Heat Shock Proteins and their clinical Implications

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Abstract

Knowledge of the physiological role of heat shock proteins is currently limited; however better understanding of their function and thereby the acquisition of the capacity to harness their power might lead to their use as therapeutic agents and revolutionize clinical practice in a number of areas. Future work is needed to translate the experimental data on the capacity of heat shock proteins to induce tumor protection and immunity to infectious agents into the clinical environment. Approach to cancer vaccine is based on the role of HSP in the presentation of antigens. In several infections and especially autoimmune diseases, the implications of immune responses against HSP are still not properly or fully understood. HSP have clinical significance in conditions such as cardiac hypertrophy, vascular wall injury, cardiac surgery, ischemic preconditioning and ageing.

Keywords: Heat Shock, Protein, Physiology, Therapeutic agent, Vaccine Vehicle, Cancer, Reproduction, Immune system, Atherosclerosis, Cardiovascular Biology.

Introduction

Stresses are defined as forces that on their own, or in combination produce, or sustain strain. In biology, stress is the driving force behind the process of adaptation and evolution. A unique class of proteins known as “Heat shock proteins” (HSP) plays important role to cope up with the stress and strain. The first products of these genes were identified in 1974 and termed as 'heat shock protein' (Tissieres et at.1974). Heat shock proteins are group of proteins which expression is increased when cells are exposed to elevated temperature or other stress. This dramatic up regulation of the HSP by Heat Shock Factor (HSF) is the key part of the heat shock response. They are the most stable biologically active proteins and don’t denature due to their stronger hydrogen bonds, adequate hydrophobic internal packing and enhanced secondary structure. Heat shock proteins also known as stress proteins are present in all cells making up 5-10% of the total protein content under normal growth conditions, and can be markedly induced up to 15% of the total cellular protein content by a range of cellular insults. They appear when the cell is under heat stress or other stress. Production of high levels of heat shock proteins can also be triggered by exposure to different kinds of environmental stress conditions, such as infection, inflammation, exposure of the cell to toxins (ethanol, arsenic, trace metals and ultraviolet light etc.) starvation, hypoxia, nitrogen deficiency (in plants), or water deprivation. Under non-stressful condition HSP carry the old proteins to the cells “recycling bin” and also help in proper folding to newly synthesized proteins and thus act as ‘monitor’ of the cellular proteins.

Importance of Heat Shock Proteins

The function of a protein is determined by its three-dimensional structure. When excessive heat is applied to proteins, chains of amino acids, which are folded into spirals, loops and sheets, begin to loose their shapes. When the interior of these proteins gets exposed, proteins can adhere and form globs. This can make them dysfunctional. Protein conformational defects are responsible for a number of pathologies, ranging from Alzheimer's disease and oncogenic transformation in humans to heat and drought susceptibility in plants. HSP acts as chaperones and bind to denatured proteins to prevent aggregation and some of them have the ability to rescue already aggregated proteins.

Regulation of transcription of Heat Shock Protein

Stressors that cause protein unfolding, misfolding or aggregation trigger a stress response that leads to the induction of gene transcription for proteins with the capacity to stabilize and refold proteins, thereby re-establishing the balance between protein synthesis, assembly and degradation. Regulation of HSP gene transcription is mediated by

the interaction of the HSF, transcription factors (of which the principal one in vertebrates is HSF1) with heat shock elements (HSEs) in the HSP gene promoter regions. In the unstressed state, HSF1 is present in the cytoplasm as a latent monomeric molecule that is unable to bind to DNA. Under stressful conditions, HSF1 is hyperphosphorylated in a ras-dependent manner by members of the mitogen-activated protein kinase (MAPK) subfamilies (e.g. ERKI, JNK/SAPK, p38 protein kinase). HSF1 is converted to phosphorylated trimers with the capacity to bind DNA, and translocates from the cytoplasm to the nucleus. The signal that activates HSF 1 is thought to be a flux of newly synthesized non-native proteins.

Classification

HSPs are classified in to different families on the basis of their apparent molecular sizes (kilo Daltons), structure and function. Those families include: The HSP100 and higher mw, HSP90 family, HSP70 family, HSP60 family (chaperonin), "small" HSP family / alpha –crystallin proteins.

Heat Shock Proteins and Immune Response

HSPs trigger immune response through activities that occur both inside the cell (Intracellular) and outside the cell (extracellular).

Intracellular Activities: Inside the cell HSP functions normally by helping proteins to fold, preparing proteins for disposal and end up binding virtually every proteins in the cell. Research suggests that inside the sick cell, HSP takes the abnormal peptide-an antigen and move them from inside the cell to the outside cell surface. When the abnormal peptides are displayed in this way, they act as red flags, warning the immune system that the cell has become sick.

Extra cellular activities: When the sick cell dies and ruptures, spilling out the HSP-peptide complexes, which are detected by circulating antigen presenting cells (APCs). HSP complexes first bind to the CD91 receptor, which is present on the surface of the APC, and with the help of this receptor APC can take in this HSP complex. Once the APCs have taken in the HSP complexes, they travel to the lymph nodes of the immune system tissue that are where T cells 'see' these peptides and are then programmed to seek out cells bearing these specific, abnormal peptides.

Role of Heat Shock Protein as a Vaccine Vehicle

The need for more effective immunological prophylaxis (vaccines) and therapies for cancer and infectious diseases caused by intracellular pathogens has spurred intense investigation of immunogens and immunization strategies that elicit effective CD8+ cytotoxic T lymphocyte (CTL). It has been found out that immunization with antigens genetically fused to HSP70 elicits strong and long-lived humoral and cellular immune responses in the absence of adjuvant. HSP70 fusion proteins elicit antigen-specific CTL responses and protect mice from tumor challenge (Suzue et al., 1997). We have now shown the ability to elicit CTL resides in a 200-amino acid domain of HSP70 and is independent of CD4 (Huang et al., 2000). There is now substantial evidence that native HSPs isolated from tumors can be used as adjuvant-free anti-tumor vaccines in animal models; HSP70 and the distantly related chaperones gp96 and calreticulin share this vaccine activity (Udono and Srivastav, 1993). In addition, chemical conjugation or genetic fusion of antigens to mycobacterial HSP70 creates potent and customized immunogens that can elicit MHC class I-restricted, CD8+ cytotoxic T cell responses sufficient to mediate rejection of tumors expressing the fusion partner (Suzue et al., 1997). Most of this work has been done in mice, however, HSP conjugate vaccines have elicited immune responses in monkeys and HSP fusion vaccines are being tested in humans.

Role of Heat Shock Proteins in Reproduction

HSPs have the profound role in reproduction. HSP production is enhanced during in-vitro embryo culture and they are among the first proteins produced during mammalian embryo growth. HSP expression can be detected in the deciduas during the first trimester of pregnancy (Nouer et al., 1996). Maximum values of HSP27, HSP60 and Heat Shock Cognate 70 (HSC70) in the endometrium are expressed after ovulation and in the early secretory phase, which is the critical period of endometrial receptivity for an implanting embryo. Prevention of cytotoxic damage by cytokines has been proposed as another function of HSP in the endometrium. In the endometrium leukocytes can produce high levels of reactive oxygen species and cytokines. Both products can modulate the expression of HSP. Since leucocytes and cytokines, viz. Tumor necrosis factor-a (TNF-a) accumulate progressively during the recovery phase, it is possible that HSP protect endometrial cells from the adverse side effect of this leukocyte accumulation and cytokine release.

Spermatogenesis is accompanied by the expression of different HSP. During mouse and rat spermatogenesis, the constitutive form of HSP70 (HSC70) accumulates. HSP expression is an integral process during oogenesis in a number of species, growing oocyte spontaneously express high levels of the constitutive 70 KDa HSP (HSC70), thus HSC70 is formed at high levels in the pre-ovulatory oocyte (Curci et al., 1991). HSP also plays a role in the ovulation process and the maintenance of the post-ovulatory metabolic activity and survival of the oocyte.

Role of Heat Shock Proteins in Cancer

Heat-shock proteins are of potential interest to cancer researchers. This is based on the observations that animals may respond to cancer "vaccinations". Tumor cells were "attenuated" or weakened and injected in small quantities into a rodent, causing the rodent to become immune to future full-fledged tumor-cell injections. Some researchers are conducting research, using heat shock proteins in the treatment of cancer. While others speculated that HSPs may be involved in binding protein fragments from dead malignant cells and presenting them to the immune system. Recently, it was discovered that Heat Shock Factor 1 (HSF1) is a powerful multifaceted modifier of carcinogenesis. Hsp90 participates in many key processes in oncogenesis such as self-sufficiency in growth signals, stabilization of mutant proteins, angiogenesis and metastasis. HSP 70 is over expressed in malignant melanoma and in renal cell cancer. HSP60 has been shown to influence apoptosis in tumor cells which seems to be associated with a change in expression levels.

Role of Heat Shock Proteins in Atherosclerosis

Atherosclerosis is a chronic inflammatory disease. Risk factors for atherosclerosis are infections, oxidized low density lipoprotein, oxidative stress, hypertensions and biochemical stress. These factors directly stimulate cells of the arterial wall and/or other tissues to express high levels of HSPs. The physiological functions of these HSPs are to protect cells against apoptosis. But when they are stimulated by the risk factors means pathologically, the cells are dying; this releases intracellular HSPs into intercellular spaces to form soluble HSPs (sHSPs). sHSPs bind to TLR4/CD14 receptors, resulting in endothelial cells expressing adhesion molecules in smooth muscle cells leading to proliferation, and in macrophages inducing a range of pro inflammatory cytokines. Simultaneously, macrophages present antigens to T and B cells, which produce autoantibodies and autoreactive cells against HSPs. All contribute to the development of atherosclerosis.

Role of Heat Shock Proteins in Cardiovascular Biology

How a cell responds to cell is the central problem in cardiovascular biology. Diverse physiological stress (eg. Heat, haemodynamics, mutant proteins and oxidative injury) produce multiple changes in a cell that ultimately affect protein structures and functions. HSP chaperones have clinical significance in conditions such as cardiac hypertrophy, vascular wall injury, cardiac surgery, ischemic preconditioning and aging. HSP70 has potential role in ischemic preconditioning. Specifically over expression of the major 70-KDa heat shock protein (HSP70) in the transgenic mice improve myocardial function (Plumer, et al., 1995), it also preserved metabolic functional recovery and reduced infarct size after ischemia/ reperfusion. HSP70, HSP27 and Gamma-crystalin can protect primary cardiomyocytes against ischemic damage.

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