Gynecologic Oncology 117 (2010) 177–182

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review

Heat shock proteins, cell survival and drug resistance: The mitochondrial chaperone TRAP1, a potential novel target for ovarian cancer therapy

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ARTICLE INFO

Article history:
Received 30 July 2009
Available online 25 November 2009

Keywords:
Ovarian carcinoma
Heat shock proteins
TRAP1
Drug resistance
Apoptosis

ABSTRACT

Background. Protein homeostasis is a highly complex network of molecular interactions governing the health and life span of the organism. Molecular chaperones, mainly heat shock proteins (HSP) and other stress-inducible proteins abundantly expressed in multiple compartments of the cell, are major modulators of protein homeostasis. TRAP1 is a mitochondrial HSP involved in protection against oxidant-induced DNA damage and apoptosis. It was recently described as a component of a mitochondrial pathway selectively up-regulated in tumor cells which antagonizes the proapoptotic activity of cyclophilin D, a mitochondrial permeability transition pore regulator, and is responsible for the maintenance of mitochondrial integrity, thus favoring cell survival. Interestingly, novel TRAP1 antagonists cause sudden collapse of mitochondrial function and selective tumor cell death, suggesting that this pathway may represent a novel molecular target to improve anticancer therapy. Preliminary data suggest that TRAP1 may be a valuable biomarker in ovarian cancers: in fact, TRAP1 levels are significantly higher in cisplatin-resistant ovarian tumors and ovarian carcinoma cell lines.

Conclusions. While major advances have been made in understanding the genetics and molecular biology of cancer, given the considerable heterogeneity of ovarian cancer, the introduction of novel targeted therapies and the consequent selection of treatments based on the molecular profile of each tumor may have a major impact on the management of this malignancy and might contribute to building a new era of personalized medicine.

Contents

Heat shock proteins in cell survival

A highly conserved and functionally interactive network of intracellular "chaperones" disaggregate, refold and renature mis-folded proteins following different environmental, physical and chemical stress. Heat shock proteins (HSPs), and other HSP-controlled cellular responses limit the damage caused by stress, thus facilitating cellular recovery. The major HSPs interact with components of the apoptotic pathways and promote cell survival by preventing mitochondrial outer membrane permeabilization and subsequent cytochrome *c* release, caspase activation and apoptosome assembly [1]. As a result of protein misfolding, protein aggregation, or disruption of regulatory complexes, inappropriate

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0090-8258/$ – see front matter
doi:10.1016/j.ygyno.2009.10.078

activation of signaling pathways could occur in several pathophysiological conditions, mainly during acute or chronic stress. Consequently, the levels of HSPs are elevated in many cancers, and HSP overexpression results in a poor prognosis in terms of patient survival and response to therapy in specific cancer types [2,3]. Indeed, elevated HSP expression in malignant cells plays a key role in protecting against the spontaneous apoptosis associated with malignancy as well as the apoptosis generated by therapy, mechanisms which may underlie the role of HSPs in tumor progression and resistance to treatment [3,4].

The 90-kDa heat shock proteins (HSP90), which are integrally involved in cell signaling, proliferation, and survival, are ubiquitously expressed in cells. Many proteins in tumor cells are dependent upon the HSP90 protein folding machinery for their stability, refolding, and maturation [5]. Thus, HSP90 has emerged as a promising target for the treatment of cancer [6]. HSP90 exists as a homodimer, containing three domains. Interestingly, while the N-terminal domain contains an ATP-binding site that binds the natural products geldanamycin and radicicol, a second ATP-binding site in the C-terminus of HSP90 has been identified which not only binds ATP, but also cisplatin (CDDP), novobiocin, epilgallocatechin-3-gallate and taxol [7], all well-known HSP90 inhibitors and powerful antitumor agents.

Several lines of evidence suggest a direct correlation between HSP27 overexpression and resistance to chemotherapy in several human malignancies, such as ovarian cancer, head and neck cancer, esophageal squamous-cell carcinoma, and leukemia [3]. Similarly, HSP70 and HSP27 are emerging as predictors of resistance to chemotherapy and shorter disease-free survival in breast cancer [3,8].

The molecular mechanisms involving HSPs in resistance to cancer therapies can be explained in several ways: (i) as molecular chaperones they can confer cytoprotection by more efficiently repairing the damaged proteins resulting from cytotoxic drug administration; (ii) protecting cancer cells against apoptosis [9], (iii) protecting the microvasculature inside tumors, because HSP27 is found in endothelial cells [10], and (iv) enhancing DNA repair [11].

In such a perspective, neutralizing HSPs is therefore an attractive strategy for anticancer therapy. Up to now, the only inhibitors to have been developed are against HSP90 and they are now under clinical evaluation However, an inhibitor of HSP70 or other HSPs would be very useful in cancer therapy alone and in combination with the above-mentioned inhibitors of HSP90. Indeed, several reports suggest that HSP70 or HSP27 antisense constructs have chemosensitizing properties and may even kill cancer cell lines in the absence of additional stimuli [12,13]. Interestingly, the cytotoxic effect of HSP70 down-modulation is particularly strong in transformed cells yet undetectable in normal, non transformed cell lines or primary cells [14]. This body of evidence suggests that targeting HSPs is one of the most promising approaches to anticancer therapy.

TRAP1 as a candidate biomarker in cancer

TRAP1 function

TRAP1 (TNF receptor-associated protein 1) is a mitochondrial heath shock protein 75 with antioxidant and antiapoptotic functions [15,16]. Several lines of evidence suggest that TRAP1 is part of a complex network involved in protecting cells against oxidative stress and apoptosis. Indeed, TRAP1 and HSP90 were recently described as components of a mitochondrial pathway selectively up-regulated in tumor cells which antagonizes the proapoptotic activity of cyclophilin D (CypD), a regulator of the mitochondrial permeability transition

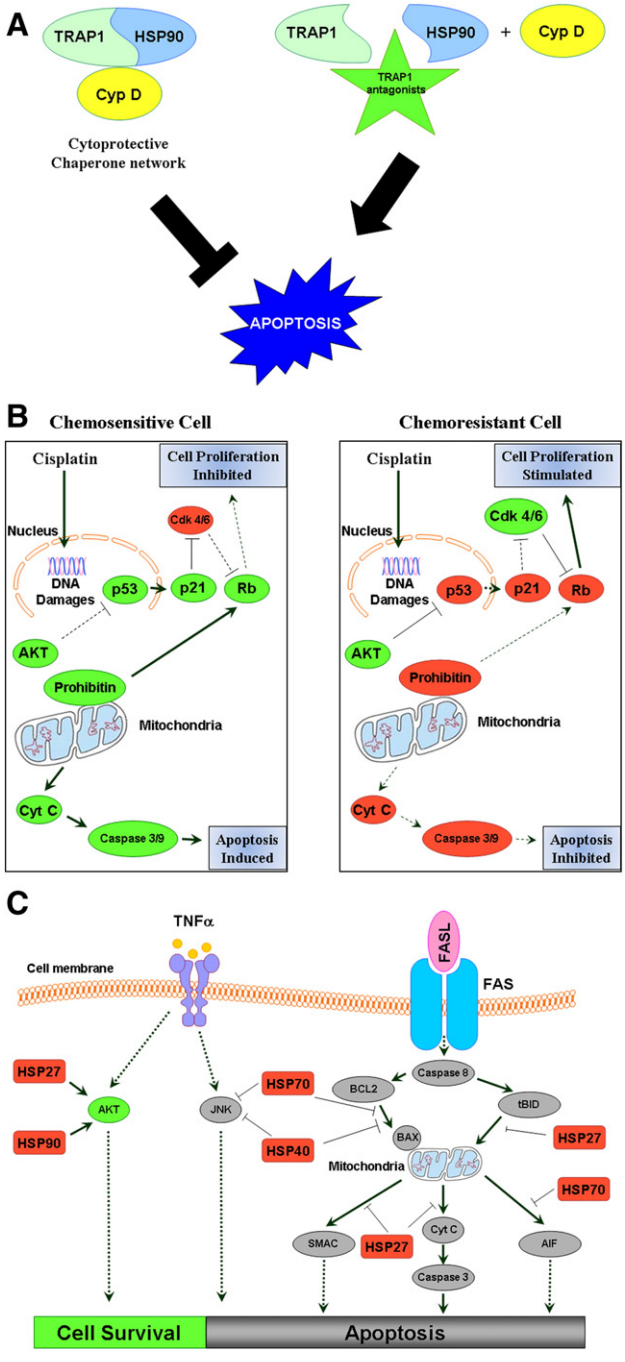

Fig. 1. Examples of signaling pathways and target molecules altered in ovarian cancer. Panel A. Regulation of tumor cell mitochondrial homeostasis by a Hsp90/TRAP1/cyclophilin D network. TRAP1 antagonists include novel agents (known and/or unknown) directed to mitochondria which induce apoptosis by disabling the cytoprotective pathway (for details see the text and Ref. [22]). CypD, cyclophilin D. Panel B. Regulation of cell proliferation and apoptosis in cisplatin chemosensitive/chemoresistant human ovarian cancer cells. Examples of target molecules undergoing quali-quantitative activation (green/grey) or inhibition (red/white). (A) Cisplatin treatment induces cell cycle arrest through a p53-dependent up-regulation of cell cycle-regulatory proteins, such as p21, and of pro-apoptotic proteins (green/grey colors). This activates programmed cell death pathways, (i.e. activation of the caspases). In these cells, cell survival mediators such as Akt, are downregulated or are in their inactive state. Prohibitin may also play a role in inhibiting cell cycle progression through the Rb-E2F pathway by binding to Rb. (B) In the presence of low levels of p53 (upon ubiquitination and/or inactivation) pathways involving Akt and other proteins with pro-survival/cytoprotective roles are in an active state despite the presence of cisplatin. Overall, failure to activate apoptosis in response to chemotherapeutic agents is a major cause of uncontrolled cell proliferation and chemoresistance. Panel C. Key role of heat shock proteins (HSPs) in the regulation of cell survival and apoptotic pathways. Most HSPs function as inhibitors of crucial molecules in the apoptosis pathway such as JNK, Cyt C, caspase-3 and other proteins with cytoprotective roles. Meanwhile, Hsp27 and Hsp90 can also promote the function of AKT in maintaining cell survival.