Cell Stress and Chaperones (2008) 13:253–262
DOI 10.1007/s12192-008-0030-8

MINI REVIEW

Heat shock proteins in animal neoplasms and human tumours—a comparison

Mariarita Romanucci · Tania Bastow · Leonardo Della Salda

Received: 18 December 2007 / Accepted: 7 February 2008 / Published online: 12 March 2008

Abstract Heat shock proteins (HSPs) are implicated in all phases of cancer from proliferation, impaired apoptosis and sustained angiogenesis to invasion and metastasis. The presence of abnormal HSP levels in several human tumours suggests that these proteins could be used as diagnostic and/or prognostic markers, whilst the direct correlation between HSP expression and drug resistance in neoplastic tissues means they could also be used to predict cancer response to specific treatment. HSPs have also been successfully targeted in clinical trials modifying their expression or chaperone activity. Preliminary studies in veterinary medicine have also demonstrated the presence of altered HSP expression in neoplasms, and the study of carcinogenesis and the role of HSPs in animal models will surely be an additional source of information for clinical cancer research.

Keywords Heat shock protein · Cancer · Animal · HSP · Stress protein · Neoplasia

Introduction

Heat shock proteins (HSPs), also known as "stress proteins", are a large class of proteins that have been highly conserved throughout evolution and are expressed by prokaryote and eukaryote organisms. HSPs control protein biogenesis by assisting in the correct folding of newly formed polypeptides, oligomeric assembly and intracellular translocation (Mathew and Morimoto 1998; Nollen and Morimoto 2002) and are thus crucial in the maintenance of cellular homeostasis. HSPs also prevent inappropriate stress-induced protein aggregation by assisting in the repair of denatured proteins or by promoting their degradation. As a result of these roles, HSPs have also been referred to as molecular "chaperones" (Whitley et al. 1999). HSPs can be classified according to their molecular weight, expressed in kDa: HSP15–30, HSP40, HSP60, HSP70, HSP90 and HSP100. Each HSP family consists of several molecules, all sharing a similar primary structure and able to perform analogous functions in different subcellular compartments.

HSPs were so-called because their expression was induced by heat shock (Ritossa 1962; Tissieres et al. 1974). However, since then, a wide variety of environmental and metabolic factors including hypoxia, oxidative injury, glucose starvation, exposure to heavy metals or anti-cancer agents have been shown to elicit stress protein expression. Cellular stress response is a unique and important defence mechanism put into act by the cell to cope with a wide range of harmful conditions (Whitley et al. 1999). This response includes increased HSP synthesis, which has been detected in many pathophysiological conditions such as tissue injury and repair, hypertrophy, fever, inflammation, viral and bacterial infections (Morimoto 1998).

A growing body of evidence suggests that HSPs are also closely involved in a number of crucial processes in tumour development such as the regulation of cell cycle progression (Helmbrecht et al. 2000), control of apoptotic pathways (Didelot et al. 2006; Garrido et al. 2006; Schmitt et al. 2007) and immunosurveillance against cancer (Li 2001; Multhoff 2006). Indeed, studies are underway to determine whether these proteins could be used as diagnostic and/or prognostic markers or represent new targets for therapy.

M. Romanucci · T. Bastow · L. Della Salda (✉)
Department of Comparative Biomedical Sciences,
Faculty of Veterinary Medicine, University of Teramo,
Teramo, Italy
e-mail: ldellasalda@unite.it

Altered HSP expression has been observed in preliminary studies on rodent and canine neoplasms suggesting a similar pattern of tumour development. These parallel findings underline the relevance of animal models in studies aimed at elucidating the multiple roles of HSPs in carcinogenesis both in animals and humans.

Comparative evaluation of altered HSPs expression in animal and human tumours

Since HSPs are overexpressed in many kinds of human malignant cells, from a diagnostic point of view, their immunodetection does not help in identifying the lineage of origin (Ciocca and Calderwood 2005). However, anti-αBcrystallin might be included in a panel of antibodies for the identification of renal cell carcinomas when a metastatic deposit or a small biopsy is evaluated (Pinder et al. 1994). Plasma levels of Hsp70, along with PSA, might also prove useful in the identification of patients with early-stage prostate cancer (Abe et al. 2004). In addition, serum levels of autoantibodies directed against HSPs in cancer patients could be of significance as tumour markers in different kinds of tumour (Korneeva et al. 2000; Trieb et al. 2000; Oka et al. 2001; Luo et al. 2002; Zhong et al. 2003).

In veterinary literature, high levels of Hsp60 and Hsp70 were reported in canine transmissible venereal tumour (CTVT), and it was thought that these HSPs could be considered potential markers for CTVT cells (Chu et al. 2001). However, more recent studies have shown high levels Hsp70 expression in canine mammary tumours (Kumaraguruparan et al. 2006; Romanucci et al. 2006), confirming that HSP expression cannot be relied upon for the recognition of a specific tumour histological type. Nevertheless, increased levels of Hsp60 have been linked to CTVT regression (Chu et al. 2001).

Many further studies have looked at the potential prognostic value of HSP expression; however, the data obtained so far are controversial and strictly linked to tumour type and organ. This is without doubt a reflection of the multiple and still unidentified roles exerted by HSPs both in different normal tissues and in cancer.

Hsp27 expression has been extensively studied in human breast cancer: Hsp27 overexpression has been correlated with oestrogen receptor levels (Thor et al. 1991; Hurlimann et al. 1993; Love and King 1994; Takahashi et al. 1995; O'Neill et al. 2004) and better differentiation of cancer cells (Love and King 1994; Têtu et al. 1995). However, other findings indicate that some but not all oestrogen receptor-positive breast tumours express Hsp27 (Ciocca et al. 1993b). In vitro data suggest that Hsp27 expression is associated with resistance to chemotherapeutic drugs (Oesterreich et al. 1993; Conroy and Latchman 1996; Hansen et al. 1999). In fact, despite the positive link with oestrogen receptors, suggesting a correlation between high amount of Hsp27 and better prognosis, an association between Hsp27 overexpression and more aggressive tumours has also been detected (Thor et al. 1991). Likewise, Hsp27 positivity in tumours from node-negative patients was correlated to lower overall survival and survival after first recurrence (Thanner et al. 2005). We have also observed a similar correlation between Hsp27 expression and tumour invasiveness in association with reduced overall survival in canine malignant mammary neoplasms (Romanucci et al. 2006). The detection of Hsp27, particularly in canine mammary infiltrating neoplastic cells, supports the theory that Hsp27 overexpression may influence the invasive and metastatic potential of human breast cancer cells (Lemieux et al. 1997) by controlling their migration on laminin-5 (Rust et al. 1999). In fact, treatment of tumour cells with a synthetic inhibitor of Hsp27 phosphorylation (Shin et al. 2005) and knock-down of such HSP using transfection with short interference RNA (Shin et al. 2005; Bausero et al. 2006) has been found to halt tumour cell migration. In Hsp27-overexpressing human breast cancer cells, an increased expression of matrix metalloproteinase 9 has also been observed and appears to be correlated with a down-regulated expression of the Src family tyrosine protein kinase Yes (Hansen et al. 2001). However, Hsp27 levels have also been correlated with different biological features in early and advanced human breast cancer such as short disease-free survival in node-negative patients but with prolonged survival from first recurrence. It is thought that the high levels of Hsp27 in advanced cancer are indicative of long survival because of the link to hormone response; however, the biological explanation for the switch from Hsp27 being a bad to a good prognostic factor in early and advanced breast cancer remains to be clarified (Love and King 1994). Moreover, Hsp27 seems to sort out cases with a better prognosis from the oestrogen receptor-negative group of patients with a poor prognosis (Hurlimann et al. 1993). Nevertheless, other findings reveal a lack of association between Hsp27 expression and the clinical outcome of this kind of neoplasm (Hurlimann et al. 1993; Têtu et al. 1995; Oesterreich et al. 1996; Ioachim et al. 2003) and its response to hormone therapy (Hurlimann et al. 1993; Ciocca et al. 1998). Antibodies to Hsp27, on the other hand, have been associated with improved survival in patients with breast cancer (Conroy et al. 1998a).

Overexpression of Hsp70 has been frequently observed in several kinds of human tumours and, in particular, breast cancer where Hsp70 expression has been correlated to adverse prognostic indicators, such as high tumour grade and presence of nodal metastasis (Lazaris et al. 1997), and appears to negatively influence overall survival and

survival after recurrence (Thanner et al. 2003). It could well prove useful in sorting out node-negative patients at high risk of recurrence, thus influencing decisions regarding treatment (Ciocca et al. 1993a). A strict correlation between Hsp70 levels and oestrogen receptors has also been detected, which is in agreement with other research demonstrating the association of this protein with steroid hormone receptors (Takahashi et al. 1994).

Hsp90 expression has also been extensively studied in tumours, predominantly in breast cancer where a positive relationship with oestrogen receptor levels has been found (Shyamala et al. 1993). Hsp90 is a fundamental component of the multi-molecular, steroid receptor complex (Cheung and Smith 2000). Similarly to Hsp70 (Vargas-Roig et al. 1997), this Hsp also seems to be involved in the proliferation of human breast cancer, as levels of Hsp90α, an isoform of the HSP90 family, appears positively correlated with cyclin D1 expression in this type of tumour (Yano et al. 1999). In addition, the presence of autoantibodies to Hsp90 in the sera of breast cancer patients has been associated with poor survival (Conroy et al. 1998b). Hsp90 overexpression has also been reported to indicate a poor prognosis in human breast cancer (Jameel et al. 1992), defining a population of patients with decreased survival (Pick et al. 2007).

In canine malignant mammary tumours, although Hsp70 and Hsp90 levels were not of significant prognostic value, the high Hsp90 expression levels detected in neoplastic tissues, independently of tumour histological type or aggressiveness (Romanucci et al. 2006), suggest that such proteins could play a fundamental role in the multiple processes leading to malignant transformation and tumour progression in the canine mammary gland. Many of the mutations in oncogenes and tumour suppressor genes commonly found in cancer result in the expression of defective proteins that display unusually stable physical association with molecular chaperones. These molecular chaperones, particularly Hsp90, seem to serve as biochemical buffers at the phenotypical level for the multiple genetic lesions which usually characterize tumours, thus permitting cells to tolerate the mutations of crucial signalling molecules that would otherwise be lethal (Whitesell and Lindquist 2005). Furthermore, in breast cancer cells, Hsp90 is essential for the stability and function of steroid hormone receptors (Pratt and Toft 1997), whose expression has been found in both normal and neoplastic canine mammary tissues (Donnay et al. 1993). Likewise, the membrane receptor tyrosine kinase ErbB2 is also a Hsp90 client protein (Xu et al. 2001), whose enhanced expression correlates with malignancy of breast cancer progression (Miyata 2005) and which might also exert an important role in carcinogenesis of canine mammary gland (Ahern et al. 1996; Matsuyama et al. 2001; Martin de las Mulas et al. 2003; Dutra et al. 2004).

The elevated expression of the HSP70 family members in both cytoplasm and nucleus of canine mammary tumour cells, characterised by intense proliferation activity and/or stromal invasion (Romanucci et al. 2006), could be correlated to the roles exerted by these chaperones in cell cycle control (Helmbrecht et al. 2000). In addition, several mammalian cells typically show an increase and a nuclear translocation of Hsp72/73 (respectively, the inducible and constitutive member of HSP70 family) during S-phase, which suggests an enhanced requirement for nuclear protein transport during this phase (Milarski and Morimoto 1986; Shi and Thomas 1992; Zeise et al. 1998). These cells could also be manifesting the symptoms of environmental stress, such as lack of nutrients or hypoxia (Kaur et al. 1998; Jolly and Morimoto 2000), particularly in the more aggressive tumour areas. However, little information is available to support this latter hypothesis and in contrast, HSP expression, induced through the stress protein response, appears to interfere with other gene expression programmes in the cell, such as mitogenic signal transduction pathways (Calderwood 2005).

Increased transcription of *hsp* genes, on the other hand, may be directly induced by basic oncogenic pathways (Calderwood et al. 2006), such as those involving the c-*myc* oncogene or p53 protein. Whereas c-*myc* does not appear to exert a prominent role in oncogenesis of canine mammary gland (Engstrom et al. 1987), the p53 tumour suppressor gene results to be involved in both human and canine mammary tumour development and progression (Van Leeuwen et al. 1996; Kumar et al. 2007). Regulation of HSP expression in normal cells also involves the tumour suppressor protein p53, which represses transcription of the *hsp70* gene through the inhibition of CBF/HSP70, a transcription factor binding to the CCAAT box on the *hsp70* promoter (Agoff et al. 1993; Chae et al. 2005). In fact, mutation of the *p53* gene reverses this effect with consequent transactivation of the *hsp70* promoter (Tsutsumi-Ishii et al. 1995). Furthermore, both Hsp72/73 and Hsp90 have been found to be associated with the conformational mutant form of p53 forming a multi-chaperone complex which mediates the stabilisation, cytoplasmic sequestration and accumulation of mutated p53 by masking the p53 nuclear localisation signal (Akakura et al. 2001) and preventing its MDM2-mediated ubiquitination (Peng et al. 2001).

A recent study has also demonstrated a similar pattern of change in Hsp70, Hsp90 and apoptosis-associated proteins, such as Bcl-2, Bcl-X_L, Bax, Caspases 3 and 8, in both human and canine mammary tumours. The resulting shift of balance towards expression of HSPs and anti-apoptotic proteins suggests the existence of similar mechanisms to evade apoptosis in both humans and canines (Kumaraguruparan et al. 2006). In this connection, an increasing number of studies have greatly contributed in defining the anti-apoptotic

activity of several HSPs, including Hsp70 and Hsp90, which can interfere with both the mitochondrial ("intrinsic") and death receptor-mediated ("extrinsic") apoptotic pathways (Didelot et al. 2006; Garrido et al. 2006; Schmitt et al. 2007). It seems to be conceivable that HSPs might play analogous functions both in humans and animals, as the amino acid sequence of the canine hsp70 gene shares 90–95% sequence similarity to the bovine, human and mouse Hsp70 proteins (Kano et al. 2004).

HSPs expression has also been investigated in human, mouse and canine cutaneous squamous cell carcinoma (SCC). The data obtained from these studies indicate that Hsp27 expression is strictly correlated to keratinocyte differentiation, suggesting that the absence of this protein in epidermal cells could be regarded as a marker of epidermal malignancy in all the species so far investigated (Trautinger et al. 1995; Kiriyama et al. 2001; Romanucci et al. 2005). As a matter of fact, canine Hsp27 is also very similar to the human form with its primary structure deduced from nucleotide sequence revealing a 209 amino acid protein sharing 86–89% homology with human, mouse, rat and hamster small Hsp (Larsen et al. 1995). In human epidermis, Hsp27 appears to operate as a chaperone of cornification, as it colocalises with keratins and proteins of the cornified cell envelope (Jonak et al. 2002), whilst another study suggests that Hsp27 could be also involved in the regulation of differentiation-associated gene expression (Hell-Pourmojib et al. 2002).

Finally, in both canine mammary tumours and cutaneous SCC, Hsp90 and Hsp73 exhibit a clear-cut expression in mitotic cells (Romanucci et al. 2005, 2006), lending further support to the role of HSPs in regulating the assembly of mitotic apparatus. In fact, Hsp73 has been found to localise on centrosomes where it probably assists the centrosomal chaperonine tailless complex protein-1 (TCP-1) in tubulin folding (Brown et al. 1996a, b). It has also been found on the fibres of spindles and asters during metaphase (Agueli et al. 2001). Hsp90 is also a core centrosomal component, and it has been found that HeLa cells treated with a specific competitive inhibitor of Hsp90, geldanamycin, tend to stop at metaphase (Lange et al. 2000). Hsp90 seems to regulate metaphase–anaphase transition (de Carcer 2004) by promoting the stabilisation of the Polo kinase, an essential centrosomal protein which regulates several aspects of cell division including centrosome maturation and function (de Carcer et al. 2001).

Animal models in HSP-based cancer therapy

Although potentially dangerous, the ability of HSPs to stabilise altered conformations of signal transduction molecules and to impair apoptotic pathways also represents a weakness as far as tumour cells are concerned, as the inhibition of their chaperone function can be expected to affect the survival of such cells, independently of the alteration responsible for the oncogenic phenotype (Mosser and Morimoto 2004). Therefore, HSPs have become targets for anti-cancer drug design: in particular, Hsp90 has emerged as an especially promising molecular target, given its interaction with over 100 client proteins, many of which are involved in cancer-associated signalling pathways. Consequently, inhibition of Hsp90 functions can affect multiple oncogenic substrates simultaneously, thus helping to circumvent the genetic plasticity that may allow cancer cells to escape the toxic effects of most molecularly targeted agents which attack on a single signalling node (Neckers 2006). Although the combinatorial action of Hsp90 inhibitors is a major advantage of this class of anti-cancer drugs, this does not exclude a role for their action against a specific oncogene product in particular tumours (Sharp and Workman 2006), such as ErbB2 in breast cancer or B-Raf in melanoma. Furthermore, as Hsp90 has been demonstrated to play crucial roles in regulating angiogenic responses, evidence suggests that Hsp90 inhibitors may provide therapeutic benefit not only via direct effects on tumour cells but also by interfering with several steps of tumour angiogenesis (Kaur et al. 2004; Sanderson et al. 2006).

Even if Hsp90 represents 1–2% of the total cellular protein content and chaperones several proteins that are essential for maintaining homeostasis of healthy cells, Hsp90 inhibitors have proven to be well tolerated. One possible explanation for their therapeutic selectivity against neoplastic cells is that oncogene-addicted tumour cells are far more sensitive that normal cells, which are responsive to a plethora of pathways and stimuli (Pearl 2005). Then, given the genetic instability which is a common event in tumour genesis, and the ability of Hsp90 to function as a biochemical buffer of the multiple genetic lesions, which usually characterise tumour cells, it is likely that Hsp90 in cancers could be far more involved in the constitution of multi-chaperone complexes, thus displaying a higher ATPase activity with an apparently higher affinity for Hsp90 inhibitors than does "free" Hsp90 in normal cells (Kamal et al. 2003; Pearl 2005). In fact, most Hsp90 inhibitors act by docking in the N-terminal nucleotide binding domain, thereby inhibiting intrinsic ATPase activity and thus blocking the formation of mature complexes. Such inhibitors include the benzoquinone ansamycin antibiotic geldanamycin and its derivatives, the macrocyclic antibiotic radicicol and its analogues, purine-scaffold derivatives and shepherdin (Sharp and Workman 2006; Xiao et al. 2006). The latter is specifically designed to block the interaction between Hsp90 and survivin (Plescia et al. 2005). 17-Allylamino, 17-demethoxygeldanamycin (17-AAG) has

recently completed several phase I clinical trials (Banerji et al. 2005; Goetz et al. 2005; Grem et al. 2005; Ramanathan et al. 2005; Nowakowski et al. 2006) and entered phase II single agent therapy in various tumour types including melanoma, breast cancers and paediatric (Sharp and Workman 2006) and genitourinary (Lattouf et al. 2006) malignancies. There is also great interest in combining 17-AAG treatment with other cancer therapies, such as radiation (Bisht et al. 2003; Enmon et al. 2003; Russell et al. 2003; Machida et al. 2005; Shintani et al. 2006) or various cytotoxic agents (Nguyen et al. 2001; Rahmani et al. 2003; Solit et al. 2003; George et al. 2004, 2005; Mesa et al. 2005; Vasilevskaya and O'Dwyer 2005; Yao et al. 2005; Barker et al. 2006; Sain et al. 2006; Premkumar et al. 2006), as 17-AAG can sensitise tumour cells to the induction of apoptosis by other treatments.

The most limiting factor in clinical trials is that 17-AAG has poor solubility in water and lacks oral bioavailability. Thus, its highly soluble hydroquinone hydrochloride derivative IP-504 has been synthesised as an Hsp90 inhibitor and appears to be effective in cellular and mouse models of myeloma (Sydor et al. 2006). In addition, a second generation analogue of geldanamycin, 17-(dimetylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) has been developed, which is water soluble and orally bioavailable. A series of preclinical studies has been carried out to establish its in vitro and in vivo anti-tumour activity and spectrum of toxicity (Bull et al. 2004; Eiseman et al. 2005; Glaze et al. 2005; Hollingshead et al. 2005; Smith et al. 2005; Robles et al. 2006), which appears to be similar to 17-AAG. 17-DMAG is currently in phase I clinical trials (Shadad and Ramanathan 2006; Sharp and Workman 2006).

Despite their promising anti-cancer properties, one concern in the clinical application of Hsp90 inhibitors is that they may induce the expression of HSPs, including Hsp70, via the activation of HSF1 (Bagatell et al. 2000). The blocking of Hsp70 induction has been observed to significantly enhance the anti-leukaemia activity of 17-AAG (Guo et al. 2005). Hsp27 up-regulation could also play a significant role in 17-AAG resistance which may be mediated, in part, through glutathione regulation (McCollum et al. 2006). Further evaluation of Hsp90-targeted cancer therapy also appears to be essential, as a potential contraindication to this therapy has been found: 17-AAG appears to enhance bone metastasis of a human breast cancer cell line following intracardiac inoculation in the nude mouse (Price et al. 2005). Such findings underline the importance of in vivo models for further testing of Hsp90-targeted cancer treatments, and the abundant Hsp90 expression detected in canine malignant mammary tumours (Romanucci et al. 2006) suggests that the canine model may well prove useful in the testing of new breast cancer therapy.

In veterinary medicine, mammary tumours constitute the most common malignant neoplasms in the bitch (Misdorp 2002), showing wide pathological and clinical heterogeneity similar to the disease in humans. Similarities between human and canine mammary neoplasms on a molecular level allow more significant comparative evaluations of the molecular mechanisms involved in carcinogenesis with respect to the classical rodent model (Kumaraguruparan et al. 2006). As a matter of fact, translation of a therapeutic into the clinic requires the use of animal models that parallel the biological, genetic, etiological, immunological and therapeutic properties of human cancer (Talmadge et al. 2007). Several characteristics allow to consider spontaneously occurring tumours in dogs as an attractive model for human cancer (Vail and MacEwen 2000; Sutter and Ostrander 2004). In this respect, there is a greater genetic homology between dogs and humans than between either species and the mouse (Kirkness et al. 2003; Switonski et al. 2004). Furthermore, companion animals live in the same environment as humans and share similar environmental risk factors (Mueller et al. 2007). Naturally occurring canine neoplasms also represent autochthonous tumour models which are believed to reproduce human tumours more closely than transplanted tumours, as they show orthotopic growth, tumour histology devoid of transplantation induced changes, metastasis via lymphatic and vascular vessels surrounding and within the primary tumour (Talmadge et al. 2007). Since adjuvant treatments are mainly aimed at controlling micrometastases, the strong Hsp90 and Hsp73 immunolabelling detected in canine mammary neoplastic emboli (Romanucci et al. 2006) is significant as it suggests that these HSPs are necessary to cells with metastatic potential and that the inhibition of their functions could affect the survival of such cells, which does not always show the same pattern of expression respect to the primary tumour (Cardoso et al. 2001).

The anti-apoptotic relevance of Hsp70 in cancer cells has been confirmed, both in vitro and in vivo, by evaluating the effects of "antisense Hsp70 sequences" (AsHsp70) (Gibbons et al. 2000; Kaur et al. 2000; Nylandsted et al. 2002; He et al. 2005; Zhao and Shen 2005). The AsHsp70-induced apoptosis seems to be caspase-independent and not rescued by the Bcl-2 anti-apoptotic protein (Nylandsted et al. 2000). Thus, Hsp70 depletion may provide a new target for cancer therapy (Jones et al. 2004), especially when acquired chemoresistance occurs (Gabai et al. 2005). AsHsp70 could be particularly useful in the therapy of tumours characterised by local tissue infiltration and invasion without metastasis (Nylandsted et al. 2002). In addition, a peptide containing the AIF sequence involved in its interaction with Hsp70, called the AIF-derived decoy for Hsp70 (ADD70), has been shown to bind to and neutralise Hsp70 in the cytosol, thereby sensitising cancer cells to apoptosis induced by a variety of stimuli (Schmitt et al. 2003) and exerting anti-tumour effects

in rodent models of colon cancer and melanoma (Schmitt et al. 2006). Notwithstanding this, drugs selectively inhibiting Hsp70 have not yet been identified.

Concluding remarks

Even if the roles of HSPs in cancer have not yet been completely clarified, the data so far obtained clearly indicate that they are involved in all the aspects of tumour biology. HSPs are essential for the survival and proliferation of neoplastic cells and represent targets for anti-cancer therapy. Preliminary studies carried out on animal tumours have identified similar changes in HSP expression with respect to their human counterparts, thus indicating similar roles/functions during human and animal carcinogenesis. Recent data suggests that the canine model would make a more suitable model with respect to the traditional rodent model to investigate the molecular mechanisms of tumour development and progression and to test the efficacy of new anti-cancer treatments.

References

Abe M, Manola JB, Oh WK, Parslow DL, George DJ, Austin CL, Kantoff PW (2004) Plasma levels of heat shock protein 70 in patients with prostate cancer: a potential biomarker for prostate cancer. Clin Prostate Cancer 3:49–53

Agoff SN, Hou J, Linzer DI, Wu B (1993) Regulation of the human hsp70 promoter by p53. Science 259:84–87

Agueli C, Geraci F, Giudice G, Cimenti L, Cascino D, Sconzo G (2001) A constitutive 70 kDa heat shock protein is localized on the fibres of spindles and asters at metaphase in an ATP-dependent manner: a new role is proposed. Biochem J 360:413–419

Ahern TE, Bird RC, Bird AC, Wolfe LG (1996) Expression of the oncogene c-erbB-2 in canine mammary cancers and tumour-derived cell lines. Am J Vet Res 57:693–696

Akakura S, Yoshida M, Yoneda Y, Horinouchi S (2001) A role for Hsc70 in regulating nucleocytoplasmic transport of a temperature-sensitive p53 ($p53^{Val\text{-}135}$). J Biol Chem 276:14649–14657

Bagatell R, Paine-Murrieta GD, Taylor CW, Pulcini EJ, Akinaga S, Benjamin IJ, Whitesell L (2000) Induction of a heat shock factor 1-dependent stress response alters the cytotoxic activity of Hsp90-binding agents. Clin Cancer Res 6:3312–3318

Banerji U, O'Donnell A, Scurr M et al (2005) Phase I pharmacokinetic and pharmacodynamic study of 17-allylamino, 17-demethoxygeldanamycin in patients with advanced malignancies. J Clin Oncol 23:4152–4161

Barker CR, McNamara AV, Rackstraw SA, Nelson DE, Whire MR, Watson AJM, Jenkins JR (2006) Inhibition of Hsp90 acts synergistically with topoisomerase II poisons to increase the apoptotic killing of cells due to an increase in topoisomerase II mediated DNA damage. Nucleic Acids Res 34:1148–1157

Bausero MA, Bharti A, Page DT et al (2006) Silencing the hsp25 gene eliminates migration capability of the highly metastatic murine 4T1 breast adenocarcinoma cell. Tumour Biol 27:17–26

Bisht KS, Bradbury CM, Mattson D et al (2003) Geldanamycin and 17-allylamino-17-demethoxygeldanamycin potentiate the in vitro and in vivo radiation response of cervical tumor cells via the heat shock protein 90-mediated intracellular signaling and cytotoxicity. Cancer Res 63:8984–8995

Brown CR, Doxsey SJ, Hong-Brown LQ, Martin RL, Welch WJ (1996a) Molecular chaperones and the centrosome. A role for TCP-1 in microtubule nucleation. J Biol Chem 271:824–832

Brown CR, Hong-Brown LQ, Doxsey SJ, Welch WJ (1996b) Molecular chaperones and the centrosome. A role for Hsp 73 in centrosomal repair following heat shock treatment. J Biol Chem 271:833–840

Bull EE, Dote H, Brady KJ et al (2004) Enhanced tumor cell radiosensitivity and abrogation of G2 and S phase arrest by the Hsp90 inhibitor 17-(dimethylaminoethylamino)-17-demethoxy-geldanamycin. Clin Cancer Res 10:8077–8084

Calderwood SK (2005) Regulatory interfaces between the stress protein response and other gene expression programs in the cell. Methods 35:139–148

Calderwood SK, Khaleque MA, Sawyer DB, Ciocca DR (2006) Heat shock proteins in cancer: chaperones of tumorigenesis. Trends Biochem Sci 31:164–172

Cardoso F, Di Leo A, Larsimont D et al (2001) Evaluation of HER2, p53, bcl-2, topoisomerase II-alpha, heat shock proteins 27 and 70 in primary breast cancer and metastatic ipsilateral axillary lymph nodes. Ann Oncol 12:615–620

Chae H, Yun J, Shin DY (2005) Transcription repression of a CCAAT-binding transcription factor CBF/HSP70 by p53. Exp Mol Med 37:488–491

Cheung J, Smith DF (2000) Molecular chaperone interactions with steroid receptors: an update. Mol Endocrinol 14(7):939–946

Chu RM, Sun TJ, Yang HY, Wang DG, Liao KW, Chuang TF, Li CH, Lee WC (2001) Heat shock proteins in canine transmissible venereal tumor. Vet Immunol Immunopathol 82:9–21

Ciocca DR, Calderwood SK (2005) Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 10:86–103

Ciocca DR, Clark GM, Tandon AK, Fuqua SAW, Welch WJ, McGuire WL (1993a) Heat shock protein Hsp70 in patients with axillary lymph node-negative breast cancer: prognostic implications. J Natl Cancer Inst 85:570–574

Ciocca DR, Oesterreich S, Chamness GC, McGuire WL, Fuqua SAW (1993b) Biological and clinical implications of heat shock protein 27000 (Hsp27): a review. J Natl Cancer Inst 85:1558–1570

Ciocca DR, Green S, Elledge RM et al (1998) Heat shock proteins hsp27 and hsp70: lack of correlation with response to tamoxifen and clinical course of disease in estrogen receptor-positive metastatic breast cancer (A Southwest Oncology Group Study). Clin Cancer Res 5:1263–1266

Conroy SE, Latchman DS (1996) Do heat shock proteins have a role in breast cancer? Br J Cancer 74:717–721

Conroy SE, Sasieni PD, Amin V, Wang DY, Smith P, Fentiman IS, Latchman DS (1998a) Antibodies to heat-shock protein 27 are associated with improved survival in patients with breast cancer. Br J Cancer 77:1875–1879

Conroy SE, Sasieni PD, Fentiman I, Latchman DS (1998b) Autoantibodies to the 90 kDa heat shock protein and poor survival in breast cancer patients. Eur J Cancer 34:942–943

de Carcer G (2004) Heat shock protein 90 regulates the metaphase–anaphase transition in a polo-like kinase-dependent manner. Cancer Res 64:5106–5112

de Carcer G, do Carmo Avides M, Lallena MJ, Glover DM, Gonzalez G (2001) Requirement of Hsp90 for centrosomal function reflects its regulation of Polo kinase stability. EMBO J 20:2878–2884

Didelot C, Schmitt E, Brunet M, Maingret L, Parcellier A, Garrido C (2006) Heat shock proteins: endogenous modulators of apoptotic cell death. Handb Exp Pharmacol 172:171–198

Donnay I, Rauis J, Wouters-Ballman P, Devleschouwer N, Leclerq G, Versteegen JP (1993) Receptors for estrogen, progesterone and epidermal growth factors in normal and tumorous canine mammary tissues. J Reprod Fertil Suppl 47:501–512

Dutra AP, Grana NV, Schmitt FC, Cassali GD (2004) c-erbB-2 expression and nuclear pleomorphism in canine mammary tumors. Braz J Med Biol Res 37:1673–1681

Eiseman JL, Lan J, Lagattuta TF, Hamburger DR, Joseph E, Covey JM, Egorin MJ (2005) Pharmacokinetics and pharmacodynamics of 17-demethoxy 17-[[(2-dimethylamino)ethyl]amino]geldanamycin (17DMAG, NSC 707545) in C.B-17 SCID mice bearing MDA-MB-231 human breast cancer xenografts. Cancer Chemother Pharmacol 55:21–32

Engstrom WE, Barrios C, Azawedo E, Mollermark G, Kangstrom LE, Eliason I, Larsson O (1987) Expression of c-*myc* in canine mammary tumours. Anticancer Res 1:1235–1238

Enmon R, Yang WH, Ballangrud AM, Solit DB, Heller G, Rosen N, Scher HI, Sgouros G (2003) Combination treatment with 17-*N*-allylamino-17-demethoxy geldanamycin and acute irradiation produces supra-additive growth suppression in human prostate carcinoma spheroids. Cancer Res 63:8393–8399

Gabai VL, Budagova KR, Sherman MY (2005) Increased expression of the major heat shock protein Hsp72 in human prostate carcinoma cells is dispensable for their viability but confers resistance to a variety of anticancer agents. Oncogene 24:3328–3338

Garrido C, Brunet M, Didelot C, Zermati Y, Schmitt E, Kroemer G (2006) Heat shock proteins 27 and 70. Anti-apoptotic proteins with tumorigenic properties. Cell Cycle 5:2592–2601

George P, Bali P, Cohen P et al (2004) Cotreatment with 17-allylamino-demethoxygeldanamycin and FLT-3 kinase inhibitor PKC412 is highly effective against human acute myelogenous leukemia cells with mutant FLT-3. Cancer Res 64:3645–3652

George P, Bali P, Annavarapu S et al (2005) Combination of the histone deacetylase inhibitor LBH589 and the Hsp90 inhibitor 17-AAG is highly active against human CML-BC cells and AML cells with activating mutation of FLT-3. Blood 105:1768–1776

Gibbons NB, Watson RWG, Coffey RNT, Brady HP, Fitzpatrick JM (2000) Heat-shock proteins inhibit induction of prostate cancer cell apoptosis. Prostate 45:58–65

Glaze ER, Lambert AL, Smith AC et al (2005) Preclinical toxicity of a geldanamycin analog, 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG), in rats and dogs: potential clinical relevance. Cancer Chemother Pharmacol 56:637–647

Goetz MP, Toft D, Reid J et al (2005) Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. J Clin Oncol 23:1078–1087

Grem JL, Morrison G, Guo XD et al (2005) Phase I and pharmacologic study of 17-(allylamino)-17-demethoxygeldanamycin in adult patients with solid tumors. J Clin Oncol 23:1885–1893

Guo F, Rocha K, Bali P et al (2005) Abrogation of heat shock protein 70 induction as a strategy to increase antileukemia activity of heat shock protein 90 inhibitor 17-allylamino-demethoxy geldanamycin. Cancer Res 65:10536–10544

Hansen RK, Parra I, Lemieux P, Oesterreich S, Hilsenbeck SG, Fuqua SA (1999) Hsp27 overexpression inhibits doxorubicin-induced apoptosis in human breast cancer cells. Breast Cancer Res Treat 56:187–196

Hansen RK, Parra I, Hilsenbeck SG, Himelstein B, Fuqua SAW (2001) Hsp27-induced MMp-9 expression is influenced by the Src tyrosine protein kinase Yes. Biochem Biophys Res Commun 282:186–193

He LF, Guan KP, Yan Z, Ye HY, Xu KX, Ren L, Hou SK (2005) Enhanced sensitivity to mitomycin C by abating heat shock protein 70 expression in human bladder cancer cell line of BIU-87. Chin Med J 118:1965–1972

Hell-Pourmojib M, Neuner P, Fischer H, Rezaie S, Kindås-Mügge I, Knobler R, Trautinger F (2002) Differential expression of a novel gene in response to Hsp27 and cell differentiation in human keratinocytes. J Invest Dermatol 119:154–159

Helmbrecht K, Zeise E, Reinsing L (2000) Chaperones in cell cycle regulation and mitogenic signal transduction: a review. Cell Prolif 33:341–365

Hollingshead M, Alley M, Burger AM, Borgel S, Pacula-Cox C, Fiebig HH, Sausville EA (2005) In vivo antitumor efficacy of 17-DMAG (17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride), a water-soluble geldanamycin derivative. Cancer Chemother Pharmacol 56:115–125

Hurlimann J, Gebhard S, Gomez F (1993) Oestrogen receptor, progesterone receptor, pS2, Erd5, Hsp27 and cathepsin D in invasive ductal breast carcinomas. Histopathology 23:239–248

Ioachim E, Tsanou E, Briasoulis E, Batsis Ch, Karavasilis V, Charchanti A, Pavlidis N, Agnantis NJ (2003) Clinicopathological study of the expression of hsp27, pS2, cathepsin D and metallothionein in primary invasive breast cancer. Breast 12:111–1119

Jameel A, Skilton RA, Campbell TA, Chander SK, Coombes RC, Luqmani YA (1992) Clinical and biological significance of Hsp89 alpha in human breast cancer. Int J Cancer 50:409–415

Jolly C, Morimoto RI (2000) Role of the heat shock response and molecular chaperones in oncogenesis and cell death. J Natl Cancer Inst 92:1564–1572

Jonak C, Klosner G, Kokesch C, Födinger D, Hönigsmann H, Trautinger F (2002) Subcorneal colocalization of the small heat shock protein, Hsp27, with keratins and proteins of the cornified cell envelope. Br J Dermatol 147:13–19

Jones EL, Zhao MJ, Stevenson MA, Calderwood SK (2004) The 70 kilodalton heat shock protein is an inhibitor of apoptosis in prostate cancer. Int J Hyperthermia 20:835–849

Kamal A, Thao L, Sensintaffar J, Zhang L, Boehm MF, Fritz LC, Burrows FJ (2003) A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. Nature 425:407–410

Kano R, Abe K, Hasegawa A (2004) cDNA of canine heat shock protein 70 (HSP70). Vet Res Commun 28:395–405

Kaur J, Srivastava A, Ralhan R (1998) Expression of 70-kDa heat shock protein in oral lesions: marker of biological stress or pathogenicity. Oral Oncol 34:496–501

Kaur J, Kaur J, Ralhan R (2000) Induction of apoptosis by abrogation of HSP70 expression in human oral cancer cells. Int J Cancer 85:1–5

Kaur G, Belotto D, Burger AM et al (2004) Antiangiogenic properties of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin: an orally bioavailable heat shock protein 90 modulator. Clin Cancer Res 10:4813–4821

Kiriyama MT, Oka M, Takehana M, Kobayashi S (2001) Expression of a small heat shock protein 27 (Hsp27) in mouse skin tumors induced by UVB-irradiation. Biol Pharm Bull 24:197–200

Kirkness EF, Bafna V, Halpern AL et al (2003) The dog genome: survey sequencing and comparative analysis. Science 301:1898–1903

Korneeva I, Bongiovanni AM, Girotra M, Caputo TA, Witkin SS (2000) Serum antibodies to the 27-kd heat shock protein in women with gynecologic cancers. Am J Obstet Gynecol 183:18–21

Kumar S, Walia V, Ray M, Elble RC (2007) p53 in breast cancer: mutation and countermeasures. Front Biosci 12:4168–4178

Kumaraguruparan R, Karunagaran D, Balachandran C, Murali Manohar B, Nagini S (2006) Of human and canines: a comparative evaluation of heat shock and apoptosis-associated proteins in mammary tumours. Clin Chim Acta 365:168–176

Lange BMH, Bachi A, Wilm M, Gonzales C (2000) Hsp90 is a core centrosomal component and is required at different stages of the centrosome cycle in Drosophila and vertebrates. EMBO J 19:1252–1262

Larsen JK, Gerthoffer WT, Hickey E, Weber LA (1995) Cloning and sequencing of a cDNA encoding the canine Hsp27 protein. Gene 161:305–306

Lattouf JB, Srinivasan R, Pinto PA, Linehan WM, Neckers L (2006) Mechanisms of disease: the role of heat-shock protein 90 in genitourinary malignancy. Nat Clin Pract Urol 3:590–601

Lazaris AC, Chatzigianni EB, Panoussopoulos D, Tzimas GN, Davaris PS, Golematis BC (1997) Proliferating cell nuclear antigen and heat shock protein 70 immunolocalization in invasive ductal breast cancer not otherwise specified. Breast Cancer Res Treat 43:43–51

Lemieux P, Oesterreich S, Lawrence JA, Steeg PS, Hilsenbeck SG, Harvey JM, Fuqua SAW (1997) The small heat shock protein Hsp27 increases invasiveness but decreases motility of breast cancer cells. Invasion Metastasis 17:113–123

Li Z (2001) The roles of heat shock proteins in tumour immunity. In: Giaccone G, Schilsky R, Sondel P (eds) Cancer chemotherapy and biological response modifiers. Elsevier, New York, pp 371–382

Love S, King RJB (1994) A 27 kDa heat shock protein that has anomalous prognostic powers in early and advanced breast cancer. Br J Cancer 69:743–748

Luo LY, Herrera I, Soosaipillai A, Diamandis EP (2002) Identification of heat shock protein 90 and other proteins as tumour antigens by serological screening of an ovarian carcinoma expression library. Br J Cancer 87:339–343

Machida H, Nakajima S, Shikano N, Nishio J, Okada S, Asayama M, Shirai M, Kubota N (2005) Heat shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin potentiates the radiation response of tumor cells grown as monolayer cultures and spheroids by inducing apoptosis. Cancer Sci 96:911–917

Martin de las Mulas J, Ordas J, Millan Y, Fernandez-Soria V, Ramon y Cajal S (2003) Oncogene HER-2 in canine mammary gland carcinomas: an immunohistochemical and chromogenic in situ hybridization study. Breast Cancer Res Treat 80:363–367

Mathew A, Morimoto RI (1998) Role of the heat-shock response in the life and death of protein. Ann N Y Acad Sci 851:99–111

Matsuyama S, Nakamura M, Yonezawa K, Shimada T, Ohashi F, Takamori Y, Kubo K (2001) Expression patterns of the erbB subfamily mRNA in canine benign and malignant mammary tumors. J Vet Med Sci 63:949–954

McCollum AK, Teneyck CJ, Sauer BM, Toft DO, Erlichman C (2006) Up-regulation of heat shock protein 27 induces resistance to 17-allylamino-demethoxygeldanamycin through a glutathione-mediated mechanism. Cancer Res 66:10967–10975

Mesa RA, Loegering D, Powell HL et al (2005) Heat shock protein 90 inhibition sensitizes acute myelogenous leukemia cells to cytarabine. Blood 106:318–327

Milarski KL, Morimoto RI (1986) Expression of human Hsp70 during the synthetic phase of the cell cycle. Proc Natl Acad Sci U S A 83:9517–9521

Misdorp W (2002) Tumors of the mammary gland. In: Meuten DJ (ed) Tumors in domestic animals. Iowa State, Ames, IA, pp 575–606

Miyata Y (2005) Hsp90 inhibitor geldanamycin and its derivatives as novel cancer chemotherapeutic agents. Curr Pharm Des 11:1131–1138

Morimoto RI (1998) Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. Genes Dev 12:3788–3796

Mosser DD, Morimoto RI (2004) Molecular chaperones and the stress of oncogenesis. Oncogene 23:2907–2918

Mueller F, Fuchs B, Kaser-Hotz B (2007) Comparative biology of human and canine osteosarcoma. Anticancer Res 27:155–164

Multhoff G (2006) Heat shock proteins in immunity. Handb Exp Pharmacol 172:279–304

Neckers L (2006) Chaperoning oncogenes: Hsp90 as a target of geldanamycin. Handb Exp Pharmacol 172:259–277

Nguyen DM, Lorang D, Chen GA, Stewart JH 4th, Tabibi E, Schrump DS (2001) Enhancement of paclitaxel-mediated cytotoxicity in lung cancer cells by 17-allylamino geldanamycin: in vitro and in vivo analysis. Ann Thorac Surg 72:371–379

Nollen EAA, Morimoto RI (2002) Chaperoning signaling pathways: molecular chaperones as stress-sensing 'heat shock' proteins. J Cell Sci 115:2809–2816

Nowakowski GS, McCollum AK, Ames MM et al (2006) A phase I trial of twice-weekly 17-allylamino-demethoxy-geldanamycin in patients with advanced cancer. Clin Cancer Res 12:6087–6093

Nylandsted J, Rohde M, Brand K, Bastholm L, Elling F, Jäättelä M (2000) Selective depletion of heat shock protein 70 (Hsp70) activates a tumor-specific death program that is independent of caspases and bypasses Bcl-2. Proc Natl Acad Sci U S A 97:7871–7876

Nylandsted J, Wick W, Hirt UA, Brand K, Rohde M, Leist M, Weller M, Jäättelä M (2002) Eradication of glioblastoma and breast and colon carcinoma xenografts by Hsp70 depletion. Cancer Res 62:7139–7142

Oesterreich S, Weng CN, Qiu M, Hilsenbeck SG, Osborne CK, Fuqua SA (1993) The small heat shock protein hsp27 is correlated with growth and drug resistance in human breast cancer cell lines. Cancer Res 53:4443–4448

Oesterreich S, Hilsenbeck SG, Ciocca DR, Allred DC, Clark GM, Chamness GC, Osborne CK, Fuqua SAW (1996) The small heat shock protein Hsp27 is not an independent prognostic marker in axillary lymph node-negative breast cancer patients. Clin Cancer Res 2:1199–1206

Oka M, Sato S, Soda H et al (2001) Autoantibody to heat shock protein Hsp40 in sera of lung cancer patients. Jpn J Cancer Res 92:316–320

O'Neill PA, Shaaban AM, West CR et al (2004) Increased risk of malignant progression in benign proliferating breast lesions defined by expression of heat shock protein 27. Br J Cancer 90:182–188

Pearl LH (2005) Hsp90 and Cdc37—a chaperone cancer conspiracy. Curr Opin Genet Dev 15:55–61

Peng Y, Chen L, Li C, Lu W, Chen J (2001) Inhibition of MDM2 by Hsp90 contributes to mutant p53 stabilization. J Biol Chem 276:40583–40590

Pick E, Kluger Y, Giltnane JM, Moeder C, Camp RL, Rimm DL, Kluger HM (2007) High Hsp90 expression is associated with decreased survival in breast cancer. Cancer Res 67:2932–2937

Pinder SE, Balsitis M, Ellis IO, Landon M, Mayer RJ, Lowe J (1994) The expression of alpha B-crystallin in epithelial tumours: a useful tumour marker? J Pathol 174:209–215

Plescia J, Salz W, Xia F et al (2005) Rational design of shepherdin, a novel anticancer agent. Cancer Cell 7:457–468

Pratt WB, Toft DO (1997) Steroid receptor interactions with heat shock protein and immunophilin chaperones. Endocr Rev 18:306–360

Premkumar DR, Arnold B, Pollack IF (2006) Cooperative inhibitory effect of ZD1839 (Iressa) in combination with 17-AAG on glioma cell growth. Mol Carcinog 45:288–301

Price JT, Quinn JM, Sims NA et al (2005) The heat shock protein 90 inhibitor, 17-allylamino-17-demethoxygeldanamicin, enhances osteoclast formation and potentiates bone metastasis of a human breast cancer cell line. Cancer Res 65:4929–4934

Rahmani M, Yu C, Dai Y, Reese E, Ahmed W, Dent P, Grant S (2003) Coadministration of the heat shock protein 90 antagonist 17-allylamino-17-demethoxygeldanamycin with suberoylanilide hydroxamic acid or sodium butyrate synergistically induces apoptosis in human leukemia cells. Cancer Res 63:8420–8427

Ramanathan RK, Trump DL, Eiseman JL et al (2005) Phase I pharmacokinetic-pharmacodynamic study of 17-(allylamino)-17-demethoxygeldanamycin (17AAG, NSC 330507), a novel inhibitor

of heat shock protein 90, in patients with refractory advanced cancers. Clin Cancer Res 11:3385–3391

Ritossa F (1962) A new puffing pattern induced by temperature shock and DNP in Drosophila. Experientia 18:571–573

Robles AI, Wright MH, Gandhi B, Feis SS, Hanigan CL, Wiestner A, Varticovski L (2006) Schedule-dependent synergy between the heat shock protein 90 inhibitor 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin and doxorubicin restores apoptosis to p53-mutant lymphoma cell lines. Clin Cancer Res 12:6547–6556

Romanucci M, Bongiovanni L, Marruchella G, Marà M, Di Guardo G, Preziosi R, Della Salda L (2005) Heat shock proteins (HSPs) expression in canine intracutaneous cornifying epithelioma and squamous cell carcinoma. Vet Dermatol 16:108–116

Romanucci M, Marinelli A, Sarli G, Della Salda L (2006) Heat shock proteins expression in canine malignant mammary tumours. BMC Cancer 6:171

Russell JS, Burgan W, Oswald KA, Camphausen K, Tofilon PJ (2003) Enhanced cell killing induced by the combination of radiation and the heat shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin: a multitarget approach to radiosensitization. Clin Cancer Res 9:3749–3755

Rust W, Kingsley K, Petnicki T, Padmanabhan S, Carper SW, Plopper GE (1999) Heat shock protein 27 plays two distinct roles in controlling human breast cancer cell migration on laminin-5. Mol Cell Biol Res Commun 1:196–202

Sain N, Krishnan B, Ormerod MG, De Rienzo A, Liu WM, Kaye SB, Workman P, Jackman AL (2006) Potentiation of paclitaxel activity by the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin in human ovarian carcinoma cell lines with high levels of activated AKT. Mol Cancer Ther 5:1197–1208

Sanderson S, Valenti M, Gowan S, Patterson L, Ahmad Z, Workman P, Eccles SA (2006) Benzoquinone ansamycin heat shock protein 90 inhibitors modulate functions required for tumor angiogenesis. Mol Cancer Ther 5:522–532

Schmitt E, Parcellier A, Gurbuxani S et al (2003) Chemosensitization by a non-apoptogenic heat shock protein 70-binding apoptosis-inducing factor mutant. Cancer Res 63:8233–8240

Schmitt E, Maingret L, Puig PE et al (2006) Heat shock protein 70 neutralization exerts potent antitumor effects in animal models of colon cancer and melanoma. Cancer Res 66:4191–4197

Schmitt E, Gehrmann M, Brunet M, Multhoff G, Garrido C (2007) Intracellular and extracellular functions of heat shock proteins: repercussions in cancer therapy. J Leukoc Biol 81:15–27

Shadad FN, Ramanathan RH (2006) 17-dimethylaminoethylamino-17-demethoxygeldanamycin in patients with advanced-stage solid tumors and lymphoma: a phase I study. Clin Lymphoma Myeloma 6:500–501

Sharp S, Workman P (2006) Inhibitors of the Hsp90 molecular chaperone: current status. Adv Cancer Res 95:323–348

Shi Y, Thomas JO (1992) The transport of proteins into the nucleus requires the 70-kilodalton heat shock protein or its cytosolic cognate. Mol Cell Biol 12:2186–2192

Shin KD, Lee M, Shin D et al (2005) Blocking tumor cell migration and invasion with biphenyl isoxazole derivative KRIBB3, a synthetic molecule that inhibits Hsp27 phosphorylation. J Biol Chem 280:41439–41448

Shintani S, Zhang T, Aslam A, Sebastian K, Yoshimura T, Hamakawa H (2006) P53-dependent radiosensitizing effects of Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin on human oral squamous cell carcinoma cell lines. Int J Oncol 29:1111–1117

Shyamala G, Schweitzer M, Ullrich SJ (1993) Relationship between 90-kilodalton heat shock protein, estrogen receptor, and progesterone receptor in human mammary tumors. Breast Cancer Res Treat 26:95–100

Smith V, Sausville EA, Camalier RF, Fiebig HH, Burger AM (2005) Comparison of 17-dimethylaminoethylamino-17-demethoxy-geldanamycin (17DMAG) and 17-allylamino-17-demethoxygeldanamycin (17AAG) in vitro: effects on Hsp90 and client proteins in melanoma models. Cancer Chemother Pharmacol 56:126–137

Solit DB, Basso AD, Olshen AB, Scher HI, Rosen N (2003) Inhibition of heat shock proteins 90 function down-regulates Akt kinase and sensitizes tumors to taxol. Cancer Res 63:2139–2144

Sutter NB, Ostrander EA (2004) Dog star rising: the canine genetic system. Nat Rev Genet 5:900–910

Switonski M, Szczerbal I, Nowacka J (2004) The dog genome map and its use in mammalian comparative genomics. J Appl Genet 45:195–214

Sydor JR, Normant E, Pien CS et al (2006) Development of 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride (IPI-504), an anti-cancer agent directed against Hsp90. Proc Natl Acad Sci U S A 103:17408–17413

Takahashi S, Mikami T, Watanabe Y et al (1994) Correlation of heat shock protein 70 expression with estrogen receptor levels in invasive human breast cancer. Am J Clin Pathol 101:519–525

Takahashi S, Narimatsu E, Asanuma H et al (1995) Immunohistochemical detection of estrogen receptor in invasive human breast cancer: correlation with heat shock proteins, pS2 and oncogene products. Oncology 52:371–375

Talmadge JE, Singh RK, Fidler IJ, Raz A (2007) Murine models to evaluate novel and conventional therapeutic strategies for cancer. Am J Pathol 170:793–804

Têtu B, Brisson J, Landry J, Huot J (1995) Prognostic significance of heat-shock protein-27 in node-positve breast carcinoma: an immunohistochemical study. Breast Cancer Res Treat 36:93–97

Thanner F, Sutterlin MW, Kapp M, Rieger L, Kristen P, Dietl J, Gassel AM, Muller T (2003) Heat-shock protein 70 as a prognostic marker in node-negative breast cancer. Anticancer Res 23:1057–1062

Thanner F, Sutterlin MW, Kapp M et al (2005) Heat shock protein 27 is associated with decreased survival in node-negative breast cancer patients. Anticancer Res 25:1649–1653

Thor A, Benz C, Moore D et al (1991) Stress response protein (srp-27) determination in primary human breast carcinomas: clinical, histologic, and prognostic correlations. J Natl Cancer Inst 83:170–178

Tissieres A, Mitchell HK, Tracy UM (1974) Protein synthesis in salivary glands of Drosophila melanogaster. Relation to chromosome puffs. J Mol Biol 84:389–398

Trautinger F, Kindas-Mugge I, Dekrout B, Knobler RM, Metze D (1995) Expression of the 27-kDa heat shock protein in human epidermis and in epidermal neoplasms: an immunohistochemical study. Br J Dermatol 133:194–200

Trieb K, Gerth R, Windhager R, Grohs JG, Holzer G, Berger P, Kotz R (2000) Serum antibodies against the heat shock protein 60 are elevated in patients with osteosarcoma. Immunobiology 201:368–376

Tsutsumi-Ishii Y, Tadokoro K, Hanaoka F, Tsuchida N (1995) Response of heat shock element within the human hsp70 promoter to mutated p53 genes. Cell Growth Differ 6:1–8

Vail DM, MacEwen EG (2000) Spontaneously occurring tumors of companion animals as models for human cancer. Cancer Investig 18:781–792

Van Leeuwen IS, Hellmén E, Cornelisse CJ, Van der Burg B, Rutteman GR (1996) p53 mutations in mammary tumor cell lines and corresponding tumor tissues in the dog. Anticancer Res 16:3737–3743

Vargas-Roig LM, Fanelli MA, Lopez LA, Gago FE, Tello O, Aznar JC, Ciocca DR (1997) Heat shock proteins and cell proliferation in human breast cancer biopsy samples. Cancer Detect Prev 21:441–451

Vasilevskaya IA, O'Dwyer PJ (2005) 17-Allylamino-17-demethoxygeldanamycin overcomes TRAIL resistance in colon cancer cell lines. Biochem Pharmacol 70:580–589

Whitesell L, Lindquist SL (2005) Hsp90 and the chaperoning of cancer. Nat Rev Cancer 5:761–772

Whitley D, Goldberg SP, Jordan WD (1999) Heat shock proteins: a review of the molecular chaperones. J Vasc Surg 29:748–751

Xiao L, Lu X, Ruden DM (2006) Effectiveness of Hsp90 inhibitors as anti-cancer drugs. Mini Rev Med Chem 6:1137–1143

Xu W, Mimnaugh E, Rosser MFN, Nicchitta C, Marcu M, Yarden Y, Neckers L (2001) Sensitivity of mature ErbB2 to geldanamycin is conferred by its kinase domain and is mediated by the chaperone protein Hsp90. J Biol Chem 276:3702–3708

Yano M, Naito Z, Yokoyama M, Shiraki Y, Ishiwata T, Inokuchi M, Asano G (1999) Expression of Hsp90 and Cyclin D1 in human breast cancer. Cancer Lett 137:45–51

Yao Q, Nishiuchi R, Kitamura T, Kersey JH (2005) Human leukemias with mutated FLT3 kinase are synergistically sensitive to FLT3 and Hsp90 inhibitors: the key role of the STAT5 signal transduction pathway. Leukemia 19:1605–1612

Zeise E, Kuhl N, Kunz J, Rensing L (1998) Nuclear translocation of stress protein Hsc70 during S phase in rat C6 glioma cells. Cell Stress Chaperones 3:94–99

Zhao Z, Shen W (2005) Heat shock protein 70 antisense oligonucleotide inhibits cell growth and induces apoptosis in human gastric cancer cell line SGC-7901. World J Gastroenterol 11:73–78

Zhong L, Peng X, Hidalgo GE, Doherty DE, Stromberg AJ, Hirschowitz EA (2003) Antibodies to HSP70 and HSP90 in serum in non-small cell lung cancer patients. Cancer Detect Prev 27:285–290