Critical Reviews in Oncology/Hematology 97 (2016) 152–156

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Review

Jump in the fire — heat shock proteins and their impact on ovarian cancer therapy

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Contents

ARTICLE INFO

Article history:
Received 8 February 2015
Accepted 5 August 2015

Keywords:
Ovarian cancer
Heat shock protein
Diagnosis
Drug target
Chemoresistance

ABSTRACT

Ovarian cancer (OC) is a major problem in gynecological oncology. Options for diagnosis and treatment of advanced stages and thus for patient prognosis have not been improved substantially over the past decades. Heat shock proteins (HSP) are characterized as stress-induced molecular chaperones performing cell survival factor functions. In cancer cells, various crucial and clinically important cell responses are vitally influenced and modulated by HSPs, e.g., cell growth and treatment resistance. Despite the limited knowledge on HSPs in OC progression, their roles as biomarkers, prognostic factors and their drug target properties appears promising for future clinical applications and therapeutic approaches.

1. Introduction

Currently, there are more than 200,000 newly diagnosed cases of ovarian cancer (OC) per year worldwide, thereof around 66,700 European-wide, constituting a major unsolved health problem in women's health care. Unfortunately, the options for diagnosis and treatment of advanced OC and therewith the prognosis of OC patients have not been improved substantially over the past decades (Banerjee and Gore, 2009). In the majority of cases, OC occurs in post-menopausial women. Median age at diagnosis of the patients are 56 years (Mustea et al., 2009) and the vast majority of patients (75–85%) are diagnosed at an advanced disease (FIGO III–IV) (Romero et al., 2012). While early detection of ovary malignant progression enables cure rates of 90%, late stage detection of the highly metastatic disease can be cured in no more than 20% of cases (Bast et al., 2002). Advanced OC standard therapy consists of cytoreductive surgery, followed by combined taxane-platinum chemotherapy (Cannistra et al., 2003). The addition of bevacizumab has recently been shown to improved progression-free survival in women with ovarian cancer (Perren et al., 2011). Despite of high initial response rates to chemotherapy of approximately 80% most women with advanced OC relapse within 2 years after initial drug treatment and ultimately die of the disease. About 25% of patients are diagnosed with relapsed disease after 12 month, 40% after 24 month, and 70% after 36 month (Ozols et al., 2003).

Some of new biologicals such as bevacizumab und pazopanib were tested in maintenance setting in clinical phase II/III trials.

Abbreviations: OC, ovarian cancer; HSP, heat shock proteins; 17-AAG, 17-allylamino-demethoxygeldanamycin.

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http://dx.doi.org/10.1016/j.critrevonc.2015.08.008
1040-8428/

Table 1
Nomenclature of human HSP families according to Kampinga et al. 14]. HSPs were named based on their molecular weight in kDa. Best-characterized isoforms of each family are given in the column common members.

HSP family	Alternative name	No. of members	Common members
HSPA	HSP70	13	HSP70
HSPH	HSP110	4	HSP110
DNAJ	HSP40	50	DNAJB1
HSPB	small HSPs	11	HSP27
HSP90/HSPC		5	HSP90α, HSP90β
Chaperonins		14	HSP10, HSP60

Bevacizumab and pazopanib are inhibitors of angiogenesis primarily targeting appropriate cellular receptors, e. g. receptors of the vascular endothelial growth factor, the platelet-derived growth factor, and the tyrosine kinase receptor c-kit (Cannistra et al., 2007; Raja et al., 2011; Du Bios et al., 2013). Another treatment approach in women with BRCA 1or BRCA 2 mutations is based on suppressing cancer cell DNA repair machinery by olaparib, a compound binding to and subsequently inhibiting the poly-(ADP-ribose) polymerase (Sessa, 2011). Finally, the tetrahydroisoquinoline alkaloid trabectedin affect DNA integrity by direct binding to the chromosomal DNA and followed by promoting nucleic acid restriction and apoptosis initiation (D'Incalci and Galmarini, 2010). These promising biologicals have tolerable adverse effect profile and enlarge the treatment options of OC. However, preliminary data definitely demonstrate that the clinical benefit of these new generation compounds remains temporary and only with respect to progressive free survival and primary as well as secondary treatment resistance frequently arise.

Drug resistance is a major treatment obstacle in OC (Armstrong, 2002). The combination of late-stage diagnosis and moreover the pronounced heterogeity at the cellular and molecular level hinders effective diagnosis and treatment of OC. Thus, there is growing emphasis on the identification of new molecular factors for prognostication and targeted therapy of OC.

The eukaryotic cellular response to environmental and physiological stress involves the up-regulation and the activation of stress-inducible proteins which are primarily members of the heat shock protein (HSP) family. HSPs are stress-inducible factors which are highly conserved among widely divergent organisms ranging from bacteria to human beings. Initially identified as heat shock-induced factors, HSPs were characterized as molecular chaperones and classified into 6 families based on their molecular weight (Kampinga et al., 2009) (Table 1). Basically, HSPs perform comparable molecular functions of typical cell survival factors; numerous studies have demonstrated that HSPs are frequently up-regulated in malignant cells and play an important role in tumor progression. With regard on molecular activities, HSP family members govern folding/unfolding, turn-over, and transport of client proteins as well as assembly of multiprotein complexes. As a result, various crucial and clinically important cell responses are vitally influenced and modulated by HSPs, e. g. cell growth, apoptosis, metastasis, and treatment resistance (Stope et al., 2012a, 2014; Di et al., 2007; Rocchi et al., 2004). In accordance, recently in vitro and in vivo experiments using inhibitors targeting HSP27 (Song et al., 2009) and HSP90 (Banerji et al., 2008) demonstrated evidence for the efficacy of HSP inhibition in human OC models. Despite growing knowledge on the pivotal HSP properties in cancer cells, only little data are available on HSP functionality in OC progression.

2. Heat shock protein functionality in physiological ovary cells

In animal models and in tissue analysis of human ovaries, HSP27, HSP70, and HSP90 were found to control ovarian functions namely the regulation of folliculogenesis and hormone homeostasis (Sirotkin and Bauer, 2011; Juliani et al., 2008; Velazquez et al., 2010, 2011). Hormonal stimulation of ovary cells leads to an induction of HSP27 and HSP90 expression with both factors being involved in ovarian follicle development (Park et al., 2012; Maizels et al., 1998). Besides, HSP70 was demonstrated acting as an inhibitor of steroidal effects. High levels of HSP70 were correlated with the down-regulation of estrogen receptor and progesterone receptor expression (Salvetti et al., 2009). Furthermore, high concentrations of HSP70 protein were shown to directly or indirectly provoke an inhibition of the steroid biosynthesis (Khanna et al., 1994, 1995). It has been demonstrated in various tissues that HSPs, particularly HSP70 and HSP90, control nuclear steroid receptor functionality, e.g., ER, PR, and the androgen receptor (Salvetti et al., 2007; D'Haeseleer et al., 2005; Stope et al., 2012b). Therefore it is most likely, that the HSP-dependent modulation of healthy ovary physiology is mainly driven by sex steroid receptor control. Besides the hormone response system, HSPs have been shown being involved in the regulation of apoptotic mechanisms (Isobe and Yoshimura, 2007; Koshiyama et al., 1995).

3. Heat shock proteins' putative role as biomarker in ovarian cancer

During the last 20 years crucial role of HSPs in malignant processes has been described. These findings entailed the idea that HSPs could possibly be established as biomarkers for OC diagnosis and therapy responsiveness. In 1993, Kimura et al. examined mRNA levels of HSP60 (Kimura et al., 1993), which is known to control mitochondria functions and intrinsic apoptosis pathways. HSP60 was found being up-regulated in OC samples, however, HSP60 transcript occurrence appeared highly variable between individual patients. Nevertheless, Kaplan–Meier plots clearly demonstrated survival advantages for the HSP60 low level group of patients. A recent study by Hjerpe et al. confirmed these data (Hjerpe et al., 2013).

Some data are availabla on the impact of the large HSP family members HSP70 and HSP90 with respect to OC progression. The intracellular concentration of HSP70 (Koshiyama et al., 1995; Mileo et al., 1990; Athanassiadou et al., 1998; Elstrand et al., 2009; Kang et al., 2014) as well as HSP90 (Mileo et al., 1990) were found to be increased in OC compared to physiological protein amounts in normal and benign ovary tissue. Despite this general finding, HSP70 was predominantely associated with papillary serous and poorly differentiated OC subtypes (Athanassiadou et al., 1998; Kang et al., 2014). Notwithstanding, a differentiation into OC subtypes cannot be accomplished by HSP70/HSP90 analysis. Remarkably, Koshima et al. demonstrated an elevated co-expression of HSP70 and p53, suggesting HSP70 activity may be involved in processes of cell cycle regulation and apoptosis (Koshiyama et al., 1995). Accompanying the expression of HSP70 and HSP90, heat shock factor 1 levels were found to be substantially increased in OC cells (Chen et al., 2013). The activity of the transcription factor HSF1 is part of the cellular ability to respond to stress, and therefore, its presence essentially triggers HSP expression, particularly of the primary factors HSP70, HSP90, and also of the small HSP subfamily member HSP27 (Ciocca et al., 2013).

HSP27 activity is associated with various cellular pathways including proliferation, cell cycle control, apoptosis, redox homeostasis, and cell motility. Consequently, HSP27's putative predictive capability has been tested in several studies, however, evaluation of recent literature revealed conflicting data regarding the mutational expression of HSP27 and OC pathogenesis: whereas some studies demonstrated decreased HSP27 expression levels to be correlated with more advanced OC stages (Geisler et al., 1998, 2004), other studies linked an HSP27 increase with OC's progression and