JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Cell and Molecular Biology

Review Article

# Molecular Chaperones Shape Steroid Receptor Action and Pharmacologic Strategies

Gisela I Mazaira[1], Mariana Lagadari[2], Alejandra G. Erlejman[1] and Mario D. Galigniana[1,2*]

[1]*Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina*

[2]*Instituto de Biología y Medicina Experimental (IBYME-CONICET), Buenos Aires, Argentina*

**Corresponding author: Dr. Mario D. Galigniana, Int. Güiraldes 2160, Pabellón II, 4 piso, Laboratorio QB68, Ciudad Universitaria, Buenos Aires (C1428ADN), Argentina, Tel: +54 11 4576-3300 (ext. 215); Fax: +54 11 4576-3342; Email: mgaligniana@conicet.gov.ar*

*Received:* 08-04-2014

*Accepted:* 03-20-2015

*Published:* 03-31-2015



## Abstract

Chaperone oligomers exist in cell cytosols as preassembled heterocomplexes that function as protein-folding molecular machines able to assemble essential proteins related to families that embrace steroid receptors, protein-kinases, ubiquitin-ligases, and transcription factors, among other families of key proteins. Actually, steroid receptors may be considered a particular subset of transcription factors that can be activated by specific ligands. Some of them are primarily located in the cytoplasm, others are constitutively nuclear, but regardless of their subcellular distribution, they are constantly shuttling between both compartments in a highly dynamic manner. The chaperone heterocomplex associated to steroid receptors is not only involved in the stabilization of their conformation preventing their degradation by the proteasome, but it is also critical for the molecular mechanism of transport of these receptors and their subnuclear redistribution. In this article we summarized some of the general properties of molecular chaperones, in particular those belonging to a subfamily that is highly inducible by thermal shock, the heat-shock proteins, and review the most recent findings performed in the field of soluble protein trafficking, where molecular chaperones play a critical role.

**Keywords:** Hsp90; Hsp70; p23; Immunophilins; FKBP51; FKBP52; TPR Proteins; Dynein; Steroid Receptors

## Abbreviations

Hsp90: Heat-shock protein of 90-kDa;
Hsp70: Heat-shock protein of 70-kDa;
FKBP51: FK506-binding protein of 51-kDa;
FKBP52: FK506-binding protein of 52-kDa;
TPR: Tetratricopeptide Repeats;
GR: Glucocorticoid Receptor;
MR: Mineralocorticoid Receptor;
AR: Androgen Receptor;
ER: Estrogen Receptor;
PR: Progesterone Receptor;
TPR: Tetratricopeptide Repeats;
BAG-1: Bcl-2-Associated Gene Product-1;
Hip: Hsc70-interacting protein

## Introduction

Steroid receptors are a subfamily of the nuclear receptor superfamily of transcription factors that are activated by specific ligands. They are soluble proteins that exist in oligomeric form associated to molecular chaperones, which are essential for preserving a receptor conformation that shows the highest affinity for the steroid hormone and, at the same time, preserves the stability of the receptor avoiding its degradation [1]. The presence of chaperones blocks the DNA-binding domain of steroid receptors impairing the recognition of specific sequences in the target genes. Upon hormone binding, the activation of the receptor implies the dissociation of the chaperone heterocomplex (a process referred to as 'transformation').

The primary subcellular localization in the absence of ligand can be mostly cytoplasmic for some receptors such as GR, MR and AR, or constitutively nuclear in the case of others such as ER and PR. The primary location is also dependent on the cell type. Regardless of this subcellular localization, all the receptors are concentrated in the nuclear compartment upon ligand activation. This implies that these receptors must be transported towards the nucleus, even those that are primarily nuclear because they are not statically confined within the nuclear compartment, but they shuttle dynamically between the organelle and the cytoplasm. We will address this mechanism later on.

## Molecular Chaperones

During the onset of stressing and harmful conditions for life, protein synthesis is rapidly arrested with the remarkable exception of a particular set of proteins that is highly induced, the molecular chaperones [2]. Similar to those matrons that used to oversee adolescent people at a social gathering and accompanied single young ladies in public events, proteins that assist others in their appropriate folding, assembly, and biological functions are also referred to as chaperones.

The classic concept of molecular chaperone sustains that they are able to recognize structural elements of unfolded or partially denatured polypeptides preventing or rescuing the incorrect intermolecular association of improperly folded or unfolded proteins, a situation that ultimately leads to their aggregation and/or proteasome degradation. This concept is based on studies where the prevention of histone aggregation with DNA by nucleoplasmin, the first chaperone named as such, was observed during the assembly of nucleosomes [3]. Then, the term chaperone was extended to other proteins that mediate the stabilization of proteins by favoring the proper assembly of polypetides. The novel concept of 'assembly' was not always in everybody´s mind (even today) due to the fact that purified denatured proteins are able to regain activity without the need of other macromolecules when the denaturing agent was removed from the medium [4]. This was called 'self-assembly' and the notion that each protein was self-sufficient for its spontaneous folding dominated the field for decades. The concept that chaperones are essential to assist the assembly of oligomeric complexes was gaining followers, although it is a conception that stems from old studies from the 50's where viral particles could be reassembled in vitro when the individual components were incubated together [5]. A conventional definition given for molecular chaperones that was also reproduced in several text-books is the following: "*Chaperones are a functional class of unrelated families of protein that assist the correct non-covalent assembly of other polypeptide-containing structures in vivo, but are not components of these assembled structures when they are performing their normal biological actions. The words used in this definition have been chosen with some care so as not to conflict with future likely discoveries about molecular chaperones or to overlap with existing terms*" [6]. We are going to reanalyze these concepts at the end of this article.

It is accepted that a substantial proportion ranging between 20 and 30% of all proteins in eukaryotic cells seem to be intrinsically devoid of any ordered three-dimensional structure and adopt a given conformation only after interaction with chaperone partners [7]. Molecular chaperones have a key role in the regulation of protein conformation states, which often involves a number of regulatory co-chaperones that function in various combinations to interact with chaperones to facilitate protein folding, the assembly of heteromeric complexes, to confer substrate specificities, and influence subcellular trafficking. The onset of locally enhanced transcription was first inferred from the expanded appearance of chromosomal puffs after heat-shock [8], and those members of the chaperone family that are induced by heat-shock were consequently named heat-shock proteins (HSPs). Therefore, all HSPs are molecular chaperones, but not all chaperones are HSPs.

## Heat-Shock Proteins

These chaperons show highly flexible conformation such that they can adapt to different environmental conditions and interact with several client proteins. Conformational changes are triggered by slight modifications of temperature, and the expression of their genes is greatly and efficiently induced. It is accepted that nearly 50 to 200 genes are induced from archaea to human [9], and that the leading group across the species in terms of induction level are the HSPs. Actually, it has been postulated that cells cannot sense temperature per se, but they do respond to the deleterious accumulation of proteins not properly folded or denatured generating an imbalanced proteostasis [9]. In short, all these properties make possible the existence of life in hostile environments, even at extremely

high temperatures. Nonetheless, temperature is just one of the unfavorable conditions able to induce their expression. Others are UV light, nutrient deprivation, hypoxia, ischemia, metals, organic solvents, endotoxins, reactive oxygen species, radiation, etc.

According to their molecular weights, the HSP subfamily consists of six broadly conserved types of HSPs, i.e. Hsp100s, Hsp90s, Hsp70s, Hsp60s, Hsp40s, and the small heat-shock proteins. Among them, Hsp90 is the distinctive HSP because, in addition of showing all the properties that define a molecular chaperone, the principal role of Hsp90 in the cell is to provide biological activity to properly folded client proteins showing preserved tertiary structure. In other words, Hsp90 works as a delicate and refined sensor of protein function rather than a mere folding factor. Hsp90 shows intrinsic ATPase activity, is highly selective for the recognition of substrates, and it usually shows low affinity for unfolded proteins [10-12]. Hsp90 is in a dynamic equilibrium between an open (V-shaped) and a close conformation (Fig.1), a state where ATP-hydrolysis takes place, the N-terminal domains dissociate, and Hsp90 returns to the open conformation again [13].

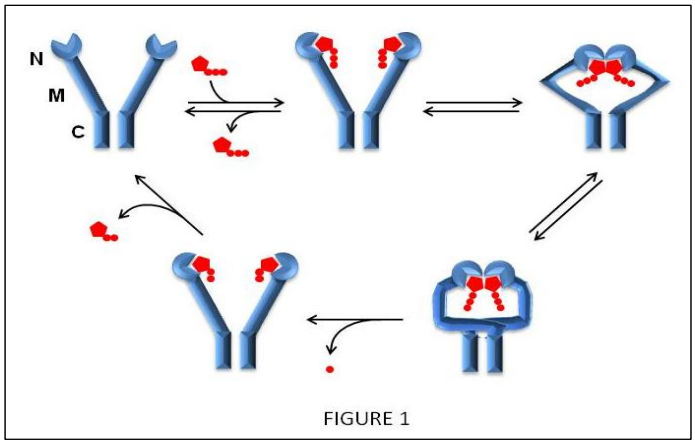


**Figure 1.** Conformational Cycle of Hsp90 Dimers.
The V-shaped open conformation of Hsp90 binds ATP at the N-terminal domain (N). The M-middle domain (M) repositions and interacts with the N-domain, and the dimer twists over itself. The intrinsic ATPase activity is favored by this close association of the M and N domains leading to the separation of the N-domains to release the products of the hydrolysis, and Hsp90 returns to the original open conformation to restart the cycle. The C-terminal domain (C) maintains Hsp90 as a dimer.

The cooperation of Hsp90 with other chaperones such as the Hsp70/Hsp40 complex and cochaperones such as p23 and TPR-domain proteins make a vital contribution to the maturation of signal-transduction proteins such as steroid receptors and protein-kinases. A recent study showed that Hsp90 has more than 400 client proteins, 60% of which are protein kinases, 7% are transcription factors and 30% are ubiquitin ligases [14]. Stability of various oncogenic mutant factors is almost entirely depend on Hsp90 binding, such that cancer cells depend on this chaperone to survive in the demanding milieu generated by the oncogenic process [15-17]. Therefore, Hsp90 has become a fashionable pharmacological target and several inhibitors are being currently tested in clinical trials.

## Mechanism of Action of Steroid Receptors

All steroid receptors exist as oligomeric heterocomplexes where the Hsp90 dimer plays a cardinal role. The stoichiometry of the receptor•$(Hsp90)_2$ complex also shows one molecule of Hsp70, one molecule of p23, and a TPR-domain cochaperone bound to the TPR acceptor site of the Hsp90 dimer. Nevertheless, this final heterocomplex must pass through a maturation cycle, which is depicted in Fig.2 using the GR as a model. Because of its hydrophobicity, the steroid binding cleft of the GR is collapsed and unable to bind steroid unless the chaperone complex is bound to the receptor making it more stable from the thermodynamic point of view. The assembly of the GR by a minimal five-protein chaperone system requires the preexistent cytosolic complex $(Hsp90)_2$•Hop•Hsp70/Hsp40•p23 called foldosome. It is transferred to the GR in an ATP-, K+-, and Mg2+-dependent manner allowing steroid binding. Note that these chaperones interact with a protein that shows a stable tertiary structure (although it is biologically inactive) and not with a denatured protein. The TPR-domain protein Hop is important to bring together Hsp90 and Hsp70. It first stabilizes the open conformation of Hsp90 dimers and prevents ATPase activity and the recruitment of p23. This closes Hsp90 conformation weakening Hop binding, which is finally released in a BAG-1/Hip-assisted mechanism [18,19]. Consequently, other TPR-domain co-chaperone such as the immunophilin FKBP52 binds to form the final mature heterocomplex (Fig.3).

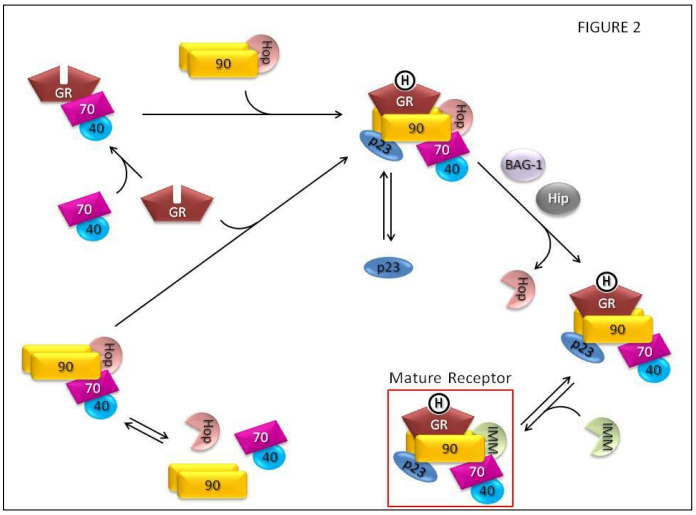


**Figure 2.** Assembly Cycle of the GR with the Chaperone Heterocomplex.
The Hsp90-based chaperone machinery called foldosome forms almost spontaneously in the cytosol thanks to the assistance of the TPR-domain protein Hop (formerly called p60). The collapsed steroid

binding cleft of the GR opens, allowing the binding of the hormone. Alternatively, GR can be primed by Hsp70•Hsp40 binding and the foldosome forms by recruitment of Hsp90•Hop complexes by the GR primed intermediary (46). Hop is then released and replaced by other TPR-domain protein, likely a high molecular weight immunophilin (IMM) such as FKBP51, FKBP52 or CyP40. The TPR domains are depicted as black domains.

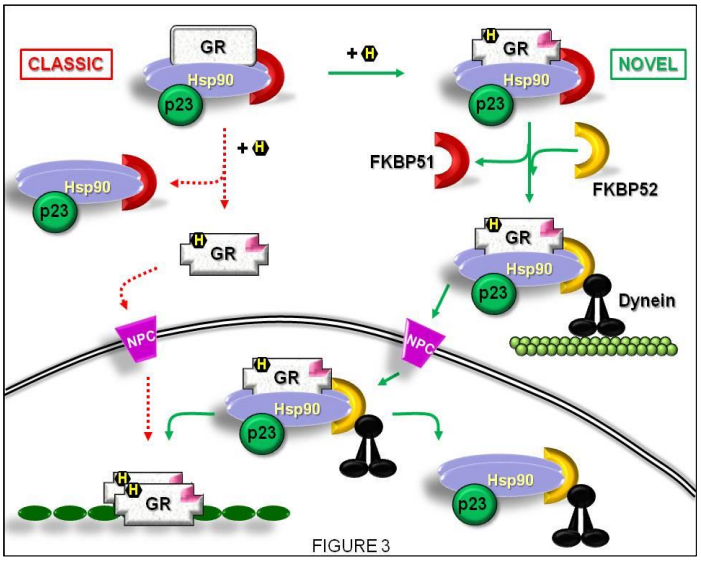


**Figure 3.** Classic and Novel Models for the Retrotransport Mechanisms of the GR.
The classic model for GR activation is depicted with dashed lines. The GR-chaperone complex dissociates after hormone (H) binding favoring the release of the Hsp90-based heterocomplex. The receptor moves by free diffusion and passes through the nuclear pore complex (NPC) in a nuclear localization signal-assisted mechanism (pink corner). According to the novel model (continuous lines), the GR heterocomplex exchanges FKBP51 by FKBP52, which recruits dynein/dynactin motor proteins and moves towards the nucleus on cytoskeletal tracts. The heterocomplex interacts with structural proteins of the nuclear pore complex. Note that the receptor transformation and receptor dimerization are nuclear events.

For decades, it was heuristically stated that Hsp90 anchors GR to the cytoplasm, such that its release from the complex was a requirement to permit the nuclear localization of the receptor. Recent evidence demonstrate that the Hsp90•FKBP52 complex is necessary for that retrotransport [20,21]. In unstimulated conditions, the immunophilin FKBP51 is bound to the GR•Hsp90 complex. Upon steroid binding, FKBP51 is exchanged by its homolog partner FKBP52, an immunophilin able to interact with the dynein/dynactin motor protein machinery. This complex retrotransports the liganded GR•Hsp90 complex throughout the cytoplasmic via microtubules, facilitates the passage of the intact heterocomplex through the nuclear pore, and also the anchorage of GR to the nuclear matrix. Therefore, the receptor transformation step (i.e., dissociation of Hsp90) takes place in the nucleoplasm rather than in the cytoplasm.

This novel mechanism of action for steroid receptors shaped by molecular chaperones noticeably collides with the posited classic dogma that Hsp90 retains receptors in the cytoplasm, and also with the classic definition of chaperone quoted in section 2: chaperones are still components of the assembled structure with the client protein when it is performing its biological action. A similar reasoning can be stated for other Hsp90-client proteins such as protein-kinases, for whom the presence of Hsp90 is a sine qua non requirement for its biological activity to the point that Hsp90 has become an attractive therapeutic target [15-17].

## Chaperones and Disease

Most HSPs are highly expressed in cancer cells, and are also implicated in several processes such as cell proliferation, differentiation, apoptosis, invasion, metastasis and the recognition of the human system [22]. One of the consequences is that cells are protected from apoptosis and develop resistance to existing therapies. Hsp27 is overexpressed in hyperplastic endometrium, breast cancer, and is a good marker of squamous metaplasia in the uterine cervix [23]. In most if not all cancer cells, Hsp27 translocates from cytoplasm to the nucleus. Other chaperones such as Hsp60 are more related to development of carcinogenesis in colon and cervix; whereas Hsp70 is highly associated to carcinogenesis of the oral epithelia and is a good marker for hepatocarcinomas. Increased expression of Hsp70 correlates with a poor prognosis in endometrial and uterine cancers, breast cancer, and transitional cell carcinoma of the bladder [24]. All of these actions are consistent with the associations of Hsp70 with increased cell proliferation, reduced differentiation, lymph node metastasis, antiapoptotic actions, and higher clinical stage, which are markers of poor clinical outcome. On the other hand, high Hsp70 expression is synonym of good prognosis in oesophageal cancer, pancreatic cancer, renal cancer, and melanoma [24].

The Hsp90 cochaperone FKBP51 is regarded as a negative regulator of steroid receptor activity in most studies reported to date [21], except for the case of AR [25], where the overexpression of FKBP51 increases AR transcriptional activity in the presence or absence of androgens in the medium, and siRNA knock-down of the immunophilin strongly impairs AR-dependent gene transcription and cell proliferation [26,27]. Interestingly, it was also demonstrated that about 505 of the cellular pool of FKBP51 is located in mitochondria [28], but undergoes a rapid nuclear accumulation accompanied by nucleolar concentration under several situation of stress (peroxides, heat-shock, UV light, serum deprivation, high osmolarity of the medium, metals, proinflammatory stimuli, etc.) [28]. Inasmuch as the cell metabolism is highly oxidative in cancer cells, it is not surprised that FKBP51 is overexpressed in tumor tissues. FKBP51 shows antiapoptotic effects, whereas its knock-down sensitizes cells to cell death.

FKBP52 is a positive regulator of steroid receptors [21], is overexpressed in breast cancer [29,30] and is also required for normal sexual differentiation and development [31-33]. Accordingly, FKBP52-deficient male mice display characteristics of partial androgen insensitivity syndrome, including dysgenic prostate [27,34]. Recently, it has been reported that FKBP52 is a strong activator of NF-κB biological actions [35]. Because many cancer types exhibit persistent activation of NF-κB, which induces an inflammatory response that is thought to favor cancer development [36], blocking the NF-κB pathway may show therapeutic benefits.

Recent studies have shown that molecular chaperones, such as Hsp70 and Hsp90 counteract the accumulation of proteins in the neurons during the neurodegeneration process [37]. While FKBP51 preserves Tau protein levels in neurons, at the same time it reduces its phosphorylation and consequently, its aggregation in neurodegenerative diseases [38]. On the other hand, FKBP52 correspond with decreased Tau stability, such that both proteins appear to show antagonistic roles [39]. A similar observation was made for the neurodifferentiation process, where FKBP52 is a required factor and FKBP51 impairs it [40,41].

As a consequence of these properties, molecular chaperones are attractive targets for pharmacologic approaches. In this regard, the most advanced studies relate to Hsp90 inhibitors, which are in advanced clinical trials (see [22] for a recent update). Immunosuppressive drugs have also been used to target high molecular weight immunophilins [42], but most ligands are still unselective to specifically recognize FKBP51 and FKBP52. A very recent publication described the biochemical properties of two new compounds named SAFit1 and SAFit2 that appear to show selective antagonistic affinity by FKBP51 [43], i.e. Ki values equal to 4 nM and 6 nM respectively, and >10,000 fold lower affinity for FKBP52, which open new trends to analyze their pharmacologic potential.

## Concluding Remarks

For many key proteins of the cell such as kinases, oncogenes, receptors, ligases, enzymes, and transcription factors, the chaperone complex-client protein interaction is an absolute requirement for its biological action and maintenance of protein signalling. This is particularly true for the case of steroid receptors since hormone binding is entirely dependent of the heterocomplex, as well as receptor trafficking. Not surprisingly, an increasing body of evidence suggests involvement of these chaperones and co-chaperones in the development of various types of malignancies and several diseases. Therefore, the original definition quoted in Section 2 that stated that chaperones are not components of these assembled structures when they are performing their normal biological actions, has clearly been modified by the subsequent findings in the field. The best example is the persistence of the entire Hsp90-based heterocomplex associated to steroid receptors even when the receptor has reached the nuclear compartment. Although chaperones should be dissociated to permit receptor-DNA recognition, they are still playing a role in the mechanism of action, for example, regulating the transcriptional response of the receptor and/or its subnuclear localization [44-46].

All these circumstances make members of the chaperone superfamily attractive therapeutic targets. To date, the results of the clinical trials, in addition to the synthesis of new generations of inhibitors, will surely impact upon the management and treatment of several diseases in the near future.

## Acknowledgements

This work and those cited here were partially funded by grants from Universidad de Buenos Aires, Agencia de Promoción Científica y Tecnológica de Argentina, and PIP-CONICET Grant Program.

## References

1. Pratt W B and Toft D O. Steroid receptor interactions with heat shock protein and immunophilin chaperones. Endocr Rev. 1997, 18: 306-360

2. Lindquist S. The heat-shock response. Annu Rev Biochem. 1986, 55: 1151-1191.

3. Laskey R A, Honda B M, Mills A D, Finch J T. Nucleosomes are assembled by an acidic protein which binds histones and transfers them to DNA. Nature. 1978, 275: 416-420.

4. Anfinsen C B. Principles that govern the folding of protein chains. Science. 1973, 181: 223-230.

5. Fraenkel-Conrat H, Williams R C. Reconstitution of Active Tobacco Mosaic Virus from Its Inactive Protein and Nucleic Acid Components. Proc Natl Acad Sci U S A. 1955, 41: 690-698.

6. Ellis R J. The general concept of molecular chaperones. Philos Trans R Soc Lond B Biol Sci. 1993, 339: 257-261.

7. Dunker A K, Silman I, Uversky V N, Sussman J L. Function and structure of inherently disordered proteins. Curr Opin Struct Biol. 2008, 18: 756-764.

8. Ritossa F. A new puffing pattern induced by temperature

shock and DNP in Drosophila. Experientia. 1962, 18: 571-573.

9. Richter K, Haslbeck M, Buchner J. The heat shock response: life on the verge of death. Mol Cell. 40: 253-266.

10. Prince T, Matts R L. Definition of protein kinase sequence motifs that trigger high affinity binding of Hsp90 and Cdc37. J Biol Chem. 2004, 279: 39975-39981.

11. Pratt W B, Morishima Y, Osawa Y. The Hsp90 chaperone machinery regulates signaling by modulating ligand binding clefts. J Biol Chem. 283: 22885-22889.

12. Hartl F U, Hayer-Hartl M. Molecular chaperones in the cytosol: from nascent chain to folded protein. Science. 2002, 295: 1852-1858.

13. Hessling M, Richter K, Buchner J. Dissection of the ATP-induced conformational cycle of the molecular chaperone Hsp90. Nat Struct Mol Biol. 2009, 16: 287-293.

14. Taipale M, Krykbaeva I, Koeva M, Kayatekin C, Westover K D, Karras G I, Lindquist S. Quantitative analysis of HSP90-client interactions reveals principles of substrate recognition. Cell. 2012, 150: 987-1001.

15. Regan P L, Jacobs J, Wang G, Torres J, Edo R et al. Hsp90 inhibition increases p53 expression and destabilizes MYCN and MYC in neuroblastoma. Int J Oncol. 2011, 38: 105-112.

16. Whitesell L, Lin N U. HSP90 as a platform for the assembly of more effective cancer chemotherapy. Biochim Biophys Acta. 2012, 1823: 756-766.

17. Trepel J, Mollapour M, Giaccone G, Neckers L. Targeting the dynamic HSP90 complex in cancer. Nat Rev Cancer. 2010, 10: 537-549.

18. Li J, Richter K, Buchner J. Mixed Hsp90-cochaperone complexes are important for the progression of the reaction cycle. Nat Struct Mol Biol. 2011, 18: 61-66.

19. Kanelakis K C, Murphy P J, Galigniana M D, Morishima Y, Takayama S et al. 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. 2000, 39: 14314-14321.

20. Galigniana M D, Erlejman A G, Monte M, Gomez-Sanchez C, Piwien-Pilipuk G. The hsp90-FKBP52 complex links the mineralocorticoid receptor to motor proteins and persists bound to the receptor in early nuclear events. Mol Cell Biol. 2010, 30: 1285-1298.

21. Storer C L, Dickey C A, Galigniana M D, Rein T, Cox M B. FKBP51 and FKBP52 in signaling and disease. Trends Endocrinol Metab. 2011, 22: 481-490.

22. Taldone T, Ochiana SO, Patel PD, Chiosis G. Selective targeting of the stress chaperome as a therapeutic strategy. Trends Pharmacol Sci. 2014, 35: 592-603.

23. Calderwood SK, Ciocca DR. Heat shock proteins: stress proteins with Janus-like properties in cancer. Int J Hyperthermia. 2008, 24: 31-39.

24. Ciocca D R, Calderwood S K. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones. 2005, 10: 86-103.

25. Kassi E, Moutsatsou P. Glucocorticoid receptor signaling and prostate cancer. Cancer Lett. 2011, 302: 1-10.

26. Periyasamy S, Hinds T Jr, Shemshedini L, Shou W, Sanchez E R. FKBP51 and Cyp40 are positive regulators of androgen-dependent prostate cancer cell growth and the targets of FK506 and cyclosporin A. Oncogene. 2011, 29: 1691-1701.

27. Yong W, Yang Z, Periyasamy S, Chen H, Yucel S et al. Essential role for Co-chaperone Fkbp52 but not Fkbp51 in androgen receptor-mediated signaling and physiology. J Biol Chem. 2007, 282: 5026-5036.

28. Gallo LI, Lagadari M, Piwien-Pilipuk G, Galigniana M D. 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. 2011, 286: 30152-30160.

29. Ward B K, Mark P J, Ingram D M, Minchin R F, Ratajczak T. Expression of the estrogen receptor-associated immu-

nophilins, cyclophilin 40 and FKBP52, in breast cancer. Breast Cancer Res Treat. 1999, 58: 267-280.

30. Shipp C, Watson K, Jones G L. Associations of HSP90 client proteins in human breast cancer. Anticancer Res. 2011, 31: 2095-2101.

31. Chen H, Yong W, Hinds T D Jr, Yang Z, Zhou Y et al. Fkbp52 regulates androgen receptor transactivation activity and male urethra morphogenesis. J Biol Chem. 2010, 285: 27776-27784.

32. Yang Z, Wolf I M, Chen H, Periyasamy S, Chen Z et al. FK506-binding protein 52 is essential to uterine reproductive physiology controlled by the progesterone receptor A isoform. Mol Endocrinol. 2006, 20: 2682-2694.

33. Tranguch S, Cheung-Flynn J, Daikoku T, Prapapanich V, Cox M B et al. Cochaperone immunophilin FKBP52 is critical to uterine receptivity for embryo implantation. Proc Natl Acad Sci U S A. 2005, 102: 14326-14331.

34. Cheung-Flynn J, Prapapanich V, Cox M B, Riggs D L, Suarez-Quian C et al. Physiological role for the cochaperone FKBP52 in androgen receptor signaling. Mol Endocrinol. 2005, 19: 1654-1666.

35. Erlejman A G, De Leo S A, Mazaira G I, Molinari A M, Camisay M F et al. NF-kappaB Transcriptional Activity Is Modulated by FK506-binding Proteins FKBP51 and FKBP52: A ROLE FOR PEPTIDYL-PROLYL ISOMERASE ACTIVITY. J Biol Chem. 2014, 289: 26263-26276.

36. Fan Y, Gupta N, Gelinas C. Molecular Basis of Oncogenesis by NF-kB: From a Bird´s Eye View to RELevant Role in Cancer. Landes Bioscience, Georgetown, Texas, USA, 2006.

37. Miyata Y, Koren J, Kiray J, Dickey C A, Gestwicki J E. Molecular chaperones and regulation of tau quality control: strategies for drug discovery in tauopathies. Future Med Chem. 2011, 3: 1523-1537.

38. Jinwal U K, Koren J, Borysov SI, Schmid AB, Abisambra JF et al. The Hsp90 cochaperone, FKBP51, increases Tau stability and polymerizes microtubules. J Neurosci. 2010, 30: 591-599.

39. Chambraud B, Sardin E, Giustiniani J, Dounane O, Schumacher M et al. A role for FKBP52 in Tau protein function. Proc Natl Acad Sci U S A. 2010, 107: 2658-2663.

40. Quintá H R, Maschi D, Gomez-Sanchez C, Piwien-Pilipuk G, Galigniana M D. Subcellular rearrangement of hsp90-binding immunophilins accompanies neuronal differentiation and neurite outgrowth. J Neurochem. 2010, 115: 716-734.

41. Quinta H R, Galigniana M D. The neuroregenerative mechanism mediated by the Hsp90-binding immunophilin FKBP52 resembles the early steps of neuronal differentiation. Br J Pharmacol. 2012, 166: 637-649.

42. Erlejman AG, Lagadari M, Galigniana M D. Hsp90-binding immunophilins as a potential new platform for drug treatment. Future Med Chem. 2013, 5: 591-607.

43. Gaali S, Kirschner A, Cuboni S, Hartmann J, Kozany C et al. Selective inhibitors of the FK506-binding protein 51 by induced fit. Nat Chem Biol. 2015, 11: 33-37.

44. Galigniana M D, Echeverria PC, Erlejman A G, Piwien-Pilipuk G. Role of molecular chaperones and TPR-domain proteins in the cytoplasmic transport of steroid receptors and their passage through the nuclear pore. Nucleus. 2010, 1: 299-308.

45. Mazaira G I, Lagadari M, Erlejman A G, Galigniana M D. The Emerging Role of TPR-Domain Immunophilins in the Mechanism of Action of Steroid Receptors. Nucl Receptor Res 1, 2014.

46. Pratt W B, Galigniana M D, Morishima Y, Murphy P J. Role of molecular chaperones in steroid receptor action. Essays Biochem. 2004, 40: 41-58.