Mini-review

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Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications

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Abstract Heat shock proteins (Hsps) are overexpressed in a wide range of human cancers and are implicated in tumor cell proliferation, differentiation, invasion, metastasis, death, and recognition by the immune system. We review the current status of the role of Hsp expression in cancer with special emphasis on the clinical setting. Although Hsp levels are not informative at the diagnostic level, they are useful biomarkers for carcinogenesis in some tissues and signal the degree of differentiation and the aggressiveness of some cancers. In addition, the circulating levels of Hsp and anti-Hsp antibodies in cancer patients may be useful in tumor diagnosis. Furthermore, several Hsp are implicated with the prognosis of specific cancers, most notably Hsp27, whose expression is associated with poor prognosis in gastric, liver, and prostate carcinoma, and osteosarcomas, and Hsp70, which is correlated with poor prognosis in breast, endometrial, uterine cervical, and bladder carcinomas. Increased Hsp expression may also predict the response to some anticancer treatments. For example, Hsp27 and Hsp70 are implicated in resistance to chemotherapy in breast cancer, Hsp27 predicts a poor response to chemotherapy in leukemia patients, whereas Hsp70 expression predicts a better response to chemotherapy in osteosarcomas. Implication of Hsp in tumor progression and response to therapy has led to its successful targeting in therapy by 2 main strategies, including: (1) pharmacological modification of Hsp expression or molecular chaperone activity and (2) use of Hsps in anticancer vaccines, exploiting their ability to act as immunological adjuvants. In conclusion, the present times are of importance for the field of Hsps in cancer, with great contributions to both basic and clinical cancer research.

INTRODUCTION

Levels of the heat Hsp molecular chaperones are elevated in many cancers, and Hsp overexpression signals a poor prognosis in terms of survival and response to therapy in specific cancer types (Ciocca et al 1993; Cornford et al 2000; Blagosklonny 2001; van de Vijver et al 2002; van 't Veer et al 2002). Elevated Hsp expression in malignant cells plays a key role in protection from spontaneous apoptosis associated with malignancy as well as the apoptosis generated by therapy, mechanisms which may underlie the role of Hsp in tumor progression and resistance to treatment (Volloch and Sherman 1999; Nylandsted et al 2000a, 2000b; Ciocca et al 2003; Gyrd-Hansen et al 2004). Hsp transcription requires activated heat shock transcription factor 1 (*hsf1*), which is itself overexpressed in cancer and plays a role in invasion and metastasis (Wu 1995; McMillan et al 1998; Hoang et al 2000; Wang et al 2004). However, the molecular mechanisms linking increased Hsp and HSF1 expression to tumor progression are not currently understood. Because Hsps are induced only under stress conditions in normal cells, some aspects of the malignant phenotype apparently cause Hsp dysregulation (Lindquist and Craig 1988).

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Heat shock proteins

Hsps were first discovered as a cohort of proteins that are powerfully induced by heat shock and other chemical and physical stresses in a wide range of species (Lindquist

and Craig 1988; Georgopolis and Welch 1993). The Hsps have been subsequently characterized as molecular chaperones, proteins, which have in common the property of modifying the structures and interactions of other proteins (Beckmann et al 1990; Gething and Sambrook 1992; Netzer and Hartl 1998; Freeman and Yamamoto 2002). Molecular chaperone function dictates that the Hsps often interact in a stoichiometric manner with their substrates, necessitating high intracellular concentrations of the proteins (Lindquist and Craig 1988; Georgopolis and Welch 1993). As proteins that shift the balance from denatured, aggregated protein conformation toward ordered, functional conformation, Hsps are particularly in demand when proteins are disordered by heat shock, oxidative stress, or other protein-damaging events (Lindquist and Craig 1988; Hightower 1991; Gething and Sambrook 1992; Georgopolis and Welch 1993). The *Hsp28, 40, 70,* and *110* genes have therefore evolved a highly efficient mechanism for mass synthesis during stress, with powerful transcriptional activation, efficient messenger RNA (mRNA) stabilization, and selective mRNA translation (Voellmy 1994). Hsp27, 70, 90, and 110 increase to become the dominantly expressed proteins after stress (Hickey and Weber 1982; Landry et al 1982; Li and Werb 1982; Subjeck et al 1982; Henics et al 1999; Zhao et al 2002). Hsp gene transcription is regulated by transcription factors belonging to the heat shock factor (HSF) family that ensure prompt transcriptional activation in stress and equally precipitous switch-off after recovery (Sorger and Pelham 1988; Wu 1995). The *hsf* gene family includes heat shock transcription factor 1 (*hsf1*), the molecular coordinator of the heat shock response, as well as 2 less well-characterized genes, heat shock transcription factor 2 (*hsf2*) and heat shock transcription factor 4 (*hsf4*) (Rabindran et al 1991; Schuetz et al 1991; Nakai et al 1997). In addition to the Hsps induced by heat, cells also contain a large number of constitutively expressed Hsps (Tang et al 2005). Recent studies have shown that the constitutive Hsps are found in a variety of multiprotein complexes containing both Hsps and cofactors (Buchner 1999). These include Hsp10 and Hsp60 complexes that mediate protein folding and Hsp70- and Hsp90-containing complexes that are involved in both generic protein-folding pathways and in specific association with key regulatory proteins within the cell (Netzer and Hartl 1998; Pratt and Toft 2003). Hsp90 plays a particularly versatile role in cell regulation, forming complexes with a large number of cellular kinases, transcription factors, and other molecules.

Mechanisms for Hsp elevation

Hsp expression is tailored for induction by the stress response, and the proximal signal for Hsp induction is apparently the accumulation of denatured proteins (Voellmy 2004). It is thus rather a mystery as to how the Hsps become overexpressed in cancer. One hypothesis is that the physiopathological features of the tumor microenvironment (low glucose, pH, and oxygen) tend toward Hsp induction. Whether this is true or not, we do not know. However, one recent study indicates that when cells are transferred from tissue culture to growth as xenografts in vivo, Hsp expression declines markedly (Tang et al 2005). Because the elevated Hsp levels associated with malignancy tend to persist when cells are grown in tissue culture, they may well be related to the genetic changes associated with tumor progression (Tang et al 2005). Oncoproteins may appear during carcinogenesis (eg, mutated p53), and these mutated and conformationally altered proteins may elicit an Hsp response. However, the exact mechanisms are yet to be determined although they likely involve molecular changes common to a wide range of cancer cells with the potential to feed into the signaling mechanisms that lead to HSF1 activation.

In this short review, we will provide an overview of the current status of the Hsps in cancer with special emphasis on the clinical setting. This is not an easy task because there are more than 200 types of cancers and there are several Hsp families, each with multiple members (Tang et al 2005). Finally, the process of carcinogenesis involves a complex array of genetic and epigenetic alterations, which contribute to cancer pathogenesis (Hahn and Weinberg 2002), leading ultimately to a unique cancer tissue (often with mixed cancer clones) within a unique molecular milieu and in this may change dramatically the Hsp context and behavior. Therefore, we need to define whether altered expression of the Hsps at genomic or proteomic level is of importance to cancer prevention, diagnosis, prognosis, prediction, and treatment.

IMPLICATIONS IN DIAGNOSIS

In these cases, Hsp expression has been analyzed in relation to the histopathological characteristics of the tumor tissues (eg, tumor type, grade of differentiation), with the expression of other molecules (eg, estrogen receptors, c-myc, mutated p53), and with patient parameters like sex and age. In addition, levels of circulating Hsps and anti-HSP antibodies have been correlated with patient and tumor characteristics. Table 1 summarizes the publications regarding the diagnostic implications of the Hsps in cancer.

Because of space limitations, we cannot perform a detailed analysis of each study (eg, adequacy of the number and homogeneity of samples incorporated). However, the following main conclusions can be made. (a) Diagnostic implications—Hsps are overexpressed in a wide range of malignant cells and tissues. Therefore, Hsp detection is not useful in diagnostic immunopathology (there are oth-

Table 1 Heat shock proteins in cancer: diagnostic implications

Hsp	Author(s)	Findings
Breast cancer		
Hsp27	Ciocca et al (1990)	+: correlation with estrogen receptors
	Vargas-Roig et al (1997)	Overexpression: low cell proliferation
	Muñoz de Toro and Luque (1997)	Lack of association with ER in male bc
	Keeling and McKee (1999)	+: smears, suspicious of malignancy
Hsp70	Tauchi et al (1991)	+ Hsp70 and c-myc: in 63% of carcinomas
	Takahashi et al (1994)	Associated with elevation of ER, but <p53
	Lemoisson et al (1994)	Association with PR isoforms
	Iwaya et al (1995)	Bound to mutant p53 in certain cases only
	Vargas-Roig et al (1997)	+: high cell proliferation, mitotic spindle
	Lazaris et al (1997)	+c: LN metastasis, poor differentiation
Hsc70	Townsend et al (2002)	No correlation: BAG-1, ER, tumour grade
Grp78	Fernandez et al (2000)	Overexpression: malignant not benign, ER−
Hsp90α	Jameel et al (1992)	Overexpression: LN involvement
	Lemoisson et al (1994)	Association with PR isoforms
	Yano et al (1999)	Higher: cancer, correlated with cyclin D1
Endometrial cancer		
Hsp27	Ciocca et al (1985)	Increased in hyperplastic endometrium
	Ciocca et al (1989)	+: correlation with ER, well different ca
	Navarro et al (1992)	Overexpression in low-grade endometrial stromal sarcomas; negative: high grade
	Korneeva et al (2000)	Antibodies: detected in cancer patients
	Wataba et al (2001)	Overexpression in hyperplasia and some ca
Hsp70	Nanbu et al (1996)	+: poor differentiation, p53 +, ER−
Hsp90	Nanbu et al (1996)	Overexpression: well diff., ER/PR+
Ovarian cancer		
Hsp27	Langdon et al (1995)	>Hsp27: malignant tumors, advanced ca
	Schneider et al (1998)	Coexpression with P-glycoprotein (MDR1)
	Korneeva et al (2000)	Antibodies: detected in cancer patients
Hsp72	Athanassiadou et al (1998)	Hsp72 and p53: in undifferentiated ca
Hsp90	Mileo et al (1990)	>: advanced stages; no cor.: ER, PR, EGFR
	Luo et al (2002)	Autoantibodies: late-stage cancer
Uterine cervix		
Hsp10	Cappello et al (2003a)	Overexpressed during carcinogenesis
Hsp27	Ciocca et al (1986)	Marker of metaplasia
	Dressler et al (1986)	Associated with squamous cell maturation
	Ciocca et al (1989)	Lack of correlation with ER, PR
	Puy LA et al (1989)	+: more differentiated tumours
	Ciocca et al (1992)	HPV-induced changes in expression
	Korneeva et al (2000)	Antibodies: detected in cancer patients
Hsp60	Cappello et al (2003b)	Higher levels during carcinogenesis
Hsp70	Ralhan and Kaur (1995)	+: cancer tissue, >in increased tumor size
	Kim et al (1998)	Correlated with proliferation, not with ER
	Abd el All et al (1998)	Correlated with c-myc, malignancy marker
	Park et al (1999)	+: stage I; no correlation: p53, ER, or HPV
Choriocarcinoma		
Hsp27	Vegh et al (1999)	Downregulation (high sensitivity to chem.)
Oral cancer		
Hsp27, . . .	Ito et al (1998)	Hsp27, 90: + in dysplastic lesions: no correlation with clinical stage, p53
Hsp27, 60, 70	Kumamoto et al (2002)	Expressed in ameloblastomas
Hsp27	Leonardi et al (2002)	Upregulation in highly differentiated scc
Hsp70	Kaur et al (1998)	Increasing levels with carcinogenesis, in poorly differentiated scc, >clinical stage
Salivary gland cancer		
Hsp27, etc	Vanmuylder et al (2000)	Hsps 27, 70, 70, 90, and 110 were less expressed in malignant tumors
Oesophageal cancer		
Hsp27	Soldes et al (1999)	Decreasing levels with carcinogenesis (Barret's metaplasia and oesophageal adenocarcinomas)
	Lambot et al (2000)	Increases with carcinogenesis (dysplastic lesions to invasive squamous ca)

Table 1 Continued

Hsp	Author(s)	Findings
Gastric cancer		
Hsp90β	Liu et al (1999)	Increased expression in cancer tissues
Liver		
Hsp27	Ciocca et al (1991)	+: some hepatocellular carcinomas, no correlation with ER and HBV
	Delhaye et al (1992)	Higher expression in hepatomas than in nontumorous liver
CCTbeta	Yokoto et al (2001)	Increased expression in hepatocellular ca
Hsp70	Chuma et al (2003)	Marker of early hepatocellular carcinoma
Pancreatic carcinoma		
Hsp47	Maitra et al (2002)	+: neoplastic epithelium, stromal desmoplasia
Hsp90α	Ogata et al (2000)	Overexpressed in carcinomas
Colorectal carcinoma		
Hsp10	Cappello et al (2003a)	Overexpressed during carcinogenesis
CCTbeta	Yokota et al (2001)	Increased expression in colonic cancer cells
Hsp60	Cappello et al (2003)	Overexpression: early event in carcinogenesis
Hsp70, 110	Hwang et al (2003)	Expression: advanced disease, +LN
gp96	Heike et al (2000)	High expression: primary and metastatic ca
Nasopharyngel cancer		
Hsp70	Jalbout et al (2003)	Hsp70-2 homozygous genotype: associated with susceptibility to cancer
Lung cancer		
Ubiquitin, etc	Michils et al (2001)	Ubiquitin, Hsp27: no increased expression; Hsp60, Hsp70: increased expression
Hsp27, 70	Malusecka et al (2001)	Hsp27+: 70% of nsclc, more in scc Nuclear Hsp70+: correlation with Ki-67
Hsp63, 70, 90	Bonay et al (1994)	Expression: no correlation with histologic type; <differentiation> Hsp70 and 90
Hsp70, 90	Zhong et al (2003)	Antibodies to Hsp70: >patients with nsclc; antibodies to Hsp90: no correlation with ca
Grp94	Wang et al (2002)	Overexpression: in cancer, poor dif., >clinical stage
Urinary system cancer		
αB crystallin	Pinder et al (1994)	High expression: renal cell carcinomas
Hsp27	Storm et al (1993)	Overexpressed in 50% bladder ca, no correlation with LN+, etc.
Hsp27, Cryst.	Takashi et al (1998)	Hsp27 levels: >in renal cell ca than normal; αB crystalline: also >but without statistical significance. Lowest Hsp27 levels in testis tumors
Hsp27, 60, 70	Kamishima et al (1997)	Differential expression of the Hsps in a bladder carcinosarcoma
Hsp70	Efferth et al (2001)	+: blastemal and epithelial components of nephroblastomas; >Hsp70 after chemother
Hsp90	Cardillo et al (2000)	Overexpression: in high-grade and muscle-invasive bladder carcinomas, cor. with IL-6
Prostate cancer		
HSF1	Hoang et al (2000)	Upregulated in prostate carcinoma
Hsp10, 60	Cappello et al (2002–2003, 2003c)	Overexpressed in early prostate carcinogenesis
Hsp27	Storm et al (1993)	Prostate: absence in normal and ca tissue
Hsp27, 60, 70	Cornford et al (2000)	Hsp27 lack of expression: early in situ ca; Hsp60 expression: >early and advanced ca; Hsp70 expression: <in advanced ca
Hsp70	Abe et al (2004)	Plasma levels might have a role in early-stage cancer
Leukemia, lymphoma		
Hsp27	Strahler et al (1991)	Phosphorylated isoform present in pre–B acute lymphoblastic leukemia
Hsp27, 70, 90	Xiao et al (1996)	Hsp27: high expression not confined to a specific type of acute leukemia; Hsp70; <expression in leukemia, Hsp90: >expression in leukemia
Hsp27, 60, 90	PL Hsu and HM Hsu (1998)	High levels in Reed-Sternberg cells
Hsp60, 70, 90	Chant et al (1995)	All showed >expression in acute myeloid leukemia compared with chronic myeloid leukemia
Nervous system tumors		
αB crystalline	Numoto (1996)	+: pineal large tumor cells
Hsp27, cryst.	Hitotsumatsu et al (1996)	High Hsp27: glioblastomas, anaplastic tu.; αB-crystallin: schwannomas, chordomas

Table 1 Continued

Hsp	Author(s)	Findings
Hsp27	Kato et al (1992)	+: 5/21 meningiomas; + in other tumors
	Yokoyama et al (1993)	+: 22/26 cases of meningiomas
	Ungar et al (1994)	>expression: >diff. neuroblastomas, inverse correlation with N-myc
	Khalid et al (1995)	>expression in high-grade astrocytomas
	Assimakopoulou et al (1997)	>expression in more malignant astrocytomas
	Assimakopoulou (2000)	Expression in meningiomas, absence of ER
	Assimakopoulou and Varakis (2001)	Expression in astrocytomas + for c-Jun and c-Fos (ascending in malignancy)
Hsp27, 79, 90	Strik et al (2000)	Expressed in all high-grade and most low-grade gliomas, + in oligodendrogliomas
Hsp27, 60, etc	Kato et al (2001)	Hsp60 is coexpressed with other Hsps in several primary and metastatic tumors
Pituitary adenoma		
Hsp27	Gandour-Edwards et al (1995)	+: in invasive adenomas
Hsp70	Kontogeorgos et al (1999)	Colocalization with cytoplasmic p53; no correlation with apoptosis
Adrenal adenoma		
Hsp27, 60, 70	Pignatelli et al (2003)	Hsp27, 70: <in Cushing's adrenal tissue, whereas Hsp60 increased
Skin cancer		
Hsp27	Kanitakis et al (1989)	Marker of differentiation of keratinocytes; basal/squamous ca showed high expression
	Trautinger et al (1995)	Marker of differentiation of keratinocytes; basal/squamous ca show low expression
Hsp27, 72	Bayerl et al (1999)	Hsp27: high expression in basal call ca (in contrast to squamous cell ca); Hsp72: low expression
Melanoma		
Hsp27, etc	Missotten et al (2003)	Hsp27 and gp96: relatively high expression, whereas Hsp70 and 90 had low expression
Hsp70	Lazaris et al (1995)	Expression: correlated with clinical stage
Osteosarcoma		
Hsp60, 70	Trieb et al (2000a, b)	Hsp60 antibodies: high in osteosarcomas; Hsp70 antibodies: patients with lung met
Chondrosarcoma		
Hsp27, etc	Trieb et al (2000c)	Hsp72 expression: low differentiation

Abbreviations: bc, breast cancer; c, cytoplasm; ca, carcinoma(s); chem, chemotherapy; cor, correlation; EGFR, epidermal growth factor receptor; ER, estrogen receptors; HBV, hepatitis B virus; HPV, human papillomavirus; LN, lymph node; met, metastases; PR, progesterone receptors; scc, squamous cell carcinoma; nsclc, non–small cell lung carcinoma.

er more restricted molecular markers to identify the lineage of origin of cancer tissues: carcinoma, sarcoma, lymphoma, etc). However, it might be useful to apply in a panel of immunopathology antibodies, the detection of αBcrystallin for identification of renal cell carcinomas (Pinder et al 1994), and the detection of Hsp27 or Hsp90 for identification of Reed-Sternberg cells (Hsu and Hsu 1998). The presence of Hsps and antibodies to the Hsps in the serum of cancer patients is still a new research area. Although it seems that autoantibodies to certain Hsps are of significance as tumor markers in osteosarcomas, ovarian cancer and others, at present, we need more studies to draw a clear conclusion on this important subject. The same applies to the study of the polymorphism of the Hsp70-2 gene. (b) Carcinogenesis—Hsp expression levels can help indicate the presence of abnormal changes during the process of carcinogenesis (in certain tissues). For example, Hsp27 is overexpressed in hyperplastic endometrium, and this protein appears as a marker of squamous metaplasia in the uterine cervix; Hsp10 and Hsp60 are related with the process of carcinogenesis of the uterine cervix and colon; and Hsp70 is associated with carcinogenesis of the oral epithelium and as a marker of early hepatocellular carcinoma. In oesophageal carcinomas, Hsp27 decreases during the carcinogenesis that ends in adenocarcinomas but increases during the carcinogenesis that ends in squamous carcinomas. Then, Hsps can be used as subrogate biomarkers of certain cancers. (c) Differentiation—Hsp expression correlates with the degree of differentiation in certain tissues. Hsps associated with higher differentiation are: Hsp27 and Hsp90 in endometrial carcinomas, Hsp27 in squamous carcinomas (uterine cervix, oral epithelium), and Hsp27 as a marker of keratinocyte differentiation in the skin. In contrast, Hsps associated with poor differentiation are Hsp70 in cancers of the breast, ovary, and oral epithelium, Grp78 in lung

carcinomas, and Hsp27 in astrocytomas. At present, we do not have a clear explanation for these disparities and associations. Hsp70 has been involved not only with poor tumor differentiation but also with increased cell proliferation (breast, uterine cervix, lung), lymph node metastasis (breast, colon), increased tumor size (uterine cervix), presence of mutated p53 (breast, endometrium), and higher clinical stage (oral, colon, melanoma). (d) Associations with other molecules—In general, several Hsps are coexpressed in cancer tissues; in addition, certain Hsps can be significantly associated with other molecules. For example, Hsp27 has been associated with ERα in female breast carcinomas and endometrial carcinomas, but this protein did not appear associated with ERα in male breast carcinomas, cervical uterine carcinomas, hepatocellular carcinomas, and meningiomas (tissues that may express ERα). It is interesting that Hsp27, which was first described as an estrogen-regulated protein, is significantly associated with ERα in the female breast and endometrium (Table 1). These 2 organs are under strong estrogen and progesterone regulation. On the other hand, Hsp70 has been described as an important molecule in the assembly and trafficking of steroid receptors, and in breast cancer, Hsp70 has been found associated with ERα (Takahashi et al 1994). It is of interest to mention that Hsp70 can increase ERα transcriptional activity and growth in MCF-7 breast cancer cells (Spears and Barnes 2003), which in turn may explain the increased cell proliferation found in breast tumor biopsy samples that express Hsp70 (Vargas-Roig et al 1997). In addition, Hsp70 has been associated and complexed with mutant p53 in cancer cell lines (Lehmann et al 1991). This association has been studied in several cancer tissues, and the results have shown this association in certain cases only.

IMPLICATIONS IN THE PROGNOSIS

We have seen that expression of certain Hsps can be correlated with the carcinogenic process as well as with the degree of differentiation and cell proliferation, and moreover, they have been implicated in the regulation of apoptosis. Therefore, it was reasonable to study the prognostic implications of Hsps, and they emerged as useful in certain cancer types. The prognosis of a particular cancer patient is very important in the clinic to individualize cancer treatments, to plan the patient's follow-up, and to answer questions from the patient or relatives. Overtherapy with cytotoxic drugs can be avoided in cancer patients if they are correctly identified as having good prognosis and vice versa (Table 2). Again, because of space limitations, we cannot perform a detailed analysis of each study; however, the following conclusions can be made about the Hsps that have been studied most. (a) Hsp27—breast cancer is one of the sites where numerous studies on prognostic factors have been reported. To date, at the proteomic level, we can establish a categorization of several prognostic factors that, integrated with the traditional clinicopathological factors, provide a very good idea of the disease outcome (Gago et al 1998). Hsp27 is not among the list of useful prognostic factors in breast cancer (Oesterreich et al 1996). Hsp27 expression has been associated with poor prognosis in ovarian, gastric, liver and prostate cancer, and osteosarcomas. In contrast, Hsp27 expression has been associated with good prognosis in endometrial adenocarcinomas, oesophageal cancer, and in malignant fibrous histiocytomas. Although there are fewer studies in other cancers, the data suggest that Hsp27 has no prognostic value in head and neck squamous cancer, bladder and renal cancer, and leukemia (except when associated with other markers). There are contradictory data in oral cancer and ovarian cancer. (b) Hsp70—Hsp70 expression is correlated with poor prognosis in breast cancer, endometrial cancer, uterine cervical cancer, and transitional cell carcinoma of the bladder. This is consistent with the Hsp70 associations with poor differentiation, lymph node metastasis, increased cell proliferation, block of apoptosis, and higher clinical stage, which are markers of poor clinical outcome. In contrast, high Hsp70 expression was correlated with good prognosis in oesophageal cancer, pancreatic cancer, renal cancer, and melanoma. Hsp70 expression showed no correlation with prognosis in ovarian cancer, oral cancer, head and neck squamous cancer, gastric and prostate cancer, and leukemia. (c) Hsp90—Hsp90 expression in cancer tissues and presence of autoantibodies to Hsp90 have been correlated with poor prognosis in breast cancer. In contrast, Hsp90 expression is associated with good prognosis in endometrial cancer. Loss of Hsp90 (and Hsp60) expression has been associated in bladder carcinoma with invasive recurrence risk. Hsp90 expression was of no prognostic value in ovarian and oral cancer.

It is evident that we need more studies on Hsps to confirm whether they have prognostic value in specific cancers. At this point, it is tempting to speculate that the unique molecular context or milieu present in each cancer type drives the correlations of Hsps with the disease prognosis. For example, in breast cancers, Hsp90 can be chaperoning the oncoprotein HER-2/neu and the mutated p53 protecting these molecules from degradation by the proteasome, which is good for the tumor but bad for the patient. In contrast, in endometrial cancers Hsp90 may be chaperoning progesterone receptors contributing to its maturation, maintaining a more differentiated and less aggressive tumor phenotype with a better response to synthetic progestational agents. Therefore, depending of the cancer type, each Hsp has unique associations with the prognosis of the disease.

Table 2 Heat shock proteins in cancer: prognostic implications

Hsp	Author(s)	Findings
Breast cancer		
Hsp27	Thor et al (1991)	+: <DFS in patients with 1–3 LN+
	Damstrup et al (1992)	No correlation with DFS or OS
	Love and King (1994)	No correlation with DFS or OS
	Têtu et al (1995)	No correlation with DFS or OS (LN+)
	Oesterreich et al (1996)	No value in prognosis (LN negative)
	Conroy et al (1998a)	Serum antibodies: improved survival
	Fanelli et al (1998)	+ in serum: no correlation with metastases
Hsp70	Ciocca et al (1993)	Shorter DFS
	Elledge et al (1994)	p53−/cytoplasmic Hsp70+: better OS
	Mestiri et al (2001)	Homozygous genotype: increased OS
	Thanner et al (2003)	Cytoplasmatic Hsp70: decreased OS
Hsp90α	Jameel et al (1992)	High expression: early recurrence, <OS
	Conroy et al (1998b)	Autoantibodies: poor survival
Endometrial cancer		
Hsp27	Geisler et al (1999)	+: better OS
	Piura et al (2002)	Overexpression: better prognosis
Hsp70	Nanbu et al (1998)	Poor survival (univariate analysis)
	Piura et al (2002)	Overexpression: worse prognosis
Hsp90	Nanbu et al (1998)	Overexpression: favorable prognosis
	Piura et al (2002)	Overexpression: better prognosis
Ovarian cancer		
Hsp27	Langdon et al (1995)	>Hsp27: <OS
	Geisler et al (1998)	Overexpression: >OS
	Schneider et al (1998)	No correlation with survival
	Arts et al (1999)	Overexpression: <OS (but not in multivariate analysis)
	Piura et al (2002)	Overexpression: worse prognosis
	Elpek et al (2003)	Expression: <OS
Hsp60	Kimura et al (1993)	High expression: <OS
	Schneider et al (1999)	Overexpression: better OS
Hsp70	Elpek et al (2003)	Expression: no correlation with OS
Hsp90	Elpek et al (2003)	Expression: no correlation with OS
	Vidal et al (2004)	Antibodies in stage IV disease
Cervical (uterine) cancer		
Hsp70	Piura et al (2002)	Expression: worse prognosis
Oral cancer		
Hsp27, . . .	Ito et al (1998)	Hsp27, 60, 70, 90: no correlation with survival
Hsp27	Mese et al (2002)	Expression: poor survival (scc)
Head and neck squamous cancer		
Hsp27, 70	Gandour-Edwards et al (1998)	Expression: no correlation with survival
Oesophageal cancer		
Hsp27, 70	Kawanishi et al (1999)	Lower expression: poor survival (scc)
	Nakajima et al (2002)	Hsp27+: better prognosis; Hsp70 low expression: poor prognosis
Hsp70	Noguchi et al (2002)	+: better prognosis (univariate analysis)
Gastric cancer		
Hsp27	Harrison et al (1991)	+: <OS
	Takeno et al (2001a)	>Hsp27 and p53: poor survival
	Kapranos et al (2002)	+: <OS (univariate analysis)
Hsp70	Maehara et al (2000)	Expression: no correlation with survival
Pancreatic cancer		
Hsp70	Sagol et al (2002)	>expression: >OS
Colorectal		
mHsp70	Dundas et al (2004)	>expression: poor survival
Liver cancer		
Hsp27	King et al (2000)	>expression: <DFS and OS
Prostate cancer		
Hsp27, 60, 70	Cornford et al (2000)	Hsp27 expression: poor clinical outcome; Hsp60 and Hsp70: no correlation
Hsp27	Bostwick (2000)	Overexpression: <survival
Renal cancer		
Hsp27	Erkizan et al (2004)	No correlation with DFS
Hsp70	Santarosa et al (1997)	Favorable prognostic factor

Table 2 Continued

Hsp	Author(s)	Findings
Bladder cancer		
Hsp27	Storm et al (1993)	No correlation with local recurrence, distant metastases, or survival (small sample number)
Hsp27, 60, 90	Watson et al (2003)	Loss of Hsp60 and 90: infiltrating recurrence risk Low Hsp27 and 60: >tumor grade
Hsp70	Syrigos et al (2003)	+: >grade, >stage and <OS
Leukemia		
Hsp27, 70	Stammler and Volm (1996)	No correlation with DFS or OS
Hsp27	Kasimir-Bauer et al (2002)	Coexpression with other molecules: <OS
Melanoma		
Hsp70	Konstadoulakis et al (1998) Ricaniadis et al (2001)	Expression: >OS +: improved OS
Osteosarcoma		
Hsp27, etc	Uozaki et al (2000)	Hsp27 overexpression: negative prognostic value (<OS, neoadjuvant-treated patients)
Malignant fibrous histiocytoma		
Hsp27	Têtu et al (1992)	Expression: >MFS, >OS

Abbreviations: DSF, disease-free survival; LN, lymph node; MFS, metastasis-free survival; OS, overall survival; scc, squamous cell carcinoma.

PREDICTIVE IMPLICATIONS

There are studies exploring the use of the Hsps to predict the response (or lack of response) of a set of cancer patients to a specific treatment(s) (Table 3). These studies are very important because they may tailor the treatment strategy to individual cancer patients. These studies may be aided by a clearer understanding of the molecular link between the malignant phenotype and Hsp expression although such studies are currently at a very early stage. The following conclusions can be deduced from the published data (considering only those papers that presented a relatively large number of patients, with an homogeneous treatment, and with a clinical follow-up). (a) Hsp27—Although the expression of Hsp27 correlated with that of ERα in breast cancer, detection of Hsp27 does not predict the response to tamoxifen. Hsp27 expression was found in 31% of prostate cancer patients refractory to hormone therapy (Bubendorf et al 1999), although we need more studies on this important subject. Regarding chemotherapy, Hsp27 overexpression has been correlated with a shorter disease-free survival in advanced breast cancer patients who received neoadjuvant chemotherapy (Vargas-Roig et al 1998). This clinical implication of Hsp27 expression with resistance to chemotherapy is in agreement with studies performed in ovarian cancer, in head and neck cancer, esophageal squamous cell carcinoma, and leukemia (in association with other molecular markers). Hsp27 has shown no predictive value to chemotherapy in rectal cancer, malignant fibrous histiocytoma, and central nervous system tumors (induction radiochemotherapy). Regarding the brain tumors, we should point out that glioblastoma multiforme is rather resistant to radiochemotherapy and that these tumors already show a high expression of Hsp27 (as well as other Hsps) and that a further elevation in Hsp content may not correlate with a more resistant phenotype. We need more studies to know whether Hsp27 is related to radioresistance or radiosensitivity in cancer. The molecular mechanisms involving Hsp27 and other Hsps in resistance to cancer therapies can be explained in several ways: (1) as molecular chaperones they can confer cytoprotection by repairing more efficiently the damaged proteins resulting from cytotoxic drug administration, (2) protecting cancer cells from apoptosis (Arrigo et al 2002), (3) protecting the microvasculature inside tumors, because Hsp27 is found in endothelial cells (Ciocca et al 2003), and (4) enhancing DNA repair (Mendez et al 2003; Nadin et al 2003). (b) Hsp70—Although Hsp70 expression is associated with ERα expression in breast cancer, Hsp70 (like Hsp27) did not show predictive value for tamoxifen administration. In contrast, Hsp70 is emerging as a predictor of resistance to chemotherapy in breast cancer. Moreover, high Hsp70 levels predicted lower response of breast cancers to radiation and hyperthermia. In a recent study in multiple myeloma cells using oligonucleotide arrays, Chauhan et al (2003) identified several members of the Hsp family (including Hsp70) among the molecules conferring resistance to the conventional treatment with dexamethasone. Interestingly, they reported a new compound that overcomes dexamethasone resistance, which decreased the levels of Hsp27, Hsp70, and Hsp90 in the myeloma cells. Cancer cells have several defense mechanisms against cytotoxic drugs, which may be redundant, and in order to predict more accurately the

Table 3 Heat shock proteins in cancer: predictive implications

Hsp	Author(s)	Findings
Breast cancer		
Hsp27	Seymour et al (1990)	+: better response to combination therapy (chemotherapy and tamoxifen for ER+)
	Damstrup et al (1992)	Does not predict response to endocrine therapy
	Ciocca et al (1998)	Does not predict response to tamoxifen
	Vargas-Roig et al (1998)	Shorter DFS (neoadjuvant chemotherapy)
Hsp70	Ciocca et al (1993)	Predictor of recurrence (adjuvant therapy)
	Liu et al (1996)	Higher: <resp. radiation and hyperthermia
	Ciocca et al (1998)	Does not predict response to tamoxifen
	Vargas-Roig et al (1998)	Shorter DFS (neoadjuvant chemotherapy)
Ovarian cancer		
Hsp27	Langdon et al (1995)	>Hsp27: resistant to chemotherapy
	Germain et al (1996)	No correlation with chemoresistance
	Arts et al (1999)	Univariate analysis: absence of Hsp27 correlated with longer median progression-free survival
	Piura et al (2002)	Overexpression: poor response to chemoth
Cervical (uterine) cancer		
Hsp27	Vargas-Roig et al (1993)	Hsp27: no correlation with response to tamoxifen
Head and neck cancer		
Hsp27	Fortin et al (2000)	Expression: did not correlate with local response to radiotherapy (transfected cells with >Hsp27: thermoresistance and chemoresistance)
Oesophageal cancer		
Hsp27	Takeno et al (2001b)	Hsp27: involved in resistance to neoadjuvant C+R (scc)
Rectal cancer		
Hsp27/70	Rau et al (1999)	No correlation with treatment (H+R+C)
Lung cancer		
Hsp70	Volm and Rittgen (2000)	Weak correlation with resistance to doxorubicin (nsclc)
Bladder cancer		
Hsp27	Kassem et al (2002)	Downregulation in radiosensitive bccl
Hsp60	Zlotta et al (1997)	Increased anti–Hsp 60 IgG after BCG therapy: >tumor recurrence
Prostate cancer		
Hsp27	Bubendorf et al (1999)	Overexpression: 31% of hormone-refractory tumors, 5% of primary tumors
Leukemia		
Hsp27	Kasimir-Bauer et al (1998)	Coexpression of Hsp27 and other molecules predicts response to induction chemother
CNS tumors		
Hsp27, 70, 90	Hermisson et al (2000)	Does not predict response to induction radiochemotherapy. However, glioblastoma cells express high levels of Hsps
Osteosarcomas		
Hsp60, 70	Trieb et al (1998)	Hsp72+: better response to neoadjuvant chemotherapy
Hsp90	Trieb et al (2000a)	Antibodies: >response to neoadjuvant chemotherapy
Malignant fibrous histiocytoma		
Hsp27	Têtu et al (1992)	Expression: no correlation with response to chemotherapy

Abbreviations: bccl, bladder carcinoma cell line; C, chemotherapy; scc, squamous cell carcinoma; H, hyperthermia; nsclc, non–small cell lung carcinoma; R, radiotherapy.

resistance of cancer cells to certain therapies, it will be necessary to examine alternative pathways. Moreover, at the proteomic level, we will need to examine not only the expression but also the localization of the Hsps because this seems to be an important factor in their predictive value (Vargas-Roig et al 1998). Depending on the type of cancer (and their molecular profile and interactions), the Hsps can have a more marginal predictive role; for instance, in lung cancer, Hsp70 showed a weak predictive value compared with other molecules (Volm and Rittgen 2000). On the other hand, in osteosarcomas, Hsp70 predicted a better response to neoadjuvant chemotherapy

Table 4 Heat shock proteins in cancer: treatment implications

Hsp	Author(s)	Findings
Examples of preclinical studies		
HSF1	Xia et al (2003)	HSF1-transfected bcc undergo apoptosis when treated with heat shock+H7 (serine-threonine kinase inhibitor)
Hsp27	Rocchi et al (2003)	Antisense oligonucleotide increased apoptosis in hpcc
	Rocchi et al (2004)	Antisense oligonucleotide enhanced apoptosis and delayed prostate tumor progression
Hsp65	Chu et al (2000)	Use of BCG Hsp65 linked to HPV16 E7
Hsp70	Ciupitu et al (2002)	Hsp70 (tumor derived) elicited protection against an induced sarcoma (vaccine)
	Nylandsted et al (2002)	Adenovirus-expressing antisense Hsp70 cDNA effective to eradicate glioblastoma, breast ca and colon ca in nude mice
	Noessner et al (2002)	Hsp70-peptide complexes: transferred to human dendritic cells by receptor-dependent uptake (vaccine)
	Feng et al (2003)	Use of Hsps from syngeneic normal tissue as adjuvant with nonimmunogenic apoptotic tumor cells
	Chauhan et al (2003)	Use of an estrogen derivative in multiple myeloma cells downregulates Hsp27/70/90
Grp78	Lee et al (2003)	Supression of grp78 (gene therapy): elimination of cancer cells
Hsp90	Chiosis et al (2001)	Molecule that binds Hsp90 causes HER-2 degradation, growth arrest, and differentiation of bcc
	Mitsiades et al (2002)	Effect of proteasome inhibitor PS-341 in cancer cells
	Lee et al (2002)	Radicicol (Hsp90 inhibitor)-induced degradation of estrogen receptor alpha
	Solit et al (2003)	Inhibition of Hsp90 (17AAG) downregulated Akt kinase and sensitized tumors to taxol
	Smith V et al (2003)	17-DMA-geldamycin: novel Hsp90 inhibitor
	Barril et al (2003)	Novel and improved Hsp90 inhibitor
Hsp110	Wang et al (2003a)	Hsp110-gp110 complex: suppressed the growth of established tumors (vaccine)
	Manjili et al (2003)	Hsp110-HER-2/neu vaccine: inhibited spontaneous mammary tumors
Grp170	Wang et al (2003b)	Tumor-derived grp170: prolonged survival of metastases-bearing mice (vaccine)
Clinical studies		
Vaccines with Hsps		
Gp96	Janetzki et al (2000)	Immunization with autologous gp96 elicited MHC I–restricted, tumor-specific CD8+ T lymphocytes
	Belli et al (2002)	Gp96-peptide complexes: in metastatic melanoma patients (17.8% CR/SD)
	Assikis et al (2003)	Phase II: metastatic renal cell carcinoma (34.4% showed PR, CR or SD)
	Mazzaferro et al (2003)	Gp96-peptide complexes in patients with metastatic (liver) colorectal cancer
Drugs/compounds targeting Hsps		
Hsp90	Solit et al (2003)	17AAG: phase I trial
	Banerji et al (2003)	17AAG: phase I trial, with evidence of tumor target inhibition

Abbreviations: ca, cancer; bcc, breast cancer cells; CR, complete response; hpcc, human prostate cancer cells; PR, partial response; SD, stable disease; 17AAG, 17-allylamino,17-demethoxygeldanamycin; 17-DMA, 17-dimethylaminoethylamino-17-demethoxygeldamycin.

(Trieb et al 1998), which may be explained by the different molecular context of these tumors. However, we need more studies regarding the predictive value of Hsps in cancer to deduce the precise significance of HSP expression.

IMPLICATIONS IN THE TREATMENT

This is an exciting new door for the field of Hsps in cancer. Hsp and the HSF family could provide a true Achilles heel for cancer therapy because they seem to be required for cell survival during tumor progression and metastasis (Volloch and Sherman 1999; Hoang et al 2000; Nylandsted et al 2000a, 2000b; Jones et al 2004). Hsps or HSFs may be targeted by drugs and new classes of drugs targeting Hsps are beginning to be deployed, most notably at this time targeting Hsp90 (Neckers and Ivy 2003). The elevated Hsps may also provide a tempting target for immunotherapy protocols because they are able to chaperone tumor antigens and act as biological adjuvants to break tolerance to tumor antigens and cause immune killing by cytotoxic CTL and tumor regression (Arnold-Schild et al 1999; Belli et al 2002; Manjili et al 2002; Noessner et al 2002; Srivastava 2002; Todryk et al 2003; Castelli et al 2004; Daniels et al 2004). Dependence on the selective advantages for growth offered by the protective effects of Hsps may thus render tumor cells vulnerable to detection through immunosurveillance and killing by chaperone-based immunotherapy. Table 4 shows the preclinical and the few clinical studies implicating Hsps in cancer treatment.

Agents that modify the molecular levels or molecular capabilities of the Hsps—this is achieved by the inhibition of Hsp90 by the natural product geldanamycin or the geldanamycin analog 17AAG. These drugs target the nucleotide-binding site in the N-terminal domain of

Hsp90, the same as the adenosine triphosphate–binding site (inhibition of the adenosine triphosphatase activity) causing inhibition of the binding of Hsp90 to the client proteins (Workman 2002). These proteins are stress response, or survival-related, or mutated proteins that without the binding to Hsp90 are not properly folded (less stable) and destroyed by the proteasome. For instance, Hsp90 has been shown to bind mutant p53 more avidly than wild-type p53 (Blagosklonny et al 1996). In normal cells most Hsp90 is not bound to other proteins. Therefore, the effect on normal cells of the Hsp90-inhibitory drugs is not so drastic as in tumor cells. In fact, these drugs are toxic, but the toxicity of 17AAG is manageable. This strategy is interesting because of its ability to affect multiple oncogenic substrates simultaneously; in the phase I clinical trials on cancer patients, 17AAG produced in some patients stable disease, higher apoptosis, and less proliferation of the tumors but with lower potency than radiotherapy or chemotherapy. Moreover, 17AAG can be used in combination with radiotherapy or chemotherapy (enhancement of sensitization). 17AAG has some limitations such as limited solubility with low oral bioavailability, complex formulation, and modest potency on targets, and it is a substrate for P-glycoprotein. This has increased the interest in the search for other Hps90 inhibitors. Finally, HSF-1, Hsp27, Hsp70, and grp78 are also targets of antisense oligonucleotide therapies or other manipulations with possibilities for anticancer therapies. These interesting approaches are still at the preclinical level.

Use of Hsps as carriers/adjuvant to present tumor molecules to the immune system—the objective is to elicit in a cancer patient a specific and active immune response against its own tumor using the Hsps as natural adjuvants that present to the immune system the molecules (usually protein fragments, polypeptides but also relatively large molecules) that have shielded the potential epitopes from immune recognition. The immunization is carried out with tumor-derived Hps (gp96, Hsp70, and others), which bring attached the specific tumor peptides. When injected as a therapeutic vaccine, the Hsps interact with receptors on the professional antigen presenting cells (dendritic cells, macrophages). These cells introduce the antigen(s) into the MHC class I and II pathways, inducing a specific cytotoxic T lymphocyte response and the production of proinflammatory cytokines (Table 4, Srivastava et al 1998). Another approach is to use recombinant Hsps with oncoproteins such as HER-2/neu or proteins from oncogenic viruses such as E7 of HPV. The tumor-derived auto-vaccines based on Hsp or the recombinant Hsp fusion proteins induce cytokine and costimulatory molecules with activation of $CD4^+$ and $CD8^+$ T cells and increases in $CD11c^+$ cells and NK cells that kill tumor cells (Table 4, Rivoltini et al 2003). So far the most promising effects are being obtained in renal cancer and melanoma patients, but several other cancer patients are being treated with the vaccines based on Hsps including patients with colorectal, gastric and pancreatic cancers, leukemia, and lymphoma. These Hsp-based vaccines exhibit minimal toxicity, and if they continue to show good results, they may ultimately be incorporated into the armamentarium against patients with limited or minimal cancer disease (the immune system has a relatively limited capacity to kill large tumor burdens).

CONCLUSIONS

Our studies indicate a profound role for Hsp in many aspects of tumor progression and response to therapy. Although at the diagnostic level Hsps are not informative, they are effective biomarkers for carcinogenesis in some tissues and signal the degree of differentiation and aggressiveness of certain cancers. In addition, the levels of Hsp and anti-Hsp antibodies in the serum of cancer patients are useful in tumor diagnosis. Furthermore, several Hsps are implicated with the prognosis of specific cancers, including Hsp27 expression, which is associated with poor prognosis in gastric, liver, and prostate carcinoma and osteosarcomas, and Hsp70, which is correlated with poor prognosis in breast, endometrial, uterine cervical, and bladder carcinomas. Hsp may also predict the response to some anticancer treatments. Implication of Hsp in tumor progression and response to therapy has led to its successful targeting in therapy by two main strategies, including: (1) pharmacological modification of Hsp expression or molecular chaperone activity and (2) use of Hsps as adjuvants to present tumor antigens to the immune system. Study of Hsp in cancer at the cell and molecular level, although promising, is still in its infancy, and we currently have little information on how Hsp regulation is subverted in cancer and how Hsp dysregulation affects the molecular events involved with tumor growth, invasiveness, and metastasis. Such studies will be essential in interpreting and directing the studies aimed at targeting Hsps in cancer therapy.

Note: we apologize to the colleagues whose works have not been cited in the present review because of space limitations and our limitations in finding their work in the literature search.

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