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Review

Heat shock proteins in oncology: Diagnostic biomarkers or therapeutic targets?

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ABSTRACT

Heat shock proteins (HSP) are a family of proteins induced in cells exposed to different insults. This induction of HSPs allows cells to survive stress conditions. Mammalian HSPs have been classified into six families according to their molecular size: HSP100, HSP90, HSP70, HSP60, HSP40 and small HSPs (15 to 30 kDa) including HSP27. These proteins act as molecular chaperones either helping in the refolding of misfolded proteins or assisting in their elimination if they become irreversibly damaged. In recent years, proteomic studies have characterized several different HSPs in various tumor types which may be putative clinical biomarkers or molecular targets for cancer therapy. This has led to the development of a series of molecules capable of inhibiting HSPs. Numerous studies speculated that over-expression of HSP is in part responsible for resistance to many anti-tumor agents and chemotherapeutics. Hence, from a pharmacological point of view, the co-administration of HSP inhibitors together with other anti-tumor agents is of major importance in overcoming therapeutic resistance. In this review, we provide an overview of the current status of HSPs in autoimmune, cardiovascular, and neurodegenerative diseases with special emphasis on cancer.

Contents

Abbreviations: 2 DE, 2D gel electrophoresis; 2DPAGE, 2D polyacrylamide gel electrophoresis; AIF, Apoptosis inducing factor; Apaf-1, Apoptotic protease activating factor 1; APC, Antigen presenting cell; ASK-1, Apoptosis Signal-regulating Kinase 1; Bag, Bcl-2-associated athanogene; BAX, Bcl-2-associated X protein; CAD, Caspase activated DNase; CARD, Caspase-recruitment domain; CCT, Cytosolic chaperonin; COPD, Chronic obstructive pulmonary disease; CRC, Colorectal carcinoma; DAXX, Death Associated Protein 6; DFF 40, DNA fragmentation factor 40; DISC, Death Inducing Signalling Complex; ds, double-stranded; EGFR, Endothelial growth factor receptor; ELISA, Enzyme linked immuno-sorbent assay; ER, Estrogen receptor; FADD, Fas Associated Death Domain; GP, Glycoprotein; GRP, Glucose regulated protein; HCC, Hepatocellular carcinoma; Her, Human epidermal growth factor receptor; Hip, HSC70 interacting protein; Hop, HSP organizing protein; HSC, Heat shock cognate; HSF, Heat shock transcription factor; HSP, Heat shock protein; ICAD, Inhibitor of caspase activated DNase; JNK, c-Jun N-terminal kinases; MAPK, Mitogen-activated protein kinase; MAPKAP, Mitogen-activated protein kinase-activated protein; MS, Mass spectrometry; MyoD, Myogenic differentiation protein; NFAT, Nuclear factor of activated T-cells; NF-KB, Nuclear factor- kappaB; NSCLC, Non small cell lung carcinoma; PET, Positron emission tomography; PKA, Protein kinase A; PKR, Protein kinase R; PP5, Protein phosphatase 5; ROS, Reactive oxygen species; SILAC, Stable isotope labelling with amino acids in cell culture; TRADD, TNF Receptor Associated Death Domain; TRAP1, Tumour necrosis factor type 1 receptor-associated protein1

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1. Introduction

Among the many changes in cellular activity and physiology, the most remarkable event in stressed cells is the production of a highly conserved set of proteins, the heat shock or stress proteins [1]. Intensive research into the structure and function of heat shock proteins (HSPs) has been ongoing for the past 20 years [2]. They are of considerable interest since they have been shown to have a pivotal role in cell cycle progression and cell death (apoptosis) and to be involved in many disease processes. The heat shock or stress response is a cellular adaptive response, which helps maintain cellular homeostasis under stress.

It has been observed that immediately after a sudden increase in temperature all cells show induced expression of a family of genes known as the HSP genes. The DNA sequence that makes up this family of genes is highly conserved across species. This family of genes was originally so named because of their expression after exposure to heat. However the same response occurs after different insults including environmental and metabolic stresses such as hypoxia, ischemia, hyperoxia, anoxia, exposure to UV light and chemicals, nicotine, surgical stress, nutritional deficiencies (e. g., glucose deprivation), emotional and mechanical stress, mechanical injury and viral agents or other stresses, such as exposure to toxic radicals and carcinogens [3–5].

Under stress conditions, such as heat shock and some pathological states, stress proteins are rapidly induced through transcription and translation mechanisms. The mechanism of HSP production and their activation are illustrated in Fig. 1. The inducible heat shock response involves a signaling pathway leading to the activation of transcription factors [6]. Transcription of HSP genes is under the control of a family of heat shock transcription factors (HSFs). Different members of the HSF family may be activated by different specific stresses [7]. Although various HSFs have been reported, HSF-1 has been shown to be the main regulator of the short-term induction of HSP. In resting cells, HSF-1 is a monomer; however in stressed cells, active HSF-1 exists as a trimer [8] which is capable of binding to the promoter site of the stress protein gene and initiating transcription and translation. HSPs play an important regulatory role in gene transcription. If HSP is over-expressed in the absence of stress it binds directly to the HSF1 trans-activation domain resulting in its suppression [9]. In addition, some members of the HSF family help the long-term induction of HSP or exhibit important roles in the regulation of gene expression and developmental processes [10].

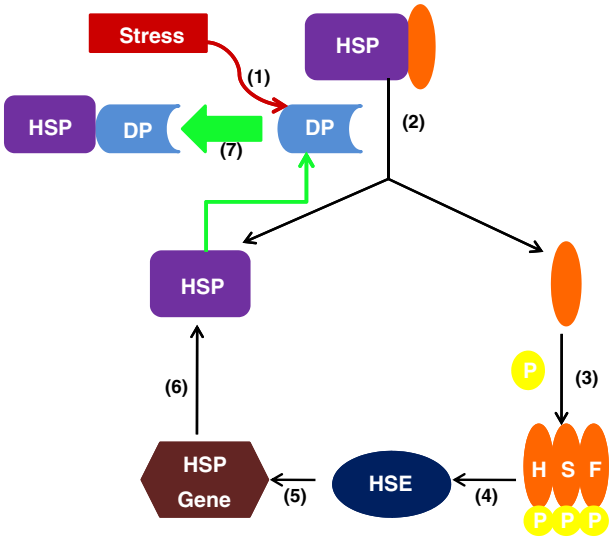

Fig. 1. Mechanism of HSP activation and repair of denatured proteins (DP): (1) Stress conditions lead to protein denaturation. (2) The presence of DP stimulates the dissociation of the HSP-HSF complex. This complex limits the transcription process in the absence of DP (3); while HSP is free to bind to DP, HSF is being activated through phosphorylation and trimerization in order to produce more HSPs. (4) Activated HSF can now bind to the heat shock element (HSE). (5) HSE is a part of the promoter region of the HSP gene. (6) Much HSP is produced. (7) Newly formed HSPs are able to bind more DPs.

HSPs are ubiquitous proteins in both prokaryotic and eukaryotic cells. As the name suggests, HSPs are induced in cells exposed to heat although stress proteins (Chaperonins) can be induced by many different kinds of insults allowing the cells to survive in otherwise lethal conditions [11]. Mammalian HSPs have been classified into six families according to their molecular size: HSP100, HSP90, HSP70, HSP60, HSP40 and small HSPs (15 to 30 kDa) including HSP27. Table 1 presents a summary of these proteins, their cellular location and function. High molecular weight HSPs are ATP-dependent chaperones, while small HSPs act in an ATP-independent fashion [12]. Each family of HSPs is composed of members expressed either constitutively or regulated inductively and is targeted to different subcellular compartments [13]. Constitutive activation of HSPs may occur in cells even in the absence of environmental stressors. For example, HSP-90 can constitute up to 1% of total cellular protein in unstressed cells [2] indicating that these proteins have a role in maintaining protein conformation even under normal conditions.

Under stress conditions, the HSP90 dimers tend to associate into tetra-, hexa-, and octamers, and even higher oligomers [14]. Under physiological conditions, HSP90 are found in association with several intracellular proteins including calmodulin, actin, tubulin, several kinases, and some receptor protein [15]. Components of HSP90 complexes like protein kinases and steroid receptors may mediate nuclear transport of HSP90 especially under heat shock stress. It is likely that HSP90 forms stable complexes with actin filaments and binds to tubulin to protect microtubules; therefore it may mediate the structural organization of the proteosome, a multicatalytic complex, when cellular ATP levels fall [6]. Similarly, HSP27 tends to oligomerize under stress conditions and it has been previously demonstrated that in cancer cells endogenous HSP27 is a major argpyrimidine modified protein and that this modification involves HSP27 oligomerization [16]. Argpyrimidine is a methylglyoxal–arginine adduct formed as a result of the non-enzymatic glycation of arginine residues of proteins in cancer cells showing increased glycolysis [17].

HSP27 and HSP70 are strongly and universally induced by different stresses while their expression is low under physiological conditions permitting constitutive cellular activities to proceed [18]. Apart from their intracellular location, HSP70 also have been found on the plasma membrane of malignantly transformed cells and in the extracellular space [19]. HSP70, HSP90, and the endoplasmic reticulum (ER)-resident chaperone protein GP96, belonging to the HSP90 family [20], have been found in the extracellular medium. This brings into consideration the dual function of HSPs: the intracellular cytoprotective/antiapoptotic function, and the extracellular immunogenic function [13]. The intracellular HSPs are known to participate in ensuring the folding of proteins into their correct tertiary structure, incorporation of polypeptides into intracellular membranes or in transport of proteins across those membranes [15] while the function of extracellular HSPs is immunogenic through the chaperoning of antigenic peptides. Members of the HSP70 and HSP90 families have been detected in the medium of antigen presenting cells (APCs). The uptake of HSP–peptide complexes by APCs was found to be specific, saturable, and concentration-dependent, and thus the existence of HSP-specific receptors has been hypothesized [13]. In this review the potential involvement of HSPs in different diseases is discussed, putting special emphasis on their apoptosis modulating functions in cancer coupled with the possibility that they are a strong candidate for therapeutic intervention.

2. HSPs as molecular chaperones and their client proteins

As stated above, HSPs are part of a group known as “molecular chaperones”, a nomenclature which clearly defines the function of