

Heat shock protein (HSP) and cancer: An overview

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ABSTRACT

Heat shock proteins (HSPs) are an evolutionary conserved family of proteins whose expression increases in response to a variety of different metabolic insults. Despite their designation, most of the HSPs are constitutively expressed and perform essential functions. Until recently, heat shock proteins (also known as heat stress proteins) have mostly been regarded as intracellular molecules that mediate a range of essential housekeeping and cytoprotective functions. However, interest in their role as intercellular signalling molecules has been fuelled by the observations that these molecules can be released and are present in the extracellular environment under physiological conditions. They can elicit cytokine production by, and adhesion molecule expression of, a range of cell types, and they can deliver maturation signals and peptides to antigen presenting cells through receptor-mediated interactions. These functions suggest that heat shock proteins could be immunoregulatory agents with potent and widely-applicable therapeutic uses. Furthermore, the induction of self heat shock protein immune reactivity can attenuate autoimmunity and delay transplant rejection, and heat shock proteins derived from tumours and pathogens can elicit specific, protective immunity. This review will focus on this rapidly evolving area of heat shock protein biology.

Keywords: Heat shock protein; Functions, therapeutic intervention

HSP AND CANCER: A OVERVIEW

Programmed cell death (PCD) forms a basic part in the developmental normal physiological conditions, where the old, worn out cells need to be eliminated. Two distinct forms of cell death, apoptosis and necrosis, have been characterized. Heat shock proteins (HSP) are highly preserved and play a major role in physiological & pathological protection. Apoptosis confrontation is associated with the expression of HSP, hence, the present discussion is focused on the functions of HSP in apoptosis regulation. Heat shock proteins (HSP) are a class of functionally related proteins, and are expressed when

cells are out in the open to increased temperatures or other stress.

HSP are practically found in all living organisms, from bacteria to humans. These proteins are so named because of their molecular weight.^{1,2,3}

CLASSIFICATION¹ (Table 1)

The principal heat-shock proteins that have chaperone activity belong to five preserved classes: HSP33, HSP60, HSP70, HSP90, HSP100, and the small heat-shock proteins (sHSPs).

| Approximate molecular weight (kDa) | Prokaryotic proteins | Eukaryotic proteins | Function |
|------------------------------------|----------------------|--|---|
| 10 kDa | GroES | Hsp10 | |
| 20-30 kDa | GrpE | The HspB group of Hsp. Ten members in mammals including Hsp27 or HspB1 | |
| 40 kDa | DnaJ | Hsp40 | Co-factor of Hsp70 |
| 60 kDa | GroEL, 60kDa antigen | Hsp60 | Involved in folding of protein after its post-translational import to the mitochondrion/chloroplast |
| 70 kDa | DnaK | The HspA group of Hsp including Hsp71, Hsp70, Hsp72, Grp78 (BiP), Hsc70 found only in primates | Protein folding and unfolding provides thermal tolerance to cell on exposure to heat stress. It also prevents protein folding during post-translational import into the mitochondria/chloroplast. |
| 90 kDa | HtpG, C62.5 | The HspC group of Hsp including Hsp90, Grp94 | Maintenance of steroid receptors and transcription factors |
| 100 kDa | ClpB, ClpA, | Hsp104, Hsp110 | Tolerance of extreme temperature |

FUNCTION¹

- (A) Upregulation in stress
- (B) Role as chaperone
- (C) Housekeeping

Heat-shock proteins also occur under non-stressful conditions, simply "monitoring" the cell's proteins. Some examples of their role as "monitors" are that they bring old proteins to the cell's "recycling bin" i.e., proteasome and they help newly synthesized proteins to fold properly. These activities are part of a cell's own restore system, called the "cellular stress response" or the "heat-shock response".

- (D) Cardiovascular
- (E) Immunity
- (F) Role in cancer

Heat shock proteins in tumor cells

Hsp, such as Hsp70, Hsp27, and Hsp90, inhibit apoptosis by direct physical interaction with apoptotic molecules, are also overexpressed in several tumor cells.^{4,5} As in case of HSP27 : it enhances the tumorigenicity of colon carcinoma cells (Garrido et al, 1998),⁶ whereas, HSP70 is highly expressed in

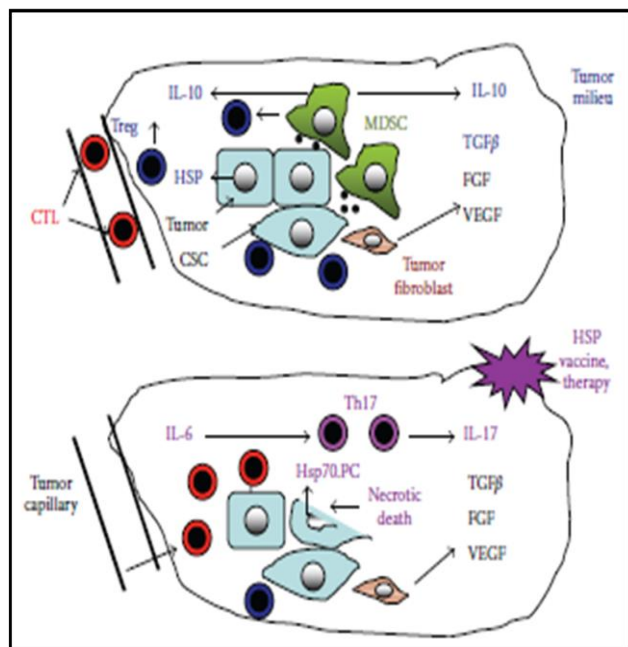
human breast tumors,⁷ & HSP90 was reported in prostate carcinomas (Akalin et al., 2001).⁸

Similarly, HSP bind to procaspases, inhibiting their activation (Beere & Green, 2001).⁹ Depletion of Hsp70 from tumor cells by various methods induces their apoptosis (Wei et al., 1995; Nylandsted et al., 2000, 2002).¹⁰ Inhibition of Hsp90 in tumor cells results in the dimerization-induced activation of death receptors, suggesting that Hsp keep death proteins in an apoptosis-resistant state by a direct association (Hulkko et al., 2000). Aging and various diseases, such as neurodegenerative diseases, induce the accumulation of damaged/misfolded proteins due to oxidative stress and/or proteotoxic insults. Moreover, chaperone function (Nardai et al., 2002),¹¹ HSP induction, and the degradation of damaged proteins are all impaired under these conditions (Soti & Csermely, 2000, 2002).^{5,12} In such cases, the increased demand of chaperone function may exceed the available chaperone capacity, which results in an unbalance of cellular homeostasis termed chaperone overload.⁵

Tumors undergo facilitated evolution due to the increased proliferation and selection pressure.

Conventional antitumor therapies (chemotherapy, radiotherapy, hyperthermia, etc.) all induce Hsp in surviving cells.^{13,14} The overexpression of Hsp may help the accumulation of hidden mutations in tumors, which can help their further progression to more aggressive types of malignant/metastatic cells (Caporale, 1999; Csermely, 2001).^{5,14} Indeed, the induction of Hsp70 by hyperthermia and anticancer drugs was reviewed and was shown to be more effective in chemoresistant tumors (Brozovic et al., 2001).¹⁵ (Fig 1)

Fig 1- defines the role of heat shock proteins. The upper part of the figure depicts tumor cells (pale blue), including cancer cells with a cuboid epithelial shape and more spindle-shaped cancer stem cells (CSCs), suggesting the EMT (epithelial-mesenchymal transition) characteristics ascribed to CSC. The tumor is represented as a heterogeneous cell colony containing myeloid suppressor cells (MDSCs; green), Treg (dark blue), and tumor-associated fibroblast



CONCLUSIONS AND PERSPECTIVES

The involvement of Hsp in a multitude of intracellular actions places them as central coordinators in deciding the fate of cell. The level of various Hsp (the Hsp pattern), as well as the amount of Hsp, which are not occupied by damaged, misfolded proteins, can be critical in cytoprotection and cell survival. We need much more comparative investigations on the

(TAF; orange). Dominant cytokines in the tumor microenvironment include IL-10 and TGF β . The growth factors FGF and VEGF are secreted by TAF. To the left of the figure is depicted a tumor capillary containing CD4⁺ T cells (red) that have stalled at the capillary wall. Tumor cells are depicted as secreting Hsp70-containing exosomes (black circles) that recruit MDSCs as well as free Hsp70 that may also trigger immunosuppressive responses. The lower section suggests the potential effects of therapy using molecular chaperone vaccines, in which IL-6 is now at high levels and the cytokine profile is proinflammatory, cognate CTL has crossed the capillary wall, penetrated the tumor interstitial spaces, and recognized MHC class I associated with tumor antigens. Such tumor cells can then be killed in an antigen-specific manner. In addition, Hsp70 peptide complexes (Hsp70.PC) are secreted from necrotic tumor cells and can trigger anticancer CTL after entering APC and cross-presentation to CD4⁺ T cells in afferent lymph nodes.

induction of various Hsp, as well as on their occupancy, to get a full picture of the optimal levels of these proteins. However, from the number of successful clinical studies, one point is already clear: Hsp can be used as novel molecular targets for pharmacological and therapeutic

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