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RESEARCH ARTICLE

Heat shock proteins in prostate cancer: from tumorigenesis to the clinic

DANIEL R. CIOCCA, MARIEL A. FANELLI, FERNANDO D. CUELLO-CARRION, & GISELA N. CASTRO

Laboratory of Oncology, Institute of Experimental Medicine and Biology of Cuyo, Scientific and Technological Centre of Mendoza, National Research Council (CONICET) and Argentina Foundation for Cancer Research, Mendoza, Argentina

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Abstract

The heat shock proteins (HSP) constitute a superfamily of chaperone proteins present in all cells and in all cell compartments, operating in a complex interplay with synergistic/overlapping multiplicity of functions, even though the common effect is cell protection. Several reasons explain the need for investigating HSP in prostate cancer: (1) these molecules function as chaperones of tumorigenesis accompanying the emergence of prostate cancer cells, (2) they appear as useful molecular markers associated with disease aggressiveness and with resistance to anticancer therapies including hormone therapy, radiotherapy, chemotherapy and hyperthermia, and (3) they can be used as targets for therapies. The latter can be accomplished by: (i) interrupting the interaction of HSP (mainly HSPC1) with various client proteins that are protected from degradation when chaperoned by the HSP; (ii) using the chaperone and adjuvant capabilities of certain HSP to present antigenic peptides to the immune system, so this system can recognise the prostate tumour cells as foreign to mount an effective antitumoral response; and (iii) using treatment planning models taking into account the HSP expression levels to obtain more effective therapies. In summary, the study of the HSP during tumorigenesis as well as during cancer progression, and the inclusion of treatment designs targeting HSP combined with other treatment modalities, should improve prostate cancer survival in the near future.

Keywords: *heat shock proteins, prostate cancer, predictive factors, prognostic factors*

Introduction

Needles to say, the diagnosis of prostate cancer is very frequent in elderly men, in fact, based on pathological studies of 'normal' prostate glands at autopsy, almost 70% of men have prostate cancer when they reach 70 years-old [1]. The difficulty is that many of these tumours are relatively indolent; they are occult causing no problems to the host, while others will grow to produce the typical aggressive cancer disease. This divergent clinical behaviour is attributed to dissimilar and largely unknown genetic and epigenetic mechanisms. Therefore, one of the main problems to be resolved is not only the early detection of the disease but also to detect those tumours with an aggressive behaviour [2]. For practical purposes this is of very high importance since the local treatments (surgery and radiotherapy) are costly and can cause urinary incontinence, sexual dysfunction and others, while on the other hand, the metastatic disease can be controlled by blocking hormone levels until the disease becomes resistant and practically incurable [3]. Nowadays, therefore, the area of early cancer detection using biomarkers, as well as their significance as prognostic and predictive factors, is under intensive re-evaluation and study (see an excellent review by Brawley et al. [4]). Researchers are concerned about utility of 'classic' screening methods such as the prostate specific antigen (PSA) and about the ways to improve the identification of

Correspondence: Daniel R. Ciocca, Laboratory of Oncology, Institute of Experimental Medicine and Biology of Cuyo, Scientific and Technological Centre of Mendoza, National Research Council (CONICET) and Argentina Foundation for Cancer Research, Casilla de Correo 855, 5500 Mendoza, Argentina. Tel: +54 261 5244153. Fax: +54 261 5244001. E-mail: dciocca@lab.cricyt.edu.ar

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aggressive tumours that will progress if left untreated. For example, the Gleason score is very useful but is not perfect. Hence, several biomarkers are being evaluated and among them are the HSP (see prognosis below).

Another reason for investigating the HSP in prostate cancer is because hyperthermia is being used in some countries (e.g. Germany, Italy, Japan) alone, or more commonly in combination with other therapies to treat patients with various types of cancer, and prostate cancer is one of the main targets for this kind of therapy [5–8]. Although we do not have yet a complete understanding of the molecular mechanisms by which hyperthermia facilitates the killing of cancer cells (we will see later that protein aggregation is of paramount importance), it is clear that when the temperature rises without cell killing there is induction of HSP. And the HSP have been implicated among others in the development of thermotolerance [9, 10]. Moreover, cancer cells need HSP to accompany many molecular events during carcinogenesis and cancer progression [11, 12] and for this reason several HSP are already over expressed in prostate cancer (as well as in many other cancer types) at the time of diagnosis and treatment.

The heat shock proteins

Briefly, the HSP constitute a superfamily of proteins characterised by their different molecular weight. In a recent publication the nomenclature of these proteins has been unified [13] and we will use this to refer to the different HSP. Table I summarises the new nomenclature to help reading. The HSP response is elicited by heat shock (this was historically the first stimulus found to induce the HSP synthesis giving rise to their name), but later it was found that several physiological and pathological conditions induce synthesis of the HSP; due to this the HSP are also known as stress responsive proteins [14–16]. In the cells there are basal constitutive levels of HSP known as constitutive or cognate HSP, for example HSPB1 is under oestrogen regulation, and at these basal levels the HSP perform 'housekeeping' functions. In contrast, when the HSP are induced by stressful situations they are known as inducible HSP. The same HSP can have both roles (e.g. there are constitutive levels of HSPB1 and when a stress occurs, the same HSP is increased), while at other times the stress can induce different but closely related HSP. For example HSPA8 is the cognate/constitutive HSPA and this was previously known as HSC70 or HSP73, while HSPA1A and HSPA1B are the inducible forms and were previously known as HSP70-1 and HSP70-2 (which differ by only two amino acids)[13]. In vertebrates the synthesis of these proteins is under control of at least four different heat shock factors (HSF1-4, with HSF1 as the main HSF activated by stress). Upon physiological or pathological stressors the inactive HSF1 (monomer) is quickly activated, the trimeric form undergoes various post-translational modifications (phosphorylation, acetylation and sumoylation) that regulate its interaction with heat shock responsive elements on the heat shock genes[17, 18]. Moreover, HSF1 is implicated in the regulation of other genes (e.g. participating in the repression of oestrogen-dependent transcription acting in combination with other molecules)[19].

Table I. New nomenclature of the main HSP (complete list in Kampinga et al. [13]).

Examples of old names	New name
Small heat shock proteins ⇒	HSPB
HSP27; HSP25; CMT2F ⇒	HSPB1
Crystalline alpha A; CRYAA ⇒	HSPB4
Crystalline alpha B; CRYAB ⇒	HSPB5
HSP20; FLJ32389 ⇒	HSPB6
HSP22; H11; HMN2 ⇒	HSPB8
HSP40 ⇒	DNAJ
DJ-2; DjA1; HSDJ ⇒	DNAJA1
HSP40; HSPF1 ⇒	DNAJB1
Hsc40 ⇒	DNAJB4
HSP70 ⇒	HSPA
HSP70-1; HSP72; HSPA1 ⇒	HSPA1A
BIP;GRP78; MIF2 ⇒	HSPA5
HSC70; HSC71; HSP71; HSP73 ⇒	HSPA8
HSP90 ⇒	HSPC
HSP90; HSP89; HSP90AA1 ⇒	HSPC1
HSP90-ALPHA; HSP90AA2 ⇒	HSPC2
HSP90-BETA; HSP90B ⇒	HSPC3
GRP94; GP96; TRA1 ⇒	HSPC4
HSP75; HSP90L; TRAP1 ⇒	HSPC5
HSP110 ⇒	HSP H
HSP105 ⇒	HSPH1
HSP110; HSPA4; APG-2 ⇒	HSPH2
HYOU1/Grp170; ORP150 ⇒	HSPH4
Chaperonins and related ⇒	HSPD and others
HSP60; GroEL ⇒	HSPD1
HSP10; chaperonin 10; GroES ⇒	HSPE1
TCP1; CCTA; CCT-alpha ⇒	CCT1
McKusick-Kaufman syndrome ⇒	MKKS
Bardet-Biedl syndrome 10 ⇒	BBS10

The HSP work as a team having overlapping functions, they are present in all cells, and in all cell compartments. Figure 1 gives an overview of the complex functions of the HSP even though the common effect is cell protection.

During carcinogenesis there are several situations that alter the cellular protein homeostasis that explain the de-repression of HSP genes: infection by oncogenic viruses (HPV, adenovirus, HCV), exposure to carcinogenic compounds, expression of mutated oncogenic or anti-oncogenic proteins, changes in the immune and endocrine systems, and the cell exposure to hypoxia, starvation and to

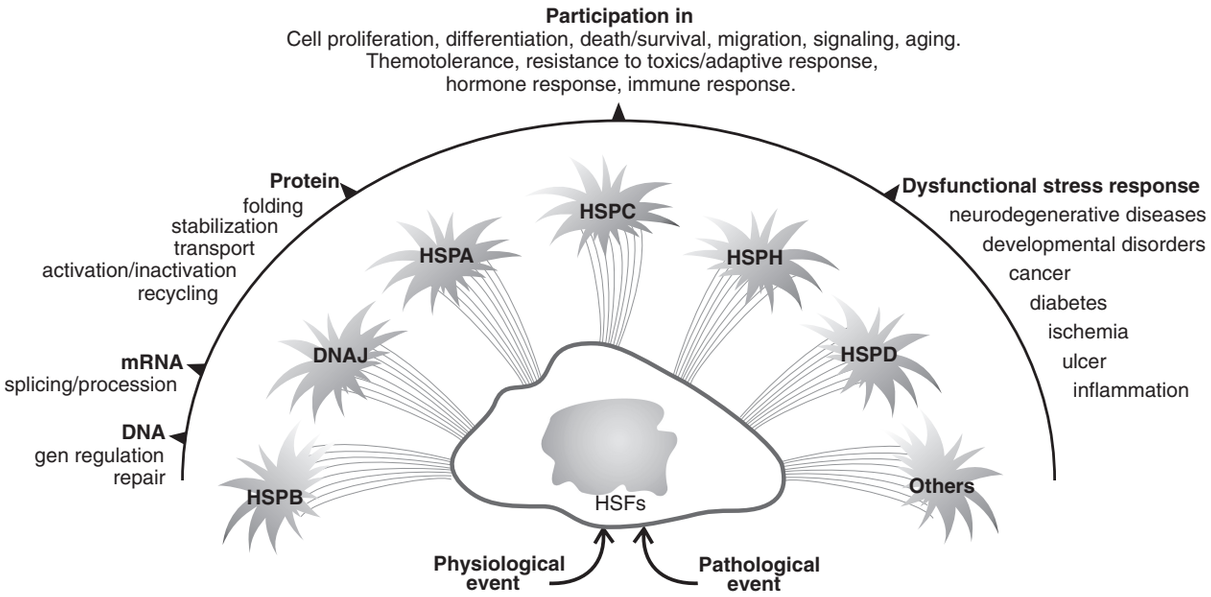

Figure 1. Schematic representation of the HSP response and the implications of these proteins in cell functions. The numerous roles of this superfamily of proteins may explain that, during evolution, gene duplication appeared as a mode of adaptation providing the cells with the functionality of the HSP. HSFs: Heat Shock Factors.

endogenous and exogenous protein-damaging stresses associated with misfolded proteins. HSP are required to maintain in a stable and active conformation important signalling proteins triggered by growth signals, and they participate in inhibitory pathways of senescence and death [11, 12]. Moreover, anticancer treatments such as cytotoxic drugs and radiotherapy can affect HSP expression levels with important clinical consequences on cell growth and survival. All of these give rise to the development of new anticancer strategies based on HSP, and to the exploration of the utility of HSP as cancer biomarkers [20, 21].

Since the synthesis of HSP is triggered by heat shock it is not surprising to find that they are implicated in thermo resistance. For example, HSPA1A is one of the important HSP implicated in thermo tolerance. It has been shown in a cultured prostate cancer cell line that higher levels of HSPA1A were associated with heat resistance [10]. On the other hand, very intense heat such as that applied to kill metastatic cancer foci in the liver produces necrosis; however, a mild or moderate heat (42°–45°C) produces breakage of bonds at protein level inducing protein instability, denaturation and finally collapse of protein structure, resulting in protein aggregation. This is a signal for a HSP response, they are in charge of further protein denaturation and they are in charge to restore protein conformation. If the proteins cannot be restored they are cleaved (ubiquitination) and recycled. Heat also produces double-strand break (DSB) formation via protein denaturation, and in addition, there is production of free radicals which can also induce DSBs in the DNA [22]. If the cell is able to mount a competent HSP response, the HSP (HSPB1 and HSPA1A) can accumulate in the nucleus contributing to DNA polymerase-beta reactivation and stimulation, which results in thermotolerance. Takahashi et al. [22] showed that thermotolerance is partially suppressed in DNA polymerase-beta (-/-) mouse fibroblasts (when compared with the wild-type cells) and also in the presence of a HSP inhibitor.

Cultured cells and animal models

Antisense design

HSPB1 is emerging as an important therapeutic target to improve the response of prostate cancer cells to different treatments, for example DU145 cells transfected with full length HSPB1 antisense cDNA showed significantly increased sensitivity to gamma radiation [23]. On the other hand, the HSPB1 siRNA developed by Rocchi et al. [24] inhibited HSPB1 expression and significantly reduced the in vitro growth of both the androgen independent (AI) PC-3 cells and the androgen dependent (AD) LNCaP cells. However, the HSPB1 knockdown inhibited more significantly the growth of the AI PC-3 cells than the androgen dependent LNCa-P cells, which may reflect a greater dependence on HSPB1 for the androgen

independent prostate cancer cell growth. Also, an increase of caspase-3 cleavage and apoptosis was observed in both cell lines by diminishing HSPB1 levels [24]. In a recent study by Andrieu et al. [25] it has been found that HSPB1 confers resistance to androgen ablation and chemotherapy through eIF4E protein (eukaryotic translation initiation factor 4E). HSPB1 down-regulation decreased eIF4E protein expression in prostate cancer cells; HSPB1 co-localized and interacted with this protein decreasing eIF4E ubiquitination and proteasomal degradation. These findings illustrate the utility of silencing the anti-apoptotic HSPB1 molecule as a form of therapy in prostate cancer cells. However, the application of RNAi depends on the efficient intracellular delivery of siRNAs [26]. Polyamidoamine (PAMAM) dendrimers are effective vectors for siRNA delivery to target HSPB1 and serve to protect the RNA molecules from enzymatic degradation, allowing effective siRNA delivery [27]. Recently it has been documented that silencing of the HSPB1 gene through PAMAM dendrimers and siRNA delivery led to induction of caspase 3/7 dependent apoptosis and inhibition of PC-3 cell growth in vitro [28]. In this manner, the siRNA delivery ensured by the dendrimers represents a great promise to further in vivo therapeutic application in cancer.

There is evidence that androgen receptor (AR) regulates HSPA1A expression in human prostatic cells. Dihydrotestosterone enhanced HSPA1A expression in AD-LNCaP cells, while this HSP was down-regulated by anti-androgens and knocking down AR [29]. The apoptosis of prostate cancer cells induced by androgen ablation could be due to, at least in part, the decrease of the anti-apoptotic HSPA1 protein. The resistance to hormone therapy could be due to the re-establishment of HSPA1A levels when this protein becomes independent of AR. Therefore, the interference of HSPA1A could also be of therapeutic interest in prostate cancer.

HSPC inhibitors

Agents that target AR expression represent an attractive treatment option for prostate cancer patients with disease progression following castration (a common element of the resistance mechanism is restoration/maintenance of AR signalling). Prior to ligand binding, AR exists in a complex with HSPC proteins and with other co-chaperones. The AR-HSPC interaction maintains AR in a high-affinity ligand-binding conformation, which is necessary for efficient hormone response. Then, HSPC 'clients' include wild-type and mutated AR and several proteins of potential importance in mediating the progression of prostate and other cancers like HER2 and Akt [30]. These data suggest that HSPC inhibitors may represent a novel strategy for the treatment of patients with prostate cancer, and clinical trials testing this hypothesis are currently ongoing (see treatment chapter below). 17-Allyamino-17-demethoxygeldanamycin (17-AAG) is an N-terminal inhibitor of the HSPC chaperone protein. Inhibition of HSPC function causes the proteasomal degradation of proteins that require this chaperone for maturation or stability. In murine models of prostate cancer, 17-AAG caused the degradation of these client proteins, at non-toxic doses, and inhibited the growth of hormone-naïve and castration-resistant tumours. Recently it has been reported a new novobiocin analogue designed to inhibit the C-terminal portion of HSPC1 (F-4) [31]. This new inhibitor demonstrated improved potency and efficacy and decreased expression of client proteins in LNCaP and PC-3 cells; PSA secretion was inhibited in a dose-dependent manner that matched with the decrease of AR expression. The dietary bioflavonoid quercetin has been involved in preventing oncogenesis, specifically in prostate cancer. Quercetin treatment of prostate cancer cell lines resulted in inhibition of HSPC, decreased cell proliferation and viability, and increased apoptosis, while exerting no quantifiable effect on normal prostate epithelia cells [32].

Other targets

On the other hand, a promising new strategy for prevention and/or treatment of castration-resistant prostate cancer is represented by Histone deacetylase 6 (HDAC6). Recent studies on C4-2 cells, and C4-2 xenograft tumour established in castrated but not in testes-intact nude mice, suggested that HDAC6 regulates AR hypersensitivity and nuclear localization, mainly via modulating HSPC1 acetylation [33]. The knockdown of HDAC6 in C4-2 cells using short hairpin RNA resulted in ligand-independent nuclear localisation of endogenous AR and inhibited PSA expression and cell growth in the absence or presence of dihydrotestosterone. Targeting HDAC6 alone, or in combination with other therapeutic approaches, represents a promising new strategy for prevention and/or treatment of castration-resistant prostate cancer.

A mitochondria-localised HSPC chaperone, tumour necrosis factor receptor-associated protein-1 (TRAP1/HSPC5), is abundantly and ubiquitously expressed in human high-grade prostatic intraepithelial neoplasia, Gleason grades 3–5 prostatic adenocarcinomas, and metastatic prostate cancer, but largely undetectable in normal prostate or benign prostatic hyperplasia in vivo [34]. Expression of HSPC5 in no transformed prostatic epithelial BPH-1 cells inhibited cell death, whereas silencing of

HSPC5 in androgen-independent PC-3 or DU145 prostate cancer cells by siRNA, enhanced apoptosis. Targeting HSPC5 with a novel class of mitochondria-directed HSPC inhibitors (e.g. Gamitrinib) caused rapid and complete killing of androgen-dependent and -independent prostate cancer, but not BPH-1 cells, whereas reintroduction of HSPC5 in BPH-1 cells conferred sensitivity to Gamitrinib-induced cell death [34].

The secreted mammalian chaperone clusterin (sCLU) can interact with and inhibit activated Bax, inhibiting cytochrome C release and caspase activation [35]. In prostate cancer, sCLU levels have previously been correlated with Gleason grade [36] and although sCLU expression is low or absent in most untreated hormone-naïve tissues, the levels increased significantly within weeks after neoadjuvant hormone therapy [37]. In this study, the authors identified sCLU as over-expressed in a docetaxel-resistant PC-3 subline (PC-3dR) and reported for the first time that sCLU knockdown using sequence-specific ASO or siRNA chemo sensitised this cell line to taxane and mitoxantrone-based chemotherapy, both in vitro and in vivo [38].

Immune-related HSP

Proteins identified by proteomic approaches have previously been associated with prostate cancer progression such as HSPA5, and HSPC4, among others [39]. Amongst the up-regulated proteins, increased HSPA5 expression has been reported in metastatic prostate cancer in the bone [40], and increased expression has been shown in metastatic LNCaP-LN3 cells compared with poorly metastatic LNCaP cells [41]. Furthermore, increased HSPA5 expression has been associated with the development of androgen-independent prostate cancer [42]. A possible mechanism for this may involve inhibition of apoptosis due to the ability of HSPA5 to interact with intermediate molecules of the apoptotic pathway [43]. Thus, the anti-apoptotic role of HSPA5 could facilitate prostate cancer progression.

Another up-regulated HSP, HSPC4, is a glycoprotein belonging to the HSP family which has a role in protein homeostasis, cell differentiation, development, and has also been shown to play a role in eliciting antitumour immunity [44, 45]. In these studies HSPC4 expression has been associated with prostate cancer progression using patient's material; additionally a previous study [41] has shown increased expression levels in LNCaP-LN3 cells compared with LNCaP cells. Furthermore, HSPC4 has been shown to undergo alterations in glycosylation associated with increased malignant behaviour [46]. Thus, their finding of significantly increased HSPC4 immunoexpression in prostate cancer and precursor lesions suggests that, in addition to altered glycosylation, up-regulation of HSPC4 may also be involved in cancer progression, and is likely to be involved at an early stage [39].

Secretion of stress protein HSPH4 promotes immune-mediated inhibition of murine prostate tumour. In a recent study it has been demonstrated that genetic modification of weakly immunogenic murine prostate tumour cells (TRAMP-C) by stable transfection with a secreteable form of endoplasmic reticulum resident chaperone HSPH4, significantly enhanced its immunogenicity *in vivo,* through the generation of tumour specific T-cell responses ($CD8^+$). Furthermore, generation of systemic anti-tumour immunity is indicated by the growth suppression of distant parental tumours, which is associated with increased tumour infiltration [47]. The systemic tumour immunity may be used to improve treatment outcomes for prostate cancer when combined with other treatment modalities. For example, adenovirally delivered nitroreductase with a prodrug that can be transformed into a cytotoxic DNA-cross-linking derivative at tumour site, induces tumour cell killing. This effect was enhanced by raising HSPA1A which caused immune stimulation [48]. The use of such cytotoxic and immunomodulatory gene combinations, possibly in conjunction with other treatments such as radiotherapy and chemotherapy, warrants optimistic results.

Finally, circulating auto antibodies against HSPA5 are present at high levels in prostate cancer patients and are potential biomarkers of aggressive tumour behaviour [40]. Thus, the epitope specificity and function of anti- HSPA5 antibodies produced by prostate cancer patients have been investigated in 1-LN, PC-3, DU145, and LNCaP prostate cancer cells. The results of this study showed that the anti- HSPA5 antibodies from prostate cancer patients bind to, and stimulate, proliferation of tumour cells expressing HSPA5 on their surface, and protected them from apoptosis induced by tumour necrosis factor α in a dose-dependent manner [49].

Implications of HSP during prostate carcinogenesis

Carcinogenesis involves a cascade of molecular events that mediate the transformation of normal cells into cancer cells. Although prostate cancer is a malignancy with a high incidence, the events associated with its initiation remain poorly understood and there are still many enigmas about the pathophysiology of prostate cancer.

Early prostate tumorigenesis appears to be associated with a dysplasia that initiates with proliferative

inflammatory atrophy (PIA), and progresses to prostatic intraepithelial neoplasia (PIN), which in some cases leads to carcinoma. Existing evidence suggests that these early lesions may be initiated by inflammation that occurs with exposure to different infectious agents and/or ingestion of carcinogens. When a premalignant lesion progresses to primary cancer, to metastatic cancer, and to androgen-independent cancer, genetic alterations continue to accumulate within the tumour cells. Moreover, normal prostate and early-stage prostate cancers cells depend on androgens for growth and survival. As the cancer advances and metastasizes, it becomes dominated by cells that proliferate and survive independently of androgens. With a practical/didactic purpose we can identify the following entities during prostate cancer progression: (1) normal prostate epithelium, (2) PIA, (3) PIN, (4) localised prostate cancer, (5) metastatic prostate cancer (all of them androgen-dependent), and (6) androgen-independent prostate cancer.

Owing to their role as molecular chaperones, HSP participate in many events related to cancer, starting from the beginning of carcinogenesis [12]. During this process, the transformed cells begin to express abnormal/elevated levels of HSP, and in some cases this induction continues during tumour progression. At present there exists an important body of evidence to support the participation of this family of proteins in the initiation and progression of prostate carcinogenesis. In accordance with the above, an interesting paper of Byun et al. [50] has demonstrated that during prostate tumorigenesis the expression of several sets of housekeeping genes (including HSP) are differentially expressed, suggesting that the process is driven by modulation of the expression of these genes. The expression of HSP was up-regulated during the transition of localised prostate cancer to metastatic prostate cancer, indicating that in advanced stages prostate tumour cells could be under cellular stress. Therefore, the authors suggest that during this period of cellular stress the prostate tumour may be more vulnerable and responsive to treatment. Table II summarises the studies about the HSP expression during the different phases of prostate cancer progression. The identification and assessment of level of these genes/proteins in the prostate tumour progression will allow the best management of prostate cancer patients and to improve the treatments that have HSP as potential targets for the therapy.

Table II. Studies evaluating HSP during the tumorigenesis of prostate cancer.

Molecule	Status/level of gene/protein expression	Authors
HSP (S)	In NP-LPC transition, 16 hsp genes were differentially expressed: 9 (56%) were up-regulated and 7 (44%) were down-regulated.	Byun et al. [50]
	In the LPC-MPC transition, 14 genes were differentially expressed; 10 of them (71%) were up-regulated	
	Differential expression in PC compared to BPH	Ummanni et al. [51]
	Different post-translationally modified isoforms of HSPB1 and HSPA1A in PNB specimens from patients with PC or BPH	Lin et al. [52]
HSPC4	Reduced expression in PC compared with benign prostate tissue (BPH). A trend for correlation between low HSPC4 and high Gleason score, supported the hypothesis that HSPC4 suppression correlates with CTC formation and metastasis.	Howard et al. [53]
HSPC	Strong expression in 95% of PIN and carcinomas without relationship with Gleason score.	Elmore et al. [54]
	Higher immunoreactivity in PC and PIN than in NPA	Cardillo et al. [55]
	In the epithelium and stroma increased expression from NAP to PIN to PC.	
HSPA	Higher expression in cancer tissue than in normal tissue	Mori et al. [56]
	HSPA1L polymorphism may be associated with a protection against PC development.	Sfar et al. [57]
	Over-expressed in PC compared with benign prostate samples.	Lexander et al. [58]
HSPD1/E1 Complex	High cytoplasmic positivity for both of these markers was present in PIN lesions as well as in carcinomas.	Capello et al. [59]
	Over-expressed in PC compared with benign prostate samples.	Lexander et al. [58]
HSPB1	The expression level highly correlated with the progression from BPH to PC, with tumour grade and stages.	Zhen et al. [60]
HSPA/HSPC Cochaperone alphaSGT	Higher AR/alphaSGT ratio en MPC samples.	Buchanan et al. [61]

(S), several; NP, normal prostate; LPC, localised prostate cancer; MPC, metastatic prostate cancer; PIN, prostatic intraepithelial neoplasia; PC, prostate cancer; BPH, benign prostate hyperplasia; PNB, prostate needle biopsy; CTC, circulating tumour cells; NPA, normal prostatic tissue adjacent to neoplasia; AR, androgen receptor; alphaSGT, small glutamine-rich tetratricopeptide repeat containing protein alpha.

Heat shock proteins in the prognosis of the disease

In a previous article our laboratory has reviewed the implications of HSP in the prognosis of cancer patients including those with prostate cancer [62]. The main conclusion was that HSPB1 expression was seen in a high percentage of hormone-refractory patients and correlated with poor clinical outcome and shorter survival. The new data confirm these observations (Table III). For example, Glaessgen et al. [65] found that, although HSPB1 did not appear as an independent predictor of disease outcome, HSPB1 immunoreactivity correlated with Gleason score and predicted biochemical disease recurrence. Due to space limitations we cannot analyse each article in depth.

Another molecule of interest is HSPD1, which appeared as an independent predictor of disease outcome. In the list of relevant HSP molecules to be evaluated in prostate cancer patients we can add HSPA5 as well as clusterin (a cytoprotective anti-apoptotic chaperone that has been reviewed by So et al. [69]) (Table III).

Figure 2 shows examples of HSP expression levels in an early cancer stage and in an advanced cancer stage. It is evident that several HSP are co-expressed in advanced disease resistant to conventional treatment. A similar situation has been reported in breast cancer patients where both HSPB1 and HSPA1A have been found highly expressed in patients with locally advanced disease displaying resistance to neoadjuvant chemotherapy [70]. In another article one of us (DRC) is reviewing the implications of the HSP in DNA repair mechanisms which has important implications in cancer cell survival both to endogenous and exogenous (i.e., chemotherapy) genotoxic stimuli [71]. The high HSP expression levels in prostate with aggressive and therapy resistant cancer cells could be exploited to detect the problematic tumours by measuring the HSP levels in urine samples after prostate massage. The newer molecular analysis should incorporate some of the HSP (i.e., HSPB1, HSPD1, HSPA5, clusterin) to improve the diagnosis and prognosis of the disease and also to guide the antitumoural designs targeting HSP in combination to conventional treatments.

Treatment designs targeting HSP

The pre-clinical and clinical therapeutic implications of HSP in cancer have been reviewed elsewhere [62]. These novel approaches still consider the HSP as key

Table III. Studies evaluating HSP in the prognosis of prostate cancer patients.

HSP	Patients	Significance	Authors
HSPB1	97 (NHT*)	>HSPB1 after NHT Associated with Gleason score >HSPB1 < biochemical RFS but not an independent predictor	Miyake et al. [63]
	172	Associated with Gleason score, with lymph node metastasis and others >HSPB1 < biochemical RFS but not an independent predictor	Kurahashi et al. [64]
	289	Associated with Gleason score >HSPB1 < biochemical RFS but not an independent predictor	Glaessgen et al. [65]
	193	>HSPB1 < biochemical RFS but not an independent predictor	Miyake et al. [63]
HSPA5	219(T3N oM0)	Associated with castration resistance >HSPA5 > recurrence, < OS	Pootrakul et al. [66]
	153 (LN+)	>HSPA5 > recurrence, < OS	Daneshmand et al. [67]
HSPD1	289	Associated with Gleason score >HSPD1 > biochemical recurrence independent predictor	Glaessgen et al. [65]
HSPA1A	172	Not associated with CP factors	Kurahashi et al. [64]
HSPC1		Lack of prognostic significance	
	193	Not prognostic significance	Miyake et al. [68]
HSPA1A	289	Not associated with Gleason score Lack of prognostic significance	Glaessgen et al. [65]
Clusterin	See review	Associated with pathological grade and biochemical recurrence	So et al. [69]

NHT, neoadjuvant hormonal therapy (HSPB1 was studied comparing pre- and post-NHT); RFS, relapse-free survival; OS, overall survival; LN+, lymph node-positive (D1 disease stage); CP, clinicopathological factors.
Biochemical recurrence evaluated by serum levels of PSA.

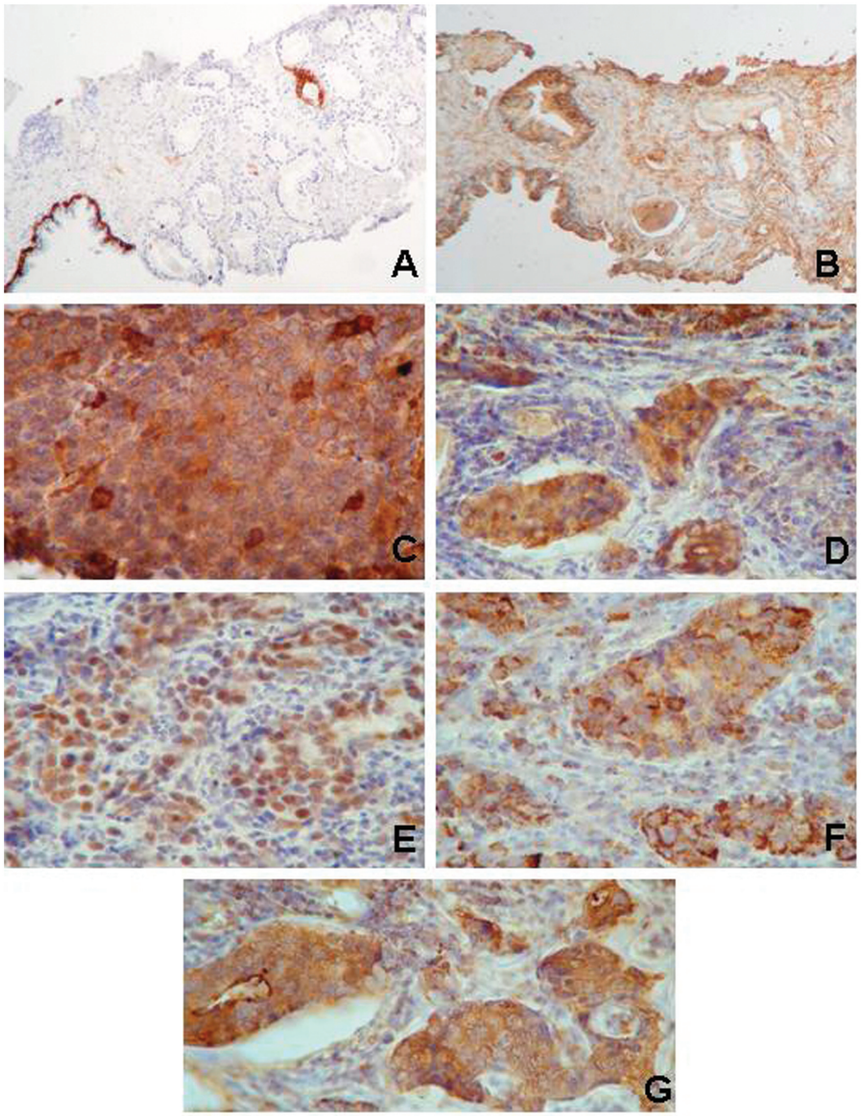

Figure 2. Examples of the expression of HSP in prostate tissues. In a patient with an early tumour (PIN in a tru-cut biopsy), the cytokeratin 7 (A) shows the basal cells in the normal gland while in the PIN (right side) these cells are lacking and there is aberrant cytokeratin 7 expression in a tumour cell clone (note the brown positive immunoreaction, diaminobenzidine). In the serial section, HSPB1 appears in the stroma and with weak immunoreactivity in the normal gland but is absent in the PIN cells (B). In contrast, HSF1 and several HSP appear in the cancer tissue from a patient with advanced disease (metastasis in a cervical lymph node). This patient failed to respond to the GnRH agonist treatment and to suffered bone metastases. (C) note the variable expression of HSPB1 in cancer cells; (D) HSPA1A and HSPA8 (these two forms are recognised by the BRM22 monoclonal antibody) appear in the nuclei and cytoplasm in the tumour cell clusters; (E) HSF1 in the nuclei of the tumour cells; (F) HSPD1 in the cytoplasm of tumour cells; and (G) HSPA5. Original magnification ×30 (A, B), ×120 (C–G). The tissues were lightly counterstained with haematoxylin to reveal nuclei.

targets for cancer therapy by: (1) interrupting the interaction of HSP (mainly HSPC1) with various client proteins that are protected from degradation when chaperoned by the HSP; (2) using the chaperone and adjuvant capabilities of certain HSP to present antigenic peptides to the immune system, so this can recognise the tumour cells as foreign to mount an effective antitumoral response; and (3) using treatment planning models taking into account the HSP expression levels to obtain more effective thermal therapies. Table IV summarises the current approaches using HSP as targets for therapies. Here we can add that the genotoxic etoposide can also disrupt the AR-HSPC association interfering with the AR signalling (impeding the binding of synthetic androgen to AR) in LNCap cells [87]. This is a good example that anticancer agents can act through multiple mechanisms involving among others

Table IV. Targeting HSP in prostate cancer.

Chaperone-client protein interactions ⇒ protection of the client from degradation
HSPC1 with: AR*, mutated p53, Her-2/neu, Akt, CDK4, C-Raf, Bcr-Abl, etc.
Interfering with: geldanamycin, 17-AAG, 17-AAG analogues and others [72–77]
HSPB1 with Stat3 ⇒ suppression of apoptosis [78]
HSPB1 with Her-2/neu ⇒ resistance to MAb treatment [79]
Interfering with: ASO, short interfering RNA
HSP-based immunotherapy ⇒ autoimmune response ⇒ rejection of tumor cells
Using HSPC4, HSPA1A, HSPH4, clusterin, others [80–85]
HSP dosimetry ⇒ HSP expression kinetics and injury data ⇒ maximize tumour destruction minimise healthy tissue injury [86]

AR, androgen receptor; MAb, immunotherapy with humanized monoclonal antibody; ASO, antisense oligonucleotides.

the HSP. These combined antitumoural strategies should improve prostate cancer survival in the near future.

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