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Review article

Heat shock proteins and cancer: How can nanomedicine be harnessed?

Félix Sauvage [a], Samir Messaoudi [b], Elias Fattal [a], Gillian Barratt [a], Juliette Vergnaud-Gauduchon [a,*]

[a] Institut Galien Paris-Sud, CNRS, UMR 8612, LabEx LERMIT, Univ. Paris-Sud/Univ. Paris-Saclay, 5 rue J.-B. Clément, Châtenay-Malabry, 92296, France
[b] BioCIS-UMR 8076, Univ. Paris-Sud, CNRS, University Paris-Saclay, Châtenay-Malabry, 92296, France

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ABSTRACT

Heat shock protein (hsp90) is an interesting target for cancer therapy because it is involved in the folding and stabilization of numerous proteins, including many that contribute to the development of cancer. It is part of the chaperone machinery that includes other heat shock proteins (hsp70, hsp27, hsp40) and is mainly localized in the cytosol, although many analogues or isoforms can be found in mitochondrion, endoplasmic reticulum and the cell membrane. Many potential inhibitors of hsp90 have been tested for cancer therapy but their usefulness is limited by their poor solubility in water and their ability to reach the target cells and the correct intracellular compartment. Nanomedicine, the incorporation of active molecules into an appropriate delivery system, could provide a solution to these drawbacks. In this review, we explain the rationale for using nanomedicine for this sort of cancer therapy, considering the properties of the chaperone machinery and of the different hsp90 analogues. We present some results that have already been obtained and put forward some strategies for delivery of hsp90 analogues to specific organelles.

Contents

Abbreviations: 17-AAG, 17-allylaminogeldanamycin; ATP, Adenosine triphosphate; AUC, Area under curve; DQ, Dequalinium; EPR, Enhanced permeation and retention effect; ER, Endoplasmic reticulum; GA, Geldanamycin; HSF-1, Heat shock factor 1; Hsp, Heat shock protein; HSR, Heat shock response; MCL, Magnetic cationic liposomes; MTD, Maximum Tolerated Doses; NP, Nanoparticle; Nvb, Novobiocin; TPP, Triphenyl phosphonium.

* Corresponding author.
E-mail address: juliette.vergnaud@u-psud.fr (J. Vergnaud-Gauduchon).

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1. Introduction

There is an urgent need for new treatments for cancer, especially because resistance to traditional cytotoxic and cytostatic drugs is now widespread. Better knowledge of the oncogenic process and cancer cell biology has revealed many potential new targets. One of these is the so-called chaperone machinery. This system of several proteins acting in concert exists in all mammalian cells and serves both to facilitate the correct folding of newly synthesized proteins and to refold proteins that have been denatured due to stress; hence some of the main components are named heat shock proteins. Many of the so-called "client" proteins of this chaperone system are involved in the oncogenic transformation or the stabilization of the cancer cell phenotype. Among the actors in the chaperone machinery, the protein hsp90 plays a central role and interference with its function can be considered as a "cluster bomb" touching many aspects of cancer cell function at the same time.

Over the last two decades, many small molecules able to inhibit hsp90 have been synthesized with a view to cancer treatment, but only a few have entered clinical trials and none have been commercialized. There are two explanations for this. Firstly, most of hsp90 inhibitors are poorly water-soluble; secondly, because hsp90 is a ubiquitous protein, effects are also seen in normal cells. Nanomedicine could give a second chance to hsp90 inhibitors by improving their apparent solubility and reducing their side effects by delivering them more specifically to cancer cells. In this review, we will first describe hsp90 in terms of its structure and cellular function and then focus on strategies to deliver hsp90 inhibitors more efficiently and on how to exploit treatment-associated biological responses in a drug delivery approach to improve cancer therapy. We will also underline the benefits in terms of intracellular targeting that nanomedicine could bring to hsp90 inhibition. Finally, the exploitation of the properties of other chaperones such as hsp70 with the aid of nanocarriers will be discussed.

1.1. The hsp90 machinery

1.1.1. Structure and function of hsp90

Hsp90 is a ubiquitous, well conserved and abundant dimeric protein that facilitates the repair and proper refolding of proteins that have undergone stress (such as pH changes, temperature variations, hypoxia or cytokine release resulting from tissue injury) that could modify their structure and thereby their function. Hsp90 has a very important role in cell homeostasis and cytoprotection in various stress situations. It is involved in the folding of more than 300 proteins (www.picard.ch/downloads); this function depends on its dimeric structure.

The hsp90 monomer consists of three main domains: a N-terminal domain, the binding site for ATP the hydrolysis of which, mediated by hsp90 and its co-chaperones [1], is the driving force for hsp90 function; a middle domain (M) where client proteins and co-chaperones bind; and a C-terminal domain, another binding site for co-chaperones, responsible for hsp90 dimerization (Fig. 1) [2]. Substrate binding to the middle domain induces conformational changes of hsp90 *via* interaction with co-chaperones and ATP hydrolysis leading to a "closed" conformation. In this state, hsp90 can exert its activity [3].

1.1.2. The chaperone cycle

The chaperone machinery consists of hsp90 associated with co-chaperones (including hsp40, hsp27, HOP, Cdc37, p23 and Aha1). Each co-chaperone has a specific role in assisting hsp90 to repair and refold proteins (Fig. 2). Many other proteins also play a role in the chaperone cycle and oncogenesis, including immunophilins and the peptidyl-prolyl cis-trans isomerases FKBP1 and 2. In this section, we will focus on the role of the co-chaperones HOP, Cdc37, p23 and Aha1 in the conformational changes of hsp90 and its ATPase activity [5].

Most of the hsp90 co-chaperones are TPR (tetratricoprotein repeat) proteins and interact with a specific sequence in the C-terminal domain of hsp90 (MEEVD motif). HOP was the first hsp90 ATPase regulatory co-chaperone to be described. It is responsible for the coupling of hsp70 and hsp90 for the activation of steroid hormone receptors mediated by hsp90. The Cdc37 adaptor is another kinase-specific co-chaperone that can arrest the ATPase cycle of hsp90. Its N-terminal region interacts with protein kinases (as client proteins) and its central and C-terminal domains interact with hsp90. This interaction maintains an open conformation of hsp90 by preventing N-domain dimerization and the N-M domain docking required for ATP hydrolysis [6]. In this way, Cdc37 inhibits ATP hydrolysis and contributes to the prolonged association of hsp90 dimers with client proteins and to effective chaperone action [7]. Due to its function as a cell cycle protein and because of its client proteins, Cdc37 could play a transforming role in tumorigenesis, particularly in prostate cancer. A protein with a different structure, p23, expressed in most mammalian tissues, also forms a complex with hsp90 like the TPR co-chaperones. Although it was first discovered complexed with hsp90 and progesterone receptors, the functions of p23 have been extended to other steroid hormone receptors. This protein can bind to dimers of hsp90 (N-terminal dimers) and is involved in the hsp90 cycle after HOP exchange for the folding of steroid hormone receptors. By stabilizing the complex, p23 allows the ligands of steroid receptors to be maintained in contact with their receptors. However, its activating or inhibiting effects can be different depending on the type of steroid receptor (for a review see [8]).

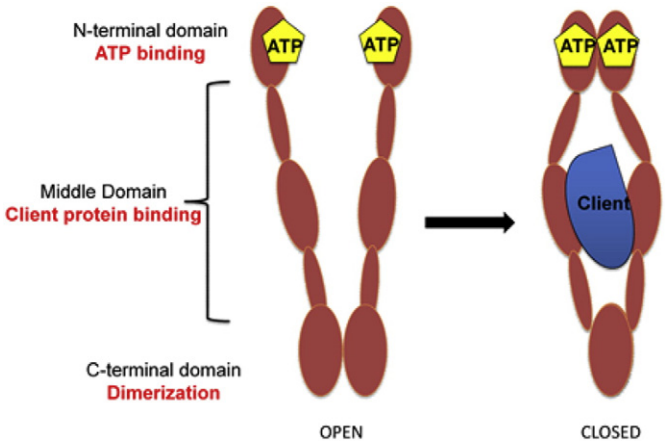

Fig. 1. Schematic representation of the structure of hsp90.

Aha1 is a recently discovered co-chaperone that interacts with hsp90 at the level of the M- and N-domains in presence or in absence of bound nucleotide. This interaction stimulates the ATPase activity of hsp90. The impact of Aha1-hsp90 complexes on client protein activation is not clearly understood, because only some ternary complexes have been described (for example CFTR, Akt Kinase). Aha1 and p23 have opposing effects on hsp90 as p23 inhibits the ATPase activity while Aha1 triggers the release of client protein by stimulating ATP hydrolysis.

When cells are undergoing stress and in some other situations such as treatment with N-terminal hsp90 inhibitors, a heat shock response (HSR) is triggered [9]. This phenomenon involves the induction of several heat shock proteins, including hsp70 and hsp27, and is regulated at the transcriptional level by heat shock factor 1 (HSF-1), which acts as the "conductor" of the HSR. In normal situations, HSF-1 is bound to hsp90 in the form of inactive monomers. Under stress situations, this complex dissociates and HSF-1 is released, hyperphosphorylated and binds to DNA in the form of an active trimer, resulting in the transcription of hsp genes [10]. During recovery periods, when the stress situation is over, activated HSF-1 is repressed by the pool of chaperones. There are several hypotheses regarding this phenomenon, including that some chaperones (hsp70, hsp90 and hsp40) act as sensors and are thus able to induce a negative regulation of the HSR after stress periods [11]. This suggests that accumulated chaperones may have a