



Review on Heat Shock Proteins and Their Fundamental Role in Cancer

Mahendra,G., Krishna,C. and ,Divya,B.

Department of Biochemistry,S.V.University,TIRUPATI-517502
Andhra Pradesh.

ABSTRACT

Body of living thing is a complex machine that works on multifunctional processes and needs maintenance. Heat shock protein is a specific type of protein that cares about many normal functions of the body. These proteins have many dynamic occupations to shield the body from various diseases and also a key role in the coiling and uncoiling of proteins, prevent from apoptosis and transportation of proteins. Along with these all properties, the foremost function of these proteins is prevention from cancer and a significant role in cancer diagnosis. Commonly heat shock protein known as chaperones and a wide range of their types have been discovered with their functions as well. Recently many scientists are working on additional investigation of heat shock proteins. This review concludes some basic types of heat shock proteins and their elegant purposes and also providing an open eye for new scientist about a further investigation of heat shock protein.

KEYWORDS: HSP ,Cancer, Apoptosis, HSP types

INTRODUCTION

The escalating human race has resulted in the emergence of new diseases via the imbalance between the food supply chain, global warming, and poor health status in underdeveloped countries. One of the most abruptly increasing condition in the human population with its devastating effects is “Cancer”. In 2018, about 0.6 million individuals died in the United States just because of cancer, by taking into account the alarming situation, the scientific community and research institutes are actively working to trump up an adequate solution to this disaster. The role of heat shock proteins has been proved to be effective for controlling and minimizing the effect of this catastrophe. Heat shock proteins coherently termed stress proteins, naturally present in all the cells of an organism (Lindquist,1986).

These heat shock proteins are contemporaneous in complex state among all species. A special type of heat shock proteins is “Chaperones” their chief role is the coiling and uncoiling of proteins besides they also implement other functions like protection of cells from apoptosis, cell signaling, the formation of multi-complex proteins and transportation and storing of protein in subcellular compartments. Heat-shock proteins (HSPs), or stress proteins, are present in all organisms and all cells. Recent studies have shown that heat shock proteins have exhibit antigen presentation by transferring antigen peptides to major histocompatibility complex class 1 and class 2 molecules (Li *et al.*, 2002). Moreover, heat shock proteins help to strengthen the immune system like macrophages and the dendritic cells for presentation of antigen (Srivastava, 2002). Heat shock proteins have the variable molecular size of 10 to 100 kDa (kilo Dalton) or more and they reside in different cellular compartments. Xu (2002) highlighted the accumulation of heat shock proteins in various locations within the cell such as HSP10, 60 and 75 in mitochondria while the other heat shock proteins are present on cytoplasm, nucleus, endoplasmic reticulum and cytosol under different physiological conditions. This review overlooks the different types of HSP’s and their physiological activity within the body and how they fruitfully take part in diagnosing the cancer and its treatment.

TYPES OF HEAT SHOCK PROTEIN (HSP) AND THEIR IMPRESSIVE FUNCTIONS

HSP has 10 to 30 types having a molecular weight ranging from 15 to 43 kDa (kilo Dalton) and recognized as heat shock protein β (HSPBs) with the chaperoning effect in the embryonic development process. HSPBs maintain homeostasis with the cytoskeleton proteins to preclude damage and conserving the cellular function. HSPB-1, HSPB-6, HSPB-7, and HSPB-12 have a characteristic responsibility in respiratory morphology development. The absence of HSPBs in cardiovascular diseases leads to the development of squeal like cardiomyopathy and lethal myopathy. (Juo et al., 2016) (Ke et al., 2011) (Rosenfeld et al., 2013) Heat shock proteins with a molecular size of 15-30 kDa are known as small HSP and these are 9 in numbers present in mammals (Mounier & Arrigo, 2002). HSP-27 and HSP-25 present in mice and recently identified HSP-22 is also categorized in small molecular size heat shock proteins. Other members of this family include α A- and α B crystallins, Hsp B different types like HSP β -2, HSP β -3, HSP β -7, HSP β -8, and HSP β -9.

HSP10 is released from the fetal placental unit and mainly suppresses the maternal immune system (Noonan et al., 1979). HSP10 is consisted of 101 amino acids and also used as a biomarker in endometrial cancer (Dubé et al., 2007). In mitochondria, HSP10 has a primary function in the protein folding which is supplied by the adenosine triphosphate (ATP) (Meyer et al., 2003). HSP10 is produced as a by-product during the neoplastic cell proliferation process and known as the growth factor of the cell and it plays an important role in tumor growth (Quinn et al., 1990). Human small HSPs is consist of 105 to 205 amino acids a crystalline domain which are 80 homologous and sequenced residues (Ingolia and Craig, 1982). This crystalline domain is much conserved and has an identity of 38% to 60% amino acids (Mounier and Arrigo, 2002). This crystalline structure can be changed by different factors like pH, Calcium ions, ionic strength and temperature. The structure of heat shock protein 16.5 has a crystalline domain and its basic function is similar to chaperone which helps in folding and miss-folding of proteins (Bertz et al., 2010). The small HSPs have a clear effect on the function of the enzymatic activity of myosin. At 43°C for 30 minutes, the crystalline affects ATPase performance that prevents the aggregation of protein at the same place and by maintaining the ATPase performance that involves the generation of myofibrils without myosin unfolding and muscle performance under different stress and in case of access exercise (Melkani et al., 2006). HSP-50 and HSP-40 are present in the cytosol and acts as the co-chaperone of HSP 70 which helps in protein coiling and uncoiling. HSP40 has a size of 43 kDa and has a different type of amino acid sequence with having different N terminal lengths. These heat shock proteins also have a-crystallin domains and extension of C terminal with a high amount of I-X-I/V motifs (Ghosh et al., 2005).

The HSP47 is also involved in the folding and unfolding of protein along with its involvement in atherosclerosis. HSP47 has the distinctive and pinpoint expression in the collagenous regions of atherosclerosis. The cells which are involved in pro- collagen expression are also intricate in the expression of HSP47 stimulated by the low density of lipoprotein and heat shock protein in the smooth muscle cells. It has been researched that HSP47 is an important part of the coronary atheroma of humans. HSP47 is also required not only for the transportation of collagen protein within cells as well as for the folding into the tertiary structure. HSP47 is present in the endoplasmic reticulum and its function is to support the folding of collagen protein and its release into the extracellular environment. The HSP60 is present in mitochondria having a size of 970 kDa which is a large hetero- oligomer protein complex known as TCP ring with several other proteins that have an important role in protein formation and structure. Besides HSP-60 beneficial effects, it causes the development of rheumatoid arthritis and systemic sclerosis in humans whereas arthritis and insulin-dependent diabetes mellitus in the mice. HSP70 belongs to the family of GRP78 (Glucose response protein 78) located in the cytosol, helps in the formation of protein, folding, transportation as well as a leading role in the prevention of protein degradation in the endoplasmic reticulum. The expression of HSP70 is done by physical exercise (Banfi et al., 2004). The expression of HSP70 and HSP90 is variable and depends on different individual abilities of athletic and regulation of these proteins is done in the response of heat acclimation (McClung et al., 2008). The HSP70 plays the role of a chaperone as in the formation, transportation of newly synthesized protein into the cell and in case of denatured proteins. It also helps the native proteins in folding and the stabilization of their functional structure (Ogawa et al., 2011). Along with HSP70, their modification with carbohydrates also helps in the GRP78 (Glucose response protein 78) to maintain the structure of native proteins and folding of these native proteins into their functional structure.

GRP78 has a supreme ability to resist the ultraviolet rays and form cisplatin which is a very famous anticancerous drug. HSP90 is present in the cytosol and nucleus of cells (Shastry et al., 2002). When muscles are under load which increases the muscle damage chances and causes different problems like muscle soreness. It elevates the hot conditions and due to its elevation, HSP72 and HSP90 expression increases (Tuttle et al., 2015). HSP90 has also a key role in the folding of myosin and the construction of sarcomere (Du et al., 2008)

(Etard *et al.*, 2007) (Hawkins *et al.*, 2008) (Srikakulam *et al.*, 2008). The structure of HSP90 consists of the N-terminal binding of ATP, substrate interacting middle domain, and C-terminal dimerization domain (Jackson, 2012). Due to the binding of ATP to the N-terminal ATP binding domain, the regulation of myosin filament construction and the myofibrillogenesis is done by HSP90 (Hawkins *et al.*, 2008). HSP90 can bind with different types of receptors in a specific manner such as binding with steroid receptors, actin microfilaments, intermediate filaments, microtubules, and protein kinases. Besides these, HSP90 is an active component of glucocorticoid receptors which are found in the form of several protein complexes. HSP40 and HSP70 act as co-chaperone with heat shock protein 90. HSP90s are also present in the cytoplasm as well as in endoplasmic reticulum which play significant features in the folding of newly synthesized proteins. HSP100 is present in the cytoplasm of the cell and acts as co-chaperone with the collaboration of different heat shock proteins like HSP40, HSP70 and HSP90 and these combinations play a vital role in the aggregation and refolding of proteins. HSP110 is located in the cytosol and the nucleus of cells (Dimauro *et al.*, 2016). The HSP110 and HSP70 have a distinctive loop structure that helps the immune system to produce an immune response in different conditions (Zuo *et al.*, 2016). HSP110 with the collaboration of HSP70 and GRP79 helps in the folding of protein structure and survival of cells in different stress conditions (Hartl, 1996) (Gething and Sambrook, 1992).

HEAT SHOCK PROTEIN ROLE IN CANCER

HSP90 is the type of molecular chaperone which has a function in the stability and ultimate functioning of mutated cells and overexpressed signal proteins for the better growth of cancer cell or the survival of the cancerous cell. HSP90 includes various types of proteins such as p53, Akt, Raf-1, HIF-1 α , HER/2Neeu (ErbB2) and Bcr-Abl. The inhibitory protein of HSP90 causes the loss of stability and degradation process of different types of HSP90 such as allylamino-17 demethoxygeldanamycin (17AAG) which is inhibitory HSP90 protein. The HSP90 fraction is present on cell surfaces which has a role in the progression of melanoma. Antibodies and cell impermeable HSP90 cause the inhibition of these cell surface fractions of HSP90 and block the invasion and cell progression as well as the metastasis process in vivo. So that, HSP90 cell surface proteins have an intense role in the tumor metastasis and can cause interaction with the intracellular function. HSP27 is the type of heat shock protein that has a role as a chaperone which not ATP dependent and discovered for the refolding of damaged proteins (Kim *et al.*, 1998). HSP27 mostly located in the cytosol and possess properties like antioxidant and against apoptotic activity (Simioni *et al.*, 2009). On the other side, heat shock protein has a role in cell growth, cytoskeleton architecture, cell migration and as well as in the progression of the tumor. It is the reason that HSP27 has protective and counter protective properties in case of different diseases (Khalil *et al.*, 2011).

This type of heat shock protein is different from the other heat shock proteins due to its response in case of stress. HSP27 also responds to oxidative stress as well as chemical stress. In the case of oxidative stress, the HSP27 plays a role as an antioxidant by reducing the amount of reactive oxygen in response to increased glutathione level and lowered iron concentration into the cell. HSP27 show anti-apoptotic activity by the interaction with dependent and independent apoptotic pathway related to mitochondria. It is also stated that HSP27 is also involved against the apoptotic activity by inhibiting the caspase-dependent apoptotic process (Havasi *et al.*, 2008). Apart from its presence in the cytosol HSP27 is also present in the intra and extracellular environment. Various studies had shown that in different categories of cancer like brain, ovarian, prostate and breast cancer, there was an increase in the amount of HSP27 (Calderwood, 2010). In Brain tumors case study, cytoplasmic immunoreactivity of HSP27 had to be found in meningiomas. HSP27 has been detected in every case study of meningioma tissues. Even overexpression has been seen in the cases of meningiomas (Assimakopoulou, 2000). HSP27 is also correlated with cancer of glial cells and with the Ki-67 index (Schmitt *et al.*, 2007).

In the case of colorectal cancer, HSP27 overexpression and accumulation also reduce the apoptotic mechanism which is induced by the alkylating agents (Graner *et al.*, 2007). Recent research has shown that in the case of prostate cancer, the overexpression of HSP27 has been analyzed as compared with the control group (MIYAKE *et al.*, 2006). As it was analyzed by ELISA, the HSP27 level is also found in tumor microenvironment and serum. This overexpression of HSP27 is also noted in breast cancer as compared to the control group (Banerjee *et al.*, 2011). Interesting results had been obtained that the breast tumor cells produce more HSP27 level rather than serum (Mischak *et al.*, 2010).

CONCLUSION

Heat shock proteins coherently called as chaperone, with a chief role in the body is the maintenance of the normal structure of the protein. Recent studies have shown that heat shock protein has a role in cell protection from abnormal functions like oxidation, apoptosis, and formation of complex protein structures. Heat shock proteins are classified into different groups, according to the function they perform like identification of several diseases and cancer diagnosis. This review throws light on the functioning of heat- shock proteins in neonatal and later ages according to the types. Further research studies are needed to expressively declare heat shock proteins as a tool for the treatment of cancer and other diseases.

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