ARTICLE
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Heat shock proteins (HSP) - As vaccines vehicle

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Since the report on the heat-induced appearance of chromosomal puffings in salivary gland tissue of *Drosophila busckii* in 1962, a new research domain has been intensively explored. This research resulted in the discovery of large number of related proteins and their physiological role in many prokaryotic and eukaryotic organisms, tissues and individual cells and at the level of sub-cellular structures. These proteins were originally called "heat shock proteins", because they were discovered in salivary glands and other tissues of *Drosophila melanogaster* recovering from a so-called transient sublethal heat shock, during which body temperature was increased nearly 5°C above normal body temperature care.

Heat shock proteins (HSPs) are highly conserved, ubiquitous and abundant proteins, essential for cellular viability. Their expression increases in response to a variety of different metabolic insults. HSPs are induced when a cell undergoes various types of environmental stresses like heat, cold and oxygen deprivation. HSPs are also present in cells under perfectly normal conditions. This increase in regulation in transcritionally regulated. The dramatic upregulation of HSPs is a key part of the heat shock response and is induced primarily by heat shock factor (HSF). HSPs are found in virtually all living organisms, from bacteria to humans. These are named according to their molecular weights. Most notable is their role as molecular chaperons, facilititating the synthesis and folding of proteins throughout the cell. In addition HSPs have been shown to participate in protein assembly, secretion, trafficking, protein degradation and the regulation of transcription factors and protein kinases. Increased level of HSPs after stress plays a central role in homeostasis. Increased expression of HSPs is mediated at multiple levels: mRNA synthesis, mRNA stability, and translation efficiency. In fact, accumulation of unfolded or misfolded proteins is a form of stress that induces expression of HSPs. HSPs 60, 70 and 90 are generally found in the cytosol and mitochondria. A more distantly related family of chaperons, including group 96 and calreticulin, are located in the endoplasmic reticulum.

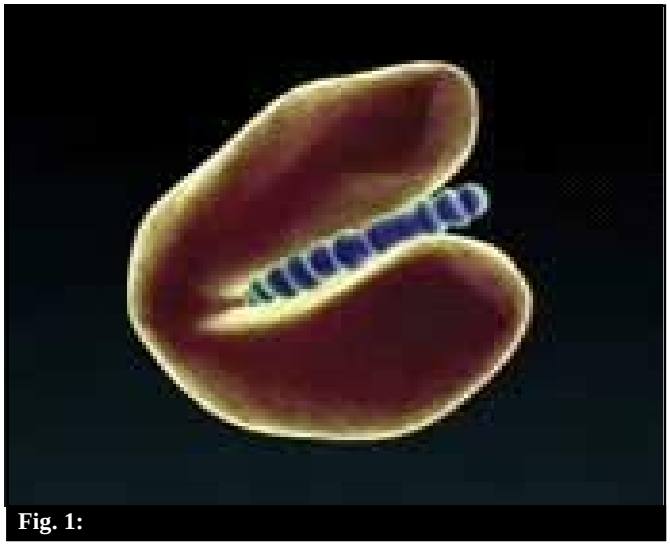

Fig. 1:

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 disfunctional. 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. Chaperones protect against denaturization. Heat Shock Proteins bind to denatured proteins to prevent aggregation. Some Heat Shock Proteins, like Hsp104, have the ability to rescue already aggregated proteins.

Different types of heat shock proteins:

Human, fruit flies and plants all have HSPs very similar in sequence and in structure. Heat Shock Proteins are classified by their molecular weight, size, structure, and function. They are divided into several families such as.

HSP100:

– Function as chaperones solubilizes protein aggregates there by dissociating them facilitates

proteolysis

– Essential in yeast for acquired thermo tolerance essential for yeast prion propagation

HSP90:

– Stabilizes proteins prior to complete folding or activation forms stable complexes with inactive glucocorticoid receptor and other transcription factors most abundant non-ribosomal protein (cytosolic version)

– Most abundant protein in endoplasmic reticulum (ER version)

HSP70:

– Assists in protein transport into mitochondria and the endoplasmic reticulum

– Protects proteins under stress. Stabilizes proteins prior to complete folding

- Transports across membranes and proteolysis

Hsp60:

Includes GroEL from bacteria, rubisco-binding protein from chloroplasts, HSP60 from mitochondria, and the t-complex polypeptide 1 from eukaryotic cytosol oligomeric structure critical composed of 14 subunits arranged in two stacked 7-membered rings, distinct ring-shape or double donut quaternary structure.

Heat shock proteins as vaccines vehicle:

Two hsp 70 genes are located within the human major histocompatability complex class III region, between the complement and tumor necrosis factor genes. An hsp 90 gene is linked to a minor histocompatability locus near murine H-2.

Hsp 60 and 70 is major targets of immune response to a wide variety of pathogens. Up to 20% of CD4 + T cells responding to mycobacterial infection are specific for hsp 60.

Immunization with a variety of pathogen HSPs induces strong immune responses and provides protection against disease caused by pathogens. HSPs appear to be fairly immunogenic; multiple B cell and T cell epitopes are found on mycobacterial hsp 60 and 70, as well as other hsps. HSPs of pathogens and mammals are very similar most people don't develop dangerous autoimmune responses to self HSPs. In fact, healthy people do posses T cells which recognize these self HSPs, but suffer no ill effects (except sometimes arthritis)

There is now substantial evidence that native HSPs isolated from tumors can be used as adjuvant-free anti-tumor vaccines in animal models. (e.g. - hsp70, gp96 and calreticulin). Chemical conjugation or genetic fusion of antigens to mycobacterial hsp 70 creates potent and customized immunogens that can elicit MHC class I restricted, CD 8+ cytotoxic T cell responses sufficient to mediate rejection of tumors expressing the fusion partners. Hsp fusion protein vaccines do not require adjuvants. A recombinant protein consisting of the HIV-1 p24 antigen fused to the amino-terminus of mycobacterial hsp 70 elicits both humoral and cellular immune responses in mice. Hsp fusion proteins elicit CTL responses in the absence of adjuvant.

Tuberculosis is another target of Hsp vaccine work. Celio Silva, professor and head of the department of parasitology at University of Sao Paulo, and his colleagues have reported successfully treating mice infected with the disease by injecting them with a vaccine based on the DNA for two HSPs from two different mycobacteria. Development of HSP vaccines to treat various cancers is the current, highly meticulous research area. Some of the cancers include: renal cancer, melanoma and pancreatic.

HSPs function as intra-cellular chaperones for other proteins. They play important role in protein-protein interactions, such as folding and assisting in the establishment of proper protein conformation and prevention of unwanted protein aggregation. Molecular chaperones are able to recognize damaged proteins and further sorting them into repair or to proteolysis. By helping to stabilize partially unfolded proteins across membranes within the cell. HSPs can regulate the life or death of cells by directly modulating certain apoptotic signaling events or indirectly, by participating in age processing. A subpopulation of HSPs is present either on the surface or within the cellular membranes. Via their special lipid interactions HSPs can control major attributes of the membrane like fluidity, permiability or non-bilayer propensity. The membrane microdomain (membrane-raft) associated HSPs can also participate in the orchestration of distinct–raft associated signaling platforms. In spite lacking a secretory signal, some HSPs are mysteriously released from cells by different secretory mechanisms. Irrespective of the secretory routes chosen, these exogenous HSPs then can stimulate both the innate and the adaptive immunity.

HSPs appear to serve a significant cardiovascular role. Hsp 90, hsp 84, hsp 70, hsp 27, hsp 20 and alpha beta crystalline all have been reported as having roles in the cardiovasculature. Hsp 90 binds both endothelial nitric oxide synthase and soluble guanylate cyclase which in turn are involved in vascular relaxation. A downstream kinase of the nitric oxide cell signaling pathway, protein kinase G, phosphorylates a small HSP, hsp 20. Hsp 20

phosphorylation correlates well with smooth muscle relaxation and is one significant phosphoprotein involved in the process. Hsp 20 appears significant in role of preventing platelet aggregation, cardiac myocyte function, prevention of apoptosis after ischemic injury, skeletal muscle function and muscle insulin response. Hsp 27 is a major phosphoprotein during muscle contraction. Hsp 27 functions in smooth muscle migration and appears to serve an integral role.