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Review Article

Investigating the Role of Thermal Shock Protein (Dank) HSP70 in Bacteria

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Abstract

Heat Shock Proteins (HSPs) are referred to as a set of proteins, which are expressed in the cell under stress conditions. These cells play a role in preventing changes in the conformation of proteins under stress conditions. HSPs are present in all living cells in bound or unbound states and are located in the nucleus and cytoplasm of the cell. HSPs as molecular chaperones are involved in various processes, such as folding of proteins and their accumulation and transportation, transition of peptides, and processing of antigen under physiological and stress conditions. HSPs bind to hydrophobic sites on polypeptides, resulting in conformation changes in them and also, preventing the formation of incorrectly folded peptides. The expression of HSPs is induced by several types of stressor agents such as fever, alcohol, inflammation, oxidative stresses and heavy metals, as well as conditions that cause injury and necrosis. The Heat Shock Protein 70 (HSP70) is considered to be the most sensitive protein among HSPs, and plays a role in various bacteria. The HSP70 family, both in eukaryotes and prokaryotes, is among the most protected structures, and in addition to being induced due to heat factors, is induced under other conditions and stresses, such as hypoxia and acidosis, viral and bacterial infections, etc. In this article, the role and function of HSP70 along with the role it plays in bacteria are briefly reviewed.

Keywords: HSP70; DnaK; Bacteria

Introduction

Heat shock protein

Heat Shock Proteins (HSPs) were first discovered and introduced by Ritosa in 1962. Based on the studies carried out in this field, researchers discovered that the Drosophila chromatin is rearranged by the heat, and the heat also causes abnormal salivary genes to appear. These investigations ultimately led to the fact that genes synthesizing HSPs are induced by stressors such as heat. In fact, the stressors such as heat induce heat shock transcription factors; accordingly, transcription begins as a result of the attachment of these factors to promoters of HSPs genes and then, they become translated into proteins at the cytoplasm level [1].

One essential question is why HSPs are necessarily important. HSPs have mechanisms; these mechanisms along with their role and necessity for use are important to be recognized. In fact, many cells have caused the production of HSP protein-producing genes to protect themselves from environmental and physiological stress conditions. HSPs have been identified and investigated in relation to a variety of environmental and physiological stresses and pathological factors [1].

HSPs are proteins that are continuously produced, and some increase with increased stress and in fact, can be induced by stresses. It should be noted that HSPs are not only induced by heat stress, and are also induced by many other stressors under certain conditions [2]. HSPs are among the most protected proteins in eukaryotes and prokaryotes, and their response also changes by a wide range of stressors. It should be noted that HSPs are expressed in two different conditions, which is discussed in the following [3].

HSPs are expressed under

1. Physiological conditions

2. Stress situations

Under physiological conditions: If a cell undergoes physiological stress conditions such as cell growth, differentiation and evolution and aging, it will have to produce a series of specific proteins, which are used to maintain cell structure. In fact, these proteins play their structural role in this way and show lower sensitivity by inducing heat stress. These proteins mostly play role of an associate and bind to polypeptides as a co-factor, preventing the torsion prior to maturation of the main proteins until they are transmitted to the final destination. Therefore, these types of proteins, which have a functional role, are called molecular chaperones [3].

Under stress conditions: Stressors are mainly environmental, metabolic or physiological. Cells are sometimes exposed to environmental and metabolic stress conditions, such as heat shock, chemotherapy agents, nutritional deficiencies, ultraviolet radiation, increased polyglutamine and anoxia frequency, hypoxia, etc., and have to produce a series of proteins that prevent the folding of proteins, as well as the structure condensation of multi-proteins and accumulation of proteins. These proteins, called HSPs, are better to be referred to as stressed proteins [3].

Molecular chaperones and their role

For a living organism's system to evolve, it requires a series of proteins to continue to grow. Proteins syntheses are associated with

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various processes. The synthesis of proteins and their evolution are accompanied by the correct folding of proteins. Folding is a process, in which the linear sequence of amino acids of a polypeptide chain obtains the structural property to become an active protein. Reaching an active structure causes proteins to reach a stable state in terms of energy level. The process of protein folding has been developed through in-cell support systems. These systems include highly protected protein families known as chaperone molecules, which are found in high concentrations in all living cells [4]. Chaperones control a various folding process during the synthesis of proteins from accumulation and transportation of them to the passage of peptides and their degradation. However, because heat stress strongly induces the synthesis of these proteins, they are called HSPs and also, chaperones. The role of chaperones is to prevent the transformation of structure of proteins by stress factors. HSPs bind to hydrophobic sites on polypeptides, resulting in conformation changes in them and also, preventing the formation of incorrectly folded peptides [4]. Chaperones, by binding to the hydrophobic section of newly emerging polypeptides or proteins that need to be refolded, undergo restructure changes through the ATP consumption and fold proteins [5].

Role of HSPs

HSPs have a dual role depending on how they are expressed inside or outside the cell. If they are expressed internally, they have a protective role that can lead to the survival of cells if they are under deadly conditions [6]. However, HSPs outside the cell are produced when the cell is exposed to long stress conditions. These types of HSPs have receptors at the surface of the cytoplasmic membrane, which are involved in the non-specific defense of the immune system [7]. In general, HSPs facilitate the synthesis and folding of proteins, structure condensation of multi-proteins, secretion, transportation and displacement of proteins across the membrane, decomposition of proteins and regulation of transcription factors and protein kinases [8].

In fact, these proteins help to reverse the denatured proteins, or cause them to decompose after stress or injury, thus preventing the metabolic effects resulting from the incorrect twist of proteins and cellular disease caused by radio toxicity [9,10].

Among other roles of HSPs, it can be pointed out that HSPs are immunodominant molecules, and many immune responses against microbial pathogens are significantly led toward these proteins. Taking into account the phylogenic similarity of these proteins in germs and mammals, HSPs are thought to act as harmful auto antigen potentials. In fact, the cross-reactive between the immune system's epitopes and HSPs causes the incidence of infection and autoimmune agents [11,12]. Various studies have shown that HSPs play an important role in cell cycle progression, embryonic development, cell differentiation and hormonal stimulation in vertebrates, as well as in growth of microorganisms [13]. Today, the role of HSPs has been used as the basis for clinical trials for the preparation of anticancer vaccines [14].

Origin of HSP production

Various studies have shown that neurons, monocytes, macrophages, B cells, and tumor cells with epithelial origin produce these types of proteins [15,16].

Types of HSPs

HSPs belong to a multigenic family and have molecular weight of 8 to 150 kDa; the naming of types of HSPs is based on their molecular weight [17]. In mammals, 4 general groups of HSPs are known to include HSP60, HSP70, HSP90, and SMALL HSPs [18]. However, in some other studies, HSPs in mammals have been divided into five groups of HSP27 (HSPB), HSP60 (HSPD), HSP70 (HSPA), HSP90 (HSPE), HSP100 (HSPC) [19, 20].

HSP70 and its role and function

HSPs in polypeptides bind to hydrophobic sites and as a result, cause structural changes in them. HSPs also prevent incorrect folding. HSP70 can be said to play a role in folding of proteins that have been destroyed and damaged by stress. What HSPs necessarily perform in these damaged and abnormal proteins is divided into several parts: firstly, they prevent the accumulation of these damaged proteins and secondly, they lead to correct folding of these proteins so that the proteins return to normal state. Thirdly, they result in correct folding of the previous accumulated proteins. Accordingly, the most important roles of HSP70 are the management of folding of damaged and abnormal proteins and proper conduction of newly synthesized proteins [21]. Various studies have shown that HSP70 cooperates with HSP100 and subsequently, naturally refolds [22,23].

Structurally, HSP70 has two isoforms of 66 and 76 kDa, both of which are called HSP70, which is derived from a gene with the same name [24]. In prokaryotes, the Hsp70 protein is a product of the dnaK gene, which is approximately 50% similar to the Hsp70 eukaryotic protein in the amino acid sequence [25]. In *E. coli*, it is one of the most common cytoplasmic proteins, and is about 1% of all cell protein in the optimum temperature. The first Hsp70 gene (dnaK) was detected at the Costa and Paulus laboratory, when a mutation was found on a *E. coli* λP propagation genome, since it was mutated in locus dnaK [26]. This protein has a half-life of 48 hours [27]. This protein is either continuously expressed or sometimes severely induced by stressors [28]. The family of HSPs, and especially HSP70, leads to folding through binding to ATP and can react with other proteins [29,30]. Overall, it can be said that HSP70 together with dnaJ and grpE genes are located in one operon, and thus can contribute to proteins in eliminating the damage caused by the heat [15]. In addition to the DnaK-DnaJ-GrpE system in *E.coli*, there are two other newly discovered proteins that are part of the chaperone system of the Hsp70 type: Hsc66 (the second Hsp70 protein in *E. coli*) and Hsc20 (another complementary protein). However, studies have shown that these proteins are part of a distinct molecular chaperone system, since their cellular functions are completely separate from the DnaK-DnaJ-GrpE system [30]. In various studies, the role of HSP70 in apoptosis inhibition and cellular resistance is mentioned [31,32]. The DnaK protein, or HSP70, consists of about 650 amino acids, and has two functional domains.

HSP70 has two sequences of N and C, whose N sequence is named Nucleotide-Binding Domain (NBD), which weighs about 40 kDa, that is, a protected or nucleotide binding sequence. This sequence also has the role of ATPase. This domain has two parts with an open space between them, and the nucleotide can bind to the open space in the

end section. In fact, each part has two subunits. For example, Part A is divided into two parts of a1 and a2, and Part B is divided into two parts of b1 and b2. There is a gap between Parts A and B where ATP enters, and it is involved in regulations [32].

However, the C sequence, also called Substra Binding Domain (SBD), has a molecular weight of 25 kDa and has a binding site for the polypeptide substrate [33,34]. In general, this part also consists of two subunits. including a base made up of two four-stranded anti-β β-sheets with 15 kDa and a lid that is the second subdomain of α-helical C-terminal, consisting of five helices, called A, B, C, D, and E [34]. It actually looks like a lidded box, with the substrate being located between the box and the lid [35]. At the end of the part C, there are four amino acids that have been shown to be important for regulation against stress [36,37].

However, the performance of the two parts of N and C in the interaction with one another is that when ATP enters the part N, i.e., NBD, it causes induction in the part C, i.e., SBD, and this creates flexibility property and causes the lid of the SBD box to open and thus, the substrate binding site opens. In this case, when the substrate is placed in this site, ATP in turn is hydrolyzed in the first section, i.e., NBD, and in fact, with this change, HSP70 is more inclined to bind to the substrate [30,38,39].

However, it should be noted that the active ATPase activity of Hsp70 proteins is essential in bacteria, which is controlled by the cooperation and coordination of the J-domain proteins. These domains are known as J proteins, called based on the *E. coli* DnaJ family from molecular chaperones. The J-domain proteins belong to different classes of multi-domain proteins that exist in the a-helical region of the *E. coli* D-NJ N-terminus [40]. These DanJ proteins play an important role in increasing the ATPase activity of the hsp70 protein [41] and also, are involved in prevention of the accumulation of other proteins and better performance of hsp70. Among other collaborative genes with hsp70, which produce active chaperone proteins for collaboration with DnaK is grpE. GrpE acts as a Nucleotide Exchange Factor (NEF) that eliminates ADP from DnaK and therefore, controls ATPase activity and the response cycle [45]. The dnaK gene, along with the dnaJ and grpE genes, are located in one operon, and can therefore contribute to proteins for elimination of heat-induced stresses [43].

The activation of Hsp70 is accomplished by two cycles performed by two sections of the protein. Initially, the SBD and ATP binding is performed [43,44]. According to the studies carried out, it has been predicted that DnaJ is initially converted into a free polypropylene or protein in order to prevent the accumulation of proteins [44]. The prepared substrate is delivered to DnaK without any combination [45]. In this case, the correlation between DnaK and the substrate is carried out by the J domain; in fact, the presence of the J domain results in the hydrolysis of DnaK-ATP and its conversion to DnaK-ADP. In the second case where the opposite occurs, the binding of the second substrate causes the ADP nucleotide exchange to ATP and then, the dimeric binding of GrpE to DnaK, which weakens and finally stops the DnaK polypeptide interaction. This sequence of events leads to a hypothesis that how Hsp70, DnaJ and NEF can be combined to help proteins in their self-activation process [46].

HSP70 regulation

In stress-free cells, the concentration of heat-shock proteins is low; however, stress-bearing cells tend to accumulate at high levels. The main role of the Hsp70 protein in non-stressed conditions is to close and not to affect other genes. Thus, some other proteins are activated in these conditions regulated in various conditions. Under normal growth conditions, the concentration of DnaK (HSP70) in *E.coli* (the most optimal growth at 37°C) is approximately equivalent to that of the ribosomes (~ 50 μm) in order to interact with the newly synthesized polypeptides [47].

The heat shock response level is established by the interaction of DnaK-DnaJ-GrpE chaperones with the sigma factor (σ32) of the RNA polymerase unit (encoded by the rpoH gene). The σ32 is a transcriptional activator that detects heat stress in heat-shock genes [48,49]. Hence, the expressed proteins would access their functional 3D configuration without actually interacting with the folded protein. The σ32 has a short lifespan because it is decomposed through proteins encoded by the hflB (ftsH) gene. Stress causes the σ32 to be released from the DnaK-DnaJ-GrpE-σ32, resulting in the expression of the heat-shock genes [50,51].

Performance of HSP70 in pathogen bacteria

Under adverse conditions and stresses such as unfavorable temperatures, pH, antibiotics, heavy metals free radicals, and prokaryotes, especially bacteria, the DnaK gene activates to enhance the bacterial survival. Pathogens take benefits from the heat shock protein 70 (HSP70), which is a product of the DnaK gene. This was investigated by Henderson et al. [50,51]. The microbial HSP70 can be involved in microbial pathogenesis, immune response and cell death or apoptosis responses. These concepts are consistent with a lot of studies conducted in this regard [51].

HSP70 binding to host surface membrane

The HSP70 binds to the surface membranes of the microbial host cell, thereby facilitating its binding to the pathogen. The interaction between bacteria and host epithelial cells is the first step in any bacterial infection. After penetrating into the host, the pathogens transmitted to the food should address the stress factors in the host's gastrointestinal tract, including low pH, high temperature, bile salt, osmotic factors, etc. These interactions affect the expression of stress proteins in the bacteria.

The DnaK gene mutation causes the Staphylococcus aureus infection and produces biofilms by the streptococcus mutans [52]. It is reported that the helicobacter pylori can use the cell surface HSP70 as an adhesion tool and the host molecules act as the receptors of these ligands [53]. The H.pylori binds to the HSP70 to bind the ligand sulfate and enter pathogenic *E. coli* HSP70 to the ligand 3'-Sulfogalactosylceramide inside the host. The destruction of the dnaK-dnaJ operon in the salmonella creates the mutants, indicating a significant growth decrease in the culture medium. The mutated bacteria survived after the removal of the DnaK and DnaJ genes in the non-cultured epithelial cells [54]. However, functional impairment in pathogenesis can be reversed by introducing a functional version of the DnaK-DnaJ operon. This indicates that the HSP70 is a major contributor to the pathogenesis. The high levels of both GroEL and DnaK have shown that they play a protective role in the growth of *E.*

coli at a temperature between 20˚C and 40˚C [55]. The better function of the host, i.e. better placement and growth, regarding the probiotic bacteria of the lactic acid bacteria was observed when they could express proteins such as the HSP70 and other similar genes [56].

Role of HSP70

After passing the epithelial barrier of the host, the bacteria encounter immunological molecules such as macrophages, which are known as a hypertension culture for the pathogens. Because of the properties of phagosomes in many other bacteria, the protein HSP70 acts as cell surface receptor for various molecules. The Hsp70 protein binds to human plasminogen in Neisseria meingitidis [57] and *Bifidobaceterium* animal is [58]. In *Lactococcus lactis*, the DnaK binds to the invertase of the host cell. These superficial interactions of the protein result in the destruction of the pathogen because it activates the immune system to counteract the pathogen [57].

Studies have shown that a recent approach to overcome bacterial infections is to use the HSP70 and homologous as a potential drug to make the prokaryotes sensitive through producing host responses.

Conclusion

Responding to stresses in the bacteria is of paramount importance for reconciliation with environmental changes to balance and maintain a physiological state. It should be noted that the HSP70 along with other chaperone proteins forms a complex network of flexible proteins both in prokaryotes and eukaryotic cells, which are induced in both normal and stress conditions.

In fact, many microbial pathogens use the chaperone system of the HSP70 to overcome the host immune system. On the other hand, these proteins cause pathogenic bacteria not to pass through the host body barriers by these proteins. Today, the HSP70 is used to overcome microbial infections and as a potential drug in inducing immune systems to fight against bacterial infections. In the future, this protein may be used as a medicine or as a vaccine against germs.

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