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Review Article

MICROBIAL STRESS RESPONSE REGULATORY ENZYME AND THEIR PHARMACEUTICAL APPLICATION

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Abstract

Ability of adaptation according to variable environmental conditions is essential for bacterial surveillance; those don't have ability to face the challenge is eliminated. To counter the damaging effect of reactive oxygen species, cells have evolved anti-oxidant defense systems, whose expression is usually induced by reactive oxygen species and/or oxidants. Bacteria survive in several kind of environmental stress condition due to alteration in cell membrane and genetic material by fatal enzyme. Other inducers of the general stress response might also cause transient genetic instability and so promote bacterial adaptation to stressful environments. Regulatory mechanisms which help bacteria to maintain their balanced and rather constant cellular composition mostly occur at the genetic level. Many studies clarified the efficacy of stress enzyme as a therapy in the treatment of many diseases, in addition to their inclusion in cosmetic products to reduce free radical damage to skin.

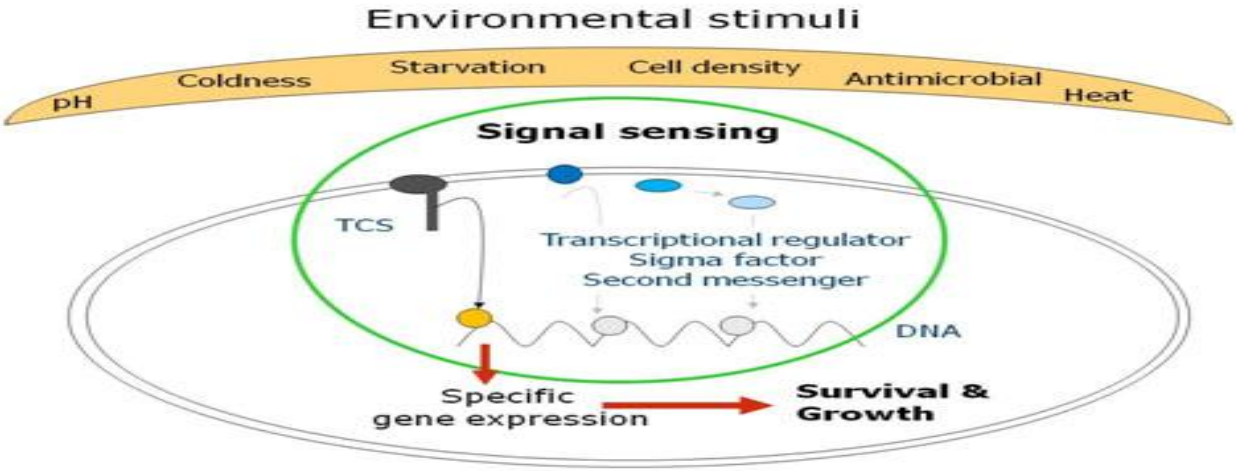
Keywords: Bacterial response, Environmental stress and regulatory enzyme.

Introduction

The bacteria have ability to survive adverse and fluctuating conditions in their changing surround due to regulatory system. Bacteria survive in almost all environmental condition on Earth, like from the steaming hot springs of Yellowstone to the frozen tundra of the arctic to the barren desert of Chile, microbes have been found thriving [1]. Tenacious nature of bacteria to survive in harsh and diverse conditions allows them to play important roles in nutrient cycle regulation. Microbe cause several types of fatal human diseases and can survive harsh conditions found in the human body [26]. Bacteria have several mechanisms to distinguish environmental changes and build up an appropriate response. A bacterial cell enable to react simultaneously in wide variety of stresses, various stress response systems interact with each other by a complex of global regulatory networks [22]. Bacteria can survive under diverse environmental conditions and in order to overcome these adverse and changing conditions, bacteria must sense the changes and rise appropriate responses in gene expression and protein activity [32].

The stress response in bacteria involves a complex network of elements that acts against the external stimulus. A complex network of global regulatory systems leads to a coordinated and effective response. These regulatory systems govern the expression of more effectors that maintain stability of the cellular equilibrium under the various conditions. Stress response systems can play an important role in the virulence of pathogenic organisms [3]. Stress response systems make capable microorganism to survive adverse and fluctuating conditions and possess several defense mechanisms to recognize adverse environmental changes and escalate an appropriate response. Microorganisms react simultaneously in a wide variety of stress situation and the various stress response systems interact with each other by a complex regulatory network [33]. Stress response systems can play an important role in the virulence of pathogenic organisms.

Regulatory networks enable bacteria to adapt almost every environmental situation on earth. Regulation is achieved by a network of interactions among diverse types of molecules including DNA, RNA, proteins and metabolites [34]. The primary role of regulatory networks in bacteria is to control the response to environmental changes, such as nutritional status and environmental stress [31]. A complex organization of networks allows the organism to coordinate and integrate with multiple environmental signals, e.g. In *Escherichia coli* several response mechanism is regulated by sigma network like bacterial virulence, ECF sigma factors, quorum sensing, cyclic di-GMP, RNA-mediated regulation, two-component regulatory systems, bacterial chemotaxis, regulation of iron homeostasis, anaerobic regulatory networks, bacterial bistable regulatory networks, and evolution of transcription factors and regulatory networks[28]. Bacteria have evolved extraordinary abilities to regulate aspects of their behavior (such as gene expression) in response to signals in the intracellular and extracellular environment. Direct interactions with chemical or physical stimuli alter the sense of diverse macromolecules (proteins or RNA) [9].



Graph1: Bacterial adaptation and stress response networks [49]

Specific stress response

Heat shock response: The cellular response to heat shock includes the transcriptional up-regulation of genes encoded by heat shock proteins (HSPs) as part of internal repair mechanism of the cell called stress-proteins present in cells under absolutely usual situation. It responds to heat, cold and oxygen deficiency by activating several cascade pathways [38]. Some HSPs, called chaperones, make sure that the cell's proteins are in the accurate shape and in the right place and at the right time, e.g. HSPs help new or misfolded proteins to fold into their correct three-dimensional conformations, which is essential for their function. They also shuttle proteins from one compartment to another inside the cell, and target old or terminally misfolded proteins to proteases for degradation [17]. Heat shock proteins are also believed to play a role in the presentation of pieces of proteins (or peptides) on the cell surface to help the immune system recognize diseased cells. The up-regulation of HSPs during heat shock is usually restricted by a single transcription factor; in eukaryotes this regulation is performed by heat shock factor (HSF), while heat shock sigma factor in prokaryote [11]. The link between aminoglycosides and heat shock is that components of the heat shock response charged with eliminating misfolded proteins might target the aberrant mistranslated polypeptides that are produced by aminoglycoside-disrupted ribosomes and that insert into and disrupt bacterial membranes [42]. Aminoglycoside mediated membrane damage has been reported and is likely a key step in the lethal activity of these agents and thus elimination of aberrant polypeptides that may be responsible would certainly reduce their toxicity to cells [41].

Envelope stress response: The cell envelope is the chief line of defense against environmental threats. It is a vital but susceptible structure that shapes the cell and counteracts the turgor pressure. It provides a sensory interface, a molecular sieve and a structural support, mediating information flow, transport and assembly of supra-molecular structures [26]. Therefore, maintenance of cell envelope integrity in the presence of lethal conditions is crucial for survival. Several envelope stress responses, including two components regulatory systems (TCRS), of bacteria are involved in the maintenance, adaptation and protection of the bacterial cell wall in response to a variety of stresses. Fastidious emphasis has been made on the recognized TCRS and their activating signals [31]. Another aspect of stress response is the generation of morphological modifications mainly

controlled by the sigma factor sigma E. Most bacteria alter shape when growth conditions change and upon symbiotic or parasitic processes. Any modification in cell shape is connected with cell wall metabolism and requires specific regulatory mechanisms [9]. Advances support the existence of complex mechanisms mediating morphological responses to stress involving inter and intra-specific signaling.

Cold shock response: Exposure of an organism to a abrupt decrease in temperature and cellular response to this is termed as cold shock response. Bacteria live in extreme condition such as Cold Ocean, alpine region and natural environmental exposed to the winter season. Most of the bacteria have ability to survive in extremely low temperature due to their resistance mechanism and sigma factor which governs expression of RNA chaperones and ribosomal factors [45]. There is a low temperature limit that even cold adopted microorganisms are unable to grow at, they are clearly genetically and physiological geared for coping with the cold. It may therefore explain that they would posses novel gene involved in cold adaptation [5]. In general gene that is cold shock gene in psychrophilic or psychrotolerant microorganism (e.g. cspA in *E.coli* compared with *Arthobacter globiformis*).

General stress response: The general stress response that responds to nutrient starvation, hyperosmolarity, pH downshift, non-optimal high and low temperature in *E. coli* and heat shock, hyperosmolarity and prolonged peroxide exposure in *P. aeruginosa* has been linked to antibiotic resistance in both *E. coli* and *P. aeruginosa* depends on the sigma factor sigma S, which is encoded by rpoS gene [19]. Since the stress-induced mutations are random, however, and unrelated to the initial stress that triggered mutagenesis, non-selected mutations, including those that impact antimicrobial resistance, also arise Interestingly, RpoS was also shown to be required for a heat shock-promoted increase in carbapenem resistance in *P. aeruginosa* a clear example of a stress response sigma factor mediating stress-promoted antimicrobial resistance[3].

(p)ppGpp-dependent stringent response: (p)ppGpp, guanosine pentaphosphate is an alarmone which take part in the stringent response in bacteria, causing the inhibition of RNA synthesis when there is a shortage of amino acids present causing translation to decrease. Furthermore, ppGpp causes the up-regulation of many other genes involved in stress response such as the genes for amino acid uptake (from surrounding media) and biosynthesis [44]. During the stringent response, (p)ppGpp accumulation affects the resource-consuming cell processes replication, transcription, and translation[23]. A complete absence of (p)ppGpp causes multiple amino acid requirements, poor survival of aged cultures, aberrant cell division, morphology, and immortality, as well as being locked in a growth mode during entry into starvation which reduces the cellular protein synthesis capacity and controls further global responses upon nutritional downshift [40] .The stringent response, also called stringent control, is a stress response of bacteria and plant chloroplasts in reaction to amino-acid starvation, fatty acid limitation, iron limitation, heat shock and other stress conditions. In other bacteria the stringent response is mediated by a diversity of RelA/SpoT Homologue (RSH) proteins, with some having only synthetic or hydrolytic or both (Rel) activities [43].

Oxidative stress: It is the disturbance between the systemic expression of reactive oxygen species and a biological system's ability to readily detoxify or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Further, some reactive oxidative species act as cellular messengers in redox signaling [31]. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling. Production of reactive oxygen species is a particularly destructive aspect of oxidative stress. Such species include free radicals and peroxides. Some of the less reactive of these species (such as superoxide) can be converted by oxidoreduction reactions with transition metals or other redox cycling compounds (including quinones) into more aggressive radical species that can cause extensive cellular damage [22]. Most long term effects are caused by damage to DNA. It is the inevitable consequence of living in an oxygen-rich environment, occurs when the cellular redox balance is upset by increased doses of reactive oxygen species (ROS). Microorganisms living in aerobic environments are constantly exposed to ROS, which are generated by the aerobic metabolism and environmental agents. ROS, including superoxide radical (O2), hydrogen peroxide (H2O2) and hydroxyl radical (NOH), are highly reactive molecules that can damage key cellular components, including DNA, proteins, carbohydrates and lipids [16].

Chemistry of Oxidative stress: is defined as interference in the balance between the production of reactive oxygen species (ROS), including free radicals, oxides and peroxides, and the ability of biological systems to readily detect their presence and detoxify ROS or repair the resulting damage [3]. A common feature among the different ROS types is their capacity to cause oxidative damage to macromolecules, proteins, DNA, and lipids leading to

an increased rate of mutagenesis, and cell death [31]. Chemically, oxidative stress is associated with increased production of oxidizing species or a significant decrease in the effectiveness of antioxidant defenses, such as glutathione [15]. The possessions of oxidative stress depend upon the size of these changes, with a cell being able to overcome small agitate and recover its original state. However, more severe oxidative stress can cause cell death and even moderate oxidation can trigger apoptosis, while more passionate stresses may cause necrosis. Production of reactive oxygen species is a negative aspect of oxidative stress. Such species include free radicals and peroxides [16]. Some of the less reactive of these species (such as superoxide) can be converted by oxidoreduction reactions with transition metals into more aggressive radical species that can cause wide range of bacterial cellular and genetic material (DNA) damage.

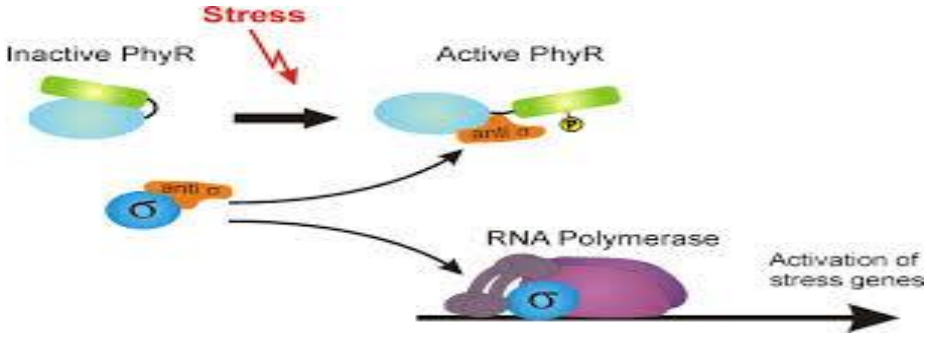
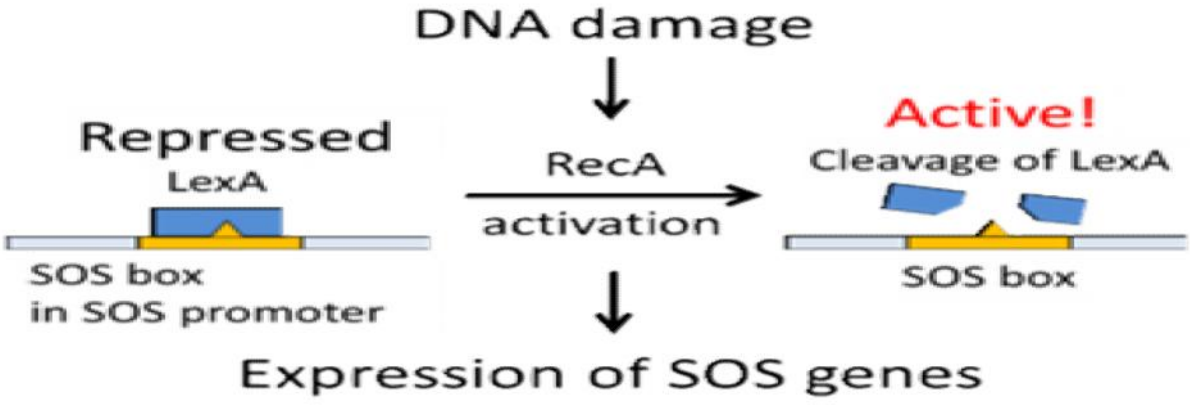


Figure1. Diagrammatic presentation of activation of stress gene [1]

SOS Response to DNA damage: It is a global response to DNA damage in which the cell cycle is arrested and DNA repair and mutagenesis are induced. It is the essential pathway of bacterial acquisition of bacterial mutation which leads to resistance of oxidative stress condition. The increase rate of mutation during SOS response is caused by their low fidelity of DNA polymerase enzyme [13]. DNA repair enzyme includes endonuclease IV, which is induced by oxidative stress, and exonuclease III, which is induced in the stationary phase and in starving cells. During normal growth, the SOS genes are negatively regulated by LexA repressor protein dimers. Under normal conditions, LexA binds to a 20-bp consensus sequence (the SOS box) in the operator region for those genes [37]. Some of these SOS genes are expressed at certain levels even in the repressed state, according to the affinity of LexA for their SOS box. Activation of the SOS genes occurs after DNA damage by the accumulation of single stranded (ssDNA) regions generated at replication forks, where DNA polymerase is blocked. RecA forms a filament around these ssDNA regions in an ATP-dependent fashion, and becomes activated [20]. The activated form of RecA interacts with the LexA repressor to facilitate the LexA repressor's self-cleavage from the operator. Once the pool of LexA decreases, repression of the SOS genes goes down according to the level of LexA affinity for the SOS boxes. Operators that bind LexA weakly are the first to be fully expressed. In this way LexA can sequentially activate different mechanisms of repair [28].



Graph3: Diagrammatic drawn of SOS expression [28]

Enzyme release due to stress

Oxidative stress is a state characterized by elevated levels of intracellular reactive oxygen species (ROS) form free radicals. ROS consist of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) reacting and damaging lipids, proteins, and DNA [6]. Several type of enzyme released due to Oxidative stress like glutathione peroxidase (GPX), nitric oxide synthase (eNOS, iNOS, and nNOS), peroxiredoxins, supra oxide dismutase (SOD), thioredoxins (Trx) etc. Some of these enzymes have antioxidant properties and other involved in generating fatal free radical species [29]. For example, nitric oxide syntheses (NOS) generates nitric oxide (NO) which is a pleiotropic signaling molecule implicated in diverse biological processes including inhibition of platelet aggregation, regulation of neurotransmission, vasodilatation, immune responses, and inflammation. In contrast, antioxidant enzymes, such as the glutathione peroxidase family, protect cell surfaces, extracellular fluid components, and other enzymes from oxidative stress by catalyzing the reduction of hydrogen peroxide, lipid peroxides, and organic hydroperoxide using reduced glutathione [4].

Pharmaceutical uses of stress enzyme

Glutathione is a powerful antioxidant found within every cell where it plays important role in nutrient metabolism, regulation of cellular actions including immune response, protein synthesis, cell growth, gene expression and DNA. Taken as a supplement, it may not be able to across the cell membrane and thus it is not well known how much effective as supplement would be if taken orally as a pill [36]. Regard as acetylcysteine which is an antioxidant that can regenerate glutathione within cells. Another antioxidant to consider is the mineral selenium. This antioxidant, made from the combination of three amino acids cysteine, glutamate, and glycine, forms part of the powerful natural antioxidant glutathione peroxidase which is found in our cells.

Glutathione peroxidase plays a several roles in cells, including DNA synthesis and repair, metabolism of toxins and carcinogens enhance capacity of immune system, and prevent lipid oxidation [35]. However, this antioxidant is mainly known for protecting our cells from damage caused by the free radical hydrogen peroxide. It also helps the other antioxidants in cells stay in their active form. Brain glutathione levels have been found to be lower in patients with Parkinson's disease [15].

Superoxide dismutase: free oxygen radical's scavenger, might interrupt inflammatory cascades and thereby limit further disease progression. Superoxide dismutase was reported for the treatment of not only systemic inflammatory diseases but also skin ulcer lesions, especially due to burn and wounds, where liposomal-encapsulated SOD injection was effective. SOD help in direct inhibition of joint tissue destruction, the mechanism of action of SOD in reducing the severity of arthritic inflammation [39]. SOD in its pharmaceutical form "Orgotein" is a potent anti-inflammatory agent approved in many countries, and because of their effectiveness in the general treatment of inflammatory and degenerative diseases. SOD might be proposed as a potent antagonist of this major fibrogenic growth factor, and as a potential antifibrotic drug for hepatitis C related fibrosis. In addition SODs are used for preparation of many pharmaceutical compositions for treatment of many diseases including myocardial ischemi, Peyronie's Disease multiple sclerosis colitis and in improving a clinical irradiation treatment of malignant diseases such as breast cancer. There is also increasing evidence that radical scavengers like superoxide dismutase may influence the outcome and progression of diabetic retinopathy.

Nitric oxide has a variety of functions in vivo and is typically produced where needed by members of a group of enzymes known as Nitric Oxide Synthase (NOS) enzymes [12]. One function of NO is as a neuromodulator, for example in the hippocampus of the brain, where it is implicated in the development of short-term memory. Another important function of NO is to regulate the dilation of the blood vessels in the cardiovascular system [46]. Excessive production of NO in response to infection or injury can result in arterial expansion and may ultimately lead to cardiovascular collapse. In order to maintain acceptable cardiovascular function under such conditions, it is important for the availability of NO to be controlled efficiently. This can be achieved using inhibitors for the enzymes producing NO in vivo but NO scavenging by suitable metal complexes offers another possible treatment [21]. Nitroglycerin, amyl nitrite, "poppers" (isobutyl nitrite or similar), and other nitrite derivatives are used in the treatment of heart disease: The compounds are converted to nitric oxide (by a process that is not completely understood), which in turn dilates the coronary artery (blood vessels around the heart), thereby increasing its blood supply [12].

Peroxiredoxins (Prxs) are a ubiquitous family of antioxidant enzymes that also control cytokine-induced peroxide levels and thereby mediate signal transduction in mammalian cells. The physiological importance of peroxiredoxins is illustrated by their relative abundance (one of the most abundant proteins in erythrocytes after hemoglobin is peroxiredoxin 2)

[47]. Peroxiredoxins can be regulated by changes to phosphorylation, redox and possibly oligomerization states. These enzymes share the same basic catalytic mechanism, in which a redox-active cysteine (the peroxidatic cysteine) in the active site is oxidized to a sulfenic acid by the peroxide substrate [24]. Lacking peroxiredoxin 1 or 2 develop severe haemolytic anemia, and are predisposed to certain haematopoietic cancers [8].

Peroxiredoxin-1 protein found in humans which is encoded by the *PRDX1* gene [27] . This gene encodes a member of the peroxiredoxin family of antioxidant enzymes, which reduce alkyl hydroperoxides and hydrogen peroxide. A chemoproteomic approach has exposed that peroxiredoxin 1 is the main target of theonellasterone. As enzymes that contest oxidative stress, peroxiredoxins play an important role in health and disease[18] . The levels of peroxiredoxin 1 are elevated in pancreatic cancer and it can potentially act as a marker for the diagnosis and prognosis of this disease [14]. In some types of cancer, peroxiredoxin 1 has been determined to act as a tumor suppressor and other studies show that peroxiredoxin 1 is overexpressed in certain human cancers. A recent study has found that peroxiredoxin 1 may play a role in tumorigenesisby regulating the mTOR/p70S6K pathway in esophageal squamous cell carcinoma. The expression patterns of peroxiredoxin 1 along with peroxiredoxin 4 are involved in human lung cancer malignancy [10]. It has also been shown that peroxiredoxin 1 may be an important player in the pathogenesis of acute respiratory distress syndrome because of its role in promoting inflammation.

Peroxiredoxin-2 .It is a member of the peroxiredoxin family of antioxidant enzymes, which reduce hydrogen peroxide and alkyl hydroperoxides. The encoded protein may play an antioxidant protective role in cells, and may contribute to the antiviral activity of CD8 T-cells. This protein may have a proliferative effect and play a role in cancer development. Transcript variants encoding the same protein have been identified for this gene[25].The mechanism by which oxidative stress induces inflammation and vice versa is unclear but is of great importance, being apparently linked to many chronic inflammatory diseases. We show here that inflammatory stimuli induce release of oxidized peroxiredoxin-2 (PRDX2), a ubiquitous redox-active intracellular enzyme. Once released, the extracellular PRDX2 acts as a redox-dependent inflammatory mediator, triggering macrophages to produce and release TNF-α. The oxidative coupling of glutathione (GSH) to PRDX2 cysteine residues (i.e., protein glutathionylation) occurs before or during PRDX2 release, a process central to the regulation of immunity [29]. Consistent with being part of an inflammatory cascade, we find that PRDX2 then induces TNF-α release. Unlike classical inflammatory cytokines, PRDX2 release does not reflect LPS-mediated induction of mRNA or protein synthesis; instead, PRDX2 is constitutively present in macrophages, mainly in the reduced form, and is released in the oxidized form on LPS stimulation. Release of PRDX2 is also observed in human embryonic kidney cells treated with TNF-α. Importantly, the PRDX2 substrate thioredoxin (TRX) is also released along with PRDX2, enabling an oxidative cascade that can alter the -SH status of surface proteins and thereby facilitate activation via cytokine and Toll-like receptors [36].

Peroxiredoxin 3 (PRX3), a typical 2-Cys peroxiredoxin located exclusively in the mitochondrial matrix, is the principal peroxidase responsible for metabolizing mitochondrial hydrogen peroxide, a byproduct of cellular respiration originating from the mitochondrial electron transport chain [47]. Mitochondrial oxidants are produced in excess in cancer cells due to oncogenic transformation and metabolic reorganization, and signals through FOXM1 and other redox-responsive factors to support a hyper-proliferative state. Over-expression of PRX3 in cancer cells has been shown to counteract oncogene-induced senescence and support tumor cell growth and survival making PRX3 a credible therapeutic target. Using malignant mesothelioma (MM) cells stably expressing shRNAs to PRX3 we show that decreased expression of PRX3 alters mitochondrial structure, function and cell cycle kinetic [7].

Conclusion

Bacterial stress response is mediated by global regulatory mechanisms affecting various pathways. Several regulatory mechanisms operated by transcriptional control, translational control, and proteolysis mechanism of bacteria in extreme condition. The fact that antimicrobials themselves are growth compromising agents also that activate bacterial stress responses has important implications for antimicrobial resistance development, given the link between stress and resistance. Studies clarified the efficacy of stress enzyme as a therapy agent in the treatment of many diseases such as myocardial ischemia, Peyronie's disease, hemolytic anemia, multiple sclerosis, Behçet's syndrome, respiratory distress syndrome and hemolytic anemia etc and in improving the clinical irradiation treatment of malignant diseases such as breast cancer. There is also increasing evidence that radical scavengers like superoxide dismutase may influence the outcome and progression of diabetic retinopathy. These stress enzymes also used successfully as an antifibrotic drug

and anti-inflammatory agent. In addition these enzymes are included in cosmetic products to reduce free radical damage to skin.

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