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Rising to the challenge: Role of stress responses and molecular chaperones in bacteria

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ABSTRACT

The survival of bacteria, in their often unfavourable and frequently changing immediate environment, is enabled mainly by two factors: the bacterial stress responses and the bacterial molecular chaperones. This review article comprehensively explores the most significant bacterial stress response systems known so far and the part played by and the working mechanism of the bacterial chaperones in ensuring the survival of the bacteria in their immediate surroundings. The principal bacterial stress response systems explored in this review include: heat shock response (which is governed by Sigma 32 factor), pppGpp-dependent strict response (which decreases the synthesis of cellular proteins), cold shock response (which controls the expression of ribosomal and RNA chaperones factors), engulf stress response (which is controlled by sigma factor E) and the general stress response (which depends on sigma S factor). On the other hand, the paper explores the bacterial molecular chaperones as the bacteria's dynamic evasive mechanism of protecting themselves in adverse environment, for instance within the host organism, and thus controlling the entire infection process To this effect, the review focuses on the bacteria's response to a number of stressful environments, examples of bacteria that are well adapted to the intracellular environment within macrophages (this is considered to be the most stressful environment for bacteria) and finally, the various bacterial molecular chaperones and the role they play in the survival of the pathogenic bacteria within the host. ! 2015 Trade Science Inc. - INDIA

KEYWORDS

Bacteria;
Environment;
Chaperones;
Molecular chaperones;
Stress response.

INTRODUCTION

Bacteria are often exposed to constant change in the environmental factors that exist in their given surroundings[1]. These factors impact and influence them either positively or negatively making them very susceptible and easily affected[2]. To ensure their survival, they have to come up with well-structured and sophisticated mechanisms of survival and adaptation[3]. In response to these factors, therefore, bacterial organisms start processes within their cells that lead to massive remodelling of protein sequences and through signal transductions that are dependent on phosphorylation. As a result, the signalling systems that notify occurrences of stress affect the individual transcriptional regulons through

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activation of the sigma factors of RNA polymerase[4]. Ultimately the cell responds to gene expression alterations that best fit it to survive in the same habitat with new prevailing conditions in the surrounding. These are as detailed below[2].

Bacterial stress response systems

Bacteria experience several stresses in their natural environments[5]. These stresses induce a range of precise and extremely controlled adaptive responses that protect the bacteria from the stresses exposed to it and also adapt the bacteria's cells for future sustainability[6]. The survival of the bacteria, therefore, depends on, at least to some extent, the bacteria's capability to sense and respond to the changes made in the environment[2]. The survival responses help in combating and offering resistance to antibacterial agents initiated by mainly the host and the environment at large. There are many reaction mechanisms exhibited by organisms for survival[4]. These include among others: the heat shock response, pppGpp-dependent strict response, the cold shock response, enveloping Stress Response and the general stress responses. The mentioned stress response systems lead to administration of resistance determinants by the bacteria and encourage physiological alterations that undermine antimicrobial actions and activities[7]. The mentioned stress resistance mechanisms ensure the sustainability of the bacteria in the chosen environment and enable their perforations aiding their survival and evolution process[8].

The heat-shock response

The heat-shock response is a combination of properly organised and controlled responses to particular stresses in a cell[7]. Of significant importance or major feature, the heat-shock response leads to the manufacture of a class of proteins referred to as the heat-shock proteins[5]. The prime function of these proteins is to insulate, cushion and preserve the bacteria cell by aiding it to survive under dire conditions that would otherwise be harmful under most circumstances[5]. The heat shock proteins are found in many organisms both at the cellular and molecular level provided their combative use of heat shock response is required[9]. This implies that the need for the heat-shock protein invokes its generation in the cell. These requirements for the production of the heat-shock proteins include among many: first when the temperature varies within a range[10]. That is when it reduces or increases above a certain range that the bacteria is accustomed to or fully optimised to work around. Secondly, as a result of extreme exposure to toxic chemicals and substances that is harmful to the bacteria's cells[2]. Thirdly respond to the depletion of energy at the cellular level and help to bring it back to optimum levels for optimum function of the cell. Fourthly, the gathering of gases, ions, osmolytes and various other substances that is toxic to the cell[4]. Lastly, the heat-shock proteins can also be prompted for release when someone contracts a fever, catches a cold, has cancer through exposure to carcinogens or has an ailment that degenerates the neurons that is has a neurodegenerative disease[11]. In other cases, the heat-shock proteins may be generated in early natural stages of cell growth as is elicited by nature for survival and combating of evolution processes[5]. The heat-shock proteins, therefore, work at the molecular level of genetics in that they initiate interactions with other proteins leading to a massive decline of the possibility of these other proteins having an interaction with each other[12]. This limits the interaction of an individual set of proteins with each other.

Heat-shock proteins form a subsection of a broader class of proteins referred to as molecular chaperones. Their functions as a sub-set, in essence, therefore, involve a drastic increase in number during the heat-shock response[14]. The primary role of the much wider molecular chaperone family is to help in making sure that protein folding is done through the correct possess possible and the desired results of the arrangement reached[13]. Also, they ensure that the process is indeed efficient and the eventual quantity of proteins is maintained at a minimum or low range[14]. The heat shock proteins function by perfectly determining and attaching themselves to other proteins when these proteins are in a state of non-native conformity[5]. This non-native conformation state of proteins is their inactive state that may be partly caused by protein denaturing stress or because the peptides that they are made of have not fully folded, manufactured, arranged or localised to an appropriate cellular section[15]. The association

and eventual hydrolysis by nucleotides regulates and efficiently controls the binding and release of these other proteins that the heat -shock proteins bind themselves to[7].

It is of significant importance to acknowledge that some amounts of heat-shock proteins exist in a cell even when the environment doesn't expose the bacteria to stress conditions. The major classes of heat –shock proteins include among many: heat-shock protein 40, heat-shock protein 60, heat-shock protein 70, heat-shock protein90, heat-shock protein 100, and the ''small heat-shock protein''[16]. Note that the numbers mentioned above that separate them from each other denote to their respective protein sizes[9]. That is heat-shock protein 40 means that they are roughly forty thousand Daltons in size[4].

In essence, heat-shock proteins act as oligomers or as a combination of various other dissimilar chaperones, co-chaperones and nucleotide exchange factors[17]. The practical cooperation with chaperones leads to the following results: First, it leads to the efficient import, export and localization of organellar[2]. Secondly, retain the heat-shock proteins partner proteins in a state that is either, folded, non-folded or even folding competent that is a state that does not impede or offer barriers to successive folding[18]. It limits the aggressive nature of non-native proteins preventing their progression into proteins[19]. Lastly, it focusses on aggregated proteins for a reduction in their properties and efficient elimination from the cell[5].

It should be noted that the stimulation of several signalling pathways within the cell result in the production and eventual action of the heat-shock protein[20]. Therefore, the heat-shock proteins are induced when any known stress process affect the bacteria. On recognition of an occurrence of various proteins that are misfolded or arranged in a way that might impede alignment, the cell triggers the heat –shock response[5]. The first process is to activate a transcription factor referred to as the heat shock factor. This heat shock factor can be activated very fast provided the stress has attained recognition making it be a very potential mechanism for protection of the cell[7].

Although there is a common occurrence of heat-shock proteins in natures, such behaviours like movement of bacteria impede and or prevent heat-shock protein inducing stresses through exploitation of equitable microhabitats in environments that could however in most cases be inhabitable[9]. They, therefore, make the bacteria stronger eliminating the need to invoke the heat-shock proteins. This is an evolutionary advantage equipping the bacteria with the much-needed benefits to being in favour of evolutionary characteristics[9]. Besides, other biochemical characteristics other than heat-shock protein responses can cushion the bacteria throughout its lifespan to prevent environmental extremes from directly impacting and affecting it.

pppGpp-dependent strict response

The pppGpp-dependent strict answer is another response mechanism exhibited by bacteria. PppGpp arbitrates a universal programming of gene articulation upon which nutrient limitation and several other stresses deal with these unfavourable conditions. The manufacture of pppGpp, in a significant number of bacteria is influenced by the RelA/SpoT Homologue (Rsh) proteins which are made up of a massive number of enzymes that hydrolyse and/or efficiently hydrolyse the nucleotide alarmone pppGpp. The several types of stresses that trigger the pppGpp-dependent strict response include among many: the inadequacy of fatty acids for the use in the cells of the bacteria, amino acids and also the presence of iron[2]. The function of pppGpp is, therefore, to impose a controlling role through modulating and binding activity of various targets to reach the desired objectives. These targets include among several others: The ribonucleic acid polymerase, lysine decarboxylase Ldc1, DnaG primase, translational GTPases IF2 and EF G and polynucleotide phosphorylase[7].

The RelA/SpoT Homologue (Rsh) proteins determine starvation of amino acid by the bacteria by precisely communicating with the ribosome of the 70s kind and monitoring the aminoacylation state of the A site tRNA[20]. Besides the RelA/SpoT, Homologue (Rsh) proteins also answer to the availability of tRNA that is deacylated as a result of the processing of pppGpp. SpoT is an enzyme that has two functions; thusit is a bifunctionalenzyme. These two features comprise of sensing several processes that

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modulate the net activity of pppGpp and also it handles the synthesis and hydrolytic activities of pppGpp[5]. Through phylogenetic analysis, there are three major groups of the RSH, protein family[2]. These mainly include; small alarmone synthesises abbreviated as (SASs), long RSHs for example SpoT and ReiA, and lastly and small alarmone hydrolases abbreviated (SAHs)[4].

The regulatory nature of pppGpp is seen in the bacteria Escherichia coli and Rhizobium etli. This occurs when amino acids reach their limit and t-RNA that has not been charged and that binds itself to ribosomes stimulates the ribosome associated with RelA to manufacture pppGpp[21]. SpoT catalyses and, therefore, acts as an enzyme facilitating the degradation of the alarmone when conditions requiring its degradation are acquired[2]. Therefore, the prime function of pppGpp is to control and regulate gene transcription[20]. This is done through theoretical propositions that have been brought forward. In these models exists, the models known as the affinity models which asserts that a direct relationship exists between the availability free RNA polymerase and increasing pppGpp numbers[22]. That is a positive rise in the occurrence of free RNA polymerase (RNAP) leads to a subsequent increase in the level of pppGpp. About this, the increase in pppGpp level will initiate promoters with a little affinity to free RNA polymerase (RNAP) for example stress response genes and maintenance of the cell[23]. Another model attests and associates the sigma factor competition model. It stipulates that the affinity to bind to other sigma factors that alternate increase with increasing pppGpp levels in comparison to the standard sigma factor σ[5]. This leads to a decrease of sigma bound free RNA polymerase (RNAP) and a reduction of promoters that are related to growth and are in most cases favoured by the presence of a high sigma bound free RNA polymerase (RNAP) concentration[2]. PppGpp dependent stringent response, therefore, reduced the capacity of cellular organisms to synthesise cellular proteins leading to massive downgrading of nutrition required for growth[4].

The cold-shock response mechanism

The cold shock response mechanism is another sub –set of stress responses in bacteria. Optimum temperature is a much needed environmental factor for molecular processes, motion and activities. Maintenance of an optimum temperature level is therefore required as it Leeds to the maintenance of cell properties and methods[5]. When there is a sudden downgrading in temperature in the environment surrounding the bacteria, some alterations are exhibited in its cellular physiology to counter these changes[2]. These include the following; first, balancing and maintenance of secondary structures of nucleic acids that prompt the reduction in the efficiency level of the messenger ribonucleic acid that is mRNA[24]. The energy processes of mRNA that are reduced include both its translation and transcription process. Secondly, reduce the amount and function of membrane fluids which impacts negatively on the transport of nutrients and membrane fluidity[9]. Thirdly, it leads to the inefficient folding of some proteins and lastly inhibits and prevents the ease of function for ribosomes[1].

The cold shock response of bacteria leads to the immediate production of certain proteins known as cold-shock proteins that initiate the above processes to counter a sudden decrease in the temperature of the surrounding[20]. This is because an immediate reduction in temperature can lead to a stop in protein synthesis. Although this cessation commences immediately, the production of other cold shock proteins continues for the bacterial organism to counter environmental changes[5]. The sole purpose of this cold shock mechanism in plants is to aid and facilitate continual growth during the cold period. The proteins associated with the cold shock response mechanism include among many: nucleases, helicases and components related to the ribosome that interact either directly or indirectly with the molecules that transfer and transport biological information. These are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)[7].

Therefore due to an abrupt shift in temperature to lower temperatures, a pattern is initiated. The model involves first, the immediate synthesis of proteins that are involved in and associated with transcription and translation[9]. Secondly, induction of cold- shock proteins and lastly the repression of heat shock proteins because their need has been elimi-

nated[20]. These cold –shock proteins generated spring into action immediately supercoiling the DNA to initiation of translation[25]. An essential cold shock protein is known as the CspA and exhibits sequences that can be closely related to proteins CspB, CspC and CspD[26].

The enveloping stress response

The enveloping stress response constitutes another subsection of stress responses in bacteria. The cell envelope acts as the foremost and most important defence mechanism that the cells of a bacteria have in relations to the outside environment[2]. This cell engulfing helps in protecting the cell from outside threats[27]. The cell envelope also acts as a necessary interface for sensors and sieves all molecules that go in or out of the cell[28]. This makes it act as a mediator controlling both the transportation of both information in and out of the cell and transportation of soluble substances[3]. Moreover, the cell envelope also handles giving the cell its shape and combats the high osmotic pressure within[5].

This engulfs stress response controlled by sigma factor E handles the maintenance, adaptation and protection of bacterial envelope in response to a broad range of responses that affect the bacteria[20]. Recent in-depth research into this type or response indicates that the sigma factor E response is prevalent mostly in many Gram-negative bacterial pathogens[2]. The cell envelope in this particular case is of prime importance since most of the virulence determinants live in or are passed through this cellular structure[7].

Further analysis and research show that the engulf stress response signified by sigma factor E pathway has been found and determined to handle protection of the cell from oxidative stress and intracellular survival[8]. The Homologues of the engulf stress response handle full virulence in many pathogens and also appear to confer resistance to intracellular survival capacity and stress exhibited through oxidation[20]. The process through which deoxyribonucleic acid (DNA) that is foreign is introduced into the cell by viral vectors in this response mechanism is controlled by two principles, two-component systems and an extracytoplasmic function of sigma (σ) factors found in the Actinobacteria (high-GC) and the Firmicutes (low-GC)[9]. The Firmicutes and Actinobacteria are both branches of Gram-positive bacteria (Henderson, 2008). This cell response, therefore, leads to the maintenance of the state of the environment that the bacteria finds itself in and aids in homoeostasis[5].

Cells that exhibit the enveloping stress response have dramatic effects on virulence since the sigma factor E response induces resistance to a large number of envelope stresses. This helps in protecting the cells of the bacteria from lethal hosts and pathogens[2]. Cells that have this response mechanism are said to exhibit sigma factor E mutation since they have to mutate so as to defend themselves from external stresses that possess major concerns to them. Due to this mutation, other multiple stress mechanisms are induced to protect the cell from stresses in the environment[5].

The general stress response

The general stress response which depends on the sigma S factor (RpoS) that is, a subsection of the ribonucleic acid polymerase is the chief controller of the general stress response exhibited in the bacteria Escherichia coli[20]. The need for this stress response is as a result of the bacteria not being able to experience optimal growth conditions suitable for growth in their respective habitats. This stress response is first induced into the cell when it enters into its stationary phase[5]. Escherichia coli and other related bacteria, therefore, increase the accumulation of RpoS in them when they enter the stationary phase of growth[2]. This occurs in most circumstances under cases of deprivation of nutrients or deprivation of stress[21]. This makes the cells become resistant.

When the cell starts exhibiting rapid growth because of being in the quick growth phase, the translation of RpoS which initiates the general stress response is inhibited and all the processes that aid in the synthesis of RpoS are quickly reduced[20]. This is due to the bacteria attaining optimal growth[2]. It is of important to note therefore that many bacteria have several single stress-induced responses that they initiate so as to cope with speciûc stress situations through the acute elimination of the agents causing the stress and initiate the repair of the damaged

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part of the cell[9]. This allows the cell to resume its previous functions with normalcy[7].

Bacterial molecular chaperones

Molecular chaperones handle folding of proteins within a cell. Although for a long time, researchers have known protein folding to be a natural process that takes place spontaneously, recent research in the genome sequencing field has determined that indeed molecular chaperones play a much greater role. Bacterial molecular chaperonesact as folding modulators that regulate the folding process of proteins. The close monitoring is necessary since an incorrect aggregation and rapid folding as is characterised by crowded environments can be very dangerous to the cell[4]. In particular, molecular chaperones are involved in the following process in bacterial cells: firstly they offer assistance in the secretion of proteins. Secondly, when proteins are newly synthesised, bacterial molecular chaperones are involved in their subsequent folding during and after their translation process. Thirdly, they offer prevention of aggregation of proteins during heat shock. This is when there is a rapid and uncalled for increase in temperature above the environmental optimum. Lastly, they are involved in the repair of proteins that have undergone miss -folding or damage due to environmental stresses such as heat shock[29]. These proteins are done away with since they may be harmful to the cell. In summary, it should be noted, therefore, that bacterial molecular chaperones offer a conformational type of assurance that is aimed towards successively regulating and modulating proteins[4].

Besides, bacterial molecular chaperones play an essential role in maintaining the balance between the refolding of proteins and their proteolytic degradation. The primary chaperone system found in the cells of bacteria is DnaK and GroE chaperones. GroE chaperone system supplies the cell with a safeguarded environment for the efficient and successful folding of individual molecules of proteins[30]. Alternatively, the DnaK chaperone system spring into action through preserving a[31]nd binding the uncovered and unprotected areas mainly found in the protein chains that are either unfolded of folded partly. Also, the DnaK chaperones communicate with the alerting and causative factor in the translation of proteins and with ClpB which is found in reactive proteins that combined due to a sudden increase in temperature above optimum in the surrounding environment of the cell. ClpB, in this case, is a third set of bacterial molecular chaperones whose role is to encourage the presence of well-balanced proteins that have been aggregated due to stress from the surrounding environment.

In most cases, the actions of bacterial molecular chaperones take place in the endoplasmic reticulum[3]. It is here that the right folding mechanism of proteins is administered and monitored. The folding mechanism is followed by and dependent on the disposition of the real bonds that are of a disulfide nature and their subsequent addition into the lipid bilayer. These two processes that are the placement of disulphide bonds and their addition to the lipid bilayer occur at a rather slow pace about other conformation changes that follow up the folding process of proteins[4]. The endoplasmic reticulum provides an environment highly optimised for facing challenges that may affect protein folding in a negative manner[32]. Moreover, it offers a range of adaptations structurally altered to help in the folding process of secretory proteins. The endoplasmic reticulum also contributes to keeping and repossesses secretion proteins that have not yet attained their native state in bacterial cells[3]. All this is possible for the endoplasmic reticulum since it administers two separate mechanisms to act on an occurrence of miss folded or unfolded proteins[32]. Firstly, the unfolded protein response (UPR) remodels the endoplasmic reticulum working to rearrange it in order to increase its capacity for folding proteins[6]. Secondly, ER-associated degradation (ERAD)determines the proteins that have misfolded terminally and proceeds to retro translocate them through the endoplasmic reticulum's membrane and into the cytol for degradation processes[8].

CONCLUSION

Bacteria increase the rate of variation in their cell characteristics to cope up with and adequately counter the prevailing harsh conditions in their environment. These stress responses initiated increase their mutation and adaptability rates. The stress re-

sponses noted include the following among others; Bacterial Stress Response Systems; Heat shock response, Cold shock response, Enveloping Stress Response and lastly General stress response. All these stress responses arerequired for the eventual survival of the bacteria. Moreover, bacterial chaperones also offer a hand in increasing bacterial adaptability by positively affecting proteins, altering their complexities in a way to better equip the cell.

REFERENCES

[1] A.Melnyk, H.Rieger, R.Zimmermann; Co-chaperones of the mammalian endoplasmic reticulum, In The Networking of Chaperones by Co-chaperones. Springer, 179-200 **(2015)**.
[2] S.Mongkolsuk, W.Schumann; Stress goes far east: meeting report of the sixth international workshop on the molecular biology of stress responses, Cell Stress Chaperone., **14(3)**, 227-231 **(2009)**.
[3] M.E.Tóth, L.Vígh, M.Sántha; Alcohol stress, Membranes, and chaperones, Cell Stress Chaperone, **19(3)**, 299-309 **(2014)**.
[4] I.Milisav; Cellular stress responses, Adv Regen Med., 215-232 **(2011)**.
[5] B.Henderson; Novartis foundation symposium, 2008, Chichester, New York, John Wiley, 1999, 141 **(2008)**.
[6] S.Marzi, W.Knight, L.Brandi, E.Caserta, N.Soboleva, W.E.Hill, C.O.Gualerzi, J.S.Lodmell; Ribosomal localization of translation initiation factor IF2, Rna, **9(8)**, 958-969 **(2003)**.
[7] De A.Maio, R.M.Tanguay, H.Kampinga, E.Lee, C.D.Kim, L.Hightower; Stress at the korean mountains: Meeting report of the 8th international workshop on the molecular biology of stress responses, Cell Stress Chaperone, **16(2)**, 113-118 **(2011)**.
[8] W.Ni, O.O.Odunuga; UCS Proteins: Chaperones for myosin and co-chaperones for Hsp90, In The Networking of Chaperones by Co-chaperones, Springer, 133-152 **(2015)**.
[9] K.J.Travers, C.K.Patil, J.Weissman; Functional genomic approaches to understanding molecular chaperones and stress responses, Adv protein chem., **59**, 345-390 **(2002)**.
[10] R.M.Jenvert, L.H.Schiavone; The flexible N-terminal domain of ribosomal protein L11 from escherichia coli is necessary for the activation of stringent factor, J.mol.biol., **365(3)**, 764-772 **(2007)**.
[11] L.Pan, R.B.Borgens; Strict perpendicular orientation of neural crest derived neurons in vitro is dependent on an extracellular gradient of voltage, J neurosci.res., **90(7)**, 1335-1346 **(2012)**.
[12] Regev N.Rudzki, K.Gabriel, D.Bursać; The evolution and function of co-chaperones in mitochondria, In The Networking of Chaperones by Co-chaperones, Springer, 201-217 **(2015)**.
[13] J.L.Borger; Dark spot syndrome: a scleractinian coral disease or a general stress response?Coral reefs, **24(1)**, 139-144 **(2005)**.
[14] M.Inouye; Cold-shock response and adaptation, J Mol.Microbiol.Biotechnol., **1(2)**, 191 **(1999)**.
[15] J.Duan, L.Nilsson; Thermal unfolding simulations of a multimeric protein—transition state and unfolding pathways, Proteins, **59(2)**, 170-182 **(2005)**.
[16] F.Schmid; Spectroscopic techniques to study protein folding and stability, Protein Folding Handbook, 22-44 **(2005)**.
[17] G.Liu, C.Jiang, M.Zhou; Networking, Sensing and control (ICNSC), 2011 IEEE international conference on: 2011, IEEE, 2011, 359-364 **(2005)**.
[18] W.Jin, Y.G.Ryu, S.G.Kang, S.K.Kim, N.Saito, K.Ochi, S.H.Lee, K.J.Lee; Two relA/spoT homologous genes are involved in the morphological and physiological differentiation of Streptomyces clavuligerus, Microbiology, **150(5)**, 1485-1493 **(2004)**.
[19] S.M.Keyse; Protein phosphatases and the regulation of mitogen-activated protein kinase signaling, Curr.opin.cell.biol., **12(2)**, 186-192 **(2000)**.
[20] M.D.Galigniana; When the cell stress society international became South American: Meeting report of the IX international workshop on the molecular biology of stress responses, Cell Stress Chaperone, **18(1)**, 3-9 **(2013)**.
[21] P.Fareleira, B.S.Santos, C.António, Moradas P.Ferreira, J.LeGall, A.V.Xavier, H.Santos; Response of a strict anaerobe to oxygen: survival strategies in desulfovibrio gigas, Microbiology, **149(6)**, 1513-1522 **(2003)**.
[22] J.Gert; Response-dependent theories, In international encyclopedia of ethics, Blackwell Publishing Ltd., **(2013)**.
[23] B.Enjalbert, A.Nantel, M.Whiteway; Stress-induced gene expression in Candida albicans: Absence of a general stress response, Mol.biol.cell., **14(4)**, 1460-1467 **(2003)**.
[24] K.Ochi, T.Nishizawa, T.Inaoka, A.Yamada, K.Hashimoto, T.Hosaka, S.Okamoto, Y.Ozeki; Heterologous expression of a plant RelA-SpoT homologue results in increased stress tolerance in Sac-

Review

charomyces cerevisiae by accumulation of the bacterial alarmone ppGpp, Microbiology, **158(8)**, 2213-2224 **(2012)**.

[25] Y.Hu, M.J.Benedik, T.K.Wood; Antitoxin dinJ influences the general stress response through transcript stabilizer CspE, Environ microbial., **14(3)**, 669-679 **(2012)**.

[26] A.Kanai; Disrupted tRNA genes and tRNA fragments, A perspective on tRNA gene evolution, Life (Basel), **5(1)**, 321-331 **(2015)**.

[27] A.Staroń, T.Mascher; General stress response in α proteobacteria: PhyR and beyond, Mol.microbiol., **78(2)**, 271-277 **(2010)**.

[28] A.Falah, A.Elkholy; Load sharing and stress analysis of single enveloping worm gearing considering transmission errors, Int.J.Adv.Manuf.Tech., **37(3-4)**, 211-220 **(2008)**.

[29] P.N.Bryan; Protein folding catalysis by pro domains, Protein Folding Handbook, 1032-1058.

[30] K.Kasai, S.Usami, T.Yamada, Y.Endo, K.Ochi, Y.Tozawa; A RelA–SpoT homolog (Cr RSH) identified in chlamydomonas reinhardtii generates stringent factor in vivo and localizes to chloroplasts in vitro, Nucl.acid res., **30(22)**, 4985-4992 **(2002)**.

[31] I.Abaza, F.Gebauer;Trading translation with RNA-binding proteins, Rna, **14(3)**, 404-409 **(2008)**.

[32] A.Battesti, E.Bouveret; Bacteria possessing two RelA/SpoT-like proteins have evolved a specific stringent response involving the acyl carrier protein-SpoT interaction, J bacterial., **191(2)**, 616-624 **(2009)**.