid binding affinity, receptor retrotransport, and protein stability are favored	[4,250]
VDR	Ligand-dependent transcriptional response and receptor stability are enhanced	[251,252]
AhR	Xenobiotics binding, receptor stability and nuclear translocation are favored	[253,254]
HSF1	Retains the factor inactivated in the cytoplasm. HsfB1 is targeted to degradation in plants	[255,256]
PPARα/β	Transcriptional activity is repressed	[257]
CAR	Cytoplasmic retention bound to microtubules	[258,259]
PXR	Nuclear translocation and transcriptional inactivation are inhibited	[260]
STATs	STAT3 nuclear translocation and IL-6 induction are enhanced. STAT5 activity is favored	[219,261]
Nanog	Proteasomal degradation is inhibited and pluripotency of stem cells is preserved	[262]
Oct4	Proteasomal degradation is inhibited and pluripotency of stem cells is preserved	[262]
p300	Hsp90α is hyperacetylated increasing tumor cell invasiveness	[78]
Swi/Snf	Opens chromatin conformation at the promoter region of heat shock-induced genes	[92]
Pih1/Tah1	Chromatin remodeling complexes and small nucleolar RNP maturation	[143,144]
SmyD	Increases levels of methylated H3K4	[108]
Bcl6	Preserves BCL-6 stability while it is actively repressing target genes	[155]
TPR-domain proteins		
Hop/p60	Intermediates assembly of several client factors. Inhibits methylation of Hsp90α by SmyD	[4,113]
FKBP51	Regulates transcriptional activity of steroid receptors. Antiapoptotic action	[183,263]
FKBP52	Regulates localization and activity of steroid receptors. Neurotrophic action	[160,172]
FKBP38	Regulates PHD2/HIF transcriptional activity. Antiapoptotic action	[264,265]
CyP40	Regulates nuclear receptor transcriptional activity.	[266–268]
FKBPL/Wisp39	Stabilizes p21 favoring growth arrest	[269]
PP5	Favors Ser/Thr-phosphatase activity	[270]
XAP2/ARA9/AIP	Stabilizes ligand binding. Prevents heterodimerization with HIF-1β.	[271]
CCRP	Retains CAR and PXR in the cytoplasm associated to microtubules	[258]
UNC-45	Favors assembly of myosin and myogenesis	[272]
Tom70	Facilitates mitochondrial import of proteins	[273]
CHIP	Remodels Hsp90-client proteins targeting them to proteosomal degradation	[274]
SGT1	Required for kinetochore complex assembly and innate immunity in plants and animals	[275,276]
Kinases		
pp60-vSrc	Required for Src-mediated cell transformation	[277]
Raf1	Essential for Raf-kinase activity and ternary assembly with Cdc37	[278]
eEF2-K	Prevents aggregation and activates kinase activity	[279]
$p210^{Bcr\text{-}Abl}$	Stabilizes de complex preventing its proteosomal degradation	[280]
Akt	Essential for kinase activity and stability of complexes with Cdc37	[281]
Chk1	Favors kinase activity	[282]
ErB2	Stabilizes and restrains ErbB2 from interacting with other ErbBs in the absence of ligand	[283,284]
PDK	Stabilizes PDK without affecting the intrinsic enzymatic activity of kinase	[285]
IκB kinase (IKK)	Favors assembly, translocation, and activation of IKKs	[286]
IGF1R	Permits the transduction of the signaling cascade of the receptor	[287]
Insulin R	Receptor trafficking to cytosol. Mobility in the endoplasmic reticulum during maturation	[288,289]
VEGFR	Favors the development of focal contacts at the receptor site via FAK activation	[290]
PDGFR	Required for receptor maturation and oligomerization with cdc37	[291,292]
TrkA	Favors the localization of the receptor in the cell surface	[293]
Cdk1	Forms complexes with cdc37	[294]
JAK	Forms complexes with cdc37	[295]
p38	Forms complexes with cdc37 attenuating p38 autophosphorylation	[296]
PKC	Required for phosphorylation, stability, mitochondrial and nuclear import	[94,297,298]
DNA-PK	Proapoptotic response	[217]
PARK	Possible enhancer of Akt-dependent actions	[299]
CMDKs	Required for fungus transformation	[300]
Cdk4	Stabilizes complexes with cdc37	[301]
MEKK (o MAP3k)	Stabilizes complexes and favors kinase activity	[302]
EPHA7-R	Required for kinase activity	[303]
GSK3	Required for autophosphorylation and stability	[235,304]
Structural proteins		
Histones	Induces chromatin condensation	[305]
Actin	Modulates microfilaments assembly	[306]
Myosin	Favors myofilaments assembly and myogenesis	[307]
Tubulin	Protects against thermal denaturation and preserves microtubule polymerization	[308]
Lamin A/C	Possible post-translational modifications	[309]
Vimentin	Prevents cleavage by caspases	[310]
Keratins	Enables protein unfolding and translocation to lysosomes	[311]
Neurofilaments	Prevents protein aggregation and axonal degeneration	[312]
Nup62	Favors interaction of the GR with the nuclear pore complex and its nuclear translocation	[171]
Others		
p23	Client protein stabilization/maturation. Prostaglandin E2 synthase activity is enhanced	[313,314]
Hsp70	Regulates client protein function, trafficking and turnover.	[315]
Hsp40	Forms the five members foldosome complex along with Hsp70, Hop, and p23	[316]
NOS	Stimulates enzymatic activity and protein stability	[317]
Calmodulin	Required for degradation of oxidized calmodulin	[318]
Aha1	The dynamic of chaperone-dependent folding and assembly of client factors is accelerated	[319]

Table 1 (*continued*)

Client protein	Biological consequence of Hsp90-binding	References
Others		
Mdm2	Promotes p53 tetramer unfolding activity	[320]
p53	Stabilizes mutant variants in cancer cells	[321]
Proteosome 20S	Favors assembly. Protein degradation is inhibited or favored according to the substrate	[322,323]
Perilipin	Possible involvement in membrane dynamics	[324]
SV40-large T-Ag	Favors proper folding of the infected particle	[325]
APAF1	Inhibits cytochrome c-dependent oligomerization	[326]
Bcl2	Favors hypoxia-induced stabilization	[327]
TERT	Required for assembly and activity	[328]
DNA pol η	Required for proper folding and DNA repair activity	[186]
Improtins	Possible involvement in cargo delivery to the nuclear pore complex	[171,329]
HDAC6	Required for activity	[41]

proteins. While p300 is a known acetyltransferase capable of Hps90 acetylation, there are several HDACs that are able to deacetylate the chaperone, including HDAC1 and HDAC10 [79–81]. HDAC1 deacetylates Hsp90 in the nucleus of human breast cancer cells [82] which results in conditions favoring the proteosomal degradation of DNA methyltransferase I, a highly active epigenetic DNA modifier involved in tumor suppressor gene silencing by DNA methylation in breast cells.

To date, it is not clear whether a particular HDAC influences the acetylation status of individual lysine residues or whether functional redundancy exists for the deacetylation of various sites. Interestingly, during neuronal differentiation, the subcellular relocalization of Hsp90 appears to be regulated by its level of acetylation (H.R. Quinta, L.T. Ballmer and M.D. Galigniana, unpublished results).

S-Nitrosylation also affects the conformation and function of Hsp90 [83]. Nitrosylation occurs in Cys^{597} of the chaperone [42], which is located nearby the switch region of the C-terminus and able to transmit its conformational change to the N-terminal domain. As a consequence, Hsp90 loses its ATPase activity and its affinity for client proteins [84]. Interestingly, one could speculate that the anti-tumor activity nitric oxide is due to its inhibitory action on Hsp90 at several levels, including telomerase activity [85].

Cys^{597} can also be targeted by reactive oxygen species, promoting similar effects to those described for nitrosylation. Accordingly, glutathione depletion impairs mineralocorticoid receptor (MR)-dependent biological effects [28,86], and while the functional activity of the glucocorticoid receptor (GR) is suppressed under oxidative conditions, it is restored in the presence of reducing reagents [87,88]. The biological actions of these steroid-regulated transcription factors are entirely dependent on Hsp90, and cell proliferation is impaired by oxidation of heat-shock proteins [89].

5. Epigenomic derivations of Hsp90 modifications

Epigenomics is perhaps one of the most intriguing and novel cutting-edge fields at the crossroad of genomics and epigenetics. It assures unexpected new insights into the genome given its potential to detect regulatory sequences outside of genes, quali-quantitative gene alterations, and multiplex genome modifications. Even though the modern notion of "genetic assimilation" was born in the previously referenced paper by Waddington in 1942 [15], the original concept can be traced to the 19th Century [90]. Nonetheless, it is still unclear how phenotypes are translated from genotypes, and how the genome of any living being answers to the selective pressure over evolutionary time. Regarding this conundrum, a broader level of understanding could be achieved if the knowledge of different fields is properly integrated. In this regard, there is growing evidence of the close relationship between participation of molecular chaperones in the biological action of chromatin remodeling and selective transcriptional regulation mechanisms. This fact is often overlooked by researchers of all fields due to our tendency to minimize the complexity of the biological system under study. As it was introduced above, Hsp90 and its cochaperone p23 promote disassembly of steroid receptor-mediated transcriptional complexes allowing the precise regulation of the biological response to changes in hormone levels. A similar phenomenon has been attributed to the action of the Swi/Snf complex of chromatin remodeling factors [91], and it is possible that both processes are indeed part of the same mechanism. It has been shown that the Swi/Snf chromatin remodeler complex is rapidly recruited to Hsp90 upon the onset of heat shock [92]. Interestingly, the transcription activator brahma-related gene 1 (Brg1) ATPase subunit of Swi/Snf is recruited to responsive heat-shock element sequences (HSE) by transcription factors such as HSF1 and Stat1 at the Hsp90β gene, which confers an open chromatin conformation at the promoter region that is pivotal to the heat shock-induced activation of the gene [93]. ChIP/ReChIP assays have shown that the association of Brg1 with HSE is strongly dependent on the activation of Stat1, which in turn is dependent on phosphorylation by both PKC and Jak2 [93]. Both kinases are Hsp90-regulated proteins [93–95], indicating that Hsp90 is required for its own induction in a positive autoregulatory cycle. While the activation of kinases related to chromatin remodeling requires Hsp90, key components of chromatin remodeling complexes, such as RvB1/RvB2, Ino80, SWR-C and Tah1/Pih1, are also physically associated and functionally dependent on Hsp90 [96]. This will be addressed in more detail in a subsequent section of this manuscript.

One intriguing question is how epigenetic modifications of a chromatin state are subject of inheritance through cell division. Histone modifications are informational events and have their own code, which could be compared to the genetic code [97]. Recently, it was proposed that nucleosomes can be reconstituted several times during the cell cycle from newly synthesized histones. This is possible due to the fact that histone modifications are erased. This makes it unlikely that the modifications are themselves capable of transmitting information [98]. As a consequence, an optional model contends that the intrinsic stability of a given nucleosome is affected by histone modifications along with the secondary effector proteins. Effector proteins are able to recognize the modifications and could regulate nucleosome architecture and stability, which in turn could facilitate its susceptibility to remodeling [99]. It remains essential to resolve how likely nucleosomes can be disassembled or modified in their relative arrangement within the nuclear milieu, which leads to the exposing of underlying sequences for specific regulators that control genome output. According to this possibility, histone modifications along with the influence of nucleosome remodeler factors and other chromatin-associated proteins, could function in an integrated manner to provide a dynamic, mechanistic system that is able to regulate both nucleosome turnover and DNA exposure to nuclear regulatory factors.

Inasmuch as increasing or decreasing accessibility of DNA to sequence-specific binding proteins may be a mechanism to enable active or repressed gene expression conditions, it is clear that some other factors would be required to facilitate this type of regulatory mechanism. Involvement of molecular chaperones would provide a reasonable explanation, and among them, Hsp90 is the best candidate. Early findings showing that histones are able to modulate Hsp90 autophosphorylation [100] prompted further investigations into their

potential interactions. In effect, Hsp90 is able to bind histones and enhance histone binding to DNA. This agrees with the existence of comparable domains between the chaperone and the polyglutamic acid sequence of nucleoplasmin, a protein involved in nucleosomal assembly [101]. Hsp90 also favors chromatin condensation with the consequent delay in the dissociation rate of histones upon treatment of isolated chromatin with high ionic strength buffers [102,103]. More recent evidence demonstrates that altered chromatin architecture impairs the response to heat-shock [104] and may even influence emotional behavior [105].

Hsp90 inhibition promotes both the inheritance and enrichment of atypical phenotypes [11,16,106]. Importantly, such inhibition favors not only the inbreeding of progenies during successive generations, but also the frequencies of the abnormal phenotypes to increase in a non-Mendelian manner. In a similar fashion to the pioneering studies performed in *Drosophila* and *Arabidopsis* that have been discussed above, it was also reported that impairment of Hsp90 function in flies following genetic mutation or pharmacological inhibition with geldanamycin resulted in the inheritance of a specific eye phenotype in isogenic fly lines [106]. At variance of the first studies, the Hsp90 functions as capacitor was revealed by the fact that the depletion of Hsp90 generated an altered chromatin state where histone H3 global acetylation was affected. Importantly, it was also demonstrated that the eye outgrowth phenotype was reversed with the use of trichostatin A or sodium butyrate, two well known inhibitors of HDACs.

Additional evidence that connects the previous phenomena with the acetylation status of chromatin came from modified selection experiments where F6 fruit flies were selected for the geldanamycin-induced phenotype and fed with trichostatin A and sodium butyrate. Interestingly, both HDAC inhibitors suppressed the ability of the organism to recover phenotypic characteristics similar to those of the original individuals. These observations provided powerful proof that heritable chromatin acetylation states could be closely linked to Hsp90-induced phenotypic inheritance.

The evidence implies that genetic variations in protein encoding genes may have a slight or neutral effect on the final phenotype if the conformation of the protein would have been preserved by the assistance of Hsp90 and associated proteins. Populations subject to high mutational loads are prone to experience reduced cellular fitness, mostly due to protein misfolding that results from destabilizing mutations in protein folding genes. The implication that Hsp90 is a mediator of phenotypic stability indicates that its role is critical for cell survival under adverse circumstances. Nonetheless, there is no definitive molecular model to date that has been able to give a full explanation for these experimental phenomena. In order to elucidate these features, models favoring a genetically based mold or an epigenetically based model could be helpful, although neither has been able to provide a definitive answer to date.

6. SmyD proteins

The balance of histone demethylation and methylation helps to turn on and off genes, respectively, by mechanisms such as relaxing their tails and altering the extent to which transcription factors are able to gain access to the DNA. Alternatively, the mechanism may be due to entwining histone tails around the DNA, which restricts access to DNA [107]. SmyD is a novel family of four chromatin regulators associated with histone methylation that has been recently characterized [108–110]. These proteins show two domains, the SET domain, an evolutionarily conserved motif responsible for transferring methyl groups from S-adenosylmethionine to lysine residues of proteins, and the MYND domain, a Zn-finger motif related to protein–protein interactions. These methyl-transferases are directly related to transcriptional control mechanisms during cell differentiation and proliferation. They are also able to methylate non-histone proteins such as the tumor suppressor p53, and methylation at K^{370} represses p53-dependent transcriptional activity [111]. A similar effect is also observed for methylation at K^{860} of the retinoblastoma tumor suppressor (Rb) [112]. In mice and humans, the cytoplasmic isoforms of Hsp90 itself is methylated by the SmyD family member SmyD2 at K^{616} and K^{615}, respectively [45,113].

Steroid receptor heterocomplexes show Hsp90-interacting proteins that contain TPR domains formed by sequences of 34 amino acids repeated in tandems and organized in antiparallel α-helixes. These domains serve as Hsp90 anchoring points. Examples of TPR proteins are the high molecular weight immunophilins recovered with steroid receptors (CyP40, FKBP51, and FKBP52); the heat-shock organizing protein, Hop/p60; and the Ser/Thr-phosphatase, PP5. [114,115] (see Table 1). Recent evidence demonstrates that the C-terminal end of SmyD is structurally similar to those TPR domains and is able to recognize the presence of Hsp90 in steroid receptor heterocomplexes [116,117]. Such physical interaction has been demonstrated and results in a positive regulation of SmyD functional activity by the chaperone [113]. Accordingly, higher levels of methylated H3K4 are achieved in an Hsp90-dependent manner [108] and there are changes in the expression of genes associated with chromatin remodeling, transcriptional regulation, and cell cycle progression. Importantly, most of those genes are up-regulated by SmyD and H3K4 methylation.

The three members of the Swi/Snf protein complex are counted among the SmyD substrates implicated in chromatin remodeling. They are up-regulated by SmyD and able to remodel nucleosomes using ATP as a source of energy [118,119]. They have also been implicated in cancer processes through several mechanisms [120,121].

Another factor that is also affected by the activity of the SmyD·Hsp90 complex is WRD9 (bromodomain and WD-repeat domain-containing 1). WRD9 is preferentially down-regulated and capable of forming complexes with SMARCA4 (SWI2-related gene 1) [122] and the acetylated form of histone H3 [123]. Also, the chromatin-related mesenchymal modulator CHD9, the transcription factor MEF2C [108], and several other Zn-finger factors are known to be up-regulated by SmyD activity, such that they are indirectly dependent on Hsp90 for their activation.

It is thought that the methyl-transferase activity of SmyD proteins is regulated by autoinhibition via the intra- and inter-domain bending of its conserved Hsp90-interacting C-terminal domain. Based on the recently elucidated crystal structures of these TPR-like domains, it has been suggested a mechanism for SmyD activation is one that resembles the association of the TPR-domain cochaperone PP5. PP5 is a prominent Hsp90-associated member of steroid receptor heterocomplexes [124–126]. The crystal structure of the autoinhibited conformation of PP5 shows that the TPR domain of the enzyme engages with the catalytic channel of the Ser/Thr-phosphatase domain, such that access to the catalytic site is restricted [127]. This self-inhibited biological conformation of PP5 is stabilized by the C-terminal helix, which interacts with the Hsp90-binding groove on the TPR domain. In short, Hsp90 favors PP5 activity by disrupting these TPR-phosphatase domain interactions, a structural modification that permits access of the substrate protein to the active Ser/Thr-phosphatase domain. Based on this mechanism of self-regulation by Hsp90, a similar model of action was postulated for SmyD proteins in which Hsp90 interacts with the TPR-like domain present at the C-terminal end of SmyD and induces a gain-function conformational change [116].

7. HDAC6

Acetylation in lysine residues is a commonly occurring post-translational modification of proteins that impact in their biological function. The acetylation of histones and transcription factors is particularly relevant for the regulatory mechanisms of gene expression in that this post-translational modification affects chromatin architecture and consequently nuclear processes that could be passed to daughter cells as epigenetic markers. Independently of transcription, the balance between histone acetyl-transferases and histone deacetylases controls a broader scope of basic cellular processes when it is compared with other

major posttranslational modifications and in many ways is comparable to phosphorylation [128–130].

To date, 18 mammalian HDACs have been characterized. They are classified into four different types. HDACs belonging to class I include HDAC1, HDAC2, HDAC3, and HDAC8; class IIa includes HDAC4, HDAC5, HDAC7, and HDAC9; class IIb contains HDAC6 and HDAC10; class III includes seven SIRT proteins (consecutively numbered SIRT1 through SIRT7), and class IV consists of only one member, HDAC11 [130]. Perhaps one of the most interesting subfamilies of HDACs is IIb since HDAC6 shows a unique characteristic—it is located at the crossroads between cytoskeleton architecture and signaling cascades. The finding that HDAC6 is a client protein of Hsp90, which is in turn substrate for the deacetylase, adds to the multifunctional properties of the chaperone [41,77]. The other known cytoplasmic substrate of HDAC6 is α-tubulin [131], although the biological significance of this modification is still unclear. While early studies showed that HDAC6 is primarily located in the cytoplasm thanks to a unique cytoplasmic anchoring domain with TPR motifs and a conserved nuclear export signal, under certain circumstances such as the arrest of cell proliferation, HDAC6 is also found in the nucleus, and this nuclear accumulation has been further detected in the presence of the CRM-1 inhibitor leptomycin B [132]. HDAC6 is acetylated by p300 [133], including a lysine located at the N-terminal nuclear localization signal (NLS) region. To determine the contributions of the NLS region acetylated lysine residue, an HDAC6 mutant was designed in which the lysine was converted into glutamine. The mutant demonstrated significantly reduced HDAC6 tubulin deacetylase activity and further impaired cell motility; however, the mutant had no effect on histone deacetylation. Interestingly, these mutations retained HDAC6 in the cytoplasm by blocking the interaction with the nuclear import protein importin-α [133]. Therefore, it could be speculated that the acetylation status of HDAC6 should affect the histone acetylation level. This is in agreement with the fact that nuclear HDAC6 forms complexes with HDAC11 [134], which could be the factor responsible for HDAC6 deacetylation and subsequent stabilization of the nuclear pool. Importantly, a study on the subcellular localization of HDAC6 in mammary epithelial cells demonstrated a strong correlation between the localization of the enzyme and the grade of cell malignancy, such that a strong cytoplasmic staining was observed in cancer cells and a preferential nuclear localization was observed in normal cells [135].

The fact that Hsp90 is a substrate of HDAC6 makes it a master regulator of several essential nuclear regulatory processes, including chromatin rearrangement and transcriptional response. Acetylation of Hsp90 promotes the dissociation of p23 from the GR·Hsp90 heterocomplex and the receptor becomes unable to bind steroid or translocate into the nucleus [41,77]. Other examples can be found in the stability properties of at least a dozen essential regulatory nuclear factors, whose stability is usually increased by acetylation of particular lysine residues (i.e., p53, p73, Smad7, SREBP1a, SREBP2, Runx3, SF-1, ER81, FOXO4, NF-E4, HNF6 and E2F1) [136].

It is important to emphasize that, in addition to their recognized function as transcriptional activators, the histone acetyltransferases p300 and CBP also exhibit the capability to repress transcription, a property shared with HDAC6. Sumoylation of the CRD1 domain (C-terminal regulatory domain-1) of p300 accounts for its activity as a transcriptional repressor, and the direct binding of HDAC6 to SUMO-CRD1 accounts for the transcriptional repression of the CRD1 domain of p300 [137]. Interestingly, HDAC6 can also form complexes with corepressors. A known representative case is HDAC6 association with LCoR, a factor related to the ligand-dependent repressor activity of various nuclear receptors [138]. Another known association occurs between ETO-2, a constituent of N-CoR, SMRT, and mSin3A complexes [139]. Many transcription factors show individual activity as repressors, and this property was assigned to their capacity to interact with HDAC6. A typical example of a protein that is capable of antagonistic activities on both transcriptional activation and repression is Runx2. Direct recruitment of HDAC6 to Runx2 from cytoplasm to chromatin is thought to be responsible for the functional repression of p21CIP/WAF [140].

The NF-κB subunits p50 and p65 can also recruit HDAC6 to repress the expression of a subunit of the H^+/K^+-ATPase [141]. On the other hand, HDAC6 knockdown studies have shown a weak effect on the double-stranded RNA (dsRNA)-induced activation of NF-κB. Even though HDAC6 knockdown shows negligible effect on dsRNA-induced activation of NF-κB, it greatly impairs the activity of IRF3 (interferon regulatory factor 3), suggesting a potential dynamic role of the HDAC6·Hsp90 complex in the activation of IRF3 and the β-interferon gene response [142].

8. The Pih1-Tah1 heterocomplex

Tah1 (TPR-containing protein associated with Hsp90) and Pih1 (Protein interacting with Hsp90) have been identified as novel Hsp90 cochaperones implicated in chromatin remodeling complexes and small nucleolar RNP maturation [143,144]. Although Pih1 is a very unstable protein and is rapidly degraded, its association with Tah1 forms a stable heterodimeric complex that is capable to regulate the intrinsic ATPase activity of Hsp90 [145]. In other words, Pih1·Tah1 dimers regulate the ability of Hsp90 to interact with other regulatory client factors in the nuclear compartment. A similar interaction has recently been described involving the two stable TPR domains in Tah1 [146].

Hsp90 binds to the Pih1·Tah1 heterodimer with the identical affinity and stoichiometry as Hsp90 binds to a Tah1 monomer [145,147]. However, the Pih1·Tah1 heterocomplex antagonizes Tah1 activity on Hsp90 and inhibits chaperone ATPase activity [145]. The heterocomplex bound to Hsp90 is also linked to the L7ae RNP assembly. This consequently leads to decreased levels of newly synthesized RNPs, such as U4 and telomerase, and loss of several core RNP proteins (15.5 K and Nop58) upon inhibition of the chaperone function by geldanamycin [148]. The Hsp90 client protein Pih1 can also interact with these core proteins [148]. Taken together, these observations suggest that the Pih1·Tah1 complex can act as a platform for the recruitment and loading of client proteins involved in RNP assembly onto the Hsp90 chaperone system.

Rvb1 and Rvb2 are two highly conserved members of the AAA + (ATPase associated with diverse cellular activities) family of ATPases that are present in various protein and nucleoprotein complexes implicated in key cellular processes such as transcription, DNA damage response, snoRNP assembly, cellular transformation, and cancer metastasis [149]. Rvb proteins have been shown to associate with Pih1 and Tah1 in the so-called R2TP complex [150], so it could be entirely possible that Rvb1/Rvb2 cooperate with the Hsp90·Pih1·Tah1machinery in remodeling RNA moieties of RNPs during their assembly, during RNP maturation, and chromatin remodeling. It should be noted that the members of the Rbv family are known histone interactors involved in the organization of structurally and functionally distinct chromatin regions, histone acetylation and chromatin decondensation [149].

9. BCL6

The transcription factor B cell lymphoma-6 protein (BCL6) belongs to the BTB/POZ-Zinc finger family of proteins. It was identified in B-cell lymphoma [151], where it plays an essential role as a repressive factor blocking the transcription of specific target genes by recruiting corepressors. Thus, BCL6 suppresses cell cycle by repressing various genes such as *p27*. BCL6 also up-regulates pro-growth genes, such as *c-myc* [152], favoring cell survival and proliferation. There is a constitutive expression of BCL6 in about 70% of patients suffering diffuse large B cell lymphomas [153], a rapidly progressive and aggressive disease that represents the most frequent type of non-Hodgkin lymphoma. This disease can be curable, but approximately 40% of patients are resistant to all types of known treatments [154]. Recent studies demonstrated that the selective inhibition of Hsp90 with the drug PU-H71 kills

lymphoma cells [155], which appears to be a direct consequence of lowering BCL6 stability by disrupting its association with Hsp90. In these B cell lymphomas, Hsp90 is concentrated in the nucleus rather than showing the typical cytoplasmic localization, and this phenomenon is presumably linked to the higher nuclear accumulation of BCL6. The presence of the chaperone at BCL6 target genes implies that Hsp90 might preserve BCL-6 stability while it is actively repressing target genes [155]. Also, the BCL6·Hsp90 complex represses the expression of two related genes, i.e., *EP300*, whose product is the coactivator p300, and *BAT3*, that encodes for the p300 cofactor HLA-B-associated transcript 3, which is required to increase p53 recruitment to p300 in response to DNA damage [156]. Inhibitors of Hsp90 action induce the expression of both proteins, p300 and BAT3, resulting in increased acetylation of p53 and Hsp90. Importantly, this treatment prevented and even eradicated established human B-cell lymphoma xenografts in murine models [157].

10. Immunophilins

Immunophilin is the collective name given to a family of proteins that bind immunosuppressive drugs and show peptidyl-prolyl-(*cis*/*trans*)-isomerase enzymatic activity. Despite the fact that these proteins constitute a family of thirty-six members [158], only the low molecular weight immunophilins CyPA and FKBP12 are responsible for the immunosuppressive effects observed by the binding of the immunosuppressive drug cyclosporine-A or FK506 (tacrolimus), respectively [159].

In addition to the isomerase domain, larger immunophilins also have TPR-domains and are usually associated with Hsp90. These immunophilins compete with each other and with Hop for binding to the Hsp90 TPR acceptor site of Hsp90, and the general consensus is that only one TPR-containing protein is physically able to bind to Hsp90 at a given time. Most of the biological actions of the large immunophilins are coupled to Hsp90 function. It was shown that the TPR-domain immunophilin FKBP52 links steroid receptors and other cytoplasmic proteins with the motor protein dynein in order to facilitate their retrotransport [160–162]. This mechanism is also shared with homologous immunophilins present in plant [163] and insect [164] models. Interestingly, the capacity to interact with motor proteins has also been reported for the low molecular weight immunophilin, CyPA [165], but this protein does not interact with steroid receptor complexes. It is still unclear whether or not CyPA participates in protein transport, although some recent evidence supports this possibility [166,167].

Two highly homologous family members, FKBP51 and FKBP52, have always shown antagonistic biological actions [168]. Both proteins are also nuclear factors related to several essential processes such as transcriptional regulation, cell differentiation, histone chaperone activity, and modification of chromatin structure [169]. Inefficient retrotransport of nuclear factors was observed when the FKBP52·Hsp90 interaction was impaired or the Hsp90 function was disrupted with specific inhibitors [50,162,170]. Immunophilins are also required for the efficient passage of proteins through the nuclear pore complex [50,171], and show regulatory actions on transcriptional activity [126,172].

Even though these proteins are poorly characterized in their biological actions, it appears that they also have their own effects in the cell, which seem to be independent of their association with Hsp90. For example, some immunophilins function as histone chaperones by binding histones and regulating the assembly and disassembly of nucleosomes. FKBP25/Fpr3 is an immunophilin that shows preferential binding for rapamycin rather than FK506 [173] and binds directly histone H2B [174], mediates the prevention of premature adaptation to DNA damage, and serves to maintain recombination check-point activity [175]. It seems that FKBP25/Fpr3 is important in the response to DNA damage since a loss of check-point function was observed during meiosis of cells lacking the immunophilin. The closely related protein in *S. cerevisiae*, FKBP25/Fpr4, forms complexes with histones [176] and provided the first epigenetic evidence connecting the peptidyl-prolyl isomerase activity of an FKBP immunophilin with histone methylation. FKBP25/Fpr4 catalyzes proline isomerization of histones H3 and H4, leading to a decrease in the level of Set2-mediated histone H3K36 trimethylation [177]. Importantly, FKBP25 interacts with HDAC1 and HDAC2. FKBP25 also interacts with other chromatin-related proteins involved in the regulation of DNA transcription, such as casein kinase II and nucleolin, as well as with the high-mobility group, HMB II protein, which possesses DNA-binding activity (see [169] for a recent review) and is not found associated with Hsp90.

FKBP52 is an immunophilin that has a peptidylprolyl (*cis*/*trans*)-isomerase domain highly homologous to that present in FKBP25, and also has multiple TPR domains through which Hsp90·FKBP52 complexes are formed. It appears as though the involvement of FKBP52 in gene regulation is not as prolific as it is for FKBP25, but there are several lines of evidence in favor of this possibility. FKBP52 association with the transcription factor IRF-4 impaired the DNA-binding capacity of IRF-4 in a peptidyl-prolyl isomerase-dependent manner [178]. Structural modifications of IRF-4 were detectable by immunoblotting and by IRF-4 partial proteolysis. This was the first direct evidence suggesting that immunophilins may function as transcriptional coregulators. In view of the ubiquitous expression of immunophilins, it is noteworthy to emphasize that they may act as inducible coregulators. FKBP52 colocalizes with Hsp90 in perinuclear structures of undifferentiated neuronal cells [58,179,180] and redistributes to terminal axons and ramification bodies during early differentiation steps. Those perinuclear areas where the Hsp90·FKBP52 complexes are primarily located are associated with the nuclear lamin and are transcriptionally silent, whereas they become very active transcriptionally during the early differentiation. This suggests that the heterocomplex can regulate expression of key genes due to chromatin refolding [58,180]. It is unclear at this point whether the association of Hsp90 with FKBP52 modifies the intrinsic biological properties of the isolated immunophilin.

Nuclear mobility of some transcription factors, such as the GR, is Hsp90-dependent. By using a fluorescence recovery after the photobleaching technique, it was shown that nuclear mobility of the receptor was inhibited by the Hsp90 antagonist geldanamycin [181]. In the same study, a more direct proof of molecular chaperone involvement in steroid receptor subnuclear trafficking was provided by an ATP-dependent recovery method for studying nuclear mobility by incubating various combinations of purified chaperones and associated proteins. Among those purified factors, Hsp90 and FKBP51 were assayed, but not FKBP52. Those results are consistent with previous studies were Hsp90 inhibitors were used and also with a more recent evidence showing that the overexpression of FKBP52 retains receptors in the nuclear compartment, whereas FKBP51 antagonizes this effect favoring receptor export [160]. These data are further supported by experiments performed with FKBP52 KO cells (Gallo LI and Galigniana MD, unpublished results). Accordingly, the transcriptional activity of the receptors was impaired by overexpression of FKBP51 and favored by FKBP52 [168]. In short, the nuclear Hsp90-immunophilin complex is able to regulate the expression of genes. A recent publication reported that FKBP51 transfected in melanoma cells was recovered bound to chromatin after performing chromatin immunoprecipitation assays [182]. A similar observation was done for endogenous FKBP51 and FKBP52 when the NF-κB cascade was activated (Erlejman AG, De Leo S, Mazaira G., Molinari AM, Camisay MF, Cox M, Piwien-Pilipuk, G, and Galigniana MD, unpublished results). Moreover, mitochondrial FKBP51 concentrates in the nucleus due to a number of stressing stimuli [183] as well as during the early steps of preadipocyte differentiation [184]. In the latter case, FKBP51 is retained in the nucleus associated with chromatin, the nuclear matrix, and the nuclear lamina [184]. A similar observation was performed during the early steps of neuronal differentiation, where FKBP51 migrated to the nuclear envelope colocalizing with lamin [179] and occupying areas where FKBP52 resided in the undifferentiated state. Taken together, these observations suggest that the expression balance

between FKBP51 and FKBP52 may play important roles in the regulation of gene expression and could also modify chromatin architecture.

11. DNA stability

Genomic DNA is continually exposed to a number of damaging stimuli such as oxidants, harmful chemicals, UV light, and radiation. When damaged DNA eludes the cellular repair mechanisms, the progress of replication forks catalyzed by high-fidelity DNA polymerases is habitually blocked [185]. One of these key sentinels is DNA polymerase-η (DNA pol η). A recent study [186] demonstrated that Hsp90 assists the folding of DNA pol η into an active conformation. Consistent with this, it was shown that the activity of DNA pol η is inhibited by geldanamycin derivatives, thus sensitizing cells to the cytotoxic effects of UV radiation. Similarly, the hypersensitivity of Hsp90 inhibitor-treated cancer cells to other DNA-damaging agents could follow the same principle. Hsp90 inhibition might retard DNA pol η-mediated mutagenic events that allow cancer cells to acquire more malignant phenotypes [186]. Nonetheless, the disruption of Hsp90 activity not always suppresses DNA mutation. In effect, Hsp90 appears to be required for the suppression of transposon activity in germ cells of *Drosophila* [187], where transposons are suppressed by a discrete RNA-silencing mechanism mediated by piRNAs (*Piwi-interacting RNAs*) [188]. The biogenesis of these small RNAs does require Hsp90, and Hsp90 inhibition has been shown to decrease the expression of piRNAs, improve transposon mobility, and result in de novo mutations [187]. The lack or loss of activity of PRMT5 (chromatin-modifying arginine methyl-transferase), which is in turn another Hsp90 client factor [189], results in a decreased methylation level of several piRNA-interacting proteins and decreases piRNA expression in *Drosophila* germ cells [190]. Therefore, the effect of Hsp90 disrupting agents on PRMT5 may contribute to their ability to abrogate piRNA-mediated regulation of transposon mobility.

The recognition of Hsp90 as a suppressor of transposable element-induced mutations raises the possibility that Hsp90 inhibitors could enlarge the frequency of mutations under specific circumstances, which opposites the effect of those compounds on DNA pol η-produced mutations.

In addition to these mechanisms, eukaryotic cells have also developed other defense systems against DNA damage and gene mutations that involve the action of protein kinases, many of which are Hsp90-regulated. Among them, one of the most interesting and best studied kinases is the family of phosphatidylinositol 3-kinase-related protein kinases (PIKK), a topic that is addressed in the next Section.

12. Hsp90-associated protein kinases and gene expression

As stated above, a large number of the Hsp90-modulated client proteins belong to the protein-kinase family, representing one of the largest groups of known Hsp90 partners [191–193]. Not by chance, one of the first isolations of Hsp90 was achieved during the affinity purification steps for a tyrosine kinase factor, v-Src [194]. Almost 200 kinases are regulated by Hsp90 [195], including many oncoproteins (Raf1, JAK, ErbB, PKB/Akt, CDK, Chk1, CAMK, KIT, Met, Fak, Plk, etc.) [192,193]. Accordingly, the disruption of the Hsp90 function is currently being pursued as a novel therapeutic strategy for treating several types of cancer [196,197]. Multiple lines of evidence support models where the activation of tyrosine kinases is an essential step for steroid receptor-mediated intercellular signaling, and also for phosphorylation of several other transcriptional factors, cofactors, and histones [198–200].

It is noteworthy that the recruitment of many protein kinases to the Hsp90 complex depends on the cochaperone $p50^{cdc37}$ (also known as cell cycle division protein 37, Cdc37, and p50 or pp50) [191], a protein that binds Hsp90 and is oncogenic itself. Accordingly, a recent study showed a perfectly linear correlation of Hsp90 interaction profiles where $p50^{cdc37}$ and protein kinase association with the chaperone were compared [195], suggesting that the $p50^{cdc37}$·Hsp90 complex is essential for the proper folding of other kinases.

$p50^{cdc37}$ was first discovered in mammalian cells as a member of the $pp60^{v\text{-}src}$·Hsp90 heterocomplex [201,202]. The association of $p50^{cdc37}$ with Hsp90 was first thought to be exclusive regarding the presence of TPR-domain proteins [203,204]. Further evidence showed that Hop [205] and PP5 [206] form oligomeric structures with the $p50^{cdc37}$·Hsp90 complex, and $p50^{cdc37}$ is not able to bind Hsp90 if p23 is associated to the chaperone [207].

From an evolutionary perspective, perhaps one of the most interesting cases of regulation of transcription by $p50^{cdc37}$-managed protein kinases is the Ser/Thr protein kinase Gcn2, which is homologous to the eIF2α (eukaryotic initiation factor-2α) kinase in *S. cerevisiae*. Gcn2 requires Hsp90 for its proper regulation [208] and forms part of a crucial mechanism responsible for sensing amino acid deprivation. More than 40 genes involved in amino acid metabolism are affected by induction of Gcn4 [209], a transcriptional activator. This is possible due to the phosphorylation of the α subunit of eIF2 (or eIF2α subunit) by Gcn2, which is in turn activated by direct binding of 'uncharged' tRNA [210]. As a direct consequence of the known role of Cdc37 in regulating Gcn2, general amino acid control is defective in yeast strains carrying Cdc37 mutations [208]. Mammalian cells have developed a more complex response pathway to these types of stresses by inclusion of additional eIF2α kinases that are able to respond to different environmental stresses [211]. This mechanism blocks global translation and is accompanied by a grater expression of ATF4, a basic leucine zipper transcription factor related to yeast Gcn4 [212,213].

A second interesting group of Hsp90-binding protein kinases is the PIKK subfamily. These kinases are related to repairing mechanisms of defense against errors in gene expression, protective responses for gene mutations and/or transcriptional blundering during environmental stresses [214]. Vertebrates express various types of PIKKs—ATM (ataxia telangiectasia mutated) [215], ATR (ATM- and Rad3-related) [216], DNA-PKcs (DNA-dependent protein kinase catalytic subunit) [217], SMG-1 (suppressor with morphogenetic effect on genitalia-1) [218], and TOR (target of rapamycin) [219]. All these factors are Hsp90-binding proteins that are activated as a defensive shield against various types of cellular stresses, and exhibit activity of Ser/Thr-protein kinase. There is a sixth member, TRRAP (transformation/transcription domain associated protein), which shows some differential features. TRRAP is actually classified as a pseudokinase since it lacks key residues required for ATP binding and shows no enzymatic activity [220]. There is no direct evidence to date for interactions with Hsp90, although it has been suggested that the interactions could take place indirectly when TRRAP forms heterocomplexes with other Hsp90-interacting factors [214]. The functional disruption of Hsp90 activity leads to a decreased amount of cellular PIKKs (supposedly due to the classical destabilization of Hsp90-binding clients) and a significant reduction of the phosphorylation status of PIKK substrates [218,221]. Consequently, transcriptional activity is impaired.

Besides being identified as a protein that forms physical complexes with Hsp90 [214,218], the PIKK family member SMG-1 also forms complexes with other Hsp90-interacting factors, such as Tel-2 [216], a scaffold protein that is required for proper assembly of PPIKs and Hsp90 [215]. Thus, it is thought that Tel-2 cooperates with Hsp90 to favor the proper expression of some PPIKs, such as ATM, ATR, and DNA-PK, all of which are lost in geldanamycin-treated cells [222]. In addition, Tel2 is implicated in several signaling cascades that influence transcriptional regulation, telomere maintenance, DNA damage checkpoints, and DNA repair mechanisms [214,222,223]. This complex network provides representative evidence of the intricate arrangement of Hsp90-binding regulatory factors with kinase activities that separately affect gene expression and the cell cycle. It also demonstrates how cautious the interpretation of experimental data must be when it is assigned from a direct role to a specific protein after using a pharmacological approach such as, Hsp90 inhibition with geldanamycin.

In addition to the two previously described types of protein kinases, it is also important to discuss the specific case of the RuvB-like 1 and 2 complexes (RuvB-1 and RuvB-2, also known as Pontin and Reptin, respectively), whose biological actions are closely integrated to some of the PIKK members, Tel-2, and Hsp90. Mammalian RuvB kinases show high homology with the bacterial DNA-helicase RuvB [224], intrinsic ATPase activity, and are modulated by the protein kinase Hint1, that disrupts the association of RuvB subunits [225]. RuvB-1 and RuvB-2 can interact with one another to form hexameric complexes, but they also show individual functions such as binding capacity to tubulins α and γ and regulating spindle assembly (RuvB-1) [226] and cytokinesis events (RuvB-2) [227]. Nonetheless, they are best characterized as transcriptional regulators and chromatin-remodeling factors [149]. These complexes can reorganize nucleosomes and participate in histone exchanges and/or the recruitment of factors that affect transcription [228]. RuvB proteins are themselves Hsp90-interacting proteins [150] and also interact with other Hsp90-interacting nuclear factors such as SMG-1 [218] and Tah1/Pih1 complexes [150]. SMG-1 is activated by several stresses (oxidative stress, radiation, DNA damage, UV light, etc.) and activates p53 by phosphorylation [229]. Therefore, the impairment of SMG-1 function increases the spontaneous rate of DNA damage and cells show increased sensitivity to genotoxic injuries.

It has also been suggested that RuvB proteins have a functional relationship with mTOR [230] and members of the PIKK family [218], most likely via the C-terminal end of these proteins [231]. RuvB proteins are members of the chromatin remodeling complex INO80 [96,232] and the histone acetyltransferase TIP60, proteins that are consequently dependent in an indirect manner of the regulatory action of Hsp90 on RuvB complexes. In turn, RuvB regulates the transcriptional activity of β-catenin in cancer cells [233,234], which is activated by GSK3β, a classical Hsp90 client kinase [235]. Thus, RuvB-1 and RuvB-2 are recruited along with TIP60 to the promoter regions of transcriptional targets of NF-κB [236], c-Myc and E2F1 [237]. Since the last two transcription factors favor the translation of target mRNAs because the increase cap methylation [238], RuvB proteins are also directly involved in the translational activity of mRNAs for PIKKs. On the other hand, their association to NF-κB target genes in metastatic prostate cancer cells turns off the expression of a subset of genes encoding for tumor metastasis suppressors (for example, KAI1), favoring the metastatic progression of specific cancer types [236].

13. Cancer treatment

Epigenetic modifications of DNA, such as methylation and those involving histone modifications, can generate genomic instability that, in the end, lead to the repression of tumor suppressor genes or aberrant expression of oncogenes. As a consequence, these processes contribute to aggravating the pathogenesis of several diseases. Since many of the disease states, including cancer, are related to epigenetic changes, the attempt to counteract these modifications with epigenetic treatments appears to be a reasonable strategy. Unlike the case of mutations in DNA sequences, epigenetic modifications are an ideal target since they are naturally reversible. Some of the most frequent treatments currently employed intend to modify DNA methylation amounts and histone acetylation status. Thus, genes that have been silenced may be reactivated by DNA methylation inhibitors. Examples of inhibitory drugs currently used in these therapies include 5-azacytidine and 5-aza-2′-deoxycytidine [239]. These compounds mimic the structure of the cytosine nucleoside and are consequently incorporated in a very efficient manner into DNA during replication. This leads to the blockade of methyltransferase (DNMT) enzymatic activity and, as a result, inhibition of DNA methylation.

Acetylation is a post-translational modification that neutralizes the positive charge of histones, thereby impairing the interaction of DNA phosphate groups with the N-terminal end of histones. Hence, relatively inactive, condensed chromatin becomes a more 'relaxed' structure that permits more efficient transcriptional activity. The general mechanism for DNA relaxation requires alterations in HDAC activity, which is a further reason that transforming these enzymes is a desirable therapeutic target. In line with this principle, several HDAC inhibitors have been tested at the present time. Among the most common pharmacological agents currently used and known to modify HDAC activity are valproic acid, phenylbutyric acid, SAHA, and depsipeptide [10,239]. However, these approaches to therapy require great caution, since epigenetic modifications represent a very extensive pharmacological approach. Clearly, the potential success of any epigenetic anticancer treatment lies on its pharmacological selectivity for malignant tissue or the deregulated transformed cell; otherwise, the treatment could cause the very disorders they are trying to counteract. Despite this possible disadvantage, new drugs are being developed to specifically target anomalous cells and generating minimal damage to healthy cells, such that epigenetic therapy is becoming an increasingly promising therapeutic strategy. In this regard, the combined therapy of drugs targeting simultaneously HDACs and Hsp90 is an attractive alternative approach to treatment that is currently being evaluated in clinical trials [240]. Conventional cytotoxic drugs, such as cisplatin, cytarabine taxanes, gemcitabine, proteasome inhibitors, are being co-administered along with Hsp90 disrupting derivatives to synergistically promote apoptosis in several types of disorders [241–244]. Many times, the detailed mechanistic insights of synergistic drug actions are not readily apparent, but nonetheless likely involve interference in the survival mechanisms and cell cycle progression by targeting specific pathways like those described above.

14. Envoy

The number of Hsp90 client proteins has grown exponentially during the last ten years. Most of these interacting proteins behave as cardinal factors in key signaling cascades and are consequently related to basic biological processes. In turn, it should be realized that post-translational modifications of Hsp90 add more complex implications to the already intricate regulation of signaling proteins, transcriptional factors, and chromatin modifiers. Fig. 2 summarizes a schematic network of some Hsp90 client proteins, where the chaperone functions like a hub upon the onset of various stimuli. The interrelated molecular actions of these Hsp90-modulated proteins result in a number of physiologic responses, some of them in a potentiated manner for the same biological end, whereas others work in an antagonistic fashion according to the set of involved proteins.

Hsp90 has a unique role in safeguarding the general homeostatic mechanisms of the cell, especially in the maintenance of cellular proteostasis. As such, Hsp90 has played critical roles during the evolutionary process by preserving the biological activity of modified proteins and serving as a capacitor to buffer acquired phenotypic variations. In this sense, those pioneering studies discussed here on the potential role of the chaperone in the genetic assimilation have changed the current perception of evolution. Fig. 3 attempts to summarize the putative roles of Hsp90 in this phenomenon, and depicts its influence on the stabilization of the structure of certain client factors and gene expression by its recruitment to the initiation sites of transcription. These sites usually correspond with those promoter sites that show RNA pol II pausing properties, and could potentially generate a stable conformational variant of the client protein (perhaps favoring the translation of a given isoform of the client protein). Importantly, it seems that both above-hypothesized processes converge in the generation of phenotypic variants without the need to modify the intrinsic properties of the gene and are suited to the disadvantageous conditions of a harsh environment.

Even though this article has addressed only a limited number of cases due to page limitations, it is clear that the amount of nuclear factors commanded by Hsp90 is remarkable, and the network of Hsp90-dependent regulations has become a rather crowded and complex

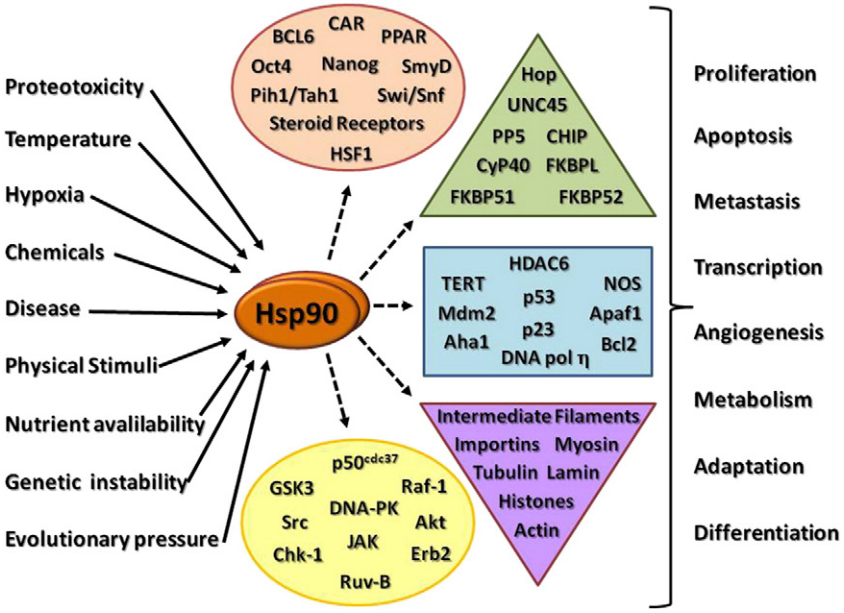

Fig. 2. Hsp90 interactions with client proteins. Hsp90 regulates cellular homeostasis against environmental modifications, biological signals, and by preserving essential biological process during the life span of the cell. To accomplish this, Hsp90 modulates the functions of hundreds of client factors influencing every aspect of the cell existence, some of them grouped here as transcription factors (pink), protein-kinases (yellow), TPR-domain proteins (green), structural proteins (purple), and miscellaneous (blue).

picture, even though we are still only in the adolescence of the field. It should be noted that the extent of Hsp90 post-translational modifications is larger in metazoans than in single eukaryote cells [245]. This suggests that this method of biological regulation could have furnished evolution with additional levels of protein control as the diversity of Hsp90 clients expanded. In this regard, besides those researchers who are close related to the molecular chaperone field, there is no doubt that little attention has been paid to the potential roles of Hsp90 in the nucleus, even though the well known functions played by Hsp90 in the structure of chromatin, its abundance in the cell, the fact that it concentrates close to the transcription start sites of about one third of genes [246,247], and plays a key role in the cytosolic turnover of nucleosomal histones [248]. For example, of the nearly 1000 publications on BCL6 shown by PubMed from the time it was first reported as an Hsp90 client protein (January 2000), only four subsequent papers have addressed the biological properties of this transcription factor from the perspective of being an Hsp90-regulated client. In contrast to that academic perspective, the pharmaceutical industry appreciated early on that direct manipulation of Hsp90 properties and functions has the potential to impact several cellular pathways simultaneously. Therefore, cutting edge research related to the development of Hsp90-targetted drugs is perhaps one of the most recurrent fields of corporate research and development investment. Nevertheless, this promising and exciting field still requires studies in greater detail to be conclusive. The conventional approach for studying the putative synergistic action of Hsp90 inhibitors with other drugs such as HDAC inhibitors has not currently reached the necessary development in order to analyze the natural genetic variation and types of polymorphisms of key genes in the human population.

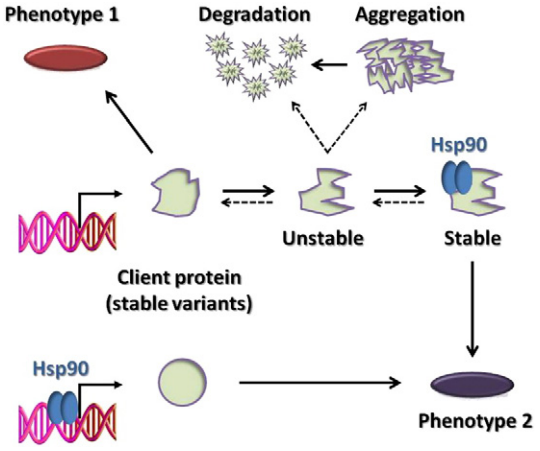

Fig. 3. Possible actions of Hsp90 during the genetic assimilation process. Hsp90 could stabilize unusual active conformations of client proteins upon the onset of harmful conditions, leading to a modification of its biological activity (for example, low protein kinase activity), which is in turn responsible for triggering unconventional signaling cascades that ultimately lead to the acquisition of a slightly different phenotype. Alternatively (but not in a mutually exclusive fashion), Hsp90 could favor the induction of a more stable protein variant for that environment leading to the accumulation of the unusual 'isoform', whose modified activity also results in the generation of the same unconventional phenotype in a convergent manner with the above-postulated mechanism.

It is noteworthy that cells treated with Hsp90 inhibitors develop a heat-shock-like response [249]. Therefore, it would not be surprising that Hsp90 could be involved in the development of drug resistance since it is a chromatin- and transcription factor-associated chaperone. Consequently, a reevaluation of the impact of the disruption of client factors and Hsp90, and the still poorly understood role of several Hsp90 cochaperones associated with Hsp90 heterocomplexes and Hsp90 sensitivity to drugs, is likely to provide novel strategies to improve therapeutic stratagems that may avoid the undesired reality of acquired drug resistance. In spite of the fact that the path appears to be longer than it was originally envisioned, it is clear that few proteins have as remarkable of a position in the multitude of molecular networks of the cell as Hsp90. Therefore, the prospects of Hsp90 targeted therapies are quite promising, and recent encouraging advances in the field lead us to think that more major breakthroughs are still to come in the near future.

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References

[1] W.B. Pratt, M.D. Galigniana, Y. Morishima, P.J. Murphy, Role of molecular chaperones in steroid receptor action, Essays Biochem. 40 (2004) 41–58.
[2] P. Csermely, T. Schnaider, C. Soti, Z. Prohaszka, G. Nardai, The 90-kDa molecular chaperone family: structure, function, and clinical applications. A comprehensive review, Pharmacol. Ther. 79 (1998) 129–168.
[3] I. Grad, D. Picard, The glucocorticoid responses are shaped by molecular chaperones, Mol. Cell. Endocrinol. 275 (2007) 2–12.
[4] W.B. Pratt, D.O. Toft, Steroid receptor interactions with heat shock protein and immunophilin chaperones, Endocr. Rev. 18 (1997) 306–360.
[5] S. Lindquist, Protein folding sculpting evolutionary change, Cold Spring Harb. Symp. Quant. Biol. 74 (2009) 103–108.
[6] F. Ritossa, A new puffing pattern induced by temperature shock and DNP in Drosophila, Experientia 18 (1962) 571–573.
[7] J. Anckar, L. Sistonen, Regulation of HSF1 function in the heat stress response: implications in aging and disease, Annu. Rev. Biochem. 80 (2011) 1089–1115.
[8] P.L. Regan, J. Jacobs, G. Wang, J. Torres, R. Edo, J. Friedmann, X.X. Tang, Hsp90 inhibition increases p53 expression and destabilizes MYCN and MYC in neuroblastoma, Int. J. Oncol. 38 (2011) 105–112.
[9] L. Whitesell, N.U. Lin, HSP90 as a platform for the assembly of more effective cancer chemotherapy, Biochim. Biophys. Acta 1823 (2012) 756–766.
[10] J. Trepel, M. Mollapour, G. Giaccone, L. Neckers, Targeting the dynamic HSP90 complex in cancer, Nat. Rev. Cancer 10 (2010) 537–549.
[11] S.L. Rutherford, S. Lindquist, Hsp90 as a capacitor for morphological evolution, Nature 396 (1998) 336–342.
[12] D.F. Jarosz, S. Lindquist, Hsp90 and environmental stress transform the adaptive value of natural genetic variation, Science 330 (2010) 1820–1824.
[13] M. Taipale, D.F. Jarosz, S. Lindquist, HSP90 at the hub of protein homeostasis: emerging mechanistic insights, Nat. Rev. Mol. Cell Biol. 11 (2010) 515–528.
[14] M. Pigliucci, Epigenetics is back! Hsp90 and phenotypic variation, Cell Cycle 2 (2003) 34–35.
[15] C.H. Waddington, Canalization of development and the inheritance of acquired characters, Nature 150 (1942) 563–565.
[16] C. Queitsch, T.A. Sangster, S. Lindquist, Hsp90 as a capacitor of phenotypic variation, Nature 417 (2002) 618–624.
[17] B. Chen, D. Zhong, A. Monteiro, Comparative genomics and evolution of the HSP90 family of genes across all kingdoms of organisms, BMC Genomics 7 (2006) 156.
[18] R.S. Gupta, Phylogenetic analysis of the 90 kD heat shock family of protein sequences and an examination of the relationship among animals, plants, and fungi species, Mol. Biol. Evol. 12 (1995) 1063–1073.
[19] E. Hickey, S.E. Brandon, G. Smale, D. Lloyd, L.A. Weber, Sequence and regulation of a gene encoding a human 89-kilodalton heat shock protein, Mol. Cell. Biol. 9 (1989) 2615–2626.
[20] K.A. Borkovich, F.W. Farrelly, D.C.B. Finkelstein, J. Taulien, S. Lindquist, hsp82 is an essential protein that is required in higher concentrations for growth of cells at higher temperatures, Mol. Cell. Biol. 9 (1989) 3919–3930.
[21] B.K. Dalley, M. Golomb, Gene expression in the Caenorhabditis elegans dauer larva: developmental regulation of Hsp90 and other genes, Dev. Biol. 151 (1992) 80–90.
[22] R.W. Hackett, J.T. Lis, Localization of the hsp83 transcript within a 3292 nucleotide sequence from the 63B heat shock locus of *D. melanogaster*, Nucleic Acids Res. 11 (1983) 7011–7030.
[23] J.L. Johnson, Evolution and function of diverse Hsp90 homologs and cochaperone proteins, Biochim. Biophys. Acta 1823 (2012) 607–613.
[24] W. Li, D. Sahu, F. Tsen, Secreted heat shock protein-90 (Hsp90) in wound healing and cancer, Biochim. Biophys. Acta 1823 (2012) 730–741.
[25] W.J. Welch, J.R. Feramisco, Purification of the major mammalian heat shock proteins, J. Biol. Chem. 257 (1982) 14949–14959.
[26] B.T. Lai, N.W. Chin, A.E. Stanek, W. Keh, K.W. Lanks, Quantitation and intracellular localization of the 85 K heat shock protein by using monoclonal and polyclonal antibodies, Mol. Cell. Biol. 4 (1984) 2802–2810.
[27] E.A. Nollen, R.I. Morimoto, Chaperoning signaling pathways: molecular chaperones as stress-sensing 'heat shock' proteins, J. Cell Sci. 115 (2002) 2809–2816.
[28] G. Piwien-Pilipuk, A. Ayala, A. Machado, M.D. Galigniana, Impairment of mineralocorticoid receptor (MR)-dependent biological response by oxidative stress and aging: correlation with post-translational modification of MR and decreased ADP-ribosylatable level of elongating factor 2 in kidney cells, J. Biol. Chem. 277 (2002) 11896–11903.
[29] R. Sawarkar, R. Paro, Hsp90@chromatin.nucleus: an emerging hub of a networker, Trends Cell Biol. 23 (2013) 193–201.
[30] F. Lamoth, P.R. Juvvadi, J.R. Fortwendel, W.J. Steinbach, Heat shock protein 90 is required for conidiation and cell wall integrity in *Aspergillus fumigatus*, Eukaryot. Cell 11 (2012) 1324–1332.
[31] D.M. Katschinski, L. Le, D. Heinrich, K.F. Wagner, T. Hofer, S.G. Schindler, R.H. Wenger, Heat induction of the unphosphorylated form of hypoxia-inducible factor-1alpha is dependent on heat shock protein-90 activity, J. Biol. Chem. 277 (2002) 9262–9267.
[32] P.M. van Bergen en Henegouwen, G. Berbers, W.A. Linnemans, R. van Wijk, Subcellular localization of the 84,000 dalton heat-shock protein in mouse neuroblastoma cells: evidence for a cytoplasmic and nuclear location, Eur. J. Cell Biol. 43 (1987) 469–478.
[33] H. Tapia, K.A. Morano, Hsp90 nuclear accumulation in quiescence is linked to chaperone function and spore development in yeast, Mol. Biol. Cell 21 (2010) 63–72.
[34] M. Mollapour, L. Neckers, Post-translational modifications of Hsp90 and their contributions to chaperone regulation, Biochim. Biophys. Acta 1823 (2012) 648–655.
[35] E.G. Mimnaugh, P.J. Worland, L. Whitesell, L.M. Neckers, Possible role for serine/threonine phosphorylation in the regulation of the heteroprotein complex between the hsp90 stress protein and the pp 60v-src tyrosine kinase, J. Biol. Chem. 270 (1995) 28654–28659.
[36] C. Garnier, D. Lafitte, T.J. Jorgensen, O.N. Jensen, C. Briand, V. Peyrot, Phosphorylation and oligomerization states of native pig brain HSP90 studied by mass spectrometry, Eur. J. Biochem. 268 (2001) 2402–2407.
[37] W. Xu, M. Mollapour, C. Prodromou, S. Wang, B.T. Scroggins, Z. Palchick, K. Beebe, M. Siderius, M.J. Lee, A. Couvillon, J.B. Trepel, Y. Miyata, R. Matts, L. Neckers, Dynamic tyrosine phosphorylation modulates cycling of the HSP90-P50(CDC37)-AHA1 chaperone machine, Mol. Cell 47 (2012) 434–443.
[38] M. Mollapour, S. Tsutsumi, A.W. Truman, W. Xu, C.K. Vaughan, K. Beebe, A. Konstantinova, S. Vourganti, B. Panaretou, P.W. Piper, J.B. Trepel, C. Prodromou, L.H. Pearl, L. Neckers, Threonine 22 phosphorylation attenuates Hsp90 interaction with cochaperones and affects its chaperone activity, Mol. Cell 41 (2011) 672–681.
[39] M. Mollapour, S. Tsutsumi, A.C. Donnelly, K. Beebe, M.J. Tokita, M.J. Lee, S. Lee, G. Morra, D. Bourboulia, B.T. Scroggins, G. Colombo, B.S. Blagg, B. Panaretou, W.G. Stetler-Stevenson, J.B. Trepel, P.W. Piper, C. Prodromou, L.H. Pearl, L. Neckers, Swe1Wee1-dependent tyrosine phosphorylation of Hsp90 regulates distinct facets of chaperone function, Mol. Cell 37 (2010) 333–343.
[40] X. Yu, Z.S. Guo, M.G. Marcu, L. Neckers, D.M. Nguyen, G.A. Chen, D.S. Schrump, Modulation of p53, ErbB1, ErbB2, and Raf-1 expression in lung cancer cells by depsipeptide FR901228, J. Natl. Cancer Inst. 94 (2002) 504–513.
[41] J.J. Kovacs, P.J. Murphy, S. Gaillard, X. Zhao, J.T. Wu, C.V. Nicchitta, M. Yoshida, D.O. Toft, W.B. Pratt, T.P. Yao, HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor, Mol. Cell 18 (2005) 601–607.
[42] A. Martinez-Ruiz, L. Villanueva, C. Gonzalez de Orduna, D. Lopez-Ferrer, M.A. Higueras, C. Tarin, I. Rodriguez-Crespo, J. Vazquez, S. Lamas, S-nitrosylation of Hsp90 promotes the inhibition of its ATPase and endothelial nitric oxide synthase regulatory activities, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 8525–8530.
[43] D.L. Carbone, J.A. Doorn, Z. Kiebler, B.R. Ickes, D.R. Petersen, Modification of heat shock protein 90 by 4-hydroxynonenal in a rat model of chronic alcoholic liver disease, J. Pharmacol. Exp. Ther. 315 (2005) 8–15.
[44] M. Blank, M. Mandel, Y. Keisari, D. Meruelo, G. Lavie, Enhanced ubiquitinylation of heat shock protein 90 as a potential mechanism for mitotic cell death in cancer cells induced with hypericin, Cancer Res. 63 (2003) 8241–8247.
[45] L.T. Donlin, C. Andresen, S. Just, E. Rudensky, C.T. Pappas, M. Kruger, E.Y. Jacobs, A. Unger, A. Zieseniss, M.W. Dobenecker, T. Voelkel, B.T. Chait, C.C. Gregorio, W. Rottbauer, A. Tarakhovsky, W.A. Linke, Smyd2 controls cytoplasmic lysine methylation of Hsp90 and myofilament organization, Genes Dev. 26 (2012) 114–119.
[46] L.H. Pearl, C. Prodromou, Structure and mechanism of the Hsp90 molecular chaperone machinery, Annu. Rev. Biochem. 75 (2006) 271–294.
[47] T. Prince, R.L. Matts, Definition of protein kinase sequence motifs that trigger high affinity binding of Hsp90 and Cdc37, J. Biol. Chem. 279 (2004) 39975–39981.
[48] W.B. Pratt, Y. Morishima, Y. Osawa, The Hsp90 chaperone machinery regulates signaling by modulating ligand binding clefts, J. Biol. Chem. 283 (2008) 22885–22889.
[49] F.U. Hartl, M. Hayer-Hartl, Molecular chaperones in the cytosol: from nascent chain to folded protein, Science 295 (2002) 1852–1858.
[50] M.D. Galigniana, P.C. Echeverria, A.G. Erlejman, G. Piwien-Pilipuk, Role of molecular chaperones and TPR-domain proteins in the cytoplasmic transport of steroid receptors and their passage through the nuclear pore, Nucleus 1 (2010) 299–308.
[51] M.D. Galigniana, Native rat kidney mineralocorticoid receptor is a phosphoprotein whose transformation to a DNA-binding form is induced by phosphatases, Biochem. J. 333 (Pt 3) (1998) 555–563.
[52] A. Chadli, I. Bouhouche, W. Sullivan, B. Stensgard, N. McMahon, M.G. Catelli, D.O. Toft, Dimerization and N-terminal domain proximity underlie the function of the molecular chaperone heat shock protein 90, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 12524–12529.
[53] W.P. Sullivan, B.A. Owen, D.O. Toft, The influence of ATP and p23 on the conformation of hsp90, J. Biol. Chem. 277 (2002) 45942–45948.
[54] Y. Morishima, K.C. Kanelakis, P.J. Murphy, D.S. Shewach, W.B. Pratt, Evidence for iterative ratcheting of receptor-bound hsp70 between its ATP and ADP conformations during assembly of glucocorticoid receptor.hsp90 heterocomplexes, Biochemistry 40 (2001) 1109–1116.
[55] W.B. Pratt, D.O. Toft, Regulation of signaling protein function and trafficking by the hsp90/hsp70-based chaperone machinery, Exp. Biol. Med. (Maywood) 228 (2003) 111–133.
[56] K.C. Kanelakis, P.J. Murphy, M.D. Galigniana, Y. Morishima, S. Takayama, J.C. Reed, D.O. Toft, W.B. Pratt, hsp70 interacting protein Hip does not affect glucocorticoid receptor folding by the hsp90-based chaperone machinery except to oppose the effect of BAG-1, Biochemistry 39 (2000) 14314–14321.
[57] G.E. Karagoz, A.M. Duarte, H. Ippel, C. Uetrecht, T. Sinnige, M. van Rosmalen, J. Hausmann, A.J. Heck, R. Boelens, S.G. Rudiger, N-terminal domain of human Hsp90 triggers binding to the cochaperone p23, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 580–585.
[58] H.R. Quinta, N.M. Galigniana, A.G. Erlejman, M. Lagadari, G. Piwien-Pilipuk, M.D. Galigniana, Management of cytoskeleton architecture by molecular chaperones and immunophilins, Cell. Signal. 23 (2011) 1907–1920.

[59] D. Picard, Heat-shock protein 90, a chaperone for folding and regulation, Cell. Mol. Life Sci. 59 (2002) 1640–1648.
[60] B.T. Scroggins, K. Robzyk, D. Wang, M.G. Marcu, S. Tsutsumi, K. Beebe, R.J. Cotter, S. Felts, D. Toft, L. Karnitz, N. Rosen, L. Neckers, An acetylation site in the middle domain of Hsp90 regulates chaperone function, Mol. Cell 25 (2007) 151–159.
[61] M. Gaestel, Molecular chaperones in signal transduction, Handb. Exp. Pharmacol. (2006) 93–109.
[62] M. Mollapour, S. Tsutsumi, Y.S. Kim, J. Trepel, L. Neckers, Casein kinase 2 phosphorylation of Hsp90 threonine 22 modulates chaperone function and drug sensitivity, Oncotarget 2 (2011) 407–417.
[63] M.D. Galigniana, P.R. Housley, D.B. DeFranco, W.B. Pratt, Inhibition of glucocorticoid receptor nucleocytoplasmic shuttling by okadaic acid requires intact cytoskeleton, J. Biol. Chem. 274 (1999) 16222–16227.
[64] G. Piwien-Pilipuk, M.D. Galigniana, Tautomycin inhibits phosphatase-dependent transformation of the rat kidney mineralocorticoid receptor, Mol. Cell. Endocrinol. 144 (1998) 119–130.
[65] S.K. Wandinger, M.H. Suhre, H. Wegele, J. Buchner, The phosphatase Ppt1 is a dedicated regulator of the molecular chaperone Hsp90, EMBO J. 25 (2006) 367–376.
[66] Y. Zhang, D.Y. Leung, S.K. Nordeen, E. Goleva, Estrogen inhibits glucocorticoid action via protein phosphatase 5 (PP5)-mediated glucocorticoid receptor dephosphorylation, J. Biol. Chem. 284 (2009) 24542–24552.
[67] M. Kurokawa, C. Zhao, T. Reya, S. Kornbluth, Inhibition of apoptosome formation by suppression of Hsp90beta phosphorylation in tyrosine kinase-induced leukemias, Mol. Cell. Biol. 28 (2008) 5494–5506.
[68] S.P. Lees-Miller, C.W. Anderson, Two human 90-kDa heat shock proteins are phosphorylated in vivo at conserved serines that are phosphorylated in vitro by casein kinase II, J. Biol. Chem. 264 (1989) 2431–2437.
[69] R. Aligue, H. Akhavan-Niak, P. Russell, A role for Hsp90 in cell cycle control: Wee1 tyrosine kinase activity requires interaction with Hsp90, EMBO J. 13 (1994) 6099–6106.
[70] C.F. Cheng, J. Fan, M. Fedesco, S. Guan, Y. Li, B. Bandyopadhyay, A.M. Bright, D. Yerushalmi, M. Liang, M. Chen, Y.P. Han, D.T. Woodley, W. Li, Transforming growth factor alpha (TGFalpha)-stimulated secretion of HSP90alpha: using the receptor LRP-1/CD91 to promote human skin cell migration against a TGFbeta-rich environment during wound healing, Mol. Cell. Biol. 28 (2008) 3344–3358.
[71] H. Lei, A. Venkatakrishnan, S. Yu, A. Kazlauskas, Protein kinase A-dependent translocation of Hsp90 alpha impairs endothelial nitric-oxide synthase activity in high glucose and diabetes, J. Biol. Chem. 282 (2007) 9364–9371.
[72] W.M. Old, J.B. Shabb, S. Houel, H. Wang, K.L. Couts, C.Y. Yen, E.S. Litman, C.H. Croy, K. Meyer-Arendt, J.G. Miranda, R.A. Brown, E.S. Witze, R.E. Schweppe, K.A. Resing, N.G. Ahn, Functional proteomics identifies targets of phosphorylation by B-Raf signaling in melanoma, Mol. Cell 34 (2009) 115–131.
[73] M.T. Barati, M.J. Rane, J.B. Klein, K.R. McLeish, A proteomic screen identified stress-induced chaperone proteins as targets of Akt phosphorylation in mesangial cells, J. Proteome Res. 5 (2006) 1636–1646.
[74] S.P. Lees-Miller, C.W. Anderson, The human double-stranded DNA-activated protein kinase phosphorylates the 90-kDa heat-shock protein, hsp90 alpha at two NH2-terminal threonine residues, J. Biol. Chem. 264 (1989) 17275–17280.
[75] S. Matsuoka, B.A. Ballif, A. Smogorzewska, E.R. McDonald III, K.E. Hurov, J. Luo, C.E. Bakalarski, Z. Zhao, N. Solimini, Y. Lerenthal, Y. Shiloh, S.P. Gygi, S.J. Elledge, ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage, Science 316 (2007) 1160–1166.
[76] P. Bali, M. Pranpat, J. Bradner, M. Balasis, W. Fiskus, F. Guo, K. Rocha, S. Kumaraswamy, S. Boyapalle, P. Atadja, E. Seto, K. Bhalla, Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors, J. Biol. Chem. 280 (2005) 26729–26734.
[77] P.J. Murphy, Y. Morishima, J.J. Kovacs, T.P. Yao, W.B. Pratt, Regulation of the dynamics of hsp90 action on the glucocorticoid receptor by acetylation/deacetylation of the chaperone, J. Biol. Chem. 280 (2005) 33792–33799.
[78] Y. Yang, R. Rao, J. Shen, Y. Tang, W. Fiskus, J. Nechtman, P. Atadja, K. Bhalla, Role of acetylation and extracellular location of heat shock protein 90alpha in tumor cell invasion, Cancer Res. 68 (2008) 4833–4842.
[79] C. Nishioka, T. Ikezoe, J. Yang, S. Takeuchi, H.P. Koeffler, A. Yokoyama, MS-275, a novel histone deacetylase inhibitor with selectivity against HDAC1, induces degradation of FLT3 via inhibition of chaperone function of heat shock protein 90 in AML cells, Leuk. Res. 32 (2008) 1382–1392.
[80] S.M. Lee, J.H. Bae, M.J. Kim, H.S. Lee, M.K. Lee, B.S. Chung, D.W. Kim, C.D. Kang, S.H. Kim, Bcr-Abl-independent imatinib-resistant K562 cells show aberrant protein acetylation and increased sensitivity to histone deacetylase inhibitors, J. Pharmacol. Exp. Ther. 322 (2007) 1084–1092.
[81] J.H. Park, S.H. Kim, M.C. Choi, J. Lee, D.Y. Oh, S.A. Im, Y.J. Bang, T.Y. Kim, Class II histone deacetylases play pivotal roles in heat shock protein 90-mediated proteasomal degradation of vascular endothelial growth factor receptors, Biochem. Biophys. Res. Commun. 368 (2008) 318–322.
[82] Q. Zhou, A.T. Agoston, P. Atadja, W.G. Nelson, N.E. Davidson, Inhibition of histone deacetylases promotes ubiquitin-dependent proteasomal degradation of DNA methyltransferase 1 in human breast cancer cells, Mol. Cancer Res. 6 (2008) 873–883.
[83] H.H. Zhang, Y.P. Wang, D.B. Chen, Analysis of nitroso-proteomes in normotensive and severe preeclamptic human placentas, Biol. Reprod. 84 (2011) 966–975.
[84] M. Retzlaff, M. Stahl, H.C. Eberl, S. Lagleder, J. Beck, H. Kessler, J. Buchner, Hsp90 is regulated by a switch point in the C-terminal domain, EMBO Rep. 10 (2009) 1147–1153.
[85] S.A. Compton, L.W. Elmore, K. Haydu, C.K. Jackson-Cook, S.E. Holt, Induction of nitric oxide synthase-dependent telomere shortening after functional inhibition of Hsp90 in human tumor cells, Mol. Cell. Biol. 26 (2006) 1452–1462.
[86] G. Piwien-Pilipuk, M.D. Galigniana, Oxidative stress induced by L-buthionine-(S, R)-sulfoximine, a selective inhibitor of glutathione metabolism, abrogates mouse kidney mineralocorticoid receptor function, Biochim. Biophys. Acta 1495 (2000) 263–280.
[87] K. Okamoto, H. Tanaka, H. Ogawa, Y. Makino, H. Eguchi, S. Hayashi, N. Yoshikawa, L. Poellinger, K. Umesono, I. Makino, Redox-dependent regulation of nuclear import of the glucocorticoid receptor, J. Biol. Chem. 274 (1999) 10363–10371.
[88] L.F. Stancato, K.A. Hutchison, P.K. Chakraborti, S.S. Simons Jr., W.B. Pratt, Differential effects of the reversible thiol-reactive agents arsenite and methyl methanethiosulfonate on steroid binding by the glucocorticoid receptor, Biochemistry 32 (1993) 3729–3736.
[89] W.Y. Chen, F.R. Chang, Z.Y. Huang, J.H. Chen, Y.C. Wu, C.C. Wu, Tubocapsenolide A, a novel withanolide, inhibits proliferation and induces apoptosis in MDA-MB-231 cells by thiol oxidation of heat shock proteins, J. Biol. Chem. 283 (2008) 17184–17193.
[90] D. Spalding, Instinct with original observations on young animals, Macmillan's Mag. 27 (1873) 282–293.
[91] T.M. Fletcher, N. Xiao, G. Mautino, C.T. Baumann, R. Wolford, B.S. Warren, G.L. Hager, ATP-dependent mobilization of the glucocorticoid receptor during chromatin remodeling, Mol. Cell. Biol. 22 (2002) 3255–3263.
[92] J. Zhao, J. Herrera-Diaz, D.S. Gross, Domain-wide displacement of histones by activated heat shock factor occurs independently of Swi/Snf and is not correlated with RNA polymerase II density, Mol. Cell. Biol. 25 (2005) 8985–8999.
[93] M.B. Cheng, Y. Zhang, X. Zhong, B. Sutter, C.Y. Cao, X.S. Chen, X.K. Cheng, L. Xiao, Y.F. Shen, Stat1 mediates an auto-regulation of hsp90beta gene in heat shock response, Cell. Signal. 22 (2010) 1206–1213.
[94] C.M. Gould, N. Kannan, S.S. Taylor, A.C. Newton, The chaperones Hsp90 and Cdc37 mediate the maturation and stabilization of protein kinase C through a conserved PXXP motif in the C-terminal tail, J. Biol. Chem. 284 (2009) 4921–4935.
[95] S. Marubayashi, P. Koppikar, T. Taldone, O. Abdel-Wahab, N. West, N. Bhagwat, E. Caldas-Lopes, K.N. Ross, M. Gonen, A. Gozman, J.H. Ahn, A. Rodina, O. Ouerfelli, G. Yang, C. Hedvat, J.E. Bradner, G. Chiosis, R.L. Levine, HSP90 is a therapeutic target in JAK2-dependent myeloproliferative neoplasms in mice and humans, J. Clin. Invest. 120 (2010) 3578–3593.
[96] R. Zhao, W.A. Houry, Hsp90: a chaperone for protein folding and gene regulation, Biochem. Cell Biol. 83 (2005) 703–710.
[97] T. Jenuwein, C.D. Allis, Translating the histone code, Science 293 (2001) 1074–1080.
[98] R.B. Deal, J.G. Henikoff, S. Henikoff, Genome-wide kinetics of nucleosome turnover determined by metabolic labeling of histones, Science 328 (2010) 1161–1164.
[99] R.B. Deal, S. Henikoff, Capturing the dynamic epigenome, Genome Biol. 11 (2010) 218.
[100] P. Csermely, C.R. Kahn, The 90-kDa heat shock protein (hsp-90) possesses an ATP binding site and autophosphorylating activity, J. Biol. Chem. 266 (1991) 4943–4950.
[101] C. Dingwall, S.M. Dilworth, S.J. Black, S.E. Kearsey, L.S. Cox, R.A. Laskey, Nucleoplasmin cDNA sequence reveals polyglutamic acid tracts and a cluster of sequences homologous to putative nuclear localization signals, EMBO J. 6 (1987) 69–74.
[102] P. Csermely, J. Kajtar, M. Hollosi, J. Oikarinen, J. Somogyi, The 90 kDa heat shock protein (hsp90) induces the condensation of the chromatin structure, Biochem. Biophys. Res. Commun. 202 (1994) 1657–1663.
[103] T. Schnaider, J. Oikarinen, H. Ishiwatari-Hayasaka, I. Yahara, P. Csermely, Interactions of Hsp90 with histones and related peptides, Life Sci. 65 (1999) 2417–2426.
[104] J. Labbadia, H. Cunliffe, A. Weiss, E. Katsyuba, K. Sathasivam, T. Seredenina, B. Woodman, S. Moussaoui, S. Frentzel, R. Luthi-Carter, P. Paganetti, G.P. Bates, Altered chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease, J. Clin. Invest. 121 (2011) 3306–3319.
[105] M. Fukada, A. Hanai, A. Nakayama, T. Suzuki, N. Miyata, R.M. Rodriguiz, W.C. Wetsel, T.P. Yao, Y. Kawaguchi, Loss of deacetylation activity of Hdac6 affects emotional behavior in mice, PLoS One 7 (2012) e30924.
[106] V. Sollars, X. Lu, L. Xiao, X. Wang, M.D. Garfinkel, D.M. Ruden, Evidence for an epigenetic mechanism by which Hsp90 acts as a capacitor for morphological evolution, Nat. Genet. 33 (2003) 70–74.
[107] J.W. Conaway, Introduction to Theme "Chromatin, Epigenetics, and Transcription", Annu. Rev. Biochem. 81 (2012) 61–64.
[108] M. Abu-Farha, J.P. Lambert, A.S. Al-Madhoun, F. Elisma, I.S. Skerjanc, D. Figeys, The tale of two domains: proteomics and genomics analysis of SMYD2, a new histone methyltransferase, Mol. Cell. Proteomics 7 (2008) 560–572.
[109] R. Hamamoto, Y. Furukawa, M. Morita, Y. Iimura, F.P. Silva, M. Li, R. Yagyu, Y. Nakamura, SMYD3 encodes a histone methyltransferase involved in the proliferation of cancer cells, Nat. Cell Biol. 6 (2004) 731–740.
[110] S. Chuikov, J.K. Kurash, J.R. Wilson, B. Xiao, N. Justin, G.S. Ivanov, K. McKinney, P. Tempst, C. Prives, S.J. Gamblin, N.A. Barlev, D. Reinberg, Regulation of p53 activity through lysine methylation, Nature 432 (2004) 353–360.
[111] J. Huang, L. Perez-Burgos, B.J. Placek, R. Sengupta, M. Richter, J.A. Dorsey, S. Kubicek, S. Opravil, T. Jenuwein, S.L. Berger, Repression of p53 activity by Smyd2-mediated methylation, Nature 444 (2006) 629–632.
[112] L.A. Saddic, L.E. West, A. Aslanian, J.R. Yates III, S.M. Rubin, O. Gozani, J. Sage, Methylation of the retinoblastoma tumor suppressor by SMYD2, J. Biol. Chem. 285 (2010) 37733–37740.
[113] M. Abu-Farha, S. Lanouette, F. Elisma, V. Tremblay, J. Butson, D. Figeys, J.F. Couture, Proteomic analyses of the SMYD family interactomes identify HSP90 as a novel target for SMYD2, J. Mol. Cell Biol. 3 (2011) 301–308.
[114] R.K. Allan, T. Ratajczak, Versatile TPR domains accommodate different modes of target protein recognition and function, Cell Stress Chaperones 16 (2011) 353–367.
[115] W.B. Pratt, M.D. Galigniana, J.M. Harrell, D.B. DeFranco, Role of hsp90 and the hsp90-binding immunophilins in signalling protein movement, Cell. Signal. 16 (2004) 857–872.

[116] Y. Jiang, N. Sirinupong, J. Brunzelle, Z. Yang, Crystal structures of histone and p53 methyltransferase SmyD2 reveal a conformational flexibility of the autoinhibitory C-terminal domain, PLoS One 6 (2011) e21640.
[117] N. Sirinupong, J. Brunzelle, E. Doko, Z. Yang, Structural insights into the autoinhibition and posttranslational activation of histone methyltransferase SmyD3, J. Mol. Biol. 406 (2011) 149–159.
[118] D.Y. Lee, C. Teyssier, B.D. Strahl, M.R. Stallcup, Role of protein methylation in regulation of transcription, Endocr. Rev. 26 (2005) 147–170.
[119] C.N. Johnson, N.L. Adkins, P. Georgel, Chromatin remodeling complexes: ATP-dependent machines in action, Biochem. Cell Biol. 83 (2005) 405–417.
[120] C.W. Roberts, S.H. Orkin, The SWI/SNF complex-chromatin and cancer, Nat. Rev. Cancer 4 (2004) 133–142.
[121] R.J. Gibbons, Histone modifying and chromatin remodelling enzymes in cancer and dysplastic syndromes, Hum. Mol. Genet. 14 (Spec No 1) (2005) R85–R92.
[122] H. Huang, I. Rambaldi, E. Daniels, M. Featherstone, Expression of the Wdr9 gene and protein products during mouse development, Dev. Dyn. 227 (2003) 608–614.
[123] X.J. Yang, Lysine acetylation and the bromodomain: a new partnership for signaling, Bioessays 26 (2004) 1076–1087.
[124] T.D. Hinds Jr., E.R. Sanchez, Protein phosphatase 5, Int. J. Biochem. Cell Biol. 40 (2008) 2358–2362.
[125] A.M. Silverstein, M.D. Galigniana, M.S. Chen, J.K. Owens-Grillo, M. Chinkers, W.B. Pratt, Protein phosphatase 5 is a major component of glucocorticoid receptor.hsp90 complexes with properties of an FK506-binding immunophilin, J. Biol. Chem. 272 (1997) 16224–16230.
[126] L.I. Gallo, A.A. Ghini, G. Piwien Pilipuk, M.D. Galigniana, Differential recruitment of tetratricorpeptide repeat domain immunophilins to the mineralocorticoid receptor influences both heat-shock protein 90-dependent retrotransport and hormone-dependent transcriptional activity, Biochemistry 46 (2007) 14044–14057.
[127] J. Yang, S.M. Roe, M.J. Cliff, M.A. Williams, J.E. Ladbury, P.T. Cohen, D. Barford, Molecular basis for TPR domain-mediated regulation of protein phosphatase 5, EMBO J. 24 (2005) 1–10.
[128] M. Yun, J. Wu, J.L. Workman, B. Li, Readers of histone modifications, Cell Res. 21 (2011) 564–578.
[129] C. Choudhary, C. Kumar, F. Gnad, M.L. Nielsen, M. Rehman, T.C. Walther, J.V. Olsen, M. Mann, Lysine acetylation targets protein complexes and co-regulates major cellular functions, Science 325 (2009) 834–840.
[130] M. Haberland, R.L. Montgomery, E.N. Olson, The many roles of histone deacetylases in development and physiology: implications for disease and therapy, Nat. Rev. Genet. 10 (2009) 32–42.
[131] C. Hubbert, A. Guardiola, R. Shao, Y. Kawaguchi, A. Ito, A. Nixon, M. Yoshida, X.F. Wang, T.P. Yao, HDAC6 is a microtubule-associated deacetylase, Nature 417 (2002) 455–458.
[132] A. Verdel, S. Curtet, M.P. Brocard, S. Rousseaux, C. Lemercier, M. Yoshida, S. Khochbin, Active maintenance of mHDA2/mHDAC6 histone-deacetylase in the cytoplasm, Curr. Biol. 10 (2000) 747–749.
[133] Y. Liu, L. Peng, E. Seto, S. Huang, Y. Qiu, Modulation of histone deacetylase 6 (HDAC6) nuclear import and tubulin deacetylase activity through acetylation, J. Biol. Chem. 287 (2012) 29168–29174.
[134] L. Gao, M.A. Cueto, F. Asselbergs, P. Atadja, Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family, J. Biol. Chem. 277 (2002) 25748–25755.
[135] N. Yoshida, Y. Omoto, A. Inoue, H. Eguchi, Y. Kobayashi, M. Kurosumi, S. Saji, K. Suemasu, T. Okazaki, K. Nakachi, T. Fujita, S. Hayashi, Prediction of prognosis of estrogen receptor-positive breast cancer with combination of selected estrogen-regulated genes, Cancer Sci. 95 (2004) 496–502.
[136] C. Caron, C. Boyault, S. Khochbin, Regulatory cross-talk between lysine acetylation and ubiquitination: role in the control of protein stability, Bioessays 27 (2005) 408–415.
[137] D. Girdwood, D. Bumpass, O.A. Vaughan, A. Thain, L.A. Anderson, A.W. Snowden, E. Garcia-Wilson, N.D. Perkins, R.T. Hay, P300 transcriptional repression is mediated by SUMO modification, Mol. Cell 11 (2003) 1043–1054.
[138] I. Fernandes, Y. Bastien, T. Wai, K. Nygard, R. Lin, O. Cormier, H.S. Lee, F. Eng, N.R. Bertos, N. Pelletier, S. Mader, V.K. Han, X.J. Yang, J.H. White, Ligand-dependent nuclear receptor corepressor LCoR functions by histone deacetylase-dependent and -independent mechanisms, Mol. Cell 11 (2003) 139–150.
[139] J.M. Amann, J. Nip, D.K. Strom, B. Lutterbach, H. Harada, N. Lenny, J.R. Downing, S. Meyers, S.W. Hiebert, ETO, a target of t(8;21) in acute leukemia, makes distinct contacts with multiple histone deacetylases and binds mSin3A through its oligomerization domain, Mol. Cell. Biol. 21 (2001) 6470–6483.
[140] J.J. Westendorf, S.K. Zaidi, J.E. Cascino, R. Kahler, A.J. van Wijnen, J.B. Lian, M. Yoshida, G.S. Stein, X. Li, Runx2 (Cbfa1, AML-3) interacts with histone deacetylase 6 and represses the p21(CIP1/WAF1) promoter, Mol. Cell. Biol. 22 (2002) 7982–7992.
[141] W. Zhang, B.C. Kone, NF-kappaB inhibits transcription of the H(+)-K(+)-ATPase alpha(2)-subunit gene: role of histone deacetylases, Am. J. Physiol. Renal Physiol. 283 (2002) F904–F911.
[142] I. Nusinzon, C.M. Horvath, Positive and negative regulation of the innate antiviral response and beta interferon gene expression by deacetylation, Mol. Cell. Biol. 26 (2006) 3106–3113.
[143] A.J. McClellan, Y. Xia, A.M. Deutschbauer, R.W. Davis, M. Gerstein, J. Frydman, Diverse cellular functions of the Hsp90 molecular chaperone uncovered using systems approaches, Cell 131 (2007) 121–135.
[144] S.H. Millson, A.W. Truman, F. Wolfram, V. King, B. Panaretou, C. Prodromou, L.H. Pearl, P.W. Piper, Investigating the protein–protein interactions of the yeast Hsp90 chaperone system by two-hybrid analysis: potential uses and limitations of this approach, Cell Stress Chaperones 9 (2004) 359–368.
[145] K. Eckert, J.M. Saliou, L. Monlezun, A. Vigouroux, N. Atmane, C. Caillat, S. Quevillon-Cheruel, K. Madiona, M. Nicaise, S. Lazereg, A. Van Dorsselaer, S. Sanglier-Cianferani, P. Meyer, S. Morera, The Pih1-Tah1 cochaperone complex inhibits Hsp90 molecular chaperone ATPase activity, J. Biol. Chem. 285 (2010) 31304–31312.
[146] B. Jimenez, F. Ugwu, R. Zhao, L. Orti, T. Makhnevych, A. Pineda-Lucena, W.A. Houry, Structure of minimal tetratricopeptide repeat domain protein Tah1 reveals mechanism of its interaction with Pih1 and Hsp90, J. Biol. Chem. 287 (2012) 5698–5709.
[147] S.H. Millson, C.K. Vaughan, C. Zhai, M.M. Ali, B. Panaretou, P.W. Piper, L.H. Pearl, C. Prodromou, Chaperone ligand-discrimination by the TPR-domain protein Tah1, Biochem. J. 413 (2008) 261–268.
[148] S. Boulon, N. Marmier-Gourrier, B. Pradet-Balade, L. Wurth, C. Verheggen, B.E. Jady, B. Rothe, C. Pescia, M.C. Robert, T. Kiss, B. Bardoni, A. Krol, C. Branlant, C. Allmang, E. Bertrand, B. Charpentier, The Hsp90 chaperone controls the biogenesis of L7Ae RNPs through conserved machinery, J. Cell Biol. 180 (2008) 579–595.
[149] S. Jha, A. Dutta, RVB1/RVB2: running rings around molecular biology, Mol. Cell 34 (2009) 521–533.
[150] R. Zhao, M. Davey, Y.C. Hsu, P. Kaplanek, A. Tong, A.B. Parsons, N. Krogan, G. Cagney, D. Mai, J. Greenblatt, C. Boone, A. Emili, W.A. Houry, Navigating the chaperone network: an integrative map of physical and genetic interactions mediated by the hsp90 chaperone, Cell 120 (2005) 715–727.
[151] B.W. Baron, G. Nucifora, N. McCabe, R. Espinosa III, M.M. Le Beau, T.W. McKeithan, Identification of the gene associated with the recurring chromosomal translocations t(3;14)(q27;q32) and t(3;22)(q27;q11) in B-cell lymphomas, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 5262–5266.
[152] A.L. Shaffer, X. Yu, Y. He, J. Boldrick, E.P. Chan, L.M. Staudt, BCL-6 represses genes that function in lymphocyte differentiation, inflammation, and cell cycle control, Immunity 13 (2000) 199–212.
[153] W. Ci, J.M. Polo, A. Melnick, B-cell lymphoma 6 and the molecular pathogenesis of diffuse large B-cell lymphoma, Curr. Opin. Hematol. 15 (2008) 381–390.
[154] T. Illidge, S. Tolan, Current treatment approaches for diffuse large B-cell lymphoma, Leuk. Lymphoma 49 (2008) 663–676.
[155] L.C. Cerchietti, E.C. Lopes, S.N. Yang, K. Hatzi, K.L. Bunting, L.A. Tsikitas, A. Mallik, A.I. Robles, J. Walling, L. Varticovski, R. Shaknovich, K.N. Bhalla, G. Chiosis, A. Melnick, A purine scaffold Hsp90 inhibitor destabilizes BCL-6 and has specific antitumor activity in BCL-6-dependent B cell lymphomas, Nat. Med. 15 (2009) 1369–1376.
[156] T. Sasaki, E.C. Gan, A. Wakeham, S. Kornbluth, T.W. Mak, H. Okada, HLA-B-associated transcript 3 (Bat3)/Scythe is essential for p300-mediated acetylation of p53, Genes Dev. 21 (2007) 848–861.
[157] L.C. Cerchietti, K. Hatzi, E. Caldas-Lopes, S.N. Yang, M.E. Figueroa, R.D. Morin, M. Hirst, L. Mendez, R. Shaknovich, P.A. Cole, K. Bhalla, R.D. Gascoyne, M. Marra, G. Chiosis, A. Melnick, BCL6 repression of EP300 in human diffuse large B cell lymphoma cells provides a basis for rational combinatorial therapy, J. Clin. Invest. 120 (2010) 4569–4582.
[158] A.G. Erlejman, M. Lagadari, M.D. Galigniana, Hsp90-binding immunophilins as a potential new platform for drug treatment, Future Med. Chem. 5 (2013) 591–607.
[159] H. Li, A. Rao, P.G. Hogan, Interaction of calcineurin with substrates and targeting proteins, Trends Cell Biol. 21 (2011) 91–103.
[160] M.D. Galigniana, A.G. Erlejman, M. Monte, C. Gomez-Sanchez, G. Piwien-Pilipuk, The hsp90-FKBP52 complex links the mineralocorticoid receptor to motor proteins and persists bound to the receptor in early nuclear events, Mol. Cell. Biol. 30 (2010) 1285–1298.
[161] G.P. Colo, M.F. Rubio, I.M. Nojek, S.E. Werbajh, P.C. Echeverria, C.V. Alvarado, V.E. Nahmod, M.D. Galigniana, M.A. Costas, The p160 nuclear receptor co-activator RAC3 exerts an anti-apoptotic role through a cytoplasmatic action, Oncogene 27 (2008) 2430–2444.
[162] M.D. Galigniana, J.M. Harrell, H.M. O'Hagen, M. Ljungman, W.B. Pratt, Hsp90-binding immunophilins link p53 to dynein during p53 transport to the nucleus, J. Biol. Chem. 279 (2004) 22483–22489.
[163] J.M. Harrell, I. Kurek, A. Breiman, C. Radanyi, J.M. Renoir, W.B. Pratt, M.D. Galigniana, All of the protein interactions that link steroid receptor.hsp90.immunophilin heterocomplexes to cytoplasmic dynein are common to plant and animal cells, Biochemistry 41 (2002) 5581–5587.
[164] X. Vafopoulou, C.G. Steel, Cytoplasmic travels of the ecdysteroid receptor in target cells: pathways for both genomic and non-genomic actions, Front. Endocrinol. (Lausanne) 3 (2012) 43.
[165] M.D. Galigniana, Y. Morishima, P.A. Gallay, W.B. Pratt, Cyclophilin-A is bound through its peptidylprolyl isomerase domain to the cytoplasmic dynein motor protein complex, J. Biol. Chem. 279 (2004) 55754–55759.
[166] T. Schaller, K.E. Ocwieja, J. Rasaiyaah, A.J. Price, T.L. Brady, S.L. Roth, S. Hue, A.J. Fletcher, K. Lee, V.N. KewalRamani, M. Noursadeghi, R.G. Jenner, L.C. James, F.D. Bushman, G.J. Towers, HIV-1 capsid-cyclophilin interactions determine nuclear import pathway, integration targeting and replication efficiency, PLoS Pathog. 7 (2011) e1002439.
[167] C. Zhu, X. Wang, J. Deinum, Z. Huang, J. Gao, N. Modjtahedi, M.R. Neagu, M. Nilsson, P.S. Eriksson, H. Hagberg, J. Luban, G. Kroemer, K. Blomgren, Cyclophilin A participates in the nuclear translocation of apoptosis-inducing factor in neurons after cerebral hypoxia–ischemia, J. Exp. Med. 204 (2007) 1741–1748.
[168] C.L. Storer, C.A. Dickey, M.D. Galigniana, T. Rein, M.B. Cox, FKBP51 and FKBP52 in signaling and disease, Trends Endocrinol. Metab. 22 (2011) 481–490.
[169] Y.L. Yao, Y.C. Liang, H.H. Huang, W.M. Yang, FKBPs in chromatin modification and cancer, Curr. Opin. Pharmacol. 11 (2011) 301–307.
[170] G. Piwien Pilipuk, G.P. Vinson, C.G. Sanchez, M.D. Galigniana, Evidence for NL1-independent nuclear translocation of the mineralocorticoid receptor, Biochemistry 46 (2007) 1389–1397.

[171] P.C. Echeverria, G. Mazaira, A. Erlejman, C. Gomez-Sanchez, G. Piwien Pilipuk, M.D. Galigniana, Nuclear import of the glucocorticoid receptor-hsp90 complex through the nuclear pore complex is mediated by its interaction with Nup62 and importin beta, Mol. Cell. Biol. 29 (2009) 4788–4797.
[172] J.C. Sivils, C.L. Storer, M.D. Galigniana, M.B. Cox, Regulation of steroid hormone receptor function by the 52-kDa FK506-binding protein (FKBP52), Curr. Opin. Pharmacol. 11 (2011) 314–319.
[173] J. Liang, D.T. Hung, S.L. Schreiber, J. Clardy, Structure of the Human 25 kDa FK506 binding protein complexed with rapamycin, J. Am. Chem. Soc. 118 (1996) 1231–1232.
[174] X. Shan, Z. Xue, T. Melese, Yeast NPI46 encodes a novel prolyl cis-trans isomerase that is located in the nucleolus, J. Cell Biol. 126 (1994) 853–862.
[175] A. Hochwagen, W.H. Tham, G.A. Brar, A. Amon, The FK506 binding protein Fpr3 counteracts protein phosphatase 1 to maintain meiotic recombination checkpoint activity, Cell 122 (2005) 861–873.
[176] H. Xiao, V. Jackson, M. Lei, The FK506-binding protein, Fpr4, is an acidic histone chaperone, FEBS Lett. 580 (2006) 4357–4364.
[177] W.M. Yang, Y.L. Yao, E. Seto, The FK506-binding protein 25 functionally associates with histone deacetylases and with transcription factor YY1, EMBO J. 20 (2001) 4814–4825.
[178] Y. Mamane, S. Sharma, L. Petropoulos, R. Lin, J. Hiscott, Posttranslational regulation of IRF-4 activity by the immunophilin FKBP52, Immunity 12 (2000) 129–140.
[179] H.R. Quintá, D. Maschi, C. Gomez-Sanchez, G. Piwien-Pilipuk, M.D. Galigniana, Subcellular rearrangement of hsp90-binding immunophilins accompanies neuronal differentiation and neurite outgrowth, J. Neurochem. 115 (2010) 716–734.
[180] N.M. Galigniana, L.T. Ballmer, J. Toneatto, A.G. Erlejman, M. Lagadari, M.D. Galigniana, Regulation of the glucocorticoid response to stress-related disorders by the Hsp90-binding immunophilin FKBP51, J. Neurochem. 122 (2012) 4–18.
[181] C. Elbi, D.A. Walker, G. Romero, W.P. Sullivan, D.O. Toft, G.L. Hager, D.B. DeFranco, Molecular chaperones function as steroid receptor nuclear mobility factors, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 2876–2881.
[182] S. Romano, S. Staibano, A. Greco, A. Brunetti, G. Nappo, G. Ilardi, R. Martinelli, A. Sorrentino, A. Di Pace, M. Mascolo, R. Bisogni, M. Scalvenzi, B. Alfano, M.F. Romano, FK506 binding protein 51 positively regulates melanoma stemness and metastatic potential, Cell Death Dis. 4 (2013) e578.
[183] L.I. Gallo, M. Lagadari, G. Piwien-Pilipuk, M.D. Galigniana, The 90-kDa heat-shock protein (Hsp90)-binding immunophilin FKBP51 is a mitochondrial protein that translocates to the nucleus to protect cells against oxidative stress, J. Biol. Chem. 286 (2011) 30152–30160.
[184] J. Toneatto, S. Guber, N.L. Charo, J. Schwartz, M.D. Galigniana, G. Piwien Pilipuk, Dynamic Mitochondrial-Nuclear Redistribution of the Immunophilin FKBP51 is Regulated by PKA Signaling Pathway in the Process of Adipocyte Differentiation, J. Cell Sci. 126 (2013) 5357–5368.
[185] C.J. Lord, A. Ashworth, The DNA damage response and cancer therapy, Nature 481 (2012) 287–294.
[186] T. Sekimoto, T. Oda, F.M. Pozo, Y. Murakumo, C. Masutani, F. Hanaoka, T. Yamashita, The molecular chaperone Hsp90 regulates accumulation of DNA polymerase eta at replication stalling sites in UV-irradiated cells, Mol. Cell 37 (2010) 79–89.
[187] V. Specchia, L. Piacentini, P. Tritto, L. Fanti, R. D'Alessandro, G. Palumbo, S. Pimpinelli, M.P. Bozzetti, Hsp90 prevents phenotypic variation by suppressing the mutagenic activity of transposons, Nature 463 (2010) 662–665.
[188] J. Brennecke, A.A. Aravin, A. Stark, M. Dus, M. Kellis, R. Sachidanandam, G.J. Hannon, Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila, Cell 128 (2007) 1089–1103.
[189] A. Maloney, P.A. Clarke, S. Naaby-Hansen, R. Stein, J.O. Koopman, A. Akpan, A. Yang, M. Zvelebil, R. Cramer, L. Stimson, W. Aherne, U. Banerji, I. Judson, S. Sharp, M. Powers, E. deBilly, J. Salmons, M. Walton, A. Burlingame, M. Waterfield, P. Workman, Gene and protein expression profiling of human ovarian cancer cells treated with the heat shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin, Cancer Res. 67 (2007) 3239–3253.
[190] K.M. Nishida, T.N. Okada, T. Kawamura, T. Mituyama, Y. Kawamura, S. Inagaki, H. Huang, D. Chen, T. Kodama, H. Siomi, M.C. Siomi, Functional involvement of Tudor and dPRMT5 in the piRNA processing pathway in Drosophila germlines, EMBO J. 28 (2009) 3820–3831.
[191] L.H. Pearl, Hsp90 and Cdc37—a chaperone cancer conspiracy, Curr. Opin. Genet. Dev. 15 (2005) 55–61.
[192] V.C. da Silva, C.H. Ramos, The network interaction of the human cytosolic 90 kDa heat shock protein Hsp90: a target for cancer therapeutics, J. Proteome 75 (2012) 2790–2802.
[193] C. Prodromou, L.H. Pearl, Structure and functional relationships of Hsp90, Curr. Cancer Drug Targets 3 (2003) 301–323.
[194] J.S. Brugge, E. Erikson, R.L. Erikson, The specific interaction of the Rous sarcoma virus transforming protein, pp60src, with two cellular proteins, Cell 25 (1981) 363–372.
[195] M. Taipale, I. Krykbaeva, M. Koeva, C. Kayatekin, K.D. Westover, G.I. Karras, S. Lindquist, Quantitative analysis of HSP90-client interactions reveals principles of substrate recognition, Cell 150 (2012) 987–1001.
[196] L. Neckers, P. Workman, Hsp90 molecular chaperone inhibitors: are we there yet? Clin. Cancer Res. 18 (2012) 64–76.
[197] K. Jhaveri, T. Taldone, S. Modi, G. Chiosis, Advances in the clinical development of heat shock protein 90 (Hsp90) inhibitors in cancers, Biochim. Biophys. Acta 1823 (2012) 742–755.
[198] S.L. Berger, Cell signaling and transcriptional regulation via histone phosphorylation, Cold Spring Harb. Symp. Quant. Biol. 75 (2010) 23–26.
[199] C.A. Zahnow, CCAAT/enhancer-binding protein beta: its role in breast cancer and associations with receptor tyrosine kinases, Expert Rev. Mol. Med. 11 (2009) e12.
[200] T. Hunter, Tyrosine phosphorylation: thirty years and counting, Curr. Opin. Cell Biol. 21 (2009) 140–146.
[201] J.S. Brugge, Interaction of the Rous sarcoma virus protein pp60src with the cellular proteins pp 50 and pp90, Curr. Top. Microbiol. Immunol. 123 (1986) 1–22.
[202] M.L. Whitelaw, K. Hutchison, G.H. Perdew, A 50-kDa cytosolic protein complexed with the 90-kDa heat shock protein (hsp90) is the same protein complexed with pp 60v-src hsp90 in cells transformed by the Rous sarcoma virus, J. Biol. Chem. 266 (1991) 16436–16440.
[203] C. Prodromou, S.M. Roe, R. O'Brien, J.E. Ladbury, P.W. Piper, L.H. Pearl, Identification and structural characterization of the ATP/ADP-binding site in the Hsp90 molecular chaperone, Cell 90 (1997) 65–75.
[204] A.M. Silverstein, N. Grammatikakis, B.H. Cochran, M. Chinkers, W.B. Pratt, p50(cdc37) binds directly to the catalytic domain of Raf as well as to a site on hsp90 that is topologically adjacent to the tetratricopeptide repeat binding site, J. Biol. Chem. 273 (1998) 20090–20095.
[205] S.D. Hartson, A.D. Irwin, J. Shao, B.T. Scroggins, L. Volk, W. Huang, R.L. Matts, p50(cdc37) is a nonexclusive Hsp90 cohort which participates intimately in Hsp90-mediated folding of immature kinase molecules, Biochemistry 39 (2000) 7631–7644.
[206] J. Shao, S.D. Hartson, R.L. Matts, Evidence that protein phosphatase 5 functions to negatively modulate the maturation of the Hsp90-dependent heme-regulated eIF2alpha kinase, Biochemistry 41 (2002) 6770–6779.
[207] G. Siligardi, B. Hu, B. Panaretou, P.W. Piper, L.H. Pearl, C. Prodromou, Co-chaperone regulation of conformational switching in the Hsp90 ATPase cycle, J. Biol. Chem. 279 (2004) 51989–51998.
[208] O. Donze, D. Picard, Hsp90 binds and regulates Gcn2, the ligand-inducible kinase of the alpha subunit of eukaryotic translation initiation factor 2 [corrected], Mol. Cell. Biol. 19 (1999) 8422–8432.
[209] A.G. Hinnebusch, The Molecular and Cellular Biology of the Yeast Saccharomyces: Gene Expression, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1992.
[210] A.G. Hinnebusch, Translational regulation of yeast GCN4. A window on factors that control initiator-trna binding to the ribosome, J. Biol. Chem. 272 (1997) 21661–21664.
[211] R.C. Wek, H.Y. Jiang, T.G. Anthony, Coping with stress: eIF2 kinases and translational control, Biochem. Soc. Trans. 34 (2006) 7–11.
[212] R.C. Wek, D.R. Cavener, Translational control and the unfolded protein response, Antioxid. Redox Signal. 9 (2007) 2357–2371.
[213] P.D. Lu, H.P. Harding, D. Ron, Translation reinitiation at alternative open reading frames regulates gene expression in an integrated stress response, J. Cell Biol. 167 (2004) 27–33.
[214] N. Izumi, A. Yamashita, S. Ohno, Integrated regulation of PIKK-mediated stress responses by AAA+ proteins RUVBL1 and RUVBL2, Nucleus 3 (2012) 29–43.
[215] Z. Horejsi, H. Takai, C.A. Adelman, S.J. Collis, H. Flynn, S. Maslen, J.M. Skehel, T. de Lange, S.J. Boulton, CK2 phospho-dependent binding of R2TP complex to TEL2 is essential for mTOR and SMG1 stability, Mol. Cell 39 (2010) 839–850.
[216] H. Takai, Y. Xie, T. de Lange, N.P. Pavletich, Tel2 structure and function in the Hsp90-dependent maturation of mTOR and ATR complexes, Genes Dev. 24 (2010) 2019–2030.
[217] S. Solier, K.W. Kohn, B. Scroggins, W. Xu, J. Trepel, L. Neckers, Y. Pommier, Heat shock protein 90alpha (HSP90alpha), a substrate and chaperone of DNA-PK necessary for the apoptotic response, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 12866–12872.
[218] N. Izumi, A. Yamashita, A. Iwamatsu, R. Kurata, H. Nakamura, B. Saari, H. Hirano, P. Anderson, S. Ohno, AAA+ proteins RUVBL1 and RUVBL2 coordinate PIKK activity and function in nonsense-mediated mRNA decay, Sci. Signal. 3 (2010) ra27.
[219] K. Moulick, J.H. Ahn, H. Zong, A. Rodina, L. Cerchietti, E.M. Gomes DaGama, E. Caldas-Lopes, K. Beebe, F. Perna, K. Hatzi, L.P. Vu, X. Zhao, D. Zatorska, T. Taldone, P. Smith-Jones, M. Alpaugh, S.S. Gross, N. Pillarsetty, T. Ku, J.S. Lewis, S.M. Larson, R. Levine, H. Erdjument-Bromage, M.L. Guzman, S.D. Nimer, A. Melnick, L. Neckers, G. Chiosis, Affinity-based proteomics reveal cancer-specific networks coordinated by Hsp90, Nat. Chem. Biol. 7 (2011) 818–826.
[220] J. Boudeau, D. Miranda-Saavedra, G.J. Barton, D.R. Alessi, Emerging roles of pseudokinases, Trends Cell Biol. 16 (2006) 443–452.
[221] N. Izumi, A. Yamashita, H. Hirano, S. Ohno, Heat shock protein 90 regulates phosphatidylinositol 3-kinase-related protein kinase family proteins together with the RUVBL1/2 and Tel2-containing co-factor complex, Cancer Sci. 103 (2012) 50–57.
[222] H. Takai, R.C. Wang, K.K. Takai, H. Yang, T. de Lange, Tel2 regulates the stability of PI3K-related protein kinases, Cell 131 (2007) 1248–1259.
[223] J. Kanoh, M. Yanagida, Tel2: a common partner of PIK-related kinases and a link between DNA checkpoint and nutritional response? Genes Cells 12 (2007) 1301–1304.
[224] X.B. Qiu, Y.L. Lin, K.C. Thome, P. Pian, B.P. Schlegel, S. Weremowicz, J.D. Parvin, A. Dutta, An eukaryotic RuvB-like protein (RUVBL1) essential for growth, J. Biol. Chem. 273 (1998) 27786–27793.
[225] J. Weiske, O. Huber, The histidine triad protein Hint1 interacts with Pontin and Reptin and inhibits TCF-beta-catenin-mediated transcription, J. Cell Sci. 118 (2005) 3117–3129.
[226] D. Ducat, S. Kawaguchi, H. Liu, J.R. Yates III, Y. Zheng, Regulation of microtubule assembly and organization in mitosis by the AAA+ ATPase Pontin, Mol. Biol. Cell 19 (2008) 3097–3110.
[227] A.R. Skop, H. Liu, J. Yates III, B.J. Meyer, R. Heald, Dissection of the mammalian midbody proteome reveals conserved cytokinesis mechanisms, Science 305 (2004) 61–66.
[228] A.J. Ruthenburg, H. Li, D.J. Patel, C.D. Allis, Multivalent engagement of chromatin modifications by linked binding modules, Nat. Rev. Mol. Cell Biol. 8 (2007) 983–994.

[229] K.M. Brumbaugh, D.M. Otterness, C. Geisen, V. Oliveira, J. Brognard, X. Li, F. Lejeune, R.S. Tibbetts, L.E. Maquat, R.T. Abraham, The mRNA surveillance protein hSMG-1 functions in genotoxic stress response pathways in mammalian cells, Mol. Cell 14 (2004) 585–598.
[230] C. Mayer, I. Grummt, Ribosome biogenesis and cell growth: mTOR coordinates transcription by all three classes of nuclear RNA polymerases, Oncogene 25 (2006) 6384–6391.
[231] T. Morita, A. Yamashita, I. Kashima, K. Ogata, S. Ishiura, S. Ohno, Distant N- and C-terminal domains are required for intrinsic kinase activity of SMG-1, a critical component of nonsense-mediated mRNA decay, J. Biol. Chem. 282 (2007) 7799–7808.
[232] X. Shen, G. Mizuguchi, A. Hamiche, C. Wu, A chromatin remodelling complex involved in transcription and DNA processing, Nature 406 (2000) 541–544.
[233] L.C. Cooper, E. Prinsloo, A.L. Edkins, G.L. Blatch, Hsp90alpha/beta associates with the GSK3beta/axin1/phospho-beta-catenin complex in the human MCF-7 epithelial breast cancer model, Biochem. Biophys. Res. Commun. 413 (2011) 550–554.
[234] R. Kurashina, J.H. Ohyashiki, C. Kobayashi, R. Hamamura, Y. Zhang, T. Hirano, K. Ohyashiki, Anti-proliferative activity of heat shock protein (Hsp) 90 inhibitors via beta-catenin/TCF7L2 pathway in adult T cell leukemia cells, Cancer Lett. 284 (2009) 62–70.
[235] P.A. Lochhead, R. Kinstrie, G. Sibbet, T. Rawjee, N. Morrice, V. Cleghon, A chaperone-dependent GSK3beta transitional intermediate mediates activation-loop autophosphorylation, Mol. Cell 24 (2006) 627–633.
[236] J.H. Kim, B. Kim, L. Cai, H.J. Choi, K.A. Ohgi, C. Tran, C. Chen, C.H. Chung, O. Huber, D.W. Rose, C.L. Sawyers, M.G. Rosenfeld, S.H. Baek, Transcriptional regulation of a metastasis suppressor gene by Tip60 and beta-catenin complexes, Nature 434 (2005) 921–926.
[237] S.R. Frank, T. Parisi, S. Taubert, P. Fernandez, M. Fuchs, H.M. Chan, D.M. Livingston, B. Amati, MYC recruits the TIP60 histone acetyltransferase complex to chromatin, EMBO Rep. 4 (2003) 575–580.
[238] M.D. Cole, V.H. Cowling, Specific regulation of mRNA cap methylation by the c-Myc and E2F1 transcription factors, Oncogene 28 (2009) 1169–1175.
[239] G. Egger, G. Liang, A. Aparicio, P.A. Jones, Epigenetics in human disease and prospects for epigenetic therapy, Nature 429 (2004) 457–463.
[240] M. Wanczyk, K. Roszczenko, K. Marcinkiewicz, K. Bojarczuk, M. Kowara, M. Winiarska, HDACi–going through the mechanisms, Front. Biosci. 16 (2011) 340–359.
[241] P. George, P. Bali, S. Annavarapu, A. Scuto, W. Fiskus, F. Guo, C. Sigua, G. Sondarva, L. Moscinski, P. Atadja, K. Bhalla, Combination of the histone deacetylase inhibitor LBH589 and the hsp90 inhibitor 17-AAG is highly active against human CML-BC cells and AML cells with activating mutation of FLT-3, Blood 105 (2005) 1768–1776.
[242] E.M. Ocio, J.F. San Miguel, The DAC system and associations with multiple myeloma, Invest. New Drugs 28 (Suppl. 1) (2010) S28–S35.
[243] A.A. Lane, B.A. Chabner, Histone deacetylase inhibitors in cancer therapy, J. Clin. Oncol. 27 (2009) 5459–5468.
[244] M. Rahmani, C. Yu, Y. Dai, E. Reese, W. Ahmed, P. Dent, S. Grant, Coadministration of the heat shock protein 90 antagonist 17-allylamino- 17-demethoxygeldanamycin with suberoylanilide hydroxamic acid or sodium butyrate synergistically induces apoptosis in human leukemia cells, Cancer Res. 63 (2003) 8420–8427.
[245] H.H. Kampinga, Chaperones in preventing protein denaturation in living cells and protecting against cellular stress, Handb. Exp. Pharmacol. (2006) 1–42.
[246] R. Sawarkar, C. Sievers, R. Paro, Hsp90 globally targets paused RNA polymerase to regulate gene expression in response to environmental stimuli, Cell 149 (2012) 807–818.
[247] L.J. Core, J.T. Lis, Transcription regulation through promoter-proximal pausing of RNA polymerase II, Science 319 (2008) 1791–1792.
[248] A.J. Cook, Z.A. Gurard-Levin, I. Vassias, G. Almouzni, A specific function for the histone chaperone NASP to fine-tune a reservoir of soluble H3–H4 in the histone supply chain, Mol. Cell 44 (2011) 918–927.
[249] P.W. Piper, S.H. Millson, Mechanisms of resistance to Hsp90 inhibitor drugs: a complex mosaic emerges, Pharmaceuticals (2011) 1400–1422.
[250] Y. Miyata, Hsp90 inhibitor geldanamycin and its derivatives as novel cancer chemotherapeutic agents, Curr. Pharm. Des. 11 (2005) 1131–1138.
[251] G. Angelo, S. Lamon-Fava, L.A. Sonna, M.L. Lindauer, R.J. Wood, Heat shock protein 90beta: a novel mediator of vitamin D action, Biochem. Biophys. Res. Commun. 367 (2008) 578–583.
[252] E. Marcinkowska, E. Gocek, Heat shock protein 90 interacts with vitamin D receptor in human leukemia cells, J. Steroid Biochem. Mol. Biol. 121 (2010) 114–116.
[253] I. Pongratz, G.G. Mason, L. Poellinger, Dual roles of the 90-kDa heat shock protein hsp90 in modulating functional activities of the dioxin receptor. Evidence that the dioxin receptor functionally belongs to a subclass of nuclear receptors which require hsp90 both for ligand binding activity and repression of intrinsic DNA binding activity, J. Biol. Chem. 267 (1992) 13728–13734.
[254] A. Kazlauskas, S. Sundstrom, L. Poellinger, I. Pongratz, The hsp90 chaperone complex regulates intracellular localization of the dioxin receptor, Mol. Cell. Biol. 21 (2001) 2594–2607.
[255] A. Hahn, D. Bublak, E. Schleiff, K.D. Scharf, Crosstalk between Hsp90 and Hsp70 chaperones and heat stress transcription factors in tomato, Plant Cell 23 (2011) 741–755.
[256] J. Zou, Y. Guo, T. Guettouche, D.F. Smith, R. Voellmy, Repression of heat shock transcription factor HSF1 activation by HSP90 (HSP90 complex) that forms a stress-sensitive complex with HSF1, Cell 94 (1998) 471–480.
[257] W.K. Sumanasekera, E.S. Tien, J.W. Davis II, R. Turpey, G.H. Perdew, J.P. Vanden Heuvel, Heat shock protein-90 (Hsp90) acts as a repressor of peroxisome proliferator-activated receptor-alpha (PPARalpha) and PPARbeta activity, Biochemistry 42 (2003) 10726–10735.
[258] K. Kobayashi, T. Sueyoshi, K. Inoue, R. Moore, M. Negishi, Cytoplasmic accumulation of the nuclear receptor CAR by a tetratricopeptide repeat protein in HepG2 cells, Mol. Pharmacol. 64 (2003) 1069–1075.
[259] Y. Kanno, Y. Miyama, M. Ando, Y. Inouye, Dependence on the microtubule network and 90-kDa heat shock protein of phenobarbital-induced nuclear translocation of the rat constitutive androstane receptor, Mol. Pharmacol. 77 (2010) 311–316.
[260] E.J. Squires, T. Sueyoshi, M. Negishi, Cytoplasmic localization of pregnane X receptor and ligand-dependent nuclear translocation in mouse liver, J. Biol. Chem. 279 (2004) 49307–49314.
[261] N. Sato, T. Yamamoto, Y. Sekine, T. Yumioka, A. Junicho, H. Fuse, T. Matsuda, Involvement of heat-shock protein 90 in the interleukin-6-mediated signaling pathway through STAT3, Biochem. Biophys. Res. Commun. 300 (2003) 847–852.
[262] E. Bradley, E. Bieberich, N.F. Mivechi, D. Tangpisuthipongsa, G. Wang, Regulation of embryonic stem cell pluripotency by heat shock protein 90, Stem Cells 30 (2012) 1624–1633.
[263] L.A. Stechschulte, E.R. Sanchez, FKBP51-a selective modulator of glucocorticoid and androgen sensitivity, Curr. Opin. Pharmacol. 11 (2011) 332–337.
[264] M. Shirane, K.I. Nakayama, Inherent calcineurin inhibitor FKBP38 targets Bcl-2 to mitochondria and inhibits apoptosis, Nat. Cell Biol. 5 (2003) 28–37.
[265] S. Barth, J. Nesper, P.A. Hasgall, R. Wirthner, K.J. Nytko, F. Edlich, D.M. Katschinski, D.P. Stiehl, R.H. Wenger, G. Camenisch, The peptidyl prolyl cis/trans isomerase FKBP38 determines hypoxia-inducible transcription factor prolyl-4-hydroxylase PHD2 protein stability, Mol. Cell. Biol. 27 (2007) 3758–3768.
[266] T. Ratajczak, B.K. Ward, R.F. Minchin, Immunophilin chaperones in steroid receptor signalling, Curr. Top. Med. Chem. 3 (2003) 1348–1357.
[267] S. Periyasamy, T. Hinds Jr., L. Shemshedini, W. Shou, E.R. Sanchez, FKBP51 and Cyp40 are positive regulators of androgen-dependent prostate cancer cell growth and the targets of FK506 and cyclosporin A, Oncogene 29 (2010) 1691–1701.
[268] T.C. Luu, P. Bhattacharya, W.K. Chan, Cyclophilin-40 has a cellular role in the aryl hydrocarbon receptor signaling, FEBS Lett. 582 (2008) 3167–3173.
[269] T. Jascur, H. Brickner, I. Salles-Passador, V. Barbier, A. El Khissiin, B. Smith, R. Fotedar, A. Fotedar, Regulation of p21(WAF1/CIP1) stability by WISp39, a Hsp90 binding TPR protein, Mol. Cell 17 (2005) 237–249.
[270] A.J. Ramsey, M. Chinkers, Identification of potential physiological activators of protein phosphatase 5, Biochemistry 41 (2002) 5625–5632.
[271] J.R. Petrulis, G.H. Perdew, The role of chaperone proteins in the aryl hydrocarbon receptor core complex, Chem. Biol. Interact. 141 (2002) 25–40.
[272] M.G. Price, M.L. Landsverk, J.M. Barral, H.F. Epstein, Two mammalian UNC-45 isoforms are related to distinct cytoskeletal and muscle-specific functions, J. Cell Sci. 115 (2002) 4013–4023.
[273] J.C. Young, N.J. Hoogenraad, F.U. Hartl, Molecular chaperones Hsp90 and Hsp70 deliver preproteins to the mitochondrial import receptor Tom70, Cell 112 (2003) 41–50.
[274] C.A. Ballinger, P. Connell, Y. Wu, Z. Hu, L.J. Thompson, L.Y. Yin, C. Patterson, Identification of CHIP, a novel tetratricopeptide repeat-containing protein that interacts with heat shock proteins and negatively regulates chaperone functions, Mol. Cell. Biol. 19 (1999) 4535–4545.
[275] P.K. Bansal, R. Abdulle, K. Kitagawa, Sgt1 associates with Hsp90: an initial step of assembly of the core kinetochore complex, Mol. Cell. Biol. 24 (2004) 8069–8079.
[276] A. Mayor, F. Martinon, T. De Smedt, V. Petrilli, J. Tschopp, A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses, Nat. Immunol. 8 (2007) 497–503.
[277] L. Whitesell, E.G. Mimnaugh, B. De Costa, C.E. Myers, L.M. Neckers, Inhibition of heat shock protein HSP90-pp 60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 8324–8328.
[278] N. Grammatikakis, J.H. Lin, A. Grammatikakis, P.N. Tsichlis, B.H. Cochran, p50(cdc37) acting in concert with Hsp90 is required for Raf-1 function, Mol. Cell. Biol. 19 (1999) 1661–1672.
[279] S. Uma, S.D. Hartson, J.J. Chen, R.L. Matts, Hsp90 is obligatory for the heme-regulated eIF-2alpha kinase to acquire and maintain an activable conformation, J. Biol. Chem. 272 (1997) 11648–11656.
[280] W.G. An, T.W. Schulte, L.M. Neckers, The heat shock protein 90 antagonist geldanamycin alters chaperone association with p210bcr-abl and v-src proteins before their degradation by the proteasome, Cell Growth Differ. 11 (2000) 355–360.
[281] A.D. Basso, D.B. Solit, G. Chiosis, B. Giri, P. Tsichlis, N. Rosen, Akt forms an intracellular complex with heat shock protein 90 (Hsp90) and Cdc37 and is destabilized by inhibitors of Hsp90 function, J. Biol. Chem. 277 (2002) 39858–39866.
[282] S.J. Arlander, S.J. Felts, J.M. Wagner, B. Stensgard, D.O. Toft, L.M. Karnitz, Chaperoning checkpoint kinase 1 (Chk1), an Hsp90 client, with purified chaperones, J. Biol. Chem. 281 (2006) 2989–2998.
[283] X. Peng, X. Guo, S.C. Borkan, A. Bharti, Y. Kuramochi, S. Calderwood, D.B. Sawyer, Heat shock protein 90 stabilization of ErbB2 expression is disrupted by ATP depletion in myocytes, J. Biol. Chem. 280 (2005) 13148–13152.
[284] A. Citri, J. Gan, Y. Mosesson, G. Vereb, J. Szollosi, Y. Yarden, Hsp90 restrains ErbB-2/HER2 signalling by limiting heterodimer formation, EMBO Rep. 5 (2004) 1165–1170.
[285] N. Fujita, S. Sato, A. Ishida, T. Tsuruo, Involvement of Hsp90 in signaling and stability of 3-phosphoinositide-dependent kinase-1, J. Biol. Chem. 277 (2002) 10346–10353.
[286] G. Chen, P. Cao, D.V. Goeddel, TNF-induced recruitment and activation of the IKK complex require Cdc37 and Hsp90, Mol. Cell 9 (2002) 401–410.
[287] A.S. Martins, J.L. Ordonez, A. Garcia-Sanchez, D. Herrero, V. Sevillano, D. Osuna, C. Mackintosh, G. Caballero, A.P. Otero, C. Poremba, J. Madoz-Gurpide, E. de Alava, A

pivotal role for heat shock protein 90 in Ewing sarcoma resistance to anti-insulin-like growth factor 1 receptor treatment: in vitro and in vivo study, Cancer Res. 68 (2008) 6260–6270.
[288] R.R. Ramos, A.J. Swanson, J. Bass, Calreticulin and Hsp90 stabilize the human insulin receptor and promote its mobility in the endoplasmic reticulum, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 10470–10475.
[289] T. Imamura, T. Haruta, Y. Takata, I. Usui, M. Iwata, H. Ishihara, M. Ishiki, O. Ishibashi, E. Ueno, T. Sasaoka, M. Kobayashi, Involvement of heat shock protein 90 in the degradation of mutant insulin receptors by the proteasome, J. Biol. Chem. 273 (1998) 11183–11188.
[290] B. Masson-Gadais, F. Houle, J. Laferriere, J. Huot, Integrin alphavbeta3, requirement for VEGFR2-mediated activation of SAPK2/p38 and for Hsp90-dependent phosphorylation of focal adhesion kinase in endothelial cells activated by VEGF, Cell Stress Chaperones 8 (2003) 37–52.
[291] M. Sakagami, P. Morrison, W.J. Welch, Benzoquinoid ansamycins (herbimycin A and geldanamycin) interfere with the maturation of growth factor receptor tyrosine kinases, Cell Stress Chaperones 4 (1999) 19–28.
[292] D. Matei, M. Satpathy, L. Cao, Y.C. Lai, H. Nakshatri, D.B. Donner, The platelet-derived growth factor receptor alpha is destabilized by geldanamycins in cancer cells, J. Biol. Chem. 282 (2007) 445–453.
[293] A.R. Farina, A. Tacconelli, L. Cappabianca, G. Cea, A. Chioda, A. Romanelli, S. Pensato, C. Pedone, A. Gulino, A.R. Mackay, The neuroblastoma tumour-suppressor TrkAI and its oncogenic alternative TrkAIII splice variant exhibit geldanamycin-sensitive interactions with Hsp90 in human neuroblastoma cells, Oncogene 28 (2009) 4075–4094.
[294] P. Garcia-Morales, E. Carrasco-Garcia, P. Ruiz-Rico, R. Martinez-Mira, M.P. Menendez-Gutierrez, J.A. Ferragut, M. Saceda, I. Martinez-Lacaci, Inhibition of Hsp90 function by ansamycins causes downregulation of cdc2 and cdc25c and G(2)/M arrest in glioblastoma cell lines, Oncogene 26 (2007) 7185–7193.
[295] L. Shang, T.B. Tomasi, The heat shock protein 90-CDC37 chaperone complex is required for signaling by types I and II interferons, J. Biol. Chem. 281 (2006) 1876–1884.
[296] A. Ota, J. Zhang, P. Ping, J. Han, Y. Wang, Specific regulation of noncanonical p38alpha activation by Hsp90-Cdc37 chaperone complex in cardiomyocyte, Circ. Res. 106 (2010) 1404–1412.
[297] T.S. Adwan, A.M. Ohm, D.N. Jones, M.J. Humphries, M.E. Reyland, Regulated binding of importin-alpha to protein kinase Cdelta in response to apoptotic signals facilitates nuclear import, J. Biol. Chem. 286 (2011) 35716–35724.
[298] G.R. Budas, E.N. Churchill, M.H. Disatnik, L. Sun, D. Mochly-Rosen, Mitochondrial import of PKCepsilon is mediated by HSP90: a role in cardioprotection from ischaemia and reperfusion injury, Cardiovasc. Res. 88 (2010) 83–92.
[299] C.B. Knobbe, T.J. Revett, Y. Bai, V. Chow, A.H. Jeon, C. Bohm, S. Ehsani, T. Kislinger, H.T. Mount, T.W. Mak, P. St George-Hyslop, G. Schmitt-Ulms, Choice of biological source material supersedes oxidative stress in its influence on DJ-1 in vivo interactions with Hsp90, J. Proteome Res. 10 (2011) 4388–4404.
[300] J. Rodriguez-Caban, W. Gonzalez-Velazquez, L. Perez-Sanchez, R. Gonzalez-Mendez, N. Rodriguez-del Valle, Calcium/calmodulin kinase1 and its relation to thermotolerance and HSP90 in *Sporothrix schenckii*: an RNAi and yeast two-hybrid study, BMC Microbiol. 11 (2011) 162.
[301] H. Wang, T. Goode, P. Iakova, J.H. Albrecht, N.A. Timchenko, C/EBPalpha triggers proteasome-dependent degradation of cdk4 during growth arrest, EMBO J. 21 (2002) 930–941.
[302] S. Fang, J. Fu, X. Yuan, C. Han, L. Shi, Y. Xin, L. Luo, Z. Yin, Heat shock protein 90 regulates the stability of MEKK3 in HEK293 cells, Cell. Immunol. 259 (2009) 49–55.
[303] W.B. Ou, C. Hubert, J.M. Corson, R. Bueno, D.L. Flynn, D.J. Sugarbaker, J.A. Fletcher, Targeted inhibition of multiple receptor tyrosine kinases in mesothelioma, Neoplasia 13 (2011) 12–22.
[304] V.M. Banz, M. Medova, A. Keogh, C. Furer, Y. Zimmer, D. Candinas, D. Stroka, Hsp90 transcriptionally and post-translationally regulates the expression of NDRG1 and maintains the stability of its modifying kinase GSK3beta, Biochim. Biophys. Acta 1793 (2009) 1597–1603.
[305] T. Schnaider, J. Somogyi, P. Csermely, M. Szamel, The Hsp90-specific inhibitor, geldanamycin, blocks CD28-mediated activation of human T lymphocytes, Life Sci. 63 (1998) 949–954.
[306] S. Koyasu, E. Nishida, T. Kadowaki, F. Matsuzaki, K. Iida, F. Harada, M. Kasuga, H. Sakai, I. Yahara, Two mammalian heat shock proteins, HSP90 and HSP100, are actin-binding proteins, Proc. Natl. Acad. Sci. U. S. A. 83 (1986) 8054–8058.
[307] R. Srikakulam, D.A. Winkelmann, Chaperone-mediated folding and assembly of myosin in striated muscle, J. Cell Sci. 117 (2004) 641–652.
[308] F. Weis, L. Moullintraffort, C. Heichette, D. Chretien, C. Garnier, The 90-kDa heat shock protein Hsp90 protects tubulin against thermal denaturation, J. Biol. Chem. 285 (2010) 9525–9534.
[309] M. Nakamura, H. Morisawa, S. Imajoh-Ohmi, C. Takamura, H. Fukuda, T. Toda, Proteomic analysis of protein complexes in human SH-SY5Y neuroblastoma cells by using blue-native gel electrophoresis: an increase in lamin A/C associated with heat shock protein 90 in response to 6-hydroxydopamine-induced oxidative stress, Exp. Gerontol. 44 (2009) 375–382.
[310] M.H. Zhang, J.S. Lee, H.J. Kim, D.I. Jin, J.I. Kim, K.J. Lee, J.S. Seo, HSP90 protects apoptotic cleavage of vimentin in geldanamycin-induced apoptosis, Mol. Cell. Biochem. 281 (2006) 111–121.
[311] P.C. Burcham, A. Raso, C.A. Thompson, Intermediate filament carbonylation during acute acrolein toxicity in A549 lung cells: functional consequences, chaperone redistribution, and protection by bisulfite, Antioxid. Redox Signal. 12 (2010) 337–347.
[312] T. Fukuda, J. Shimizu, H. Furuhata, T. Abe, K. Shimizu, T. Oishi, M. Ogihara, J. Kubota, A. Sasaki, K. Sasaki, T. Azuma, S. Umemura, Overexpression of heat shock proteins in pallido-nigral axonal spheroids of nonhuman aged primates, Acta Neuropathol. 110 (2005) 145–150.
[313] T. Tanioka, Y. Nakatani, T. Kobayashi, M. Tsujimoto, S. Oh-ishi, M. Murakami, I. Kudo, Regulation of cytosolic prostaglandin E2 synthase by 90-kDa heat shock protein, Biochem. Biophys. Res. Commun. 303 (2003) 1018–1023.
[314] J.L. Johnson, D.O. Toft, Binding of p23 and hsp90 during assembly with the progesterone receptor, Mol. Endocrinol. 9 (1995) 670–678.
[315] W.B. Pratt, Y. Morishima, H.M. Peng, Y. Osawa, Proposal for a role of the Hsp90/Hsp70-based chaperone machinery in making triage decisions when proteins undergo oxidative and toxic damage, Exp. Biol. Med. (Maywood) 235 (2010) 278–289.
[316] W.B. Pratt, K.D. Dittmar, Studies with purified chaperones advance the understanding of the mechanism of glucocorticoid receptor-hsp90 heterocomplex assembly, Trends Endocrinol. Metab. 9 (1998) 244–252.
[317] S.S. Billecke, A.T. Bender, K.C. Kanelakis, P.J. Murphy, E.R. Lowe, Y. Kamada, W.B. Pratt, Y. Osawa, hsp90 is required for heme binding and activation of apo-neuronal nitric-oxide synthase: geldanamycin-mediated oxidant generation is unrelated to any action of hsp90, J. Biol. Chem. 277 (2002) 20504–20509.
[318] J.E. Whittier, Y. Xiong, M.C. Rechsteiner, T.C. Squier, Hsp90 enhances degradation of oxidized calmodulin by the 20 S proteasome, J. Biol. Chem. 279 (2004) 46135–46142.
[319] B. Panaretou, G. Siligardi, P. Meyer, A. Maloney, J.K. Sullivan, S. Singh, S.H. Millson, P.A. Clarke, S. Naaby-Hansen, R. Stein, R. Cramer, M. Mollapour, P. Workman, P.W. Piper, L.H. Pearl, C. Prodromou, Activation of the ATPase activity of hsp90 by the stress-regulated cochaperone aha1, Mol. Cell 10 (2002) 1307–1318.
[320] L. Burch, H. Shimizu, A. Smith, C. Patterson, T.R. Hupp, Expansion of protein interaction maps by phage peptide display using MDM2 as a prototypical conformationally flexible target protein, J. Mol. Biol. 337 (2004) 129–145.
[321] M.V. Blagosklonny, J. Toretsky, S. Bohen, L. Neckers, Mutant conformation of p53 translated in vitro or in vivo requires functional HSP90, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 8379–8383.
[322] A.M. Eleuteri, M. Cuccioloni, J. Bellesi, G. Lupidi, E. Fioretti, M. Angeletti, Interaction of Hsp90 with 20S proteasome: thermodynamic and kinetic characterization, Proteins 48 (2002) 169–177.
[323] B.J. Wagner, J.W. Margolis, Age-dependent association of isolated bovine lens multicatalytic proteinase complex (proteasome) with heat-shock protein 90, an endogenous inhibitor, Arch. Biochem. Biophys. 323 (1995) 455–462.
[324] T. Yamaguchi, N. Omatsu, A. Omukae, T. Osumi, Analysis of interaction partners for perilipin and ADRP on lipid droplets, Mol. Cell. Biochem. 284 (2006) 167–173.
[325] Y. Miyata, I. Yahara, p53-independent association between SV40 large T antigen and the major cytosolic heat shock protein, HSP90, Oncogene 19 (2000) 1477–1484.
[326] P. Pandey, A. Saleh, A. Nakazawa, S. Kumar, S.M. Srinivasula, V. Kumar, R. Weichselbaum, C. Nalin, E.S. Alnemri, D. Kufe, S. Kharbanda, Negative regulation of cytochrome c-mediated oligomerization of Apaf-1 and activation of procaspase-9 by heat shock protein 90, EMBO J. 19 (2000) 4310–4322.
[327] D. Trisciuoglio, C. Gabellini, M. Desideri, E. Ziparo, G. Zupi, D. Del Bufalo, Bcl-2 regulates HIF-1alpha protein stabilization in hypoxic melanoma cells via the molecular chaperone HSP90, PLoS One 5 (2010) e11772.
[328] B.R. Keppler, A.T. Grady, M.B. Jarstfer, The biochemical role of the heat shock protein 90 chaperone complex in establishing human telomerase activity, J. Biol. Chem. 281 (2006) 19840–19848.
[329] P.C. Echeverria, A. Bernthaler, P. Dupuis, B. Mayer, D. Picard, An interaction network predicted from public data as a discovery tool: application to the Hsp90 molecular chaperone machine, PLoS One 6 (2011) e26044.