Biomedicine & Pharmacotherapy 102 (2018) 608–617

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Targeted cancer therapy through 17-DMAG as an Hsp90 inhibitor: Overview and current state of the art

Hassan Mellatyar[a,b], Sona Talaei[a,b], Younes Pilehvar-Soltanahmadi[a,b], Abolfazl Barzegar[c], Abolfazl Akbarzadeh[d], Arman Shahabi[e], Mazyar Barekati-Mowahed[f], Nosratollah Zarghami[a,b,*]

[a] Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Research Institute for Fundamental Sciences (RIFS), University of Tabriz, Tabriz, Iran
[d] Department of Medical Nanotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Department of Molecular Medicine, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA

ARTICLE INFO

Keywords:
Heat shock protein 90
17-DMAG
Cancer therapy
Inflammatory diseases

ABSTRACT

Heat shock protein 90 (Hsp90) is an evolutionary preserved molecular chaperone which mediates many cellular processes such as cell transformation, proliferation, and survival in normal and stress conditions. Hsp90 plays an important role in folding, maturation, stabilization and activation of Hsp90 client proteins which all contribute to the development, and proliferation of cancer as well as other inflammatory diseases. Functional inhibition of Hsp90 can have a massive effect on various oncogenic and inflammatory pathways, and will result in the degradation of their client proteins. This turns it into an interesting target in the treatment of different malignancies. 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG) as a semi-synthetic derivative of geldanamycin, has several advantages over 17-Allylamino-17-demethoxygeldanamycin (17-AAG) such as higher water solubility, good bioavailability, reduced metabolism, and greater anti-tumour capability. 17-DMAG binds to the Hsp90, and inhibits its function which eventually results in the degradation of Hsp90 client proteins. Here, we reviewed the pre-clinical data and clinical trial data on 17-DMAG as a single agent, in combination with other agents and loaded on nanomaterials in various cancers and inflammatory diseases.

1. Hsp90 and its biological role

Heat shock protein 90 is the most plentiful molecular chaperone in eukaryotic organisms which comprises about 1–2% of cytosolic proteins [1–3]. Hsp90 is tightly conserved in the course of evolution from bacteria to homo sapiens. This implies its essential niche in several cellular processes including cell transformation, proliferation, and survival under normal and stressed conditions [4,5]. Eukaryotic cells have three types of Hsp90s: cytosolic Hsp90 with two isoforms of Hsp90α and Hsp90β, Grp94 (glucose-regulated protein 94) of the endoplasmic reticulum (ER) and mitochondrial Trap1 (tumor necrosis receptor-associated protein 1) [6,7]. Hsp90 is composed of three functional domains: N-terminal, middle and C-terminal domains. All of the domains discussed bind to the ATP which is a primary function of Hsp90 [2,6] (Fig. 1).

Hsp90 has a primary role in folding, maturation, stabilization and activation of a wide range proteins which are known as Hsp90 client proteins in both normal and cancer cells [8]. In normal cells, Hsp90 also plays a key role in intracellular transport, cell signaling and maintenance of genome stability [9]. In these cells, freshly synthesized or stress-induced denatured client proteins achieve an innate state which is mediated via Hsp90. Hsp90 also protects these proteins from proteasomal degradation [10,11].

To materialize this, Hsp90 forms the multi-chaperone complex known as the Hsp90 chaperone machine [12]. This complex which is made up from Hsp90 juxtaposed to Hsp70, Hsp40, P23, cdc37, immunophilins (IPs) and HOP (Hsp70 and Hsp90 organizing protein) [3,13,14]. The Hsp90 chaperone machinery is regulated via the consecutive binding and hydrolysis of ATP [15] (Fig. 2). On the other hand, Hsp90 plays an essential role in the assembly and maintenance of the 26 S proteasome that is responsible for degradation of misfolded and damaged proteins marked for destruction by the polyubiquitation pathway in normal conditions of eukaryotic cells [16].

The Hsp90 client proteins can be classified into three main classes: steroid hormone receptors, tyrosine and serine/threonine kinases, and proteins with various other functions [17–20] (Table 1). These proteins

* Corresponding author at: Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, 13191-45156, Iran.
E-mail address: zarghami@tbzmed.ac.ir (N. Zarghami).

https://doi.org/10.1016/j.biopha.2018.03.102
Received 16 January 2018; Received in revised form 6 March 2018; Accepted 17 March 2018

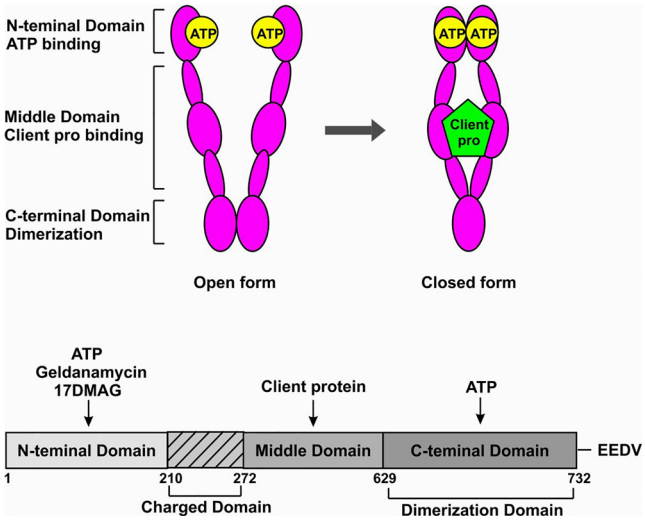

Fig. 1. Schematic structure of Hsp90. There are three functional domains in Hsp90: N-terminal domain with ATP-binding site and drugs such as geldanmycin and 17-DMAG, middle domain with binding site for client proteins, and C-terminal homodimerization domain with binding site for ATP. The charged domain provides a flexible linker in structure of Hsp90. EEVD motif within C-terminal domain is essential for the interaction, and is recognized by co-chaperones carrying a tetratricopeptide repeat (TPR) domain. Client protein binding to the middle domain induces conformational changes in structure of Hsp90, and leads to a closed form formation. In closed form, Hsp90 can exert its activity.

all possess critical roles in the signal transduction pathways as well as the cell cycle [21–23].

Hsp90 is upregulated in response to external stressors such as heat, nutrient absence and oxidative stress conditions in various human tumors [21,24]. Also its ATPase activity is enhanced 50X in a cancerous microenvironment [25].

When cells are stressed by external stressors, Hsp90 assists in the recovery from stress through at least two general ways. First, Hsp90 facilitates protein refolding (correct folding) and increases the rate at which a damaged protein is reactivated. Second, Hsp90 directs non-functional proteins toward proteasomal degradation by the poly-ubiquitation pathway. Thus, Hsp90 restores protein homeostasis and promotes cell survival in stress conditions [26,27].

On the other hand, cancer cells overexpress a number of Hsp90 client proteins, including signal transduction proteins and growth factor receptors that degradation of these proteins induce apoptosis [28]. Hsp90 also stabilizes mutant proteins that appear during cell transformation, thereby enabling malignant transformation [29].

Hsp90 significantly contributes to the microenvironment in which the cancer cells thrive. The inhibition and disruption of Hsp90 affects processes involved in the initiation of cancer which all holistically can be regarded as the “Hallmarks of Cancer”. [6,30–32] (Fig. 3).

A noticeable chunk of Hsp90 client proteins are involved in stages of carcinogenesis. Accordingly inhibition of Hsp90 by inhibitors and proteasomal degradation of these proteins can be effective in cancer therapy [17,19,33].

2. Discovery and development of 17-DMAG as an Hsp90 inhibitor

Geldanamycin is a natural product and a member of the family of benzoquinone ansamycins that was first derived from Streptomyces hygrocopicus [34,35]. Benzoquinone ansamycins have demonstrated anti-tumor and anti-proliferative characteristics [36]. Initially, the potent antitumor activity of geldanamycin on cancer cells was proposed to be done via inhibition of c-Src kinases catalytic activity, but subsequent studies have indicated that inhibition of Hsp90 was responsible for its antitumor activity [13,37].

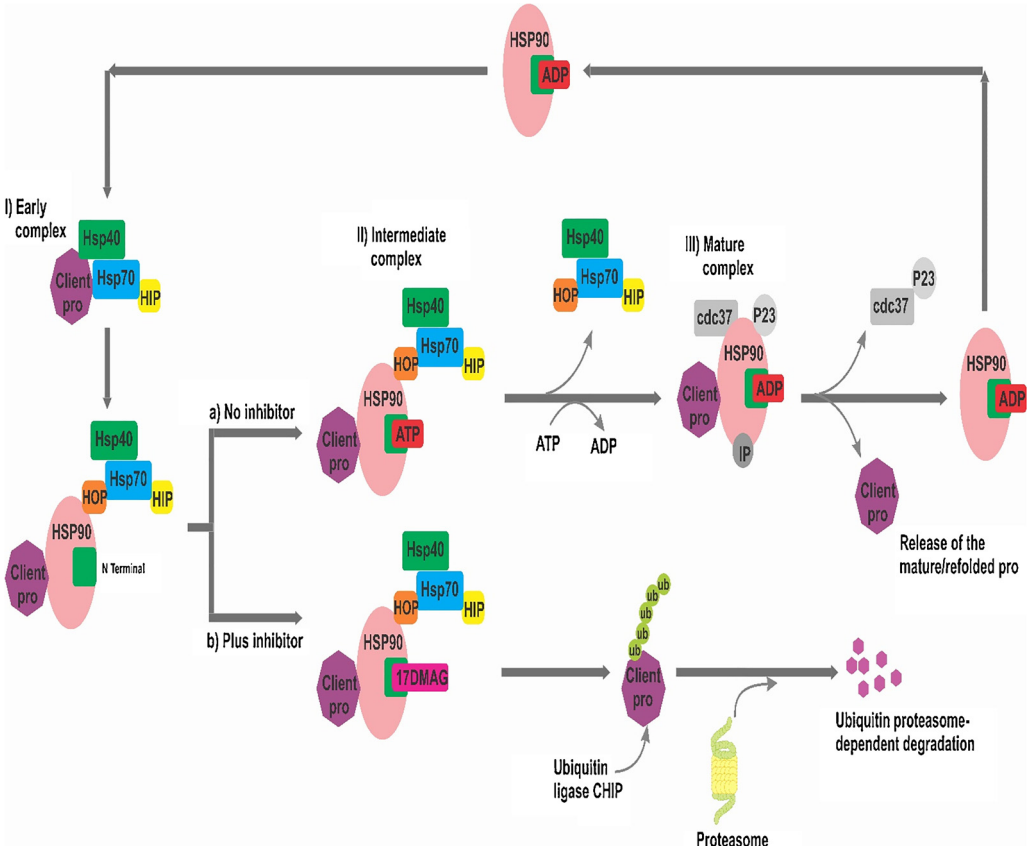

Fig. 2. The Hsp90 chaperoning cycle. Initially, HSP70, HSP40, HIP and a client protein form an early complex that interacts with the Hsp90 homodimer via the adaptor protein HOP which will result into an intermediate complex. The ATP binding at amino-terminal region of Hsp90, and its following hydrolysis detaches the HSP70, HSP40, HIP and HOP from the intermediate complex and Hsp90 forms a mature complex, containing p23, cdc37 and IPs. This prepares the structural maturation of the client protein. Binding of 17-DMAG to the ATP-binding site of Hsp90, blocks formation of mature complex and leads to the ubiquitin proteasome-dependent degradation of client proteins by the CHIP (C-terminus of HSP70-interacting protein) ligase.