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Forum Review

Small Heat Shock Proteins HSP27 and αB-Crystallin: Cytoprotective and Oncogenic Functions

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ABSTRACT

Heat shock protein-27 (HSP27) and αB-crystallin are ubiquitous small heat shock proteins whose expression is induced in response to a wide variety of physiological and environmental insults. They allow the cells to survive in otherwise lethal conditions. Various mechanisms have been proposed to account for the cytoprotective functions of these small heat shock proteins. First, these proteins are powerful molecular chaperones whose main function is to prevent the aggregation of nascent and stress-accumulated misfolded proteins. Second, they interact directly with various components of the tightly regulated programmed cell death machinery, upstream and downstream of the mitochondrial events. Third, they appear to play a role in the proteasome-mediated degradation of selected proteins. Both HSP27 and αB-crystallin were also proposed to participate in the development of neurodegenerative diseases and malignant tumors in which their overexpression could induce drug resistance. Altogether, these properties suggest that these small heat shock proteins are appropriate targets for modulating cell death pathways. *Antioxid. Redox Signal.* 7, 404–413.

INTRODUCTION

SMALL HEAT SHOCK PROTEINS (sHSPs) are a widespread and diverse class of proteins. These are low-molecular-range proteins (15–42 kDa) that form oligomeric structures ranging from 9 to 50 subunits. The mammalian sHSP family, now referred to as the HSPB family, includes 10 members: HSP27/HSPB1, MKBP (myotonic dystrophy protein kinase-binding protein)/HSPB2, HSPB3, αA-crystallin/HSPB4, αB-crystallin/HSPB5, HSP20/HSPB6, cvHSP (cardiovascular heat shock protein)/HSPB7, HSP22/HSPB8, HSPB9, and ODF1(outer dense fiber protein)/HSPB10 (22). All these proteins share a common C-terminal motif, the so-called α-crystallin domain, and two of them are stress-inducible, namely, HSP27 and αB-crystallin (Fig. 1). These two latter proteins are expressed ubiquitously and can be phosphorylated at different serine residues. Under physiological conditions, their protein level in all tissues is low, with the noticeable exception of the eye lens in which αB-crystallin is highly expressed. The expression of HSP27 and αB-crystallin can vary during development, cell cycle, and cell differentiation (2, 93). For example, HSP27 has been observed to accumulate in leukemic cells undergoing differentiation (four cell cycles). As this accumulation occurs early in the differentiation process, when the cells exit cell cycle, HSP27 accumulation has been proposed as a predifferentiation marker (five to eight cell cycles).

Stresses that transiently induce HSP27 and αB-crystallin include heat shock, anticancer drugs, radiation, and oxidative stress. For example, a shift of the redox status to an oxidative state due to loss of protein thiols or glutathione can trigger or enhance their expression in the cell. On the other hand, overexpressed HSP27 modulates reactive oxygen species intracellular content by increasing the level of glutathione (68). Oxidative stress, as well as other stresses, often induces a nuclear translocation of HSP27. The effect of this transient translocation of HSP27 protective function(s) remains unknown.

The expression of HSP27 and αB-crystallin is regulated at the transcriptional level. As observed with *hsp70* gene, bind-

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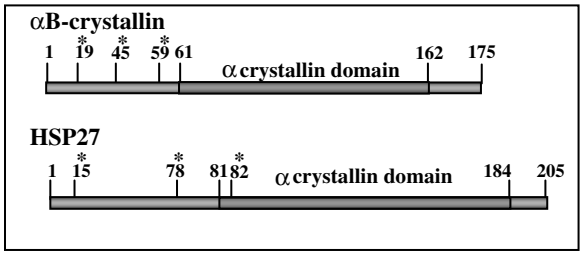

FIG. 1. Structure of HSP27 and αB-crystallin human proteins. The phosphorylation sites (*) and the α-crystallin domain are indicated.

ing of heat shock factor to the regulatory heat shock element found in the promoter region of their genes can induce their transcription (26, 71). Another transcription factor involved in their transcriptional regulation is the cyclic AMP responsive element binding protein (11), whereas the presence of an estrogen responsive element in *hsp27* gene promoter accounts for its strong induction by steroid hormones, *e.g.,* by estrogens (24). However, other mechanisms of regulation of HSP27 and αB-crystallin expression must exist because these proteins can accumulate in the absence of transcriptional induction, *e.g.,* in response to the cytotoxic drug cisplatin (19).

Both HSP27 and αB-crystallin are abundantly expressed in some cancer cells. These proteins could participate in oncogenesis, and their overexpression was suggested to limit the efficacy of cancer therapy (45), presumably due to their capacity to disable apoptosis. The different pathways through which HSP27 and αB-crystallin modulate cell death will be discussed in this review.

CYTOPROTECTIVE FUNCTIONS OF HSP27 AND αB-CRYSTALLIN

HSP27 and αB-crystallin are powerful molecular chaperones

Molecular chaperones are proteins that support the folding of other proteins during translation and translocation, as well as during stress periods, when cellular proteins are in danger of irreversible aggregation. Of the major heat shock proteins, HSP27 and αB-crystallin have been the most recently identified molecular chaperones. In contrast to other main heat shock proteins, HSP27 and αB-crystallin bind several nonnative proteins per oligomeric complex, thus representing the most efficient chaperones in terms of quantity of substrate binding (20, 59). In some cases, the release of substrate proteins from the sHSP complex is achieved in cooperation with HSP70 in an ATP-dependent reaction, suggesting that the role of sHSPs in the network of chaperones is to create a reservoir of nonnative refoldable protein. Although an influence of ATP on the chaperone function of αB-crystallin has been described (72), analysis of the chaperone function of HSP27 and αB-crystallin *in vitro* was found to be completely independent of ATP binding or hydrolysis (47).

These *in vitro* studies have demonstrated also that the main chaperone role of these sHSPs is to avoid intracellular protein aggregation, which has been confirmed by *in vivo* studies, *e.g.,* in neurodegenative diseases. A common feature of neurodegenerative disorders such as Alzheimer disease (62), Parkinson disease (44), Alexander disease (43), and Creutzfeld–Jacob syndrome (44, 80) is the deposition of improperly folded proteins in fibers, inclusion bodies, and plaques in the nervous system (87). This event has been associated with an increased expression of HSP27 and/or αB-crystallin, which were typically found in association with insoluble protein aggregates and ubiquitin (see below) (62). In scrapie-infected mouse neuroblastoma cells, induction of HSP27 by metabolic stress is blocked, whereas that of other heat shock proteins is enhanced, which could indicate a role for HSP27 in the pathogenesis of the prion disease (86). In a familial form of desmin-related myopathy, desmin aggregation was related to a missense mutation of αB-crystallin (R120G) that inhibits its chaperone function in desmin filament assembly and induces accumulation of both mutant αB-crystallin and desmin in inclusion bodies with aggresome characteristics. It was shown that wild-type αB-crystallin, HSP27, and HSPB8 could prevent the formation of these abnormal structures by cooligomerizing with the mutated αB-crystallin R120G, thus promoting an efficient folding of desmin filament (10, 42).

HSP27 and αB-crystallin as inhibitors of the apoptotic process

Another protective effect of heat shock proteins is related to their ability to interfere with apoptotic pathways. Apoptosis or programmed cell death is responsible for the removal of unwanted or supernumerary cells during development, as well as for adult tissue homeostasis (46). Apoptosis is also one of the cell death mechanisms triggered by cytotoxic drugs in tumor cells (84). Two main pathways of apoptosis have been described. One involves BH3-only members of the Bcl-2 family (including Bid, Bim, Bad, and others), which may function as context-specific sensors for cell damage and converge on the mitochondria to trigger their permeabilization (intrinsic pathway), whereas the other implicates plasma membrane proteins of the tumor necrosis factor receptor family known as death receptors (extrinsic pathway). At least in some cell types, signals originating from death receptors require the mitochondria, and thus depend on the Bcl-2 family of proteins (Fig. 2) (84). The mitochondrial pathway is initiated by the release into the cytosol of soluble apoptogenic molecules that include cytochrome *c*, apoptosis-inducing factor, and Smac/Diablo. The cytochrome *c*, once in the cytosol, interacts with apoptotic protease-activating factor-1 (Apaf-1), thereby triggering the ATP-dependent oligomerization of Apaf-1 (36, 61). Oligomerized Apaf-1 then binds to procaspase-9, thus leading to the formation of the so-called apoptosome, the caspase-9 activation complex. Activated caspase-9 triggers the proteolytic maturation of procaspase-3, and thus the caspase activation cascade responsible for apoptotic cell death (61). Smac/Diablo facilitates caspase activation by neutralizing the inhibitory activity of the IAPs (inhibitory apoptotic proteins) (18). HSP27 and αB-crystallin function at key regulatory points in the control of apoptosis by directly interacting with different apoptotic proteins (Fig. 2).

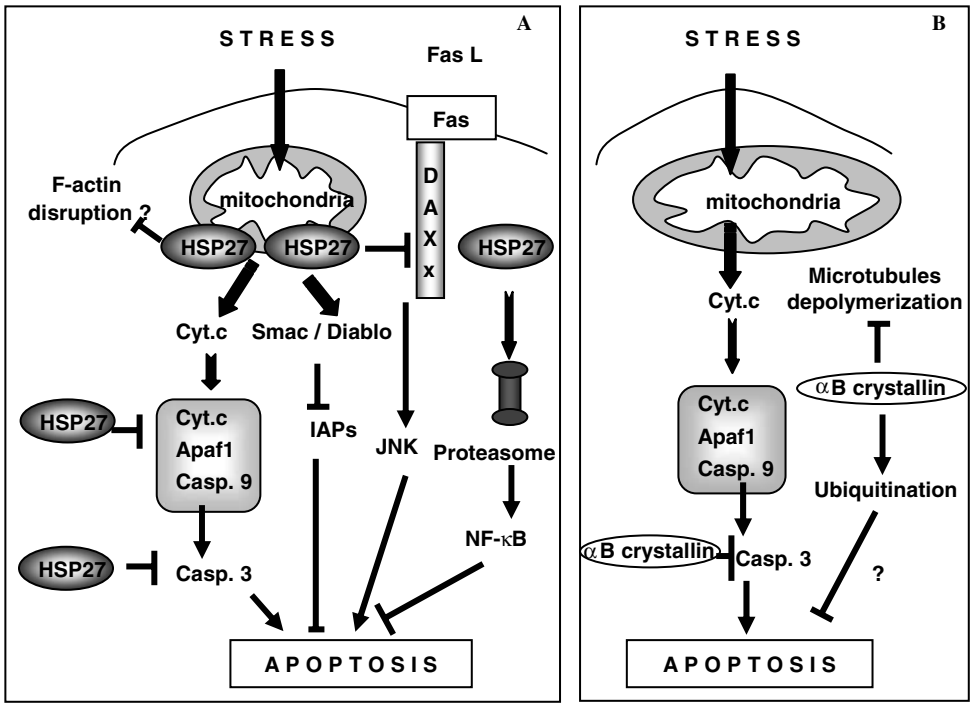

FIG. 2. Regulation of apoptotic cell death by HSP27 and αB-crystallin. (**A**) HSP27 prevents the apoptosome formation by (1) blocking the release of cytochrome *c* (cyt. c) and Smac/Diablo from the mitochondria and (2) by directly interacting with cytochrome *c* in the cytosol. HSP27 may also bind to Daxx and prevent apoptosis induced by Fas ligand (Fas L). HSP27 can bind to F-actin and prevent cytoskeleton disruption. Finally, HSP27 can enhance the proteasome-mediated degradation of I-κBα, which results in increased NF-κB activity. (**B**) αB-Crystallin interacts with pro-caspase 3 and prevents its activation. αB-Crystallin increases the resistance of microtubules against depolymerization. Finally, αB-crystallin can enhance ubiquitination of yet unknown proteins that may contribute to its antiapoptotic activity. Casp., caspase; JNK, c-Jun N-terminal kinase.

HSP27

Overexpressed HSP27 protects against apoptotic cell death triggered by various stimuli, including hyperthermia, oxidative stress, staurosporine, ligation of the Fas/Apo-1/CD95 death receptor, and cytotoxic drugs (28, 29, 69). Several of these stimuli induce HSP27 (and αB-crystallin) overexpression, providing an example of how proapoptotic stimuli, delivered below a threshold level, can elicit protective responses. HSP27 has been shown to interact and inhibit components of both stress- and receptor-induced apoptotic pathways. We have demonstrated that HSP27 could prevent the formation of the apoptosome and the subsequent activation of caspases (31). It does so by directly sequestering cytochrome *c* when released from the mitochondria into the cytosol (5). The heme group of cytochrome *c* is necessary, but not sufficient, for this interaction that involves amino acids 51 and 141 of HSP27 and requires dimerization of the stress protein. Actually, we have shown both *in vitro* and *in vivo* that the postmitochondrial antiapoptotic effect of HSP27 involved large, nonphosphorylated oligomers of HSP27 (6).

At higher HSP27 intracellular levels, the protein has been shown also to interfere with caspase activation upstream of the mitochondria. This effect seems to be related to the ability of HSP27 to stabilize actin microfilaments (57). HSP27 binds to F-actin to prevent disruption of the cytoskeleton resulting from heat shock, actin filament-disrupting agent cytochalasin D, and other stresses (32). For example, in L929 murine fibrosarcoma cells exposed to cytochalasin D or staurosporine, overexpression of HSP27 prevents the cytoskeletal disruption and Bid intracellular redistribution that precede cytochrome *c* release (77). More recently, HSP27 has been shown to inhibit the mitochondrial release of Smac and thereby to confer resistance of multiple myeloma cells to dexamethasone (9). The ability of HSP27 to interact with caspase-3 is a more controversial issue (15, 75). Initially identified in cell-free extracts from 293T cells, this interaction was not confirmed when studied in breast cancer cells (48). In addition, interaction of HSP27 with caspase-3 was described to disappear when cells were exposed to cytotoxic drugs, and thus may not account for the cytoprotective function of the protein (75).

HSP27 has been shown to increase the antioxidant defense of cells by decreasing reactive oxygen species cell content (68) and to neutralize the toxic effects of oxidized proteins (82). This latter effect may occur more specifically in neuronal cells in which HSP27 protective effect does not depend on its interaction with cytochrome *c* and is modulated by HSP27 phosphorylation status (94).

HSP27 also inhibits apoptosis by regulating upstream signaling pathways (Fig. 2). For example, the stress protein was shown to bind the protein kinase Akt, an interaction that is necessary for Akt activation in stressed cells (53, 79). In turn,

Akt could phosphorylate HSP27, thus leading to the disruption of HSP27–Akt complexes (79). HSP27 also affects one of the Fas-mediated apoptotic pathways. The phosphorylated form of HSP27 interacts directly with Daxx. This latter protein connects Fas signaling to the protein kinase Ask1 that mediates a caspase-independent cell death (8).

αB-Crystallin

The antiapoptotic effect of αB-crystallin overexpression has been demonstrated in epithelial lens cells and many other cell types. Caspase-3 processing inhibition by αB-crystallin appears to account for this antiapoptotic effect in most cells (48, 49, 64, 70). Addition of purified αB-crystallin to cell-free extracts was shown to prevent procaspase-3 processing by either cytochrome *c*-dATP or caspase-8. The small stress protein interacts with the partially processed caspase-3, thus preventing further cleavage required for the protease to be activated. Procaspase-3 processing is inhibited by αB-crystallin after separation of the small subunit from the partially processed p24 (p20) fragment composed of the large subunit and the prodomain. αB-Crystallin was shown to coimmunoprecipitate with this partially processed fragment of procaspase-3 (48, 49, 64).

In an ischemia/reperfusion mouse model, overexpresion of αB-crystallin not only protects myocardium cells from apoptosis, but also prevents necrosis (70). The phosphorylation of αB-crystallin Ser^{59} appeared to be both necessary and sufficient to provide maximal protection of cardiac myocytes from apoptosis, which could indicate that phosphorylation of αB-crystallin is required for caspase-3 inhibition (70). In cardiac myocytes, the hyperosmotic stressor sorbitol was shown to activate the p38/mitogen-activated protein kinase (MAPK) pathway through MKK6, thus leading to induction of αB-crystallin gene expression and phosphorylation of the protein on Ser^{59}, two events that contribute to sorbitol-induced cell death inhibition (35).

αB-Crystallin has been shown to protect cells also from death induced by proteasome inhibitors. Proteasome inhibition induces accumulation of unfolded proteins that are toxic to the cells. In response to proteasome inhibitors and other stressful conditions, αB-crystallin relocalizes, like HSP27, to the cytoskeleton and binds to microtubules via microtubule-associated proteins, which may protect the cells from damaged intracellular proteins by sequestering these proteins on the cytoskeleton (90). αB-Crystallin cellular redistribution also increases the resistance of microtubules against depolymerization. These results suggest that the ability of αB-crystallin to maintain microtubule dynamics may contribute to the death protective effect of this protein (Atomi Y, personal communication).

HSP27, αB-CRYSTALLIN, AND THE UBIQUITIN/PROTEASOME SYSTEM

Another recently identified function of HSP27 that could account for its protective effect toward cell death is its ability to facilitate the degradation of specific proteins by the ubiquitin/proteasome system, and thus to play a role in the so-called "protein triage" (27). The ubiquitination system labels proteins for degradation by the 26S proteasome, a multicatalytic protease composed of a catalytic 20S and two regulatory 19S subunits (12).

We have recently demonstrated that HSP27 was able to enhance the catalytic activity of the 26S proteasome machinery and to increase the degradation of ubiquitinated proteins in response to stressful stimuli. In contrast to HSP70 and HSP90, HSP27 interacts directly with ubiquitin (76). This ability to interact directly with ubiquitin could account for the recently described colocalization of HSP27 with ubiquitinated proteins (41, 52) in cytoplasmic "aggresomes" that characterize neurodegenerative diseases, a colocalization also observed with αB-crystallin (95).

αB-Crystallin has been shown to interact with one of the 14 subunits of the 20S proteasome, namely, the C8/α7 subunit (4). However, this interaction does not seem to modulate the proteasome activity. When Ser^{19} and Ser^{45} of αB-crystallin are phosphorylated, the protein can interact with FBX4, which is a component of the ubiquitin-ligase SCF (SKP1/CUL1/F-box). αB-crystallin could thereby affect the ubiquitination of yet unknown proteins (17).

We have demonstrated that HSP27 also interacts with the proteasome, more specifically with its regulatory PA700 subunit. In contrast with αB-crystallin interaction with the 20S proteasome, the HSP27/PA700 interaction appears to increase the degradation of ubiquitinated proteins (76). Interestingly, overexpressed HSP27 specifically enhances the proteasomal degradation of ubiquitinated I-κBα and cyclin E without affecting the degradation of ubiquitinated β-catenine and cyclin A (unpublished observations).

The ability of overexpressed HSP27 to increase the degradation of specific proteins through the ubiquitin/proteasome pathway may account for its antiapoptotic effect by modulating the expression of death regulatory proteins. For example, by increasing the proteasome-mediated degradation of I-κBα (and possibly the proteasome-mediated maturation of the transcription factor subunits and the proteasome-induced activation of I-κB kinases), the overexpressed HSP27 activates the transcription factor nuclear factor-κB (NF-κB) that, in turn, enhances the expression of antiapoptotic proteins. We have demonstrated that HSP27 stimulates the degradation of I-κBα and thereby increases the intracellular content of NF-κB. Accordingly, expression of a dominant negative NF-κB mutant reduces the cytoprotective action of HSP27 (76).

REGULATION OF FUNCTIONAL PROPERTIES OF HSP27 AND αB-CRYSTALLIN

The functions of most chaperones are regulated by cofactors and ATP. In the case of HSP27 and αB-crystallin, other mechanisms have to exist. An intrinsic mechanism of regulation is the oligomerization status of the protein. HSP27 and αB-crystallin can form large oligomers of up to 800 kDa. The dimer seems to be the building block for these multimeric complexes. Oligomerization is a highly dynamic process that depends on the phosphorylation status of the protein and exposure to stress (27).

Human HSP27 is phosphorylated at Ser^{15}, Ser^{78}, and Ser^{82} (55, 85) and mouse HSP27 at Ser^{15} and Ser^{86} (25). This phosphorylation is a reversible process catalyzed by the kinase MAPK-activating protein (MAPKAP) 2/3, downstream of p38 kinase and protein kinase C, more specifically its δ isoform (63). Phosphorylation of HSP27 is observed in response to a variety of stimuli, including differentiating agents, mitogens, inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, hydrogen peroxide, and other oxidants. Selectivity of phosphorylation sites in HSP27 for these enzymes is apparently absent (63, 66, 85). Dephosphorylation of HP27 *in vivo* is catalyzed by protein phosphatase 2A, although protein phosphatase 2B also demonstrated activity *in vitro* (7).

αB-Crystallin is also phosphorylated at three serine residues, namely, Ser^{19}, Ser^{45}, and Ser^{59}, and this phosphorylation has been shown to occur in response to heat, arsenite, phorbol esters, okadaic acid, anisomycin, and high concentration of sorbitol (40). In the case of αB-crystallin, the *in vivo* phosphorylation of distinct serine residue appears to be regulated independently, *i.e.,* p44/42 MAPK and MAPKAP kinase 62 are responsible for Ser^{45} and Ser^{59} phosphorylation, respectively (51).

These phosphorylating events are associated with changes in the oligomeric structure of the sHSP complexes. Studies with phosphorylation mutant proteins have demonstrate that phosphorylation favors the formation of small oligomers. Actually, depending on the extracellular stimulus and the time after stimulation, phosphorylation of HSP27 has been correlated with either the dissociation or further increase in the size of the oligomers (50, 54, 67). We have demonstrated that, although HSP27 phosphorylation is important for the regulation of its oligomerization in exponentially growing cells cultured *in vitro*, the formation of large oligomers occurs independently of the phosphorylation status of the protein in cells grown at confluence *in vitro* or grown *in vivo*. This indicates that cell–cell contact induces the formation of large oligomers independently of the phosphorylation status of the protein (6), which could explain some controversial observations on the role of HSP27 phosphorylation in its oligomerization.

That HSP27 biochemical functions may be modulated by its oligomeric (and/or phosphorylated) status is demonstrated by the fact that some biological activities of HSP27 are associated with small oligomers, whereas others require the formation of large oligomers. The dissociated and phosphorylated form of HSP27 shows no chaperone activity (82), and its thermoprotective activity is strongly decreased (65). Monomeric and phosphorylated HSP27 binds to actin (32, 57, 58), whereas phosphorylated dimers associate with Daxx to interfere negatively with the extrinsic pathway to apoptosis (8). On the other hand, large oligomers of unphosphorylated HSP27 are responsible for the stress protein-mediated inhibition of caspase-dependent apoptosis (6), as well as for its antioxidant effects (82). Thus, the nonphosphorylated, oligomeric HSP27 negatively interferes with the intrinsic, mitochondria-mediated death pathway, whereas phosphorylated, dimeric protein down-regulates the death receptor-mediated, extrinsic pathway to apoptosis. In contrast to HSP27, the protective effects of αB-crystallin appear to be mediated mostly by the phosphorylated form of the protein.

Altogether these results suggest that sHSP modulates its interaction with various cellular partners by shifting toward small or large oligomers. Phosphorylation, cell–cell contact, and probably other factors regulate this equilibrium. The different protein–protein interactions may determine the biochemical properties of the protein.

HSP27 AND αB-CRYSTALLIN PROTEINS AND CANCER

Role of HSP27

The ability of HSP27 to protect cells from stressful stimuli, together with the fact that cells or tissues from a wide range of tumors have been shown to express abnormally high levels of HSP27, has suggested that this protein could play a role in tumorigenicity. Experimental models have supported this hypothesis, *e.g.,* rat colon carcinoma cells engineered to express human HSP27 were observed to form more aggressive tumors in syngeneic animals than control cells (30), and this increased tumorigenicity correlated with a reduced rate of tumor cell apoptosis. Overexpressed HSP27 did not increase the tumorigenicity of these rat colon cancer cells in immunodeficient animals (30), suggesting that HSP27 somehow had subverted the tumor-specific immune response. However, HSP27 overexpression was also reported to increase the metastatic potential of human breast cancer cells inoculated into athymic (nude) mice (60). Thus, HSP27 may contribute to tumorigenicity through various mechanisms, including its cytoprotective activity and its molecular chaperone functions that could regulate signaling processess that influence cell growth (30).

An increased level of HSP27 has been described in breast cancer, ovarian cancer, osteosarcoma, endometrial cancer, and leukemia cells as compared with nontransformed cells of the same tissue (29). In ovarian tumors, HSP27 expression has been shown to increase with the tumor stage (56). In addition, the pattern of HSP27 phosphorylation in tumor cells differs from that observed in primary nontransformed cells and could therefore represent another convenient tumor marker (28, 56).

The molecular basis for overexpression of HSP27 in tumors is not completely understood, but may be tumor-specific. In some tumors, HSP27 accumulation could be related to a deficient environment, *e.g.,* to hypoxia in a poorly vascularized solid tumor. In other tumors, oncogenic mutations could create an increased requirement for chaperone activity toward abnormally folded protein variants. Another possibility is the occurence of gain-of-function mutations in transcription factors that increase heat shock promoter activity. In adenocarcinoma cell lines, an increased level of heat shock transcription factor 1 (HSF1) was associated with an increased HSP27 protein level (34).

Clinical studies have correlated elevated levels of HSP27 in breast, endometrial, and gastric cancer with enhanced occurrence of metastasis, poor prognosis, and resistance to cytotoxic agents (16, 23, 29, 89). Overexpressed HSP27 in tumor cells was also correlated with a poor prognosis in patients with osteosarcoma (88). However, all the clinical stud-

ies do not reach similar conclusions, *e.g.,* overexpressed HSP27 in a series of breast cancers has been correlated with the expression of estrogen receptors, small tumor size, and a low proliferation index (37). Clinicopathological studies attempting to correlate the effect of hormone therapy on HSP27 protein level in breast cancers with tumor progression and clinical outcome have provided contradictory results (73). It is therefore possible that the chemoprotective effects of HSP27 can be superseded by a variety of other modulators of drug resistance in human tumors.

Role of αB-crystallin

Overexpression of αB-crystallin has also been observed in some human malignant tumors, for example, in glial tumors such as astrocytoma, glioblastoma, and oligodendroglioma (1) and in renal carcinoma tumors (78). Highly proliferating fibroblasts do not express αB-crystallin, whereas proliferative neoplastic cells do express the protein, suggesting transformation-associated deregulation of its expression (3). Overexpression of αB-crystallin does not correlate with HSP27 overexpression (33), and its clinical significance remains poorly explored. Chemotherapy has been shown to enhance the expression of αB-crystallin in neuroblastoma cells, but the significance of this observation remains unknown (39).

HSP27 and αB-crystallin as putative drug targets in cancer therapy?

Constitutive or stress-induced overexpression of HSP27 has been shown to induce resistance of a variety of human cancer cells to anticancer agents such as doxorubicin and cisplatin, at least *in vitro* (13, 28, 81, 91). This observation makes the protein a potential target for chemosensitization of tumor cells (14, 21). The targeting of another stress protein for anticancer activity is currently being tested in clinical trials by using the benzoquinone ansamycin antibiotic geldanamycin and its analogue 17-AAG [17-(allylamino)-17-demethoxygeldanamycin], two drugs that interfere with HSP90 (74). These two drugs induce the proteasomal degradation of HSP90 client proteins and provide specific antitumor effects (38). The proapoptotic effect of geldanamycin treatment results from enhanced degradation of prosurvival oncogenes, such as Raf1 and Akt. We have recently demonstrated that specific inhibition of HSP70 can increase the sensibility of cancer cells to chemotherapeutic agents (83). Whether reduction or neutralization of small stress proteins such as HSP27 and αB-crystallin in human tumors would trigger apoptosis or sensitize tumor cells to chemotherapeutic agents remains to be demonstrated. Unfortunately, no specific inhibitor of either HSP27 or αB-crystallin has been identified so far, and the only experiment that suggests the potential interest of such a strategy has been gene therapy to decrease HSP27 expression (92).

CONCLUSION

Recent evidence indicates several connections between two sHSPs, HSP27 and αB-crystallin, and the cell death machinery. These connections involve the chaperone functions of these proteins, their ability to interact with death regulatory proteins, and probably their ability to connect the protein folding machinery to the protein degradation pathway. Ongoing studies will indicate whether these proteins are useful targets for therapeutic manipulation of the apoptotic pathways, for example, for inducing the death of cancer cells or sensitizing them to current therapeutic approaches.

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ABBREVIATIONS

Apaf-1, apoptosis protease-activating factor-1; HSP27, heat shock protein-27; IAP, inhibitory apoptotic proteins; MAPK, mitogen-activated protein kinase; MAPKAP, MAPK-activated protein; NF-κB, nuclear factor-κB; sHSP, small heat shock protein.

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