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Review Article

Biochemistry Section

Bacterial Heat Shock Protein Activity

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ABSTRACT

Bacteria are exposed to different types of stress in their growth conditions. They have developed appropriate responses, modulated by the re-modeling of protein complexes and by phosphorylation dependent signal transduction systems, to adapt and to survive in a variety range of nature. Proteins are essential components for biologic activity in the eukaryotic and prokaryotic cell. Heat Shock Proteins (HSP) have been identified from various organisms and have critical role in cell hemostasis. Chaperone can sense environment and have different potential role in the organism evolution.

Keywords: Bacterial chaperone, Heat shock protein90, Chaperone DnaK, Heat shock protein GroEL

INTRODUCTION

The Heat-shock response involves the induction of many proteins called heat-shock proteins, or HSP in response to variations of temperature. The HSPs include chaperones and proteases that are presumably essential for overcoming changes that involve protein denaturation. HSP plays an important role in pathogenesis [1]. In *Escherichia coli* the heat-shock response is controlled by a specific sigma factor-32 (σ32), this factor coded by the rpoH gene and binds to heat-shock promoters located upstream of heat-shock genes [2]. Many molecular chaperones have developed to control protein folding and protection of the cell from accelerating temperature [3]. HSP include chaperones and proteases that are necessary for maintaining the cell, in abnormal condition such protein denaturation.

The 90-kDa HSP are member of molecular chaperones family that are wide spread in prokaryote and eukaryote cell [4]. 90-KDa Heat Shock Protein (HSP90) is conserved from bacteria to eukaryotic cell with approximate 50% sequence similarity between *E.coli* and humans [5]. HSP90 has a low ATPase activity causing large conformational changes of HSP90 that cause structural changes to bound substrate protein and mediate release of nascent protein from the chaperone [6]. HSP proteins have a major role in cellular functions, such as protein trafficking, receptor maturation and signal transduction [7]. HSP90 proteins are dimeric and with each protomer contain three conserved domains: N-terminal domain that binds and hydrolyzes ATP, a C-terminal and middle domain that is important for dimerization [8]. HSP90 has kinase activity and nuclear receptor ligand binding by an unknown mechanism [9]. This activity has suggested that HSP90 can interact with unfolded or non-native protein.

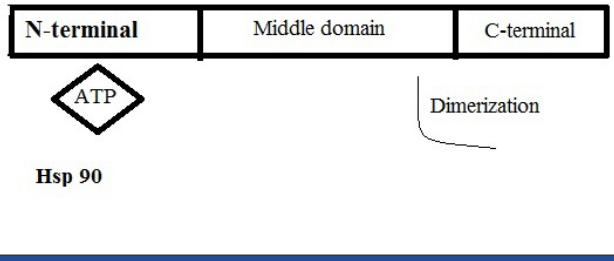
Activity role of HSP90: Cyanobacterial HSP90 fix particular protein that is required for the assembly of protein complexes called phycobilisomes [10]. Cells abrogated to induce heat shock protein to eliminate the related transcription factor, cause accumulation of large protein aggregates in bacterial cell [11]. The major classes of HSPs called chaperones have ability to identify non-native proteins such as unfolded protein. In abnormal conditions such thermal stress, bacterial HSP90 has crucial role in protein folding [12]. HSP90 is utilize the ATP in the N-terminal domains and deform as then make contacts with the middle domain [13]. Only if the ATP utilized, HSP90 returns to the open state. HSP90 is involved in assembly group of macromolecular protein that have major role in scaffolding proteins [13]. HSP90 dimer is compound of three stable domains N-terminal domain, middle domain and C-terminal domain [Table/Fig-1]. ATP hydrolyzed at the N-terminal and dimerization occurs at the C-terminal.

HSP90 have kinase activity and nuclear receptor ligand binding by an unknown pathway [9]. HSP90 is a molecular chaperone known to elevate the folding, refolding and activation of a broad range of protein substrates. This modulation suggested that HSP90 can interact with unfolded substrates that are delayed in their folding pathway [3]. HSP90 can actively effect the combination of bound substrates, which could modify the substrate folding process and cause functional outcome. If the HSP90 absence, recovery of cells from a heat shock is delayed, and this retard can be eliminated by overproduction of HSP90 [14]. Chaperones can fold the proteins which is a major role to ensure functional assembly. However, when the temperature is reduced, these proteins act mainly on the regulation of protein synthesis [15]. Two main chaperones associated with HSP90: DnaK and GroEL. DnaK (HSP70) chaperone has been found as a HSP90-interacting protein. GroEL (HSP60) chaperone is essential for growth under many environmental conditions [16-18].

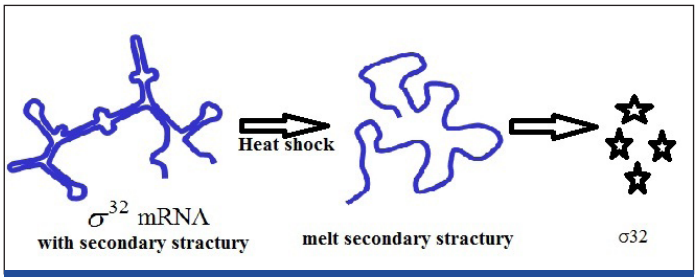
DnaK and GroEL: Major HSPs (DnaK, GroEL) are molecular chaperones that assist in correct folding and assembly of proteins and are involved in diverse cellular processes including DNA replication, UV mutagenesis, bacterial growth, RNA transcription and flagella synthesis [19,20]. GroEL together with GroES translocate protein across membrane barriers and possibility secretion. Functions of these HSPs are to prevent protein denaturation and to reactivate partially denatured proteins. The chaperone DnaK is an enzyme that uses ATP and ADP released by N-terminal, ATP catalysis and release of unfolded proteins by a C-terminal domain. DnaK can bind to nascent polypeptide chains and assistance in refolding protein and degradation [21].

Regulation of HSP: Regulation of HSP is based on alternative sigma factors that direct RNA polymerase to specific promoters that differ from the housekeeping promoters. Two major sigma factors have been described: sigma-32 and sigma-E (σE) [22]. The sigma-32 factor, encoded by the rpoH gene and regulated post transcriptionally and involves protein stability and translation efficiency. Under normal conditions, the amount of active sigma-32 is kept low [23]. Chaperones inhibit σ32 activity by sequestering

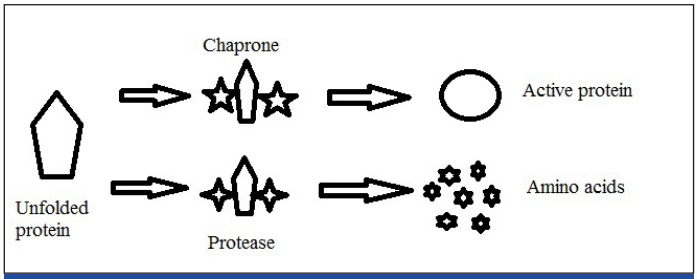
σ32 away from RNA-polymerase. This is accomplished by low translation rate of its mRNA which results from the sequestration of the Shine-Dalgarno sequence and the start codon within the secondary structure of the rpoH mRNA [23]. After a precipitate increase in temperature, the secondary structure is removed cause enhanced translation [24] [Table/Fig-2].



[Table/Fig-1]: Outline of HSP90, N-terminal: binding site of ATP, middle domain: contribute in dimerization and C-terminal: Dimerization



[Table/Fig-2]: Translational induction is due to temperature melting of rpoH mRNA secondary structure resulting to produce active σ32.



[Table/Fig-3]: Inactive, non-native or unstable proteins are recognized by either proteases or a chaperone complex which leads to degradation of the proteins to smaller peptides or formation of native proteins.

First, a temperature upshifts from 30^0 to 39^{0}C or higher results in the increased translation of rpoH gene [25]. mRNA sites within the five ′ region of rpoH gene form temperature-sensitive secondary structures that detach the ribosome-binding site but at higher temperatures, these secondary structures deliquesce, thereby enabling more efficient translation of the rpoH message [25]. Most HSPs are synthesized at low levels under normal conditions but are induced rapidly and transiently upon exposure to high temperature [26].

Clinical effect: Heat shock protein60 found in both eukaryotic and prokaryotic cell with high sequences similarity [27]. HSP can interact with immune cell and produce antibody response. This effect seen in different bacterial cells such *Helicobacter* pylari and *Mycobacterium leprae* [28,29]. One of major heat shock protein an *H.pylory* is HSP60 that anti *H.pylori* HSP60 antibody against it found in most of patients. This HSP60 can induce cytokine such a IL-8, IL-1β and TNF-α [30,31] and interact with immune system that suggested to play major role in pathogenesis of gastric cancer. HSP 60 expressed on the surface of bacterial cell and act as adhesion to host cell [32]. High titers of antibody against HSP60 were found with bad diagnosis led to gastric cancer. This effect related to secretion of TNF-α and IL-8 [33]. One of hypothesis for pathology of disease is molecular mimicry between bacterial HSP60 and human HSP60 [34]. In the other hand O_2 radical, outer membrane vesicle and pH change can damage the human cell and induce immune response [35].

DISCUSSION

Heat Shock Proteins (HSP) are a group of proteins that is induced by elevated temperature. The major members of this group are a class of functionally related proteins involved in the folding and refolding of other proteins. The expression of HSP increased when cells are exposed to elevated temperatures [36]. Several chaperones, including HSP70 and HSP90, are required for the folding and regulation of a variety of proteins [37]. Several HSP have chaperones activity for other proteins. If the protein aggregation is low, chaperon is at work, however in high protein aggregation proteases lysis the protein into amino acid [Table/Fig-3].

HSPs plays major role in protein interactions such as folding and supporting the establishment of suitable protein compound and prevention of unwanted protein aggregation [38,39].

CONCLUSION

Bacterial cells which produce HSPs can grow in more challenging temperature. Accelerated temperature in bacterial cell environment leads to damage natural protein, HSPs with refolding or degradation effect can save the bacterial cell. This effect helps the bacterial cell to survive in displacement from environment to body. In the other hands bacterial HSP with similarity to human HSP can interact with immune cells and cause autoimmune response leading to cancer such gastric cancer or leprosy lesion in leprosy disease.

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